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SPINAL CORD INJURY REHABILITATION EVIDENCE

Lower Limb, Balance and Walking Following Spinal Cord Injury

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Key Points

Neuromuscular Electrical Stimulation (NMES) programs are beneficial in preventing and restoring lower limb muscle atrophy as well as improving stimulated lower limb muscle strength and endurance but the persistence of effects after the NMES has ended is not known

Functional Electrical Stimulation (FES)-assisted exercise is beneficial in preventing and restoring lower limb muscle atrophy as well as improving lower limb muscle strength and endurance in motor complete SCI.

Community-based ambulation training that is progressively challenged may result in long-lasting benefits in incomplete SCI.

For patients less than 12 months post-SCI, Body-weight Supported Treadmill Training (BWSTT) may have similar effects on gait outcomes as overground mobility training of similar intensity.

Body weight-support gait training strategies can improve gait outcomes in chronic, incomplete SCI, but most body weight-support strategies (overground, treadmill, with FES) are equally effective at improving walking speed. Robotic training was the least effective at improving walking speed.

Down-conditioning (DC) reflex protocols of the soleus could facilitate gait outcomes.

Repetitive transcranial magnetic stimulation (rTMS) combined with overground locomotor training may not afford further benefits over overground locomotor training alone.

There is limited evidence for the benefits of combining the use of certain pharmacological agents with gait training on ambulation in individuals with SCI.

FES-assisted walking can enable walking or enhance walking speed in incomplete SCI or complete (T4-T11) SCI. Regular use of FES in gait training or activities of daily living can lead to improvement in walking even when the stimulator is not in use.

BWSTT combined with FES of the common peroneal nerve can lead to an overall enhancement of short-distance functional ambulation.

Electrical stimulation is shown to be a more effective form of locomotor training than manual assistance and braces.

Stimulation with FES while ambulating on a BWS treadmill can increase SCIM mobility scores. BWSTT combined with FES to the quadriceps and hamstrings muscles can enhance functional ambulation.

While an 8 channel neuroprosthesis system is safe and reliable, its use with rehabilitation training showed no statistically significant difference in walking outcomes.

An ankle-foot-orthosis can enhance walking function in incomplete SCI patients who have drop-foot.

Reciprocal Gait Orthosis (RGO) can enable slow walking in participants with thoracic lesions, and not at speeds sufficient for community ambulation. The advantages of RGOs appear largely

restricted to the general health, well-being and safety benefits related to practice of standing and the ability to ambulate short-distances in the home or indoor settings.

Powered Gait Orthosis (PGO), more commonly known as exoskeletons, can enable safe walking and reduce energy expenditure compared to passive bracing in patients with thoracic injuries.

There is limited evidence that a combined approach of bracing and FES results in additional benefit to functional ambulation in paraplegic patients with complete SCI.

There is limited evidence that whole body vibration improves walking function in incomplete SCI.

Electromyography (EMG) Biofeedback may improve gait outcomes in incomplete SCI.

Locomotor training programs are beneficial in improving lower limb muscle strength although in acute SCI similar strength increases may be obtained with conventional rehabilitation.

The real benefit of locomotor training on muscle strength may be realized when it is combined with conventional therapy. This should be further explored in acute, incomplete SCI where better functional outcomes may be realized with the combination of therapies.

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1.0 Executive Summary

What Lower Limb, Balance, and Walking problems occur after injury?

- Loss of function in the lower limbs due to SCI can extend from complete paralysis to varying levels of voluntary muscle activation. The rehabilitation of lower extremity function after SCI has generally focused on the recovery of gait. Even when functional ambulation may not be possible (e.g. in complete tetraplegia), lower limb interventions can be targeted to maintain muscle health as well as reduce other complications, such as decreased cardiovascular health, osteoporosis, or wounds. Minimizing the risk of these complications would ease health costs related to the treatment of these sequelae and also could promote participation in society and/or the workforce.

What are the chances of recovering from Lower Limb, Balance and Walking problems after Spinal Cord Injury?

- Most patients classified with an AIS A (complete motor and sensory) spinal cord injury have very slim chances of walking independently in the community again compared to the other AIS grading levels[1]
- Those who regain some community walking function usually have lower levels of injuries (T12-L3) [1]
- Overall ambulation recovery for AIS B (motor complete, sensory incomplete) patients is at around 33%[1]
- AIS C and AIS D patients generally have a very good prognosis for regaining ambulatory/walking function[1]
- However, the ability to recover walking function from a spinal cord injury decreases as one ages[1]

What management options are there for lower limb, balance, and walking following spinal cord injury?

Non-Pharmacological Options

- **Sitting, Standing and Balance Training:**
  - There are relatively few studies that provide information on balance as an outcome (of an intervention) in people with SCI. Early balance training does not appear to enhance the effects of standard physical therapy in either sitting or standing balance, but people that engaged in overground or BWSTT *and* were able to walk showed improvements in their balance scores.[2,9,10,11,12]
  - Visual field feedback training leads to substantial improvements in static and dynamic standing (eyes open and closed scores), and improvements in balance performance during training-irrelevant tasks.[3,4] Results from 1 RCT found that task-specific sitting balance exercises for an additional 3 weeks in acute SCI had no effect on balance outcomes.
  - In people with chronic SCI who cannot stand, sitting balance can be improved with both static and dynamic task specific training. For people with lower severity injuries (e.g., AIS C and D), BWS over ground training combined with physiotherapist-led task-specific exercises and feedback appear to be more effective to improve standing function than BWSTT alone.[5,6,7,8]
  - In studying the effects of task-specific balance exercises in acute SCI, 1 RCT showed no difference in balance outcomes after an additional 3 weeks of training.[49]

- **Strengthening Lower Limb Function:**

- Typically, studies to improve walking focus on individuals with incomplete SCI and look at walking-related outcomes (e.g., walking speed or distance). However, some investigators have also examined the relationship between changes in lower limb strength and walking ability. For the most part, these therapies include a form of body-weight supported treadmill training, and the patient's limb movements may be assisted by any (or a combination) of: therapist, electrical stimulation (i.e., FES) or a robotically controlled servo-mechanism.[13,14,15,16,17,18,19]
- In general, investigators have noted significant increases of lower limb strength following locomotor training, despite variations between training protocols and specific methods employed. [13,14,15,16,18,19]

- Despite all investigators reporting some increases in lower limb muscle strength following locomotor training (in individuals with chronic SCI, and in 1 study with subacute SCI),[20] enhanced walking capability was not necessarily associated with parallel increases in strength, nor do we know the clinical relevance of strength gains found. [15,16,17,18,19]

- However, a study that examined the effects of a 12-week resistance and plyometric training program, improvements in knee extensor and ankle plantarflexor torque production were accompanied by >30% improvement in gait speed.[21] There is also weak evidence (from 1 study, n = 3) that significant improvements in muscle strength may be realized when locomotor training is combined with conventional therapy.[14]

- **Gait Re-training Strategies**
  - Overground training can only be undertaken with higher functioning individuals with incomplete SCI. However, overground training provides an important mode of exercise for improving walking function, and likely other physical and mental functions (e.g., muscle strength, balance, bone health, cardiovascular function, depression symptoms) shown to be positively affected by exercise in the general population. Oh and Park (2013)[22] found that an intensive 6X/week, 4 week training program resulted in effects at 1 year follow-up and demonstrate the positive benefits of exercise.
  - There is evidence from 1 RCT and multiple pre-post-studies that BWSTT can improve gait outcomes in chronic, incomplete SCI, and most body weight-support strategies (overground, treadmill, with FES) are equally effective at improving walking speed. Robotic training was the least effective at improving walking speed.[9-12, 15,17,18,23,24,25,26]

- **Orthoses/Braces**
  - Two studies[27,28] examined the immediate effects of an ankle-foot-orthosis after randomizing different brace conditions. Positive effects consisted of increased gait speed, step length, cadence and improved performance on the 6 Minute Walk test. It is generally recognized in the field that effects from an AFO are attained immediately, although it is likely that practice over a few sessions may improve a participant's confidence, learning and function.
  - The Reciprocating Gait Orthosis (RGO) (or variants of it) is the most common bilateral HKAFO for people with thoracic injuries, as it permits ambulation and in some cases, stairs to be performed.
  - Most studies showed that HKAFOs may facilitate the ability of people with subacute or chronic complete paraplegia to stand independently and to achieve some functional walking skills, such as stepping up on curbs or climbing stairs.
  - It has been recommended that orthoses or braces are best for people who are well-motivated, with complete SCI at T9 or below or incomplete SCI at any level, with good postural control and good level of fitness.[29,30,31]

- **Functional Stimulation, PES, and Walking**
    - The functional benefits derived from FES are also quite variable. For instance, one study showed[32] that most people showed a modest improvement in gait speed (average: 4 m/min), with greater gains for the more severely disabled participants. Higher-functioning participants felt that this small benefit in gait speed did not warrant the daily use of FES.
    - Other research[33] reported that there was a tendency for people with initially faster gait speed to have greater absolute improvements. Thus, outcomes from FES-use also seem to be quite variable in terms of walking speed[32, 33] or distance.[34]

    - 1 RCT in people with either complete or incomplete SCI found that PES-assisted exercise increased voluntary quads strength over those with no intervention (though we don't know if strength increases were clinically important).[36]

    - PES exercise to ankle flexor muscles found stimulated leg could generate significantly higher torque and simulated muscle forces than on the untrained leg.[35, 37,38,39]

    - FES-assisted walking can enable walking or enhance walking speed in incomplete SCI or complete (T4-T11) SCI. Regular use of FES in gait training or activities of daily living can lead to improvement in walking even when the stimulator is not in use.[33,34,40,41,42,43,44]

    - There is also evidence that electrical stimulation can have increased benefits over manual assistance or braces (driven gait orthosis)[45] and that BWSTT combined with FES to the quadriceps and hamstrings muscles can enhance functional ambulation.

Pharmacological Options

- The studies on clonidine (oral or intrathecal), cyproheptadine and baclofen demonstrate improvements in various aspects of gait (i.e. walking speed, posture, spasticity), but no improvements led to significant functional changes in walking.
- The greatest improvements have been found in more severely disabled participants and in many cases, and the effects were retained following washout of clonidine.[46] Bradycardia and hypotension, common side-effects of oral clonidine can be lessened with intrathecal injection of clonidine (150-450µg).[47]
- One high-quality randomized, placebo-controlled, double-blinded crossover study[48] (N=9) provided level 1 evidence that a combination of physical therapy (including gait training) and GM-1 ganglioside improved motor scores, walking distance, and walking speed in chronic SCI participants compared to physical therapy plus placebo.

2.0 Introduction

Lower Limb, Balance and Walking Following Spinal Cord Injury

Loss of function in the lower limbs due to SCI can extend from complete paralysis to varying levels of voluntary muscle activation and sensation. The rehabilitation of lower extremity function after SCI has generally focused on the recovery of gait. Even when functional ambulation may not be possible (e.g., in complete tetraplegia), lower limb interventions can be targeted to maintain muscle health as well as reduce other complications, such as decreased cardiovascular health, osteoporosis, or wounds. Minimizing the risk of these complications would ease health costs related to the treatment of these sequelae and also to promote participation in society as productive members of the workforce. Conventional rehabilitation strategies for enhancing lower limb function after SCI have focused on range of motion and stretching, active exercises, electrical stimulation to strengthen functioning

musculature, and functional training in daily mobility tasks. Standing and overground ambulation training are also important components of conventional rehabilitation using various bracing and assistive devices (O'Sullivan and Schmitz 1994; Somers 1992). In the last several years, we have seen increasing emphasis on providing task-specific training of functional movements, such as walking, with the help of body weight support and treadmills. We have also seen exciting advances in technology applications for facilitating or augmenting gait rehabilitation strategies, such as robotic devices for treadmill gait retraining (Hesse et al., 2004; Colombo et al., 2001), the introduction of microstimulators for activating paralyzed muscles (Weber et al., 2004), and more recently, the application of epidural spinal cord stimulation in combination with intensive therapy (Harkema et al., 2011). In the following sections, we review evidence for the efficacy of these various lower limb rehabilitation interventions on lower limb muscle strength and ambulatory capacity following SCI. As will be evident from the review, injury level, severity, chronicity, as well as institutional resources must all be taken into account to help guide the clinical decision-making process and expected outcomes.

3.0 Systematic Reviews

Table 1: Systematic Reviews Lower Limb

Authors; Country Date included in the review Number of articles Level of Evidence Type of Study Score	Method: Databases:	Conclusions
Louie et al. 2015 Canada Systematic Review AMSTAR= 8/11 N= 15	**Methods:** A systematic search in computerized databases was conducted to identify articles that reported on walking outcomes when using a powered exoskeleton. Individual gait speed data from each study was extracted. Pearson correlations were performed between gait speed and 1) age, 2) years post-injury, 3) injury level, and 4) number of training sessions. **Databases:** MEDLINE (1946 to May 6, 2015), EMBASE (1980 to May 6, 2015), Cochrane Central Register of Controlled Trials (1991 to May 6, 2015), and CINAHL (1982 to May 6, 2015)	1. Gait speed, ranged from 0.031m/s to 0.71m/s. The mean gait speed attained by the 84 participants in these 12 studies was 0.26m/s (SD: 0.15m/s) 2. An aggregate mean of 19.8 (SD= 18.6, n= 79) training sessions was calculated across all studies; training sessions were 60 to 120min in duration. 3. Participants ambulated on a body weight-supported treadmill while wearing the Hybrid Assistive Limb (HAL). At the end of the intervention period, the participants improved their mean gait speed without the exoskeleton from 0.28m/s to 0.50m/s ($p< 0.05$, n= 8, effect size= 0.71). They also demonstrated an improvement in mean 6MWT distance from 70.1 m to 163.3 m ($p< 0.05$, n= 8, effect size= 0.64). 4. A significant correlation was found between increasing age and faster gait speed (r= 0.27, 95% CI 0.02–0.48, p= 0.03, n= 63). However, no relationship was found between injury duration and gait speed (r= 0.19, 95% CI−0.09–0.44, p= 0.18, n= 53) from 10 studies. From the 12 studies, we found a significant correlation between injury level and gait speed (r= 0.27, 95% CI 0.02–0.48, p = 0.03, n = 63).

		5. Those who were able to practice longer with the powered exoskeleton achieved faster gait speeds (r= 0.27, 95% CI 0.003–0.49, p= 0.048, n= 56).
Bochkezanian et al. 2015 Australia Systematic Review AMSTAR= 9/11 N= 9	**Methods**: A search was conducted for randomized controlled trials (RCTs), controlled trials, uncontrolled clinical trials, case series and cross-over studies involving exercise interventions that included a combination of aerobic and strength components, either in circuit-mode or in sequence for people with SCI. Methodological quality was independently rated using the PEDro scale and key findings were extracted from trials by two reviewers. **Databases:** PEDro, Web of Science, MEDLINE via OvidSP, AMED—Allied and Complementary Medicine via OvidSP, Cinahl via Ebsco and Scopus from earliest record till February, 2013.	1. One of the RCT studies of 'fair' quality that used a twice weekly circuit resistance in combination with arm ergometry intervention, showed a significant within-training group effect on aerobic fitness with MD (95% CI) of 13.8bpm W^{-1} (0.63–26.9) and between-group effect on aerobic fitness with MD (95% CI) value of 13.1bpm. W^{-1} (0.2–25.98) but only for participants with tetraplegia. 2. Four studies of poor quality and with no control groups found no statistically significant within-group improvements in aerobic measures. 3. Most of these studies showed statistically significant within-group differences in muscle strength on some of the muscle groups assessed. 4. The only 'fair' quality study that used a control group reported statistically significant improvements in muscle strength only on one of the muscle groups assessed. In this case, the within-group MD (95% CI) was 4.5 kg (0.93–8.06) and 4.3 kg (0.10–8.49), for right and left biceps, respectively. A significant between-group effect was found for right biceps only with a MD (95% CI) of 4.6 kg (0.38–8.8)
Federici et al. 2015 Italy Systematic Review AMSTAR= 7/11 N= 27	**Methods**: The PRISMA guidelines were used to review literature on the use of powered and active lower limb exoskeletons for neurorehabilitative training in paraplegic participants. We reviewed 27 studies published between 2001 and 2014, involving a total of 144 participants from the USA, Japan, Germany, Sweden, Israel, Italy, and Spain. Seventy percent of the studies were experimental tests of safety or efficacy and 29% evaluated rehabilitative effectiveness through uncontrolled (22%) or controlled (7%) clinical trials. **Databases**: Articles were retrieved in a search of the electronic databases PubMed, EBSCO, Web of Science, Scopus, ProQuest, and Google Scholar.	1. The studies confirmed that the HAL, Tibion Bionic Technologies, and Ekso devices were safe to use in controlled environments, and with the assistance of expert professionals. 2. Exoskeletons provide a safe and practical method of neurorehabilitation which is not physically exhausting and makes minimal demands on working memory. 3. It is easy to learn to use an exoskeleton and they increase mobility, improve functioning and reduce the risk of secondary injury by reinstating a more normal gait pattern.
Lajeunesse et al. 2015 Canada Systematic Review AMSTAR= 5/11 N= 7	**Methods:** Systematically review the usefulness of lower limb exoskeletons used for functional mobility of people with spinal cord injury. Seven articles were selected. **Databases**: A systematic review of the literature (January 2004 to April 2014) was done using the databases PubMed, CINAHL and EMBASE and groups of keywords associated with "exoskeleton", "lower limb" and "paraplegia".	1. The applicability and effectiveness of lower limb exoskeletons as assistive devices have only been demonstrated in the lab, but not yet in the community. 2. More research is needed on walking performance with these exoskeletons compared to other mobility devices and other training contexts in the community.

Wall et al. 2015 Sweden Systematic Review AMSTAR= 8/11 N= 7	**Methods:** Systematically review the literature on clinical applications of the Hybrid Assistive Limb system for gait training. Out of 37 studies, 7 studies fulfilled inclusion criteria. Six studies were single group studies and 1 was an explorative randomized controlled trial. In total, these studies involved 140 participants of whom 118 completed the interventions and 107 used HAL for gait training. **Databases**: A systematic literature search was conducted using Web of Science, PubMed, CINAHL and clinicaltrials.gov and additional search was made using reference lists in identified reports. Abstracts were screened, relevant articles were reviewed and subject to quality assessment.	1. Most studies applied HAL training ≥2 times per week during ≥4 weeks with durations of ≥20 min per session. In studies involving persons with SCI, Aach et al. (2014) used a mean of 51.75 sessions while the number of sessions for persons with SCI in the study by Kubota et al. (2013) was 16. 3. The explorative RCT (Watanabe et al., 2014) compared the effect of HAL-training to the effect of conventional training in the subacute phase after stroke and included 11 participants in each group. The study shows a significant difference (p = 0.04) according to the Functional Ambulation Categories (FAC) between groups, in favor for the HAL training group.
do Espirito Santo et al. 2014 Brazil Systematic Review AMSTAR= 8/11 N= 5	**Methods:** The systematic review explored the effectiveness of body weight-support treadmill training (BWSTT) for muscle atrophy management in people with spinal cord injury (SCI). A total of 5 studies were included. The methodological quality of the articles included was classified according to Jovell and Navarro-Rubio. **Databases**: The following databases were consulted from January to October 2013: PubMed, Institute for Scientific Information (ISI), Science Direct and Lilacs.	1. The period of intervention with BWSTT therapy ranged from 9 to 48 weeks, with a minimum and maximum session number of 45 and 144 respectively, and a mode of 48 sessions was the predominant quantity number. The frequency of therapeutic approach ranged from two to five times a week, and there was a predominance of two sessions per week, lasting a minimum of 5 min (initial sessions) and a maximum of 30 min. 2. The treadmill speed, another parameter of training intensity, was initially established at an average of 0.3m/s. For two studies, the reduction of the BWS resulted in increased speed; however, in one article, the final speed was omitted. The average of the final evaluated speed was 0.6 m/s. 3. In acute incomplete SCI, the CSA of the thigh muscles and calf increased in 12 and 14% of the participants, respectively, compared with baseline. In chronic incomplete SCI, BWSTT was also effective for increasing the muscle trophism of the lower limbs (thigh and calf), and the values increased from 2.3 to 16.8%, compared with the reference group that did not receive locomotor training muscle trophism was only observed when BWSTT was combined with NMES, where the quadriceps CSA increased from 49.81 ± 9.36 to 57.33 ±10.32 cm.
Arazpour et al. 2015 UK	**Methods:** Papers were selected from peer-reviewed journals, which demonstrated or reported temporal–spatial, kinematics, and kinetic effects or clinical efficacy by the use of relevant tests, such as the 6-min walk test, 10-m walk test, and self-efficacy measures, or by assessing physiological cost index (PCI) when SCI participants used powered orthoses after being screened for	1. Efficacy was demonstrated in producing activated motion of lower limb joints. 2. Powered gait orthoses have a beneficial effect on the kinetics, kinematics, and temporal–spatial parameters of gait, but their effect on

Systematic Review AMSTAR= 6 N= 16	relevance. To be included, the intervention involved a powered reciprocating gait orthosis (RGO), but without the use of partial bodyweight relief; the participants were all diagnosed with SCI; the assessment of gait was undertaken using recognized tests. **Databases**: ISI Web of Knowledge, PubMed, Google Scholar, Science Direct, Scopus	muscle activity in individuals with spinal cord injury is still unclear. 3. Magnitudes of the muscle activity of tibialis anterior, quadriceps, and hamstrings were higher with the new RGO with a variable constraint hip mechanism, orthosis as compared to a mechanical IRGO and normal walking
Bani et al. 2014 UK Systematic Review AMSTAR= 7/11 N= 20	**Methods:** This review examined papers which assessed purely mechanical orthosis (consisting of RGO, medial single joint orthoses and hip guidance orthoses, and also included KAFOs) on independence, energy expenditure, gait parameters, stability, system reliability, comfort and cosmesis in people with SCI. Any papers evaluating orthoses utilizing FES or actuators on other patient groups or healthy participants were excluded. Only papers written in English from 1960 to 2012 with full text available were studied. **Databases**: PubMed, ISI web of knowledge and Science Direct	1. Independence and cosmesis are improved when using MLOs 2. Gait parameters, energy expenditure and stability are all improved when using RGOs
Ibitoye et al. 2014 Malaysia Systematic Review AMSTAR= 7/11 N= 59	**Methods:** We conducted a systematic review to examine the effectiveness of eEMG potentials to assess muscle force and fatigue, particularly as a biofeedback descriptor of FES-evoked contractions in individuals with spinal cord injury. At the outset, 2867 citations were identified, and 59 trials met the inclusion criteria. **Databases**: IEEE Xplore, IOP Science, MEDLINE, Science Direct, Scopus, SpringerLink, PubMed, Nature, Google Scholar	1. eEMG is effective at quantifying muscle force and fatigue during isometric contraction, but may not be effective during dynamic contractions including cycling and stepping. 2. Positive correlation of up to $r = 0.90$ ($p < 0.05$) between the decline in the peak-to-peak amplitude of the eEMG and the decline in the force output during fatiguing isometric contractions has been reported. 3. In the available prediction models, the performance index of the eEMG signal to estimate the generated muscle force ranged from 3.8% to 34% for 18 s to 70 s ahead of the actual muscle force generation.
Panisset et al. 2015 Australia Systematic Review AMSTAR= 10/11 N= 11	**Methods:** A comprehensive search (Any-2014) of eleven databases identified studies evaluating exercise interventions initiated within 12 weeks after SCI on muscle and bone loss in paralyzed limbs and comparing with standard care or immobilization. Two reviewers assessed methodological quality. One reviewer extracted data and critiqued results according to the Spinal Cord Injury Rehabilitation Evidence body of evidence framework. **Databases**: Academic Search Complete, CINHAL, Cochrane, DOAJ, MEDLINE (OVID interface), Pedro, PhysEdIndex, PubMED, SCOPUS, Sports & Rehab and SPORTSDiscus, Google Scholar	1. Two studies found significant positive effects of high-load FES-resisted stance on physiological measures of muscle. 2. Three reported positive effects of 3 months of Functional Electrical Stimulation (FES) on muscle size. 3. Two studies found positive effects of 6-month body-weight supported treadmill training or FES on trabecular bone using pQCT.
Ellaway et al. 2014 UK	**Methods:** This article reviews the attempts that have been made to restore sensorimotor function and to obtain functional benefits from the application of repetitive transcranial magnetic	1. High-frequency (20 Hz) rTMS lead to a significant improvement in clinical lower extremity motor scores. 2. A 5 Hz rTMS protocol decreased the H-reflex to M-wave ratio for the soleus

Systematic Review AMSTAR= 3/11 N= 5	stimulation (rTMS) of the cortex following incomplete spinal cord injury. **Databases**: Not specified	muscle and, when repeated during a 2-week period, rTMS produced long-lasting (at least 1 week) clinical improvement in spasticity of lower limbs.
Wessels et al. 2010 Netherlands Systematic Review AMSTAR= 8/11 N= 17	**Methods:** In the search strategy MeSH-terms and text words for participants (paraplegia, quadriplegia, spinal cord injuries) and interventions (gait, hydrotherapy, robotics, weight bearing, body weight support, BWS, driven gait orthosis (DGO) gait training, locomotion training, locomotor training, lokomat, robotics, treadmill, weight bearing) were combined. Two of the authors (MW and SdeG) evaluated the search strategy and the initial selection criteria on the first 100 retrieved articles. The search was conducted by the first author. Reference lists of all selected trials and retrieved reviews over the past 2 years were screened. **Databases**: Cochrane Central Register of Controlled Trials (Cochrane Library), MEDLINE (PubMed and OVID), EMBASE (OVID), Cumulative Index to Nursing and Allied Health Literature (CINAHL) through OVID, the Physiotherapy Evidence Database (PEDro) and DocOnline, a reference database of the Dutch Institute of Allied Health Professions	1. Two randomized controlled trials showed that participants with injuries of less than one year duration reached higher scores on the locomotor item of the Functional Independence Measure (range 1–7) in the over-ground training group compared with the body weight-supported treadmill training group. 2. Only for persons with an American Spinal Injury Association Impairment Scale C or D was the mean difference significant, with 0.80 (95% confidence interval 0.04–1.56). 3. No differences were found regarding walking velocity, activities of daily living or quality of life.
Mehrholz et al. 2012 Germany Systematic Review AMSTAR: 9 N=5	**Method:** Review randomized controlled trials involving people with SCI that compared locomotor training to a control of any other exercise or no treatment to assess the effects of locomotor training on the improvement in walking speed and walking capacity for people with traumatic SCI. **Database:** Cochrane Injuries Group's Specialised Register (searched Nov 2011); Cochrane Central Register of Controlled Trials; MEDLINE (1966 to Nov 2011); EMBASE (1980 to Nov 2011); CINAHL (1982 to Nov 2011); Allied and Complementary Medicine Database (1985 to Nov 2011); SPORTDiscus (1949 to Nov 2011); PEDro (searched Nov 2011); COMPENDEX (1972 to Nov 2011); INSPEC (1969 to Nov 2011). Online trials databases Current Controlled Trials (www.controlled-trials.com/isrctn) and Clinical Trials (www.clinicaltrials.gov) was searched.	1. 4 trials involving a total of 274 participants measured walking speed and found that the use of bodyweight supported treadmill training (BWSTT) as locomotor training for people after SCI did not increase walking velocity. The pooled mean difference (fixed-effect model) was 0.03m/s (95%CI: -0.05-0.11). 2. 3 trials involving a total of 234 participants measured walking distance (6MWT) and found that the use of BWSTT as locomotor training for people after SCI did not significantly increase walking distance (pooled mean difference (random-effects model) = -1.25 m (95%CI: -41.26=3.77). 3. 1 trial involving 146 participants measured recovery of independent walking and found that use of BWSTT as locomotor training for people after SCI did not increase the chances of walking independently. **4.** 1 trial involving 74 participants found that the use of robotic-assisted locomotor training as locomotor training for people after SCI did not significantly increase the walking velocity (mean difference = 0.06 m/s (95%CI: 0.01-0.13)) and actually **decreased** walking distance at final follow-up (mean difference = 10.29 m (95%CI: 0.15-20.43).

		5. 1 trial involving 88 participants found that people with SCI who used functional electrical stimulation combined with BWSTT did not significantly increase walking speed (mean difference = -0.03 m/s (95%CI: -0.11-0.06)). **6.** 1 trial involving 74 participants found that people with SCI who used functional electrical stimulation combined with BWSTT did not significantly increase walking distance (mean difference = 2.43 m (95%CI: -10.82-15.67)).
Mehrholz et al. 2008 Germany Systematic Review AMSTAR=8 N=4 (n=222)	**Methods:** Literature search for articles with randomized controlled trials (RCT) that compared locomotor training to any other exercise provided with the goal of improving walking function after SCI or to a no-treatment control group. Interventions include: Lokomat, BWSTT and BWSTT+FES. Outcome measures include speed of walking, 6MWT and FIM. **Databases:** Cochrane Injuries Group Specialized Register (last searched June 2007); Cochrane Central Register of Controlled Trails (CENTRAL) (*The Cochrane Library 2007,* Issue 2); MEDLINE (1966-June 2007); EMBASE (1980- June 2007); National Research Register (2007, Issue 2); CINAHL (1982-June 2007); Allied and Complementary Medicine Database (1985- June 2007); SPORTDiscus; PEDro (the Physiotherapy Evidence Database) (searched June 2007); COMPENDEX (engineering databases) (1972-June 2007); INSPEC (1969 – June 2007); National Research Register (2007, Issue 2); Zetoc; Current Controlled Trials	1. We found 4 RCTs for inclusion 2. No statistically significant difference in the effect of various locomotor training on walking function after SCI comparing BWSTT with or without FES or robotic-assisted locomotor training. 3. Adverse events and drop- outs were not more frequent for participants who received BWSTT with or without FES or robotic-assisted locomotor training
Domingo et al. 2012 Canada Systematic Review AMSTAR: 7 N=11 (2 SCI)	**Method:** Systematically review the effects of pharmacological agents on gait in people with SCI. Studies were included if they specifically reported outcome measures associated with gait. Exclusion criteria include animal studies, non-English, less than half the reported population had a SCI, or there were no measurable outcomes associated with the intervention. **Database:** MEDLINE/PubMed, CINAHL, EMBASE, PsycINFO and hand-searching.	1. One RCT provided Level 1 evidence that GM-1 ganglioside in combination with physical therapy improved motor scores, walking velocity and distance better than placebo and physical therapy in persons with incomplete SCI. 2. Multiple studies (levels 1-5 evidence) showed that clonidine and cyproheptadine may improve locomotor function and walking speed in severely impaired individuals with incomplete SCI. 3. Gains in walking speed associated with GM-1, cyproheptadine and clonidine are low compared to those seen with locomotor training. 4. There is Level 1 evidence that 4-aminopyridine and L-dopa were no better than placebo in helping to improve gait. 5. 2 Level 5 studies showed that baclofen had little to no effect on improving

		walking in persons with incomplete SCI.
Wittwer et al. 2013 Australia Systematic Review AMSTAR: 6 N=14 (2 SCI)	**Method:** Reviewed published English articles that explored effect of intentional synchronization of overground walking to externally-generated rhythmic auditory cues on temporal and/or spatial gait measures. Only studies with adult participants (>16 yrs) and gait disorders of neurological origin (excluding Parkinson's) were included. **Database:** AGELINE, AMED, AMI, CINAHL, Current Contents, EMBASE, MEDLINE, PsycINFO, PubMed.	1. Two non-controlled studies with a total of 46 participants found no significant changes in measures of velocity, cadence, stride length or symmetry.
Morawietz & Moffat 2013 UK Systematic Review AMSTAR: 4 N=8	**Method:** Reviewed randomized controlled trials evaluating locomotor therapies after incomplete SCI in an adult population. Restricted to English, German and Dutch publications only. **Database:** Allied and Complementary Medicine Database, CINAHL, Cochrane Database of Systematic Reviews, MEDLINE, Physiotherapy Evidence Database, PubMed.	1. For acute participants, gait parameters improved slightly more after BWSTT and robotic gait training. 2. For chronic participants, improvements were greater after BWSTT with functional electrical stimulation and overground training with functional electrical stimulation/body-weight support compared with BWSTT with manual assistance, robotic gait training, or conventional physiotherapy.
Lam et al. 2007 Canada Systematic Review AMSTAR=4 N= 41	**Methods:** Literature search for published literature evaluating the effectiveness of any treatment or therapy on functional ambulation in people with SCI Interventions include: BWSTT, FES, braces/orthoses and hybrid therapies. Outcome measures include FIM, WISCI-II, walking distance, and walking speed. **Databases:** PubMed/MEDLINE, CINAHL, EMBASE, PsycINFO	1. There is level 1 evidence of an overall enhancement of functional ambulation, as measured by overground gait speed, when BWSTT was combined with FES of the common peroneal nerve 2. There is level 1 evidence that a combination of physical therapy and GM-1 ganglioside improved motor scores, walking distance, and walking speed in chronic SCI participants 3. There is level 1 evidence that different modes of gait training (BWSTT vs. overground) result in similar effects
Swinnen et al. 2010 Belgium Systematic Review AMSTAR=4 N= 6	**Methods**: Literature search for articles written in English, French, German or Dutch, that included incomplete and complete adult SCI patients, over 18 years of age, participating in robot-assisted gait training intervention Outcome measures include trials without random assignment – pre-experimental; case reports, uncontrolled clinical trials **Databases:** MEDLINE, Web of Knowledge, Cochrane Library, Physiotherapy Evidence Database (PEDro) and Digital Academic Repositories (DAREnet) (1990–2009)	1. There is currently no evidence that robot-assisted gait training improves walking function more than other locomotor training strategies 2. Some improvements were reported related to body function (i.e. motor function) and limitations in activities (i.e. walking speed)
	Method: Review the differences in performance of SCI participants standing and walking with functional electrical stimulation (FES) systems and hybrid orthoses (combine FES with structural	1. Using FES does not influence the performance of participants with SCI. The magnitude of energy consumption based on the Physiological Cost Index

Karimi 2013 Iran Systematic Review AMSTAR: 3 N=17	support of an orthosis) based on results in published literature. Inclusion criteria: study focused on SCI with specification of level of injury, type of injury, and device used. English-only articles. Mechanical orthoses were not included in the study. **Database:** PubMed, EMBASE, ISI Web of Knowledge	(PCI) increased while walking with hybrid orthosis based on reciprocal gait orthosis (RGO) compared to the mechanical orthosis. 2. There is no evidence to support the positive effect of FES on cardiovascular fitness. 3. User performance with the mechanical orthoses was generally better than that of the hybrid and FES systems based on participant stability and energy consumption while walking. Participants also reportedly experienced a higher incidence of problems with the use of hybrid orthoses and FES systems compared with mechanical orthoses.

4.0 Sitting, Standing and Balance Training

Most individuals with incomplete SCI have the potential to recover some degree of mobility and many functional activities of daily living (ADL) through rehabilitation (McKinley et al., 1999). Proper balance control is important not only for mobility and ambulation, but in fact underlies daily home and community-based functional activities in sitting and standing (Huxham et al., 2001).
SCI is accompanied by changes in sensation, loss of muscle strength, decreased cognitive reserve and spasticity amongst a host of other pathological changes that may lead to balance and gait impairments. Balance and gait impairments in turn, may lead to falls. The incidence of falls in people with SCI has been reported to be as high as 75% with loss of balance being the primary perceived factor contributing to falls in incomplete SCI (Brotherton et al., 2006). Moreover, falls are a major contributor of SCI with falls being the most common cause of SCI in individuals > 60 years old (Dohle and Reding, 2011). It is not currently known the extent to which deficits in balance may affect people with SCI.

The central nervous system (CNS) maintains balance by integrating information from visual, vestibular and sensorimotor systems (Horak and Macpherson, 2006). Greater understanding of the principles underlying the neural control of movement and functional recovery following neurological injury has resulted in increased efforts to design rehabilitation strategies based on task-specific training (Wolpaw and Tennisen, 2001; Behrman and Harkema, 2007; Fouad and Telzaff, 2012). This concept has been translated to various rehabilitation interventions, such as those targeting walking outcomes (e.g. body-weight supported treadmill training) (Mehrholz et al., 2008; Van Hedel and Dietz, 2010; Wessels et al., 2010; Harkema et al., 2012) or arm and hand function (e.g. constraint-induced movement therapy) (Taub et al., 1999; Wolf et al., 2002). For balance, task specific rehabilitation similarly focuses on the achievement of the three main functional goals encompassing balance: 1) maintaining an antigravity posture such as sitting and standing, 2) anticipatory postural control during voluntary self-initiated movements and 3) reactive postural control during an unexpected perturbation (Berg, 1989).
There has been a great deal of focus on the effectiveness of gait training in SCI rehabilitation research (Mehrholz et al., 2008; Van Hedel and Dietz, 2010; Wessels et al., 2010; Harkema et al., 2012), but there has been relatively little attention on the impact of interventions specifically targeting balance outcomes. In other neurologic populations, there is some evidence that task-specific balance training can be effective for improving functional outcomes. A systematic review in people with stroke found moderate evidence that balance could be improved with exercises such as challenging static/dynamic balance ability and practice of balance in different functional tasks, including sitting, standing, walking, and stair climbing (Lubetzky-Vilnai and Kartin, 2010). In recent years, and with the rapid development in technology (e.g., exoskeletons, virtual-reality), there has been more data available about balance outcomes following gait training (Dobkin et al., 2006; Wu et al., 2012;

Harkema et al., 2012), as well as specific sitting (Boswell-Ruys et al., 2010; Harvey et al., 2011) or standing (Alexeeva et al., 2011) balance interventions in people with SCI.

Table 2: Sitting Balance

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Sitting Balance-Acute		
Harvey et al. 2011 Australia/Bangledesh RCT PEDro=8 N=32	**Population**: 32 individuals- 30 males and 2 females; chronic SCI; motor level T1 – L1; 29 AIS A, 2 AIS B, 1 AIS C; age range= 24-31y; years post injury= 8-17 weeks **Treatment**: In the control group, individuals received 6 weeks standard in patient rehabilitation. In the experimental group, participants received 6 weeks standard in patient rehabilitation + 3 additional 30-minute sessions/wk of 84 task specific exercises with 3 levels of difficulty (252 exercises) in unsupported sitting. **Outcome Measures:** Maximal Lean Test (Maximal Balance Range), Maximal Sideward Reach Test.	1. The mean between-group differences for the Maximal Lean Test, Maximal Sideward Reach Test and the Performance Item of the COPM were –20 mm, 5% arm length, and 0.5 points respectively.
Sitting Balance-Chronic (> 1 year SCI)		
Boswell-Ruys et al. 2010 Australia RCT PEDro=8 N=30	**Population:** 30 participants- 25 males and 5 females; 25 AIS A, 15 AIS B; level of injury: T1-12; mean age=45y; mean years post injury= 14.5y **Treatment:** Participants in the experimental group receieved 1hr of 84 task specific exercises with 3 grades of difficulty in an unsupported sitting 3 times a week for 6 weeks. The control group did not receive any intervention. **Outcome Measures:** Primary measures were: Upper Body Sway Test, Maximal Balance Range Test; Secondary measures were: Alternating Reach test (supported and unsupported), Seated Reach Test 45°to right, Coordinated Stability Test (Version A), Upper Body Sway Test (lateral and antero-posterior components).	1. The between-group mean difference for the maximal balance range was 64mm.
Kim et al. 2010 Korea Prospective Controlled Trial Level 2 N=12	**Population:** 12 individuals- 9 males and 3 females; 11 AIS A, 1 AIS B; level of injury: T6-12. mean age= 40.86y **Treatment:** The control group received conventional PT. The experimental group received conventional PT and goal-oriented training on a rocker board. The patients sat on a stable surface with their legs straight on the floor. Reach forwarrd, left and right, were all measured. Sessions were 5 sets of 10 reps 5 times a week for 4 weeks.	1. There was an increase in the MFRT distance in the experimental group. 2. The experimental group showed a decrease in sway area with both opened and closed eyes after training. 3. The experimental group showed a significant difference before and after training compared to the control, as shown by MFRT distance and swaying area.

	Outcome Measures: Modified Functional Reach Test, sway area and sway velocity using the Balance Performance Monitor	
Bjerkefors et al. 2006 Sweden Pre-post Level 4 N=10	**Population:** 10 individuals- 7 males and 3 females; 7 AIS A, 2 AIS B, 1 AIS C; level of injury between T3-12; mean age= 37.6 ± 12y; median years post-injury= 11.5y **Treatment:** Participants paddled a modified kayak ergometer for 60 minutes 3 times a week for 10 weeks. **Outcome Measures:** sit and reach tests	1. Sit and reach tests significantly increased from 3.5cm at baseline to 5.8cm at the end of 10 weeks.
Bjerkefors et al. 2007 Sweden Pre-post Level 4 N=10	**Population:** 10 individuals- 7 males and 3 females; 7 AIS A, 2 AIS B, 1 AIS C; level of injury between T3-12; mean age= 37.6 ± 12y; median years post-injury= 11.5y **Treatment:** Participants paddled a modified kayak ergometer for 60 minutes 3 times a week for 10 weeks. **Outcome Measures:** anterior-posterior (A/P), medio-lateral (M/L) angular and linear and twisting (TW) displacements on support surface translations - forward (FWD), backward (BWD) and lateral (LAT); Kinematic Responses include: I-onset of acceleration (unpredictable), II-constant velocity, III-deceleration (predictable), IV-end of deceleration	1. A/P angular and linear and TW angular during LAT translations for all kinematic responses were significantly decreased except II for A/P angular 2. M/L angular displacements during LAT translations-significant decrease for kinematic response IV. 3. M/L linear displacement during LAT translations-no significant effects for all kinematic responses.
Grigorenko et al. 2004 Sweden Pre-post Level 4 N=24	**Population:** Experimental group: 12 individuals- 9 males and 3 females; chronic SCI; 6 AIS A, 5 AIS B, 1 AIS C; level of injury: T2-11; mean age=40y; median years post-injury= 17y; Control group: 12 able bodied participants who did not train **Treatment:** Participants were involved in 2-3 modified kayak sessions on open water per week for 8 weeks. **Outcome Measures:** sitting quietly on a force plate-standard deviation (SD), median velocity, median frequency	1. Small effects in all 3 variables except on the median frequency in the sagittal plane (opposite to becoming normal) 2. Before training and comparing to the control group, all variables differed. 3. Small effects on balance variables-no significant effect.

SITTING BALANCE

Acute (< 6 months) SCI

One good quality RCT examined the effect of an additional 3 weeks of task specific exercises on sitting balance in individuals with acute SCI following 6 weeks of standard inpatient rehabilitation consisting of practice of activities of daily living (N=32, AIS A=29, AIS B=2, AIS C=1) (Harvey et al., 2011). Participants were mainly motor complete paraplegics with a median time since injury of 11 weeks. Both experimental and control groups received 6 weeks of standard inpatient rehabilitation consisting of practice of activities of daily living. Despite receiving more training sessions, there was no additional benefit to the experimental group compared to the control group on functional outcomes of sitting balance.

Chronic (> 1 year) SCI

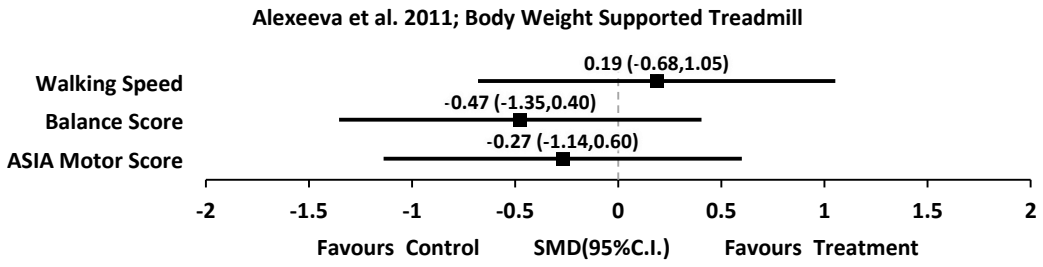
There were 5 studies that investigated the effects of various interventions (i.e. kayak ergometry, task specific exercises in unsupported sitting) on sitting balance. The majority of the participants had motor-complete SCI (N=76, AIS A=51, AIS B=23, AIS C=2). Sitting balance was significantly

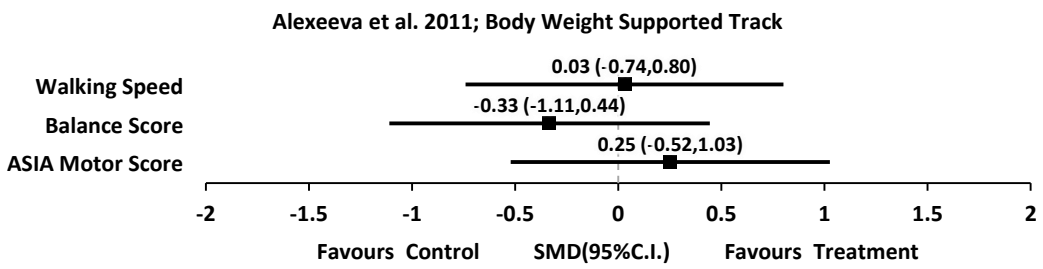
improved with kayak ergometer training in two Level 4 evidence trials with substantial transfer effects to functional tests in the wheelchair (Bjerkefors and Thorstensson, 2006; Bjerkefors et al., 2007). No significant effect was reported of 8 weeks open water kayak training vs. able-bodied control group who did not train (Grigorenko et al., 2004).

A good quality RCT assessed sitting balance in chronic SCI using the same task specific exercises as the study by Harvey *et al* (Harvey et al., 2011) in unsupported sitting for 6 weeks vs. a control group who received no training (N=30, AIS A=25, AIS B=15) (Boswell-Ruys et al., 2010). Overall improvements in both the training and control groups were reported. The addition of task-specific exercises using a rocker board to conventional physical therapy for 4 weeks yielded significant improvements in sit and reach tests as well as COP measures (N=12, AIS A=11, AIS B=1) (Kim et al. 2010). However, this was a relatively small study (N = 12) and it did not appear that participants were randomly assigned to the interventions.

Table 3: Standing Balnace

Author Year Country Score Research Design Total Sample Size	**Methods**	**Outcome**
Standing Balance-Acute		
Dobkin et al. 2006 USA RCT PEDro=2 N=146	**Population:** 146 individuals- 116 males and 30 females; 38 AIS, and 7 AIS D; level of injury: C5-L3; median age= 25y; time since injury= 1.03 months **Treatment:** The control group had 12 weeks of over ground training. The experimental group participated in 12 weeks of body weight support treadmill training. The sessions were 1 hour long for 45-60 sessions. 5 times a week for 12 weeks **Outcome Measures:** Berg Balance Scale	1. There were no differences in balance between the overground training group and the body-weight supported treadmill training group.
Standing Balance-Chronic Virtual Reality		
Villiger et al. 2013 Switzerland Pre-post Level 4 N=14	**Population:** 14 individuals- 9 males and 5 females; chronic SCI; 2 AIS C and 12 AIS D; level of injury: C4-T12. mean age= 53y; median years post-injury= 4y **Treatment:** Participants received 4-5 45-minute sessions of intensive virtual reality augmented training sessions per week for a total of 16-20 sessions. **Outcome Measures:** Berg Balance Scale	1. Significant increases were found for all patients in BBS (16.5% increase post treatment and 13% at follow up).
Sayenko et al. 2010 Canada, Japan Pre-post	**Population:** 6 participants- 5 males and 1 female; chronic SCI; 4 AIS C and 2 AIS D; level of injury: C4-T12; mean age= 41y; median years post-injury= 7y **Treatment:** Patients participated in 3 60-minute visual feedback training sessions, totalling 12 sessions. During training,	1. All participants showed substantial improvements in the scores, which varied between 236±94 and 130±14% of the initial values for different exercises. 2. Improvements were all statistically significant for both eyes open and closed except mean velocity in the medial/lateral direction.

Level 4 N=6	participants stood on a force platform and were asked to shift their center of pressure (COP) in the indicated directions as represented by a cursor on the monitor. **Outcome Measures:** Static standing eyes open and closed as measured by COP displacement; Dynamic standing as measured by voluntary COP displacement.	3. The balance performance during training-irrelevant tasks was significantly improved: for example, the area inside the stability zone after the training reached 221±86% of the pre-training values.
Tamburella et al. 2013 Italy Open-case study with retrospective matched controls Level 4 N=18	**Population:** 18 individuals- 9 males and 9 females; chronic SCI; 6 AIS D; level of injury: T9-L5; mean age= 52y; median time since injury: 2.3y **Treatment:** The control group participated in overground conventional rehabilitation including BWS standing and stepping on a treadmill and overground, balance exercises. The experimental group participated in 40 min of control group protocol and 20 min of specific vBFB (visual biofeedback task specific balance training). The sessions were 60 minutes long 5 times a week for a total of 8 weeks. **Outcome Measures:** Berg Balance Scale, COP measures, Timed Up and Go (TUG)	1. At T4, the experimental group saw an improvement in balance aned gait demonstrated by clinical and instrumental evaluation; the improvement was maintained at follow up examinations. 2. In the experimental group, the enhancement in balance that existed at T1 preceded the improvement in gait, and significant correlations between the improvements in gait and balance were observed. 3. In comparison with H data, vBFB treatment demonstrated a significant higher level of effecvtiveness than conventional rehab.
Standing Balance-Chronic Body Weight Support		
Alexeeva et al. 2011 USA RCT PEDro=7 Level 1 N=35	**Population:** 35 individuals- 30 males and 5 females; chornic SCI; 8 AIS C and 27 AIS D; level of injury: C2-T10. mean age= 38.5y; median years post injury= 4y **Treatment:** Patients participated in a 13-week training program, with three 1 hour sessions per week. The PT group is a structured rehab program individualized for each participant. The TRK group consisted of body weight supported ambulation on a fixed track. The TM group involved body weight supported ambulation on a treadmill. **Outcome Measures:** Tinetti Balance Scale	1. All three training groups showed significant improvements in maximal walking speed, muscle strength, and psychological well-being. 2. A significant improvement in balance was seen for PT and TRK groups but not for participants in the TM group.
	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%C.I.) as calculated from pre- and post-intervention data  	

		
Wu et al. 2012 USA Repeated assessment with crossover PEDro=4 Level 2 N=10	**Population:** 10 individuals- 8 males and 2 females; chronic SCI; all AIS D; level of injury: C2-T10; mean age= 47y; median time since injury=5y **Treatment:** Group 1 underwent 4 weeks of assistance training then 4 weeks of resistance training. Group 2 underwent 4 weeks of resistance training first, then 4 weeks of assistance training. Resistance was provided by a cable-driven robotic locomotor training system. Sessions were 45 minutes long, 3 times a week for 8 weeks. **Outcome Measures:** Berg Balance Scale.	1. A significant improvement in walking speed and balance in humans with SCI was observed after robotic treadmill training using the cable-driven robotic locomotor trainer.
Buehner et al. 2012 USA Prospective Cohort Study Level 2 N=225	**Population:** 225 individuals- 167 males and 58 females; chronic SCI; 57 AIS C and 167 AIS D; level of injury was not specified; mean age= 42.5y; median time since injury= 2.45y **Treatment:** NRN Locomotor Training Program consisting of manual-facilitated BWS standing and stepping on a treadmill and overground. Sessions included 1hr of treadmill training, 30 minutes overground assessment, and 15-30 minutes of community reintegration. Sessions were 5 days per week for non ambulators, 4 days per week for ambulators with pronounced assistance, and 3 days week for independent walkers. **Outcome Measures:** Berg Balance Scale, AIS classification, lower extremity pin prick, light touch and motor scores, 10MWT, 6MWT	1. Significant gains occurred in lower extremity motor scores. 2. Final Berg Balance Scale scores and initial lower extremity motor scores were positively related. 3. Although 70% of participants showed significantly improved gait speed after locomotor training, only 8% showed AIS category conversion.
Harkema et al. 2012 USA Prospective Cohort Study Level 2 N=196	**Population:** 169 individuals- 148 males and 48 females; chronic SCI; 66 AIS C and 130 AIS D; level of injury was not specified; mean age= 41y; median time since injury= 0.9y **Treatment:** NRN Locomotor Training Program consisting of manual-facilitated BWS standing and stepping on a treadmill and overground. Sessions included 1hr of treadmill training, 30 minutes overground assessment, and 15-30 minutes of community reintegration. Sessions were 5 days per week for non ambulators, 4 days per week for ambulators with pronounced assistance, and 3 days week for independent walkers. **Outcome Measures:** Berg Balance Scale, 6MWT, 10MWT	1. Outcome measures at enrollment showed high variability between patients with AIS grades C and D. 2. Significant improvement from enrollment to final evaluation was observed in balance and walking measures for patients with AIS grades C and D. 3. The magnitude of improvement significantly differed between AIS groups for all measures. 4. Time since SCI was not associated significantly with outcome measures at enrollment, but was related inversely to levels of improvement.

Lorenz et al. 2012 USA Prospective Cohort Study Level 2 N=337	**Population:** 337 participants- 255 males and 82 females; chronic SCI; 99 AIS C and 238 AIS D; level of injury: T10 or above; mean age= 40y; median time since injury= 1y **Treatment:** NRN Locomotor Training Program consisting of manual-facilitated BWS standing and stepping on a treadmill and overground. Sessions included 1hr of treadmill training, 30 minutes overground assessment, and 15-30 minutes of community reintegration. Sessions were 5 days per week for non ambulators, 4 days per week for ambulators with pronounced assistance, and 3 days week for independent walkers. **Outcome Measures:** Berg Balance Scale, 6MWT, 10MWT.	1. There was significant improvement on each outcome measure and significant attenuation of improvement over time. 2. Patients varied significantly across groups defined by recovery status and American Spinal Injury Association Impairment Scale (AIS) grade at enrollment with respect to baseline performance and rates of change over time. 3. Time since SCI was a significant determinant of the rate of recovery for all measures.
Behrman et al. 2012 USA Prospective Cohort Study Level 2 N=95	**Population:** 95 individuals- 75 males and 20 females; chronic SCI; 31 AIS C and 64 AIS D; level of injury= T11 or above; mean age= 43y; median time since injury= 1y; time since injury: <1 yr (n=47), 1-3 yrs (n=24), ≥3 yrs (n=24). **Treatment:** NRN Locomotor Training Program consisting of manual-facilitated BWS standing and stepping on a treadmill and overground. Sessions included 1hr of treadmill training, 30 minutes overground assessment, and 15-30 minutes of community reintegration. Sessions were 5 days per week for non ambulators, 4 days per week for ambulators with pronounced assistance, and 3 days week for independent walkers. **Outcome Measures:** Berg Balance Scale, 6MWT, 10MWT	1. Individuals classified within each of the 4 phases of the NRS were functionally discrete, as shown by significant differences in the mean values of balance, gait speed, walking endurance, and the variability of these measurements was significantly reduced by NRS classification. 2. The magnitude of improvements in these outcomes was also significantly different among phase groups.
Fritz et al. 2011 USA Pre-post Level 4 N=15	**Population:** 15 individuals- 11 males and 4 females; incomplete chronic SCI; <u>Lower functioning group:</u> 10 individuals- 8 males and 2 females; mean age= 38.5y; time since injury: 6.6y; AIS lower extremity score= 24; <u>Higher functioning group:</u> 5 individuals- 3 males and 2 females; mean age= 50.4y; time since injury= 5.7y; AIS lower extremity score= 44 **Treatment:** Participants received intensive mobility training (IMT) in activities that encouraged repetitive, task specific training of the lower extremities. IMT combines BWSTT, balance exercises, muscle strengthening, coordination and range of motion in a massed intensive therapy. Sessions were 3 hours a day for 3-5 days per week for a total of 10 weeks. **Outcome Measures:** Berg Balance Scale, Dynamic Gait Index (DGI)	1. Individuals in the higher functioning ISCI group (BBS score ≥45 and gait speed ≥0.6m/s) spent more time in the intensive therapy on average than individuals in the lower functioning ISCI group. 2. Effect sizes were comparable for changes in balance and mobility assessments between the lower and higher functioning groups, with the largest effect sizes observed for the DGI.
Musselman et al. 2009	**Population:** 4 participants- 2 males and 2 females; all AIS C; level of injury: C5-L1; mean age: 44.5y; Gender: median time since injury= 2.7y **Treatment:** Initial 3 months BWSTT by all 4 patients. Patients 1, 2 received 3 months skills	1. Overall improvements in walking speed met or exceeded the minimal clinically important difference for individuals with iSCI (> or = 0.05 m/s), particularly during the skill training phase (skill training: median=0.09 m/s, IQR=0.13; BWSTT: median=0.01 m/s, IQR=0.07).

Canada Case Series Level 4 N=4	training, followed by 3 months BWSTT. Patients 3, 4 received the training in reverse order. Sessions were 1 hour long, 5 days a week for 3 months. **Outcome measures:** Berg Balance Scale, Modified Emory Functional Ambulation Profile, 10MWT, 6MWT, Activities- specific Balance Confidence Scale.	2. Walking endurance, obstacle clearance, and stair climbing also improved with both types of intervention. Three of the 4 patients had retained their gains at follow-up (retention of walking speed: median=92%, IQR=63%). 3. The findings suggest that skill training was effective in this small group of individuals.

STANDING BALANCE

Acute (< 6 months) SCI

There was one lower quality RCT that compared BWSTT (experimental group) vs. over ground gait training (control group) in acute (<8 weeks post-injury) incomplete SCI (N=146, N=45 at 6 months; AIS C=38, AIS D=7, 12 weeks of training) (Dobkin et al., 2006) (Table 3). There were no significant differences in balance scores following training between the two groups. However, there was a large median difference between baseline and 6-months post-training in both groups, indicating that for people who were able to walk at six months (N=45), both types of interventions resulted in considerable improvements in balance scores.

Chronic (> 1 year) SCI

Virtual Reality

There were 3 trials that assessed standing balance in people with chronic incomplete SCI using virtual reality (VR) (N=38, AIS C=6, AIS D=20, Table 3). Two studies performed similar VR interventions consisting of standing on a force plate and performing task specific exercises while the center of pressure (COP) position signal was used for visual biofeedback for 4 and 8 weeks respectively (Sayenko et al., 2010; Tamburella et al., 2013). Pre-post studies support the feasibility and reported positive effects on balance function using this approach (Sayenko et al., 2010; Villiger et al. 2013). In the study by Tamburella *et al,* participants were randomized to receive active training with or without the visual biofeedback. After 8 weeks of training, only the experimental group showed significant improvements in BBS (Baseline= 26.0±10.69 to post-training=41.0±7.8) and Timed Up and Go test (Baseline=21.70±10.70 to post-training=15.22±6.14) (Tamburella et al., 2013).

Body Weight Support Training (BWST)

There were 4 trials that measured standing balance in incomplete SCI following body-weight supported treadmill training. One good quality RCT (Alexeeva et al., 2011), and three studies of level 4 evidence (Musselman et al., 2009; Fritz et al., 2011; Wu et al., 2012) utilized BWST in addition to various interventions such as treadmill, over ground, physical therapist (PT) skills training or a combination of these. After 8 weeks of training, PT skills training resulted in greater balance improvements than BWSTT and BWST on a track (Alexeeva et al., 2011). Small to medium effect sizes for the BBS (0.31-0.67) were reported when BWST was combined with 10 days of intensive mobility training (Fritz et al., 2011). An overall improvement in BBS was found when combining 8 weeks of BWSTT with resistance or assistance but no significant difference between the 2 interventions was reported (Wu et al., 2012).

Four level 4 evidence pre-post trials from the same clinical setting spanning reported significant improvements in balance scores following a program of 3-5 days per week of treadmill- progressing to overground-based BWST (NRN protocol; Behrman et al., 2012; Buehner et al., 2012; Harkema et al., 2012; Lorenz et al., 2012). In addition, this data set demonstrated that the Berg Balance Scale scores were significantly correlated to the severity of injury (Lorenz et al., 2012). Among the pre-post studies, effect sizes were generally small for interventions involving BWST regardless if they were combined with other types of therapy when assessed using the BBS (d=0.18-0.47) with the exception of 1 case-control trial (d=0.88) (Musselman et al., 2009).

There are some drawbacks of measuring balance with only functional outcomes. A ceiling effect was observed in BBS scores of SCI participants receiving BWST with assistance and resistance (Wu et al., 2012). Only one trial was able to use predictable and unpredictable perturbations to assess balance reactions after kayak ergometry training (Bjerkefors et al., 2007). Nonetheless, functional measures are quick, cost effective and easy to apply in both the research and clinical setting and have the added benefit of being validated for the SCI population (Lemay and Nadeau, 2009). It would be optimal that when assessing balance, where feasible, reactions to sudden movements are included in order to give a more comprehensive understanding of balance capacity in persons with SCI.

CONCLUSION

Only preliminary recommendations can be made from the results of this review as there are relatively few studies that provide information on specific balance outcomes in SCI. Early balance training does not appear to enhance the effects of standard physical therapy in either sitting or standing balance. In people with chronic SCI who cannot stand, sitting balance can be improved with both static and dynamic task specific training. For participants with lower severity injuries (e.g., AIS C and D), BWS over ground training combined with physiotherapist-led task-specific exercises and feedback appear to be more effective to improve standing function than BWSTT alone.

There is Level 2 evidence (Dobkin et al. 2006) that there were no differences in balance whether participants engaged in overground training or Body-weight supported treadmill training, but the participants that completed either training and were able to walk made considerable progress in balance.

There is Level 4 evidence (Sayenko et al., 2010; Tamburella et al., 2013) that visual field feedback training leads to substantial improvements in static and dynamic standing eyes open and closed scores, and improvements in balance performance during training-irrelevant tasks. Tamburella et al. found that the visual biofeedback task specific balance training group saw improvements in balance and gait, and that it demonstrated a significantly higher level of effectiveness than conventional rehabilitation.

There is one study with Level 1 evidence (Alexeeva et al., 2011) and 3 studies with Level 4 evidence (Musselman et al., 2009; Fritz et al., 2011; Wu et al., 2012) that found that BWSTT in addition to Physical Therapy resulted in greater balance improvements than BWSTT alone. Wu et al. found non-significant differences in balance when combining BWSTT with resistance or assistance training.

There is Level 4 evidence (Behrman et al., 2012; Buehner et al., 2012; Harkema et al., 2012; Lorenz et al., 2012) that treadmill and overground based BWST leads to improvements in balance scores.

There is level 1 evidence (Harvey et al., 2011) that task-specific sitting balance exercises for an additional 3 weeks in acute SCI resulted in no difference on balance outcomes.

5.0 Strengthening lower limb function

5.1 Enhancing Strength Following Locomotor Training in Incomplete SCI

Much research is focused on the development of effective therapies directed at enhancing locomotion. Typically, as noted earlier in this chapter, the majority of these investigations focus on individuals with incomplete SCI and also predominately employ ambulation-related outcome measures. However, some investigators have also examined the effect of locomotor training on

enhancing lower limb strength as a secondary measure, or in other cases have examined the relationship between changes in lower limb strength and walking ability. For the most part, these therapies include a form of body-weight supported treadmill training. In these therapies, the patient's limb movements may also be assisted by any (or a combination) of the following: therapist, appropriately timed electrical stimulation (i.e., FES) or a robotically controlled servo-mechanism (Hornby et al., 2005a; Hornby et al., 2005b; Wirz et al., 2005; Field-Fote, 2001; Field-Fote & Roach, 2011; Wernig et al., 1998; Wernig et al., 1995). In other locomotor studies involving strength measures, locomotor training consisted of overground walking assisted by FES (Granat et al., 1993) or a combination of this with treadmill and biofeedback training (Petrofsky, 2001). In the present section, the outcomes associated with the strength benefits of these studies will be presented.

Table 4: Locomotor Training Studies Examining Strength Measures

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
Field-Fote & Roach, 2011; USA PEDro=8 RCT Level 1 N=64	**Population:** Patients with chronic SCI at least 1-year post-injury, mean ages between 38 and 45; TM group (14 males, 3 females), TS group (14 males, 4 females), OG group (11 males, 4 females), LR group (12 males, 2 females) **Treatment:** Training 5 days/week for 12 weeks with: treadmill-based training with manual assistance (TM), treadmill-based training with stimulation (TS), overground training with stimulation (OG), or treadmill-based training with robotic assistance (LR) **Outcome Measures:** Walking speed (over 10m), distance walked in 2 minutes, lower LEMS	1. There was a significant time effect of training on the LEMS scores of the right and left leg: LEMS scores of all participants increased 8-13%, with no significant between-group differences.
Petrofsky 2001 USA Prospective Controlled Trial Level 2 N=10	**Population:** 10 males; age 22-30 yrs; incomplete, T3-T12 lesion level **Treatment:** The control group (n=5) had 2-hour daily conventional physical therapy, including 30 min biofeedback of more affected gluteus medius for 2 months. Experimental treatment (n=5) had same program and used a portable home biofeedback device. **Outcome Measures:** Muscle strength (isometric strain gauge transducer) and gait analysis.	1. Gains in strength (in quadriceps, gluteus medius and hamstring) were seen for both groups but were greater for the experimental group than controls. 2. After 2 months of therapy the reduction in Trendelenburg gait was greater for the experimental group than for the control group and the experimental group showed almost normal gait.

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
Wernig et al. 1995; Germany Case Control Level 3 N=153	**Population:** 153 participants; locomotor training group: 89 participants (44 chronic, 45 acute); control group: 64 participants (24 chronic, 40 acute) **Treatment:** BWSTT (Laufband therapy) vs conventional rehabilitation. Specific parameters for each were not described or appeared to vary within and between groups. **Outcome Measures:** Manual muscle testing, walking function and neurological examination pre and post training.	1. 6 /20 chronic individuals initially "nearly paralysed" gained bilateral muscle strength (increased manual muscle testing) 2. For acute patients, no differences in strength gains between BWSTT and conventional rehab. 3. Authors noted that locomotor gains had little correlation with strength gains.
Benito Penalva et al. 2010; Spain Case control Level 3 N=42	**Population:** 29 motor incomplete SCI patients (24 males, 5 females, mean age 47; Group A < 3 months post-injury (n=16), Group B > 3 months post-injury (n = 13) and 13 healthy volunteers (10 males, 3 females, mean age 32) with pre-test only **Treatment:** Gait training using either the Lokomat or Gait Trainer GT1 (based on availability of the system), 20-45 minutes per sessions (5 days a week for 8 weeks). **Outcome Measures:** the LEMS, WISCI II, 10MWT, H reflex modulation by TMS	1. After gait training, there was a significant improvement in LEMS for both groups
Galen et al. 2014 USA Pre-Post Test Level 4 N= 18	**Population**: 18 individuals- 14 males and 4 females; motor incomplete SCI; 5 AIS C, 13 AIS D; mean age= 49.3 ± 11 years **Treatment**: Each person participated in the study for a total period of eight weeks, including 6 weeks of RAGT using the Lokomat system. Peak torques were recorded in hip flexors, extensors, knee flexors and extensors using torque sensors that are incorporated within the Lokomat. **Outcome Measures:** peak torque, peak voluntary isometric torque at the knee and hip	1. All the tested lower limb muscle groups showed statistically significant ($p < 0.001$) increases in peak torques in the acute participants. 2. Comparison between the change in peak torque generated by a muscle and its motor score over time showed a non-linear relationship.
Jayaraman et al. 2008; USA Pre-Post Level 4 N = 5	**Population:** 5 participants with chronic SCI, age 21-58, level of injury C4-T4. **Treatment:** 45 30-min sessions of locomotor training (LT) with partial BWS spread over 9-11 weeks. **Outcome Measures:** Voluntary contractile torque; voluntary activation deficits (using twitch interpolation), muscle cross-sectional area (CSA) using MRI.	1. All participants demonstrated improved ability to generate peak isometric torque, especially in the more involved plantar flexor (PF, +43.9 + 20.0%) and knee extensor (KE,+21.1+12.3%) muscles 2. Significant improvements of activation deficit in both KE and PF muscles 3. All participants demonstrated increased muscle CSA ranging from 6.8% –21.8%

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
Gregory et al. 2007; USA Case series Level 4 N=3	**Population:** 3 males; all participants were diagnosed as AIS D; 17-27 mos post-injury. **Treatment:** 12 weeks, 2-3 sessions/week of lower extremity resistance training combined with plyometric training (RPT). Resistance exercises included unilateral leg press, knee extension/flexion, hip extension/flexion and ankle plantar flexion exercises on adjustable load weight machines. Participants performed 2-3 sets of 6-12 repetitions at an intensity of ~70-85% of predicted 1 RM. Unilateral plyometric jump-training exercises were performed in both limbs on a ballistic jump-training device (ShuttlePro MVP ®). Participants completed a total of 20 unilateral ground contacts with each limb at a resistance of ~25% of body mass. Upon successful completion of at least 20 ground contacts, resistance was increased in increments of 10 lbs. **Outcome Measures:** Maximal cross-sectional area of muscle groups, dynamometry, maximum and self-selected overground gait speed.	1. RPT resulted in an improved peak torque production in the knee extensors (KE) and ankle plantar flexors (PF). 2. Time to peak tension decreased from mean (SD) 470.8(82.2) ms to 312.0(65.7) ms in the PF and from 324.5(35.4) ms to 254.2(34.5) ms in the KE. 3. Average rate of torque development and the absolute amount of torque generated during the initial 220 ms during a maximal voluntary contraction improved; more pronounced improvements in the PF than the KE. 4. On average, training resulted in a mean (SD) 14.2(3.8) and 8.3(1.9)% increase in max-CSA for the PF and KE, respectively. 5. RPT resulted in reductions in activation deficits in both the PF and KE muscle groups. 6. Average 36.1% increase in maximum gait speed and 34.7% increase in self-selected gait speed after training.
Hornby et al. 2005b; USA Pre-post Level 4 N=3	**Population:** 2 males, 1 female; AIS C; 5 weeks/ 6 weeks/ 18 months post-injury. **Treatment:** Therapist and Robotic-assisted, body-weight-supported treadmill training (parameters varied between participants). **Outcome Measures:** LEMS, functional mobility outcomes.	1. No group statistics 2. Increase in AIS lower limb motor scores in 2/3 participants in acute phase (5 & 6 weeks) which cannot be separated from natural recovery. No changes seen in 3rd person initiated at 18 months.
Field-Fote 2001; USA Pre-post Level 4 N=19	**Population:** 13 males and 6 females; mean age 31.7 yrs; all participants were diagnosed as AIS C; >1 yr post-injury. **Treatment:** Body weight-supported treadmill walking with peroneal nerve FES of the weaker limb for 1.5 hours, 3X/week, 3 months. **Outcome Measures:** LEMS, Gait outcomes.	1. LEMS had median increases of 3 points in both the FES-assisted leg and the non-stimulated leg 2. Increase in AIS lower limb motor scores in 15 of 19 incomplete SCI (AIS C).
Wernig et al. 1998; Germany Pre-post Level 4 N=76	**Population:** Strength data reported for 25 chronic participants only **Treatment:** BWSTT (Laufband therapy). 1-2X/day for 30 minutes, 5 days/week for 8-20 weeks. **Outcome Measures:** Voluntary muscle scores and walking function.	1. No group statistics. 2. All participants showed increases in cumulative muscle scores (i.e. 8 muscles summed) indicative of increased strength.

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
Granat et al. 1993; UK Pre-post Level 4 N=6	**Population:** 3 males and 3 females; age 20-40 yrs; all participants were diagnosed as Frankel C or D; C4-L1 lesion level; 2-18 yrs post-injury. **Treatment:** FES-assisted locomotor training to quadriceps, hip abductors, hamstrings, erector spinae, common peroneal nerve, minimum 30 min, 5 days/week. **Outcome Measures:** Manual muscle tests, maximum voluntary contraction (MVC), upright motor control, spasticity, balance and gait outcomes.	1. Significant increase in strength (increase in hip flexors and knee extensor manual muscle test). 2. Increased strength as indicated by increased quadriceps torque with MVC.
Tester et al. 2011; USA Observational Level 5 N=30	**Population**: 22 males, 8 females; mean(SD) age 40(14), 23(18) months post-injury; AIS score C or D **Treatment:** 21 participants underwent a 9-week manual-assisted locomotor training (LT) with 5 sessions/week; each session entailed 20-30 minutes of partial BWS treadmill stepping with manual assistance as needed **Outcome Measures**: presence of arm swing in relation to LEMS, WISCI II presence of arm swing	1. Arm swing was absent during treadmill stepping for 18/30 (60%) of individuals 2. There was no significant difference between arm-swing vs. no arm-swing groups in the level of injury or UEMS but there was a significant difference in LEMS

Discussion

In general, investigators have noted significant increases of lower limb strength following locomotor training – despite variations between training protocols and specific methods employed. Outcome measures have included manual muscle testing of individual lower limb muscles in incomplete SCI or summated scores of several muscles (Hornby et al., 2005; Wirz et al., 2005; Field-Fote, 2001; Wernig et al., 1998; Wernig et al., 1995; Granat et al., 1993). Most recent studies have adhered to AIS international guidelines for manual muscle testing (Hornby et al., 2005a; Hornby et al., 2005b; Wirz et al., 2005; Field-Fote, 2001; Field-Fote & Roach, 2011; Tester et al., 2011; Benito-Penalva et al., 2010). Others have employed muscle torque measurements by employing strain gauge transducers (Petrofsky, 2001; Granat et al., 1993), a dynamometer, or twitch interpolation technique (Jayaraman et al., 2008).

All investigators have reported increases in lower limb muscle strength in individuals with chronic SCI. One study (Benito-Penalva et al., 2010) also found similar increases in a group with subacute SCI (< 3 months post-injury). However, several investigators have noted that enhanced walking capability was not necessarily associated with parallel increases in strength (Wirz et al. 2005; Field-Fote, 2001; Field-Fote & Roach, 2011; Wernig et al., 1998; Wernig et al., 1995). Furthermore, the clinical relevance of the small strength gains following locomotor training is questionable when considering the duration and complexity of the intervention (Field-Fote, 2001). However, there is weak evidence (from 1 study, n = 3) that significant improvements in muscle strength may be realized when locomotor training is combined with conventional therapy (Hornby et al., 2005b). In a more recent study that examined the effects of a 12-week resistance and plyometric training program, improvements in knee extensor and ankle plantarflexor torque production were accompanied by >30% improvement in gait speed (Gregory et al., 2007).

Detecting group differences in strength gains during the acute phase may be more challenging given the natural recovery. Wernig et al. (1995) found no differences between those provided locomotor training versus those treated conventionally in muscle strength gains. However, specific subject characteristics were inadequately described other than stating that body-weight supported treadmill training was initiated within a few weeks (i.e., 2-20 weeks, median 7 weeks) following injury. There was also a lack of standardized assessment, further confounding the findings.

Conclusion

There is level 1b evidence (Field-Fote & Roach 2011) that most forms of locomotor training (i.e., including body weight supported treadmill training with various assists and FES-assisted overland training) increase lower limb muscle strength in chronic SCI as indicated by overall increases in total lower extremity motor scores.

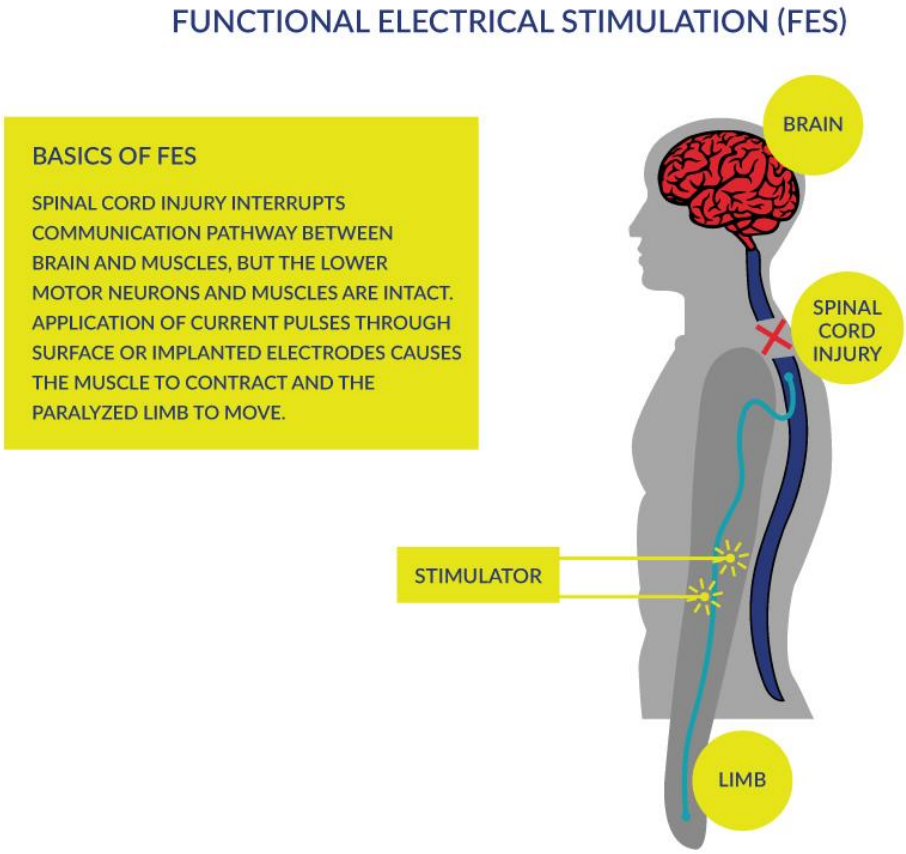
There is level 3 evidence (Wernig et al. 1995) that body weight supported treadmill training is not significantly different than conventional rehabilitation therapy in enhancing lower limb muscle strength in acute SCI, although these studies are confounded by the natural recovery that may take place in the acute period.

There is level 4 evidence (Gregory et al. 2007) that a resistance and plyometrics training program can enable improvements in overground gait speed in chronic incomplete SCI.

Locomotor training programs are beneficial in improving lower limb muscle strength although in acute SCI similar strength increases may be obtained with conventional rehabilitation.

The real benefit of locomotor training on muscle strength may be realized when it is combined with conventional therapy. This should be further explored in acute, incomplete SCI where better functional outcomes may be realized with the combination of therapies.

5.2 Electrical Stimulation to Enhance Lower Limb Muscle Function (NMES/FES non-ambulatory muscle stim)



After SCI, it is well established that muscles experience deconditioning, especially those denervated following complete SCI. The most visible effect of deconditioning is muscle atrophy, characterized by a reduction in size of individual muscle fibers (Castro et al., 1999a; Castro et al., 1999b). Deconditioning is also associated with a complex cascade of biochemical events and alterations over time in muscle composition such as changes to muscle fiber type (Stewart et al., 2004; Round et al., 1993). Functionally, these changes manifest as loss of strength and endurance of muscular contractions and have been targets for various interventions. It should be noted that there might be additional benefits to enhancing muscle structure and function in addition to the immediate functional consequences of enhancing strength and endurance. For example, muscular contractions have the added potential of ameliorating loss of bone density following SCI. In addition, Anderson (2004) noted that future treatments developed for chronic SCI may require the reversal of muscle atrophy in order for benefits of the treatment to be detectable. Others have noted the potential health benefits (e.g., reduction in secondary conditions) that may be associated with reducing muscle atrophy and enhancing muscular strength and endurance (Shields and Dudley-Javoroski, 2006). Various rehabilitation techniques have focused on reducing or reversing these detrimental changes to the muscles of the lower limb following SCI.

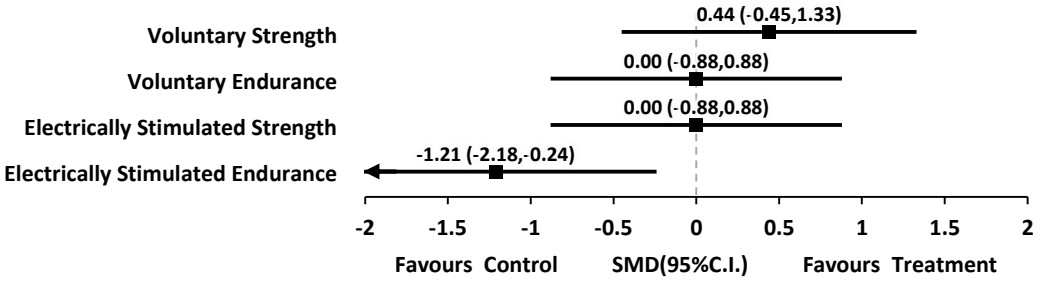
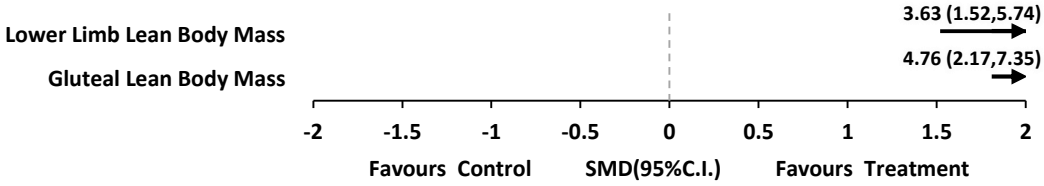
A variety of electrical stimulation techniques have been employed to enhance lower limb muscle structure and function in people with SCI. These typically involve delivering a series of electrical pulse trains to the muscle (or nerve supplying the muscle) over time such that it simulates the “normal” exercise experience. Specific stimulation parameters (i.e., pulse width, training duration, between training intervals, method of application) and other exercise-related variables (i.e., frequency, duration, intensity, and program length) may each be varied to attain an optimal training stimulus. Given the number and variety of these factors, it is not surprising that there is considerable

heterogeneity among the specific electrical stimulation interventions that have been investigated to date. In the present review we focus on two strategies: NMES and FES. Whereas both methods typically employ cyclical patterns of electrical stimulation that simulate natural muscular activity, FES is directed towards the attainment of purposeful movement such as cycling or walking, although it has also been used to address other issues such as pressure sores and spasticity (Bersch et al., 2015, Kawasaki et al., 2014). NMES, on the other hand, is focused on producing muscle contractions to generate muscle force such as in an isometric condition. In some applications, NMES techniques have been used as a training stimulus to prepare muscles for a subsequent FES training condition (e.g., Kern et al., 2005; Hjeltnes and Lannem, 1990). In situations where increased muscle torque and endurance are primary goals to improve function, for example in the quadriceps in an incomplete SCI, the outcomes of these experimental studies have direct clinical relevance.

5.3 Neuromuscular Electrical Stimulation (NMES)

Table 5: NMES Studies Examining Muscle Function and Morphology

Author Year; Country Score Research Design Total Sample Size	**Methods**	**Outcomes**
Harvey et al. 2010; Australia PEDro=10 RCT Level 1 N=20	**Population:** Complete or incomplete SCI patients Experimental group – 7 males, 3 females; mean age 40; mean YPI 3 Control group – 7 males, 3 females; mean age 39; mean YPI 4. **Treatment:** ES superimposed on PRT 3 days/week for 8 weeks (12 sets of 10 knee extension repetitions against increasing resistance, the first 6 using ES and voluntary contraction and the second 6 using only ES). **Outcome Measures:** Quadriceps strength and endurance, the performance and satisfaction scales of the Canadian Occupational Performance Measure (COPM), the ES-evoked quadriceps strength (Nm), ES-evoked quadriceps endurance (fatigue ratio), participant perception of treatment effectiveness.	1. There was a statistically significant group differences for voluntary quadriceps strength change (14 Nm), but the magnitude may not be clinically important. 2. ES group had greater perception of treatment effectiveness over control. 3. There was no group difference in any other variables.
	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%C.I.) as calculated from pre- and post-intervention data	

Author Year; Country Score Research Design Total Sample Size	Methods	Outcomes
	Harvey et al. 2010; Electrical Stimulation + Progressive Resistance Training  	
Baldi et al. 1998; USA PEDro=5 RCT Level 1 N=26	**Population:** 26 males and females; age 25-28 yrs; traumatic motor complete; cervical or thoracic lesion level; 15 wks post-injury. **Treatment:** Random assignment to 3-6 months of 1. FES-assisted cycle ergometry (n=8), 30 min, 3X/week; 2. PES-assisted isometric exercise group (n=8) (same muscle groups as FES group) for 1 hr, 5X/week and 3 control group (n=9) with no stimulation. **Outcome Measures:** lean body mass lower limb.	1. Lean body mass increased with FES-cycling at all regions and declined for control and PES group. 2. With respect to total body lean mass, lower limb lean mass and gluteal lean mass, controls lost an average of 6.1%, 10.1%, 12.4% after 3 months and 9.5%, 21.4%, 26.8% after 6 months.
	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%C.I.) as calculated from pre- and post-intervention data **Baldi et al. 1998; FES Cycle Ergometry**  **Only subjects who completed 6 months of training were analyzed. Numerical data unavailable for subjects in the 3 month program.**	
Shields & Dudley-Javoroski 2006; USA Prospective Controlled Trial Level 2 N=7	**Population:** 7 males; age 21-43 yrs; AIS A; C5-T10 lesion level; ≥ 6 weeks post-injury **Treatment:** PES exercise to unilateral ankle plantarflexion (untrained leg served as a control). Four 4 min exercise bouts, 5 days/week for 1.87-3.05 years. **Outcome Measures:** Stimulated ankle torque and soleus twitch profiles at baseline and every 6 months up to 3 years.	1. Compared to the untrained side, stimulated limb had: 2. Increased strength (increased peak stimulated ankle torque and higher torque-time integrals). 3. More resistant to fatigue (increased muscle fatigue indexes). 4. Increased twitch difference (indicative of force generating capacity), especially with successive stimulation trains.

Author Year; Country Score Research Design Total Sample Size	Methods	Outcomes
Ryan et al. 2013; USA Pre-post Level 4 N=14	**Population:** 14 participants with chronic motor complete SCI (11M 3F); 2 diabetic. Inclusion criteria included: 18-65 yrs of age; AIS A or B classification; normative range of motion in the knee and hip joints. **Treatment:** Participants performed RET of the knee extensor muscles 2 times/week for 16 weeks. 4 sets of 10 knee extensions were performed using NMES. **Outcome Measures:** Plasma glucose and insulin throughout a standard clinical oral glucose tolerance test; thigh muscle and fat mass via dual-energy x-ray absorptiometry; quadriceps and hamstrings muscle size and composition via MRI; muscle oxidative metabolism using phosphorus magnetic resonance spectroscopy.	1. After RET, thigh fat tissue (g), thigh percentage fat and bone mineral density of the femur bone was not different. Lean tissue of the thigh area increased by approximately a mean(SD) of 10(15)%g. 2. Quadriceps muscle volume (average of both legs) was increased by 39(27)% after RET (pre vs post: 618(343) vs 815(399) cm^3). No change was observed in absolute fat volume for either the quadriceps or hamstring muscles. No relation was found between the magnitude of muscle hypertrophy and improvements in glucose or insulin status. 3. 8 participants had measurements of PCr recovery kinetics. Time constants for the recovery of PCr after electrical stimulation were 102(24) and 77(18) seconds before and after RET; this represents an approximate 25% improvement in skeletal muscle oxidative capacity, which was statistically significant.
Sabatier et al. 2006; USA Pre-post Level 4 N=5	**Population:** 5 males; mean (SD) age 35.6(4.9) yrs; complete; C5-T10 lesion level; 13.4(6.5) yrs post-injury **Treatment:** 18 weeks of neuromuscular electrical stimulation resistance training for the quadriceps combined with additional weight around the shin, 2x/week with 4 sets of knee extensions. **Outcome Measures**: Weight lifted, muscle mass, muscle fatigue	1. All participants increased weight lifted during training by an average (SD) of 6.9(1.4) kg 2. Significant increases in cross-sectional area of quadriceps femoris in both thighs (right mean CSA increased from 32.6 to 44.0 cm^2, left mean increased from 34.6 to 47.9 cm^2) 3. Progressive decrease in fatigue throughout training and after 18 weeks of training. Decreases significantly at 12 weeks and 18 weeks.
Belanger et al. 2000; Canada Pre-post Level 4 N=14	**Population:** 14 males and females; age 23-42 yrs; 2 incomplete, 12 complete lesions; C5-T5 lesion level; 1.2-23 yrs post-injury **Treatment:** Bilateral functional electrical stimulation to quadriceps combined with isokinetic resistance training on left side and unresisted on right; 5 days/week, 24 weeks; each session was 1 hr or until fatigue **Outcome Measures:** knee torque, endurance	1. Average increase in knee extensor muscle torque on resisted side was 150% (average 8.1% increase/week) 2. Average increase in knee muscle torque on unresisted side was 75% (average 4.5% increase/week) 3. No change in endurance (fatigability)
Kagaya et al. 1996; Japan Pre-post Level 4 N = 5	**Population:** 5 males; age 19-68 yrs; with complete paraplegia (T5-L2 lesion level); 3-60 months post-injury. **Treatment:** Subcutaneous PES to various lower limb nerves and muscles for 6 months. Applied at 10 min, 3X/day and gradually increased to 60 min, 3X/day at 10 weeks.	1. No group statistical analysis performed, limited by heterogeneity across participants. 2. All cross-sectional muscle areas except gluteus maximus increased significantly. 3. Muscle torques generally increased after PES. 4. Manual muscle tests generally increased

Author Year; Country Score Research Design Total Sample Size	Methods	Outcomes
	Outcome Measures: Muscle cross-sectional area (CT scan), manual muscle test, stimulated muscle torque.	significantly for muscles that initially graded as poor-minus (no voluntary movement against gravity).
Hjeltnes and Lannem 1990; Norway Pre-post Level 4 N=4	**Population:** 4 males and females; age 20-36 yrs; Frankel A; T5-T12 lesion level; 3 mos-5 yrs post-injury **Treatment:** PES, 4 weeks, 2x/day, 5-10mins, isokinetic resistance to quadriceps muscles followed by 4 weeks, 30 min, 2X/day, 4-5X/day of integrated training of rising and standing. **Outcome Measures:** Knee extension torque, thigh circumference, CK, collected monthly.	1. No group statistics done. At least 2 participants had increased knee extension torque, increased muscular endurance, increased thigh circumference, increased CK (indicator of muscle injury). The more acute participant stopped training due to muscle spasms. 2. One participant progressed to the planned stage of FNS-assisted ambulation training.
Gerasimenko et al. 2015 Russia Post-test Level 4 N=10	**Population**: 10 individuals- 5 able bodied and 5 with SCI. **Treatment**: Painless transcutaneous electrical enabling motor control (pcEmc) neuromodulates the physiological state of the spinal cord. This method includes electrically activating the spinal circuitry via electrodes placed on the skin overlying the vertebrae of the lower thoracic and/or lumbosacral vertebrae. This waveform consists of 0.3- to 1.0-ms bursts with a carrier frequency of 10 kHz administered at 5 to 40 Hz. PcEmc stimulation was delivered by a 2.5-cm round electrode placed midline at the C5, T11, and/or L1 spinous processes as cathodes and two 5.0 10.2 cm2 rectangular plates made of conductive plastic placed symmetrically on the skin over the iliac crests as anodes. Biphasic rectangular 0.5- to 1.0-ms pulses with a carrier frequency of 10 kHz and at an intensity ranging from 30 to 200 mA were used. **Outcome Measures:** EMG amplitude	1. Use of the multielectrode surface array can fine-tune the control of the locomotor behavior. 2. The pcEmc strategy combined with exoskeleton technology is effective for improving motor function in paralyzed patients with SCI.

Discussion

Most studies involving NMES and strength evaluated this in individuals with complete or motor complete SCI (Hjeltnes and Lannem, 1990; Kagaya et al. 1996; Shields and Dudley-Javoroski, 2006). In general, all studies produced beneficial results on muscle size (i.e., reduced muscle atrophy). In addition to enhancing muscle bulk, most interventions also focused on improving muscle function, most notably strength and endurance, as well as contractile speed and muscle fatigue.

Studies with the strongest research design and supporting the efficacy of NMES were conducted by Harvey et al. (2010) and Shields and Dudley-Javorski (2006). Harvey et al. (2010) used an RCT design in persons with both complete and incomplete SCI and found that NMES-assisted exercise increased voluntary quadriceps strength over those that received no intervention. The increase in strength was statistically higher in the experimental group, but it was uncertain if the increase had a

clinically important effect. Shields and Dudley-Javorski (2006) employed an experimental non-RCT design to examine the effect of long-term (up to 3 years) NMES exercise to unilateral ankle plantarflexor muscles with the untrained leg serving as a control. This study examined 7 males with complete and relatively recent injuries (~6 weeks post-injury). Peak stimulated ankle torque (i.e, non-voluntary) was found to be significantly greater in the stimulated leg as compared to the untrained leg. The trained side also generated significantly higher torque-time integrals than the untrained side. Other pre-post study designs of NMES-assisted exercise also found increased stimulated muscle forces or torques following training although the participants involved in these studies were generally more chronic (Sabatier et al., 2006; Kagaya et al., 1996; Hjeltnes and Lannem, 1990).

Conclusion

There is level 1b evidence (Harvey et al., 2010) that PES-assisted exercise may increase voluntary muscle strength, but the increase may not have a clinically important treatment effect.

There is level 2 evidence (Baldi et al., 1998) that PES-assisted isometric exercise reduces the degree of lower limb muscle atrophy in individuals with recent (~10 weeks post-injury) motor complete SCI, but not to the same extent as a comparable program of FES-assisted cycling exercise.

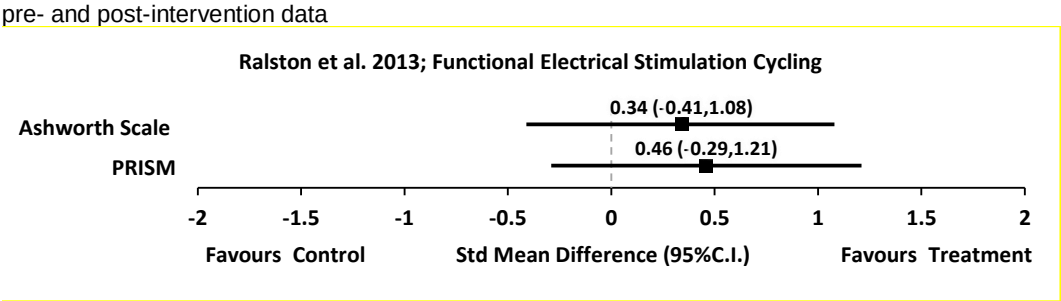
There is level 4 evidence (Sabatier et al., 2006) that PES-assisted exercise may partially reverse the lower limb muscle atrophy found in individuals with long-standing (>1 year post-injury) motor complete SCI.

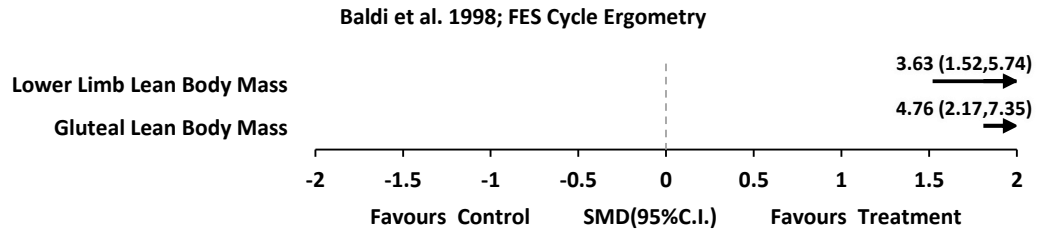
NMES programs are beneficial in preventing and restoring lower limb muscle atrophy.

5.4 Functional Electrical Stimulation

Table 6: FES Studies Examining Muscle Function and Morphology

Author Year; Country Score Research Design Total Sample Size	Methods	Outcomes
FES-assisted cycling		
Ralston et al. 2013 Australia	**Population**: 14 individuals; average age 25y; motor complete lesions between C4 and T10; AIS A, B; 118 days post injury **Treatment**: Participants were randomized to an experimental phase followed by a control phase or vice versa, with a 1-week washout period in between. The experimental phase involved FES	1. The mean between-group differences (95% CI) for lower limb swelling, spasticity (Ashworth), and PRISM were –0.1 cm (–1.5 to 1.2), –1.9 points (–4.9 to 1.2) and –5 points (–13 to 2), respectively. (Significant differences between groups were not reported).

Author Year; Country Score Research Design Total Sample Size	Methods	Outcomes
RCT Level 1 PEDro=8 N=14	cycling four times a week for two weeks and the control phase involved standard rehabilitation for two weeks. **Outcome Measures:** Primary outcome-urine output (mL/hr); Secondary outcomes- lower limb circumference, and spasticity using the Ashworth Scale, and the Patient Reported Impact of Spasticity Measure (PRISM). Participants were also asked open-ended questions to explore their perceptions about treatment effectiveness.	2. All point estimates of treatment effects favored FES cycling.
	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%C.I.) as calculated from pre- and post-intervention data 	
Kuhn et al. 2014 Germany Clinical Cohort Study Level 2 N= 30	**Population**: 30 individuals; average age 44 ± 15.5y; motor complete and incomplete spinal cord injuries in the cervical, lumbar, and thoracic regions; AIS A = 10, B = 3, C = 15, D = 2; 0-122 months post injury **Treatment**: During the 4-week study period, all patients received eight 20min FES interventions at the beginning and end of each week. At every intervention, circumferential measurement and spasticity testing before and after FES cycling (pretest/post-test) were performed. Ultrasound, walking tests, and manual muscle test were only performed at the beginning of week 1 (T1) and at the end of week 4. **Outcome Measures:** Circumferential measurement, muscular ultrasound measurement, spasticity measured by MAS, Walking (6 Minute Walk, TUG).	1. An increase in the circumference of the cross-sectional area of 15.3% on the left and of 17% on the right m. rectus femoris could be observed in group AIS A + B after 4 weeks of treatment 2. AIS C + D group, the circumference of the left m. rectus femoris increased by 25% and that of the right m. rectus femoris by 21% (for all, $P < 0.05$). 3. For the 5 patients with partial walking ability at the start of the study, the mean 6-MWT distance significantly increased from 62.3±135.3 to 94.3±167.1 m throughout the study ($P = 0.03$) and the time for TUG was reduced from 11.7±21.9 to 10.1±18.1 s ($P = 0.5$)
Duffell et al. 2008; UK Prospective Controlled Trial Level 2 N=11	**Population:** 11 participants with complete SCI, level of injury T3-T9, mean (SD) 10.7(2.1) YPI; 10 untrained AB controls, mean (SD) age 30.6(3.2) yrs **Treatment:** FES cycling, up to 1hr/day, 5 days/week for 1 year **Outcome Measures:** Maximal quadriceps torque; quadriceps fatigue resistance; power output (PO).	1. The maximal quadriceps torque increased significantly throughout training in SCI participants (+399% at 3 months, +673% at 12), but remained significantly less than that of AB controls (mean (SD) 107.0(17.9) vs. 341.0(28.6)). 2. Quadriceps fatigue resistance (76.7 (2.0)% force loss after 3 min at baseline, compared to 30.3(4.6)% after 12 months) and peak power output (+177%) improved significantly after training.

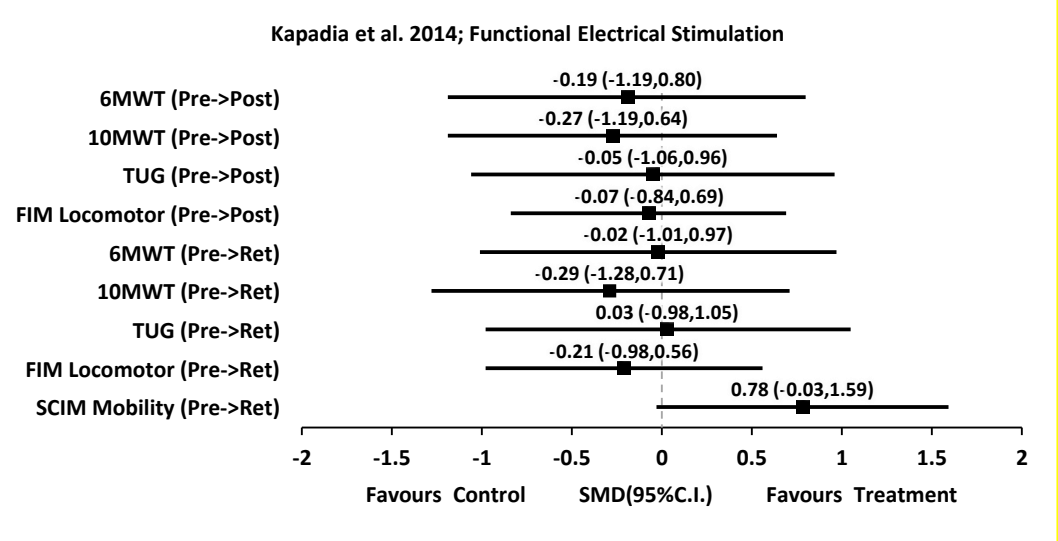
Author Year; Country Score Research Design Total Sample Size	Methods	Outcomes
Baldi et al. 1998; USA PEDro=5 RCT Level 2 N=26	**Population:** 26 males and females; age 25-28 yrs; traumatic motor complete; cervical or thoracic lesion level; 15 wks post-injury **Treatment:** Random assignment to 3-6 months of 1) FES-assisted cycle ergometry (n=8), 30 min, 3X/week; 2) PES-assisted isometric exercise group (n=8) (same muscle groups as FES group) for 1 hr, 5X/week or 3) control group (n=9) with no stimulation. **Outcome Measures:** lower limb lean body mass.	1. Lean body mass increased with FES-cycling at all regions and declined for control and PES group. 2. Lower limb lean mass and and gluteal lean mass were both significantly greater than the baseline after 6 months ($p<.05$) 3. Controls lost an average of 6.1%, 10.1%, 12.4% after 3 months and 9.5%, 21.4%, 26.8% after 6 months in total body lean mass, lower limb lean mass and gluteal lean mass, respectively.
	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%C.I.) as calculated from pre- and post-intervention data  **Only subjects who completed 6 months of training were analyzed. Numerical data unavailable for subjects in the 3 month program.**	
Deley et al. 2015 USA Pre-Post Level 4 N=10	**Population**: 10 individuals- 8m/2f; average age 34 ± 4.0y; years post injury 9.8 ± 2.7y; level of lesion between C5 and T12; 9 AIS A & 1 AIS B **Treatment:** Each participant underwent 2 testing sessions separated by at least 24h. During each testing session, isometric muscle torque was measured under 2 sequential electrical stimulation train patterns. Individuals underwent either CFT or VFT patterns until target torque was no longer produced and then switched immediately to the other pattern. **Outcome Measures:** Isometric muscle torque, CFT (constant frequency train) pattern, VFT (variable frequency train) pattern.	1. CFT needed significantly less stimulus activity than VFT in order to generate 50% maximal force ($p<.05$). 2. These findings suggest that for the same initial forces the VFT pattern is less fatiguing than CFT and that when combining train types, and thus VFT should be used first.
Gibbons et al. 2014 United Kingdom Post Test Level 4 N= 8	**Population**: 8 participants- 4 males and 4 females; chronic complete and incomplete tetraplegia; injuries between C4 and C7, 5 AIS A, 1 AIS B, 2 AIS C; mean age= 30.5 ± 11.4y; years post injury= 8.4 ± 4.2y **Treatment:** Participants completed a progressive FES-assisted training program building to three continuous 30-min FES-R sessions per week at 60–80% of their predetermined peak power output.	1. All participants were able to continuously FES-row for 30 min after completing 13±7 FES-R training sessions. 2. Each individual POav during 30 min FES-R increased over 12 months FES-training. 3. FES-R was found safe and well tolerated in this group of individuals with tetraplegia.

Author Year; Country Score Research Design Total Sample Size	Methods	Outcomes
	Thereafter, rowing performance was monitored for 12 months. **Outcome Measures:** Number and type of FES-training sessions required before achieving 30-min continuous FES-R, FES-R average power output (POav) pre and post 12 months training, participant feedback of perceived benefits.	
Gorgey et al. 2015 USA Pre-Post Level 4 N= 7	**Population**: 7 males; motor complete SCI; RT + diet group: average age= 35 ± 10y, years post injury 15 ± 9y, level of lesion between C5 and C7; Diet control group: mean age= 29 ± 4y; years post injury= 4 ± 2y **Treatment:** Seven men with motor complete SCI were randomly assigned to a resistance training plus diet (RT + diet) group (n = 4) or a diet control group (n = 3). Participants in the RT + diet group were enrolled in a 12-week leg extension weight-lifting program via surface NMES of the knee extensor muscle group. The length of mid-thigh intermuscular fascia and the patellar tendon CSA were measured using MRI. **Outcome Measures:** Length of mid-thigh intermuscular fascia and the patellar tendon CSA	1. The length of the mid-thigh intermuscular fascia increased by 19% and 23% in the right (P = .029) and left (P = .015) legs, respectively, with no changes in the diet control group. 2. Positive relationships were noted between skeletal muscle CSAs of the whole thigh (r = 0.77, P = .041) and knee extensors (r = 0.76, P = .048) and intermuscular fascial length.
Fornusek et al. 2013; Australia Pre-post Level 4 N=8	**Population:** 8 participants with chronic SCI; mean (SD) age: 39 (14); C7-T11; 7 AIS A, 1 AIS C. **Treatment:** 6 weeks (3 days/wk) of training on an isokinetic FES cycle ergometer. For each participant, 1 leg was randomly allocated to cycling at 10 rpm (LOW) for 30 min/day and the other cycling at 50rpm (HIGH) for 30 min/day. **Outcome Measures:** lower limb circumference (distal and middle position of each thigh); electrically evoked quadriceps muscle torque during isometric contraction	1. The intervention significantly increased thigh girth in both LOW and HIGH groups. At midthigh, girth increases induced by LOW (6.6% (1.2%)) were significantly greater than those by HIGH (3.6%(0.8%)). 2. LOW (87%) produced greater gains in electrically evoked isometric torque than HIGH (20%) after training.
Thrasher et al. 2013; USA Pre-post Level 4 N=11	**Population:** 11 participants with SCI (8M, 3F); 22-57 yrs; 8-95 months post-injury. **Treatment:** 40 sessions of FES-LCE at a rate of 3 sessions/wk for 13 weeks. Continuous exercise was performed at a pedal cadence of 45RPM against a constant resistance for up to 60 minutes. **Outcome Measures:** Mean power output; knee extension torque; Fatigue Index.	1. Participants demonstrated significant increases in mean power output (9.0 to 20.3W), peak isometric knee extension torque (3.8 to 16.9 Nm), and sustainable isometric knee extension torque (4.9 to 14.4 Nm) after FES-LCE training. 2. Participants with incomplete motor impairment demonstrated a decrease in Fatigue Index and improved mean power output more than those with complete motor impairment.
Reichenfelser et al. 2012; Austria	**Population:** 23 participants with SCI (20M 3F); mean(SD) age=40(14); mean(SD) DOI: 9(7) months; 7 tetraplegic, 16 paraplegic.	1. Power output test showed a monthly increase in power output of 4.4W (SD 13.7) at 30rpm and 18.2W (SD 23.9) at 60 rpm.

Author Year; Country Score Research Design Total Sample Size	Methods	Outcomes
Pre-post Level 4 N=23	**Treatment:** All participants underwent a mean(SD) of 18(14) training sessions on an instrumented tricycle combined with functional electrical stimulation. **Outcome Measures:** Power output; Modified Ashworth Test.	
Haapala et al. 2008; USA Pre-Post Level 4 N=6	**Population:** 6 SCI participants, between 20-50yrs old, complete and incomplete injury at or below C4, with previous FES cycle ergometry experience. **Treatment:** FES-LCE, progressive cycling (resistance) protocol with increasing resistance, as well as prolonged, submaximal cycling for 30min. **Outcome Measures:** Power output for ankle (APO), knee (KPO), and hip (HPO), HR	1. 4 participants successfully completed both protocols. 2. Initial and final APO for progressive protocol was lower than the submaximal protocol, but was not significantly different. There was no significant change in APO in the progressive protocol. APO significantly declined with time in the submaximal protocol. 3. The initial KPO were similar for both progressive and submaximal protocols. There was no significant change in KPO during the progressive protocol. KPO significantly declined with time in the submaximal protocol. 4. HPO for progressive protocol increased significantly with resistance. HPO for the submaximal protocol varied over time but displayed a gradual decrease overall. 5. HR was initially similar for both protocols. HR for submaximal cycling increased significantly with time. There were no significant changes in HR during the progressive protocol.
Liu et al. 2007; Taiwan Pre-post Level 4 N=18	**Population:** 18 males and females; age 26-61 yrs; AIS B-D; C3-L1 lesion level; 1-9 yrs post-injury **Treatment:** FES cycling exercises three times a week for 8 weeks; 30 minutes/session **Outcome Measures:** Muscle peak torque of knee flexors and extensors	1. Significant increase in mean thigh girth after 4 weeks 2. Significant increase in peak torque of bilateral knee flexors and right knee extensors 3. Strength gains in AIS D > AIS C > AIS B
Crameri et al. 2002; Denmark Pre-post Level 4 N=6	**Population:** 5 males, 1 female; age 28-43 yrs; complete; T4-T12 lesion level; >8 yrs post-injury **Treatment:** FES leg cycle ergometry training, 3 - 30 min/week for 10 weeks. **Outcome Measures**: Incremental exercise leg test to muscle fatigue (total work output), histological assessment, myosin heavy chain (contractile protein) (MHC), citrate synthase (a mitochondrial enzyme) and hexokinase (enzyme needed to produce muscle glycogen).	1. Total work performed increased after training. 2. Paralysed vastus lateralis muscle was altered with increased type IIA fibres, decreased type IIX fibres, decreased MHC IIx and increased MHC IIA. 3. Total mean fibre cross-sectional area increase of 129%, significantly increased cross-sectional area of type IIA and IIX fibres. 4. Increased number of capillaries surrounding each fibre. 5. Increase in citrate synthase and hexokinase activity.

Author Year; Country Score Research Design Total Sample Size	Methods	Outcomes
Gerrits et al. 2000; UK Pre-post Level 4 N=7	**Population:** 7 males; age 28-61 yrs; AIS A and B; C5-T8 lesion level; 1-27 yrs post-injury **Treatment:** FES leg cycle ergometry training, 3 - 30 minutes sessions/week for 6 weeks. **Outcome Measures:** Thigh girth, work output, contractile speed and fatigue resistance characteristics, including half relaxation time (½ Rt) and degree of fusion of electrically stimulated isometric contractions.	1. Increase in work output as training progressed. 2. More fatigue-resistant: decreased force decrement during quadriceps fatiguing stimulations. 3. No change in contractile speed (using maximal rate of rise force) but half relaxation time decreased and there was significantly less fusion. 4. Decrease in force responses at low stimulation frequencies, indicating less fusion and more relaxation. 5. No change in thigh circumference.
Koskinen et al. 2000; Finland Pre-post Level 4 N=10	**Population:** 10 males and females; age 27-45 yrs; complete; tetraplegic and paraplegic **Treatment:** 18-month FES-assisted cycling ergometry (First training period: 30 min, 3X/week, 1 year; Second training period: 1X/week, 6 months). **Outcome Measures:** Muscle morphology and protein measurement (type IV collagen, total collagen, muscle proteins).	1. Total collagen content (as indicated by hydroxyproline concentration) was increased with first training period and second training period and even more so compared to able-bodied controls. No difference in Type IV collagen content between groups. 2. This result combined with the changes seen with the other muscle proteins suggest accelerated type IV collagen turnover in skeletal muscle.
Scremin et al. 1999; USA Pre-post Level 4 N=13	**Population:** 13 males; age 24-46 yrs; AIS A; C5-L1 lesion level; 2-19 yrs post-injury. **Treatment:** A 3-phase, FES-assisted cycle ergometry exercise program leading to FES-induced cycling for 30 minutes. Average program was 2.3X/week for 52.8 weeks. **Outcome Measures**: CT-scan of legs to assess muscle cross-sectional area and proportion of muscle and adipose tissue collected (pre-test, midpoint and post-test).	1. Increase in cross-sectional area of: rectus femoris, sartorius, adductor magnus-hamstrings, vastus lateralis, vastus medialis-intermedius. No change in cross-sectional area of adductor longus and gracilis muscles. 2. No correlations between total number of sessions and magnitude of muscle hypertrophy. 3. Significant increases in the muscle/adipose tissue ratio, muscle tissue in the thigh and leg but no changes in the adipose tissue.
Yasar et al. 2015; Turkey Prospective single-arm study Pre-Post Level 4 N= 10	**Population**: 10 males and females with incomplete SCI that can ambulate more than 10m independently or with an assistive device **Treatment**: The participants underwent 1-h FES cycling sessions three times a week for 16 weeks. **Outcome Measures:** Total motor score, the Functional Independence Measure (FIM) score, the Modified Ashworth Scale for knee spasticity, temporal spatial gait parameters and oxygen consumption rate during walking.	1. There were statistically significant improvements in total motor scores, the FIM scores and spasticity level at the 6-month follow-up ($P<0.01$). 2. The changes in gait parameters reached no significant level ($P>0.05$). 3. Oxygen consumption rate of the patients showed significant reduction at only 6 months compared with baseline ($P<0.01$).

Author Year; Country Score Research Design Total Sample Size	Methods	Outcomes
Estigoni et al. 2014 Malaysia Pre-Post Level 4 N=8	**Population**: 8 males; age 45.6 ± 15.7y; complete or incomplete spinal cord lesions between C7 and T11, AIS A to C; 10.5 ± 6 y post injury **Treatment**: All participants had their quadriceps muscles group stimulated during three sessions of isometric contractions separated by 5 min of recovery. The eEMG signals, as well as the produced torque, were synchronously acquired during the contractions and during short FES bursts applied during the recovery intervals. **Outcome Measures:** A commercial muscle dynamometer (Biodex Medical Systems) was used to measure isometric torque evoked from the electrically stimulated quadriceps. A custom-made, computerized evoked EMG acquisition system (the UniSyd e^{2}MG) was utilized to control the stimulator and synchronize myoelectric signals with the torque outputs from the muscle dynamometer.	1. After the first onset of neurostimulation during c1, while PtpA and Area curves were still increasing towards their maximal values, the muscle-evoked torque was already in decline for these SCI participants. 2. Both m-waves and torque presented fast recovery during the first 20 s (b11–b12), which gradually reduced from b12 through b14. Still, the ratio *m-wave* × *torque* was fairly constant in r1with high R^2. *PtpA* also maintained a tight linear relationship with *Torque* during r2, with R^2 between 0.96 and 0.99 for all legs
FES-assisted Stand or Gait Training		
Kapadia et al. 2014 Canada RCT PEDro=5 Level 2 N= 27	**Population**: 27 individuals; traumatic (>18 months) and incomplete chronic spinal cord lesions between C2 and T12, AIS C and D. **Treatment**: 45 minutes of therapy per session, 3 days per week, for 16 weeks (48 sessions in total). Outcome measures were assessed at baseline, 4 months, 6 months, and 12 months post baseline. **Outcome Measures:** Gait Measures- 6 Minute Walk, 10 Meter Walk, Assistive Device Score (ADS), Walking Mobility Scale (WMS); Balance & Mobility Measure- Time Up and Go Test (TUG); Functional Measures- Spinal Cord Independence Measure (SCIM), Functional Independence Measure (FIM); Spasticity Measure- Modified Ashworth Scale (MAS), Pendulum Test	1. Spinal cord independence measure (SCIM) mobility sub-score significantly improved over time for the intervention group ($p<.01$) but not for the control group the control group (baseline/12 months: 17.27/21.33 vs. 19.09/17.36, respectively). 2. On all other outcome measures the intervention and control groups had similar improvements. 3. Walking speed, endurance, and balance during ambulation all improved upon completion of therapy and the majority of participants retained these gains at long-term follow-ups.
	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%C.I.) as calculated from pre- to post-intervention data and pre-intervention to retention/follow-up data	

Author Year; Country Score Research Design Total Sample Size	Methods	Outcomes
		
Carvalho de Abreu et al. 2008, 2009; Brazil Prospective Controlled Trial Level 2 N = 15	**Population:** 15 complete chronic participants with tetraplegia; injury level C4-C7; mean (SD) age 31.95(8.01) yrs with intact lower motor neurons, divided into gait training (n=8) and control (n=7) groups **Treatment:** Partial body-weight supported treadmill gait training with NMES, for 2 - 20min session every week for 6 months; control group performed conventional physiotherapy, and gait training without NMES for 6 months **Outcome Measures:** Cross-sectional area (CSA) of quadriceps, muscle hypertrophy.	1. After gait training there was a significant increase in quadriceps mean (SD) CSA (49.81(9.36) cm^2 vs. 57.33 (10.32) cm^2), whereas there was no significant difference in the control group. 2. No significant differences in muscle mass after 6 months, but the NMES group increased by 7.7%, and the control group decreased by 11.4%.
Kern et al. 2010a; Austria Pre-post Level 4 N=25	**Population:** 20 males, 5 females; 22 thoracic SCI, 3 lumbar SCI; all with complete conus/cauda equina lesions **Treatment:** Home-based functional electric stimulation (hb-FES) 30 minutes/muscle group (gluteus, thighs, and lower leg muscles), 5 days/week for two years. Stimulation was composed of long duration biphasic impulses five days a week and was adjusted every 12 weeks following assessment by a physiatrist. **Outcome Measures:** Muscle cross-sectional area (CSA), knee extension torque, vastus lateralis muscle composition.	1. Cross-sectional area of the quadriceps muscles significantly increased from mean (SD) 28.2 (8.1) to 38.1(12.7) cm^2. 2. Cross-sectional area of the hamstrings increased from 26.8(8.4) to 30.7(9.8) cm^2. 3. Mean diameter of vastus lateralis muscle fibers increased from 16.6(14.3) to 29.1(23.3) µm, and showed structural improvement. 4. Maximum knee torque with ES increased from 0.8(1.3) to 10.3(8.1) Nm after 2 years. 5. At the end of the two years, 5/20 of patients were able to perform FES-assisted standing and parallel-bars supported stepping-in-place.
Kern et al. 2010b; Austria	**Population:** 20 males, 5 females; 22 thoracic SCI, 3 lumbar SCI; all with complete conus/cauda	1. Mean muscle torque after 1 year of daily FES training increased from mean(SD)

Author Year; Country Score Research Design Total Sample Size	Methods	Outcomes
Pre-post Level 4 N=25	equina lesions **Treatment:** Home-based functional electrical stimulation training of the vastus lateralis 5 days/week for 2 years. Long duration, high intensity biphasic simulation impulses adjusted according to excitability produced by daily hb-FES over a period of one year, eventually accompanied by daily standing-up exercises **Outcome Measures:** Quadriceps muscle mass, force, and structure	0.8(1.3) to 7.21(7.18) Nm. 2. After 2 years, mean fiber size diameter significantly increased from 15.5(11.4) to 30.1(21.3) µm, with a shift toward larger muscle fibers. Muscle atrophy was delayed or reduced in both patients less than 1 year post-injury and in those over a year. 3. After the year of training, 20% of participants became able to stand, with 44% improving 1 functional class, 20% improving 2 functional classes, and 4% improving 3 functional classes.
Possover et al. 2010; Switzerland Pre-post Level 4 N=3	**Population:** 3 thoracic patients; all presenting with spasms/spasticity of the lower limbs, and bladder spasms **Treatment:** Stimulation by electrodes to the sciatic and pudendal nerves and one double extradural Brindley-Finetech electrode bilaterally to the sacral nerve roots S3 and S4. **Outcome Measures:** Spasticity and motion of the legs.	1. Contraction of the quadriceps was obtained with optimal pulse widths between 8-20µs and permitted stable standing and alternative locomotion. 2. At the post-operative follow-up points of 9, 6 and 3 months all patients reported optimal control of lower extremity spasticity with an increase in muscle mass.
Kern et al. 2005; Austria Pre-post Level 4 N=9	**Population:** 1 female, 8 males; age 20-49 yrs; complete traumatic conus cauda equina lesions; > 0.8 yrs post-injury. **Treatment:** Progressive PES to FES program for quadriceps to FES-assisted standing (n=4 trained ≥ 2.4 years); untrained controls (n=5). **Outcome Measures:** Muscle biopsy of vastus lateralis (mean fiber diameter, % area covered by muscle fibers, adipocytes, connective tissue).	1. Overall mean fiber diameter of trained group was increased vs untrained group and also had similar values to normal sedentary adults. 2. Proportion of total cross-sectional area covered by muscle fibers increased with training whereas the area covered by adipocytes and connective tissue significantly decreased.
Sharif et al. 2014 Canada Pre-Post Level 4 N= 6	**Population**: 6 individuals- 3 males and 3 females; Level of injury C5 to L4; All AIS D; mean age= 60.5 ± 13.2y; years post injury= 9.3 ± 12.0y **Treatment**: The exercise protocol consisted of 12 weeks of FES-ambulation, with the RT600 (Restorative Therapies, Baltimore, MD), at a frequency of 3 times per week. **Outcome Measures:** Locomotor function was assessed via the Walking Index for Spinal Cord Injury II (WISCI II), the 6-minute walk test (6MWT), the 10-meter walk test (10MWT), and the body-weight support required during training. HRQOL was assessed via the Short Form-36, the Perceived Stress Scale, and the Center of Epidemiological Studies for Depression scale.	1. Participants showed significant improvements in the 6MWT (223 ± 141.5 to 297.7 ± 164.5 m, P=.03) and the required body weight support (55.3% ± 12.6% to 14.7% ± 23.2%; P = .03) following the training program. 2. Four participants showed improvements on the WISCI II. 3. Participants also showed a decrease in the Short Form-36 pain score and an increase in the overall mental health score.

Discussion

In general, all studies reviewed involving FES produced beneficial results on muscle functions such as strength and endurance or muscle structure such as increased muscle size (i.e., reduced muscle atrophy). FES may have additional benefits over NMES alone. In particular, the study by Baldi et al. (1998) should be highlighted as it was the only randomized, controlled trial (n=26) which compared FES (cycle ergometry exercise), NMES (isometric exercise) and an untrained control group. These investigators assessed lean body mass in 3 distinct body areas (i.e., total body, lower limb, gluteal) as a marker of muscle atrophy in recently injured (approximately 10 weeks) individuals with motor complete SCI. Their results demonstrate that the FES-assisted cycling program is effective in reducing atrophy and resulted in relative increases in lean body mass in all areas after 3 and 6 months of participation. The NMES -assisted isometric exercise group also reduced muscle atrophy but had intermediate results between FES and no treatment (their control group actually lost lean mass).

Reversal of muscle atrophy also appears feasible in more longstanding complete or motor-complete SCI (i.e. > 2 years post-injury) as shown by increases in muscle cross-sectional area and the muscle/adipose tissue ratio using FES-cycling (Crameri et al., 2002; Scremin et al., 1999). In chronic SCI, fatigability is also a key issue due to changes in muscle fiber composition. Fornusek et al. (2013) proposed that lower FES cycling cadences may therefore be more beneficial as slower cycling could mitigate the onset of fatigue and allow greater muscle force production. Indeed, in a recent pilot study using each participant as their control, Fornusek et al (2013) provided preliminary evidence that a lower FES cycling cadence compared to a higher cadence (10 rpm vs. 50 rpm) could be more effective at improving muscle hypertrophy and isometric strength.

NMES may also be used to strengthen the atrophied muscles to some extent prior to FES (Kern et al., 2005; Kern et al., 2010a; Kern et al., 2010b) and in some cases, FES is not possible unless NMES is first used. Kern et al. (2005) used a progressive NMES - FES program for quadriceps building eventually leading to FES-assisted standing in people with longstanding complete cauda equina injuries (>1.2 years post-injury). These investigators demonstrated increases to the overall mean fiber diameter and the proportion of total cross-sectional area covered by muscle fibers with training as compared to an untrained group. Later studies showed that FES had similar results in a larger group of participants (Kern et al., 2010a, Kern et al., 2010b). However, the feasibility of providing life-long stimulation therapy to participants with denervation injuries is uncertain.

There was one null finding associated with muscle atrophy in that Gerrits et al. (2000) employed a relatively shorter program of 6 weeks of FES-assisted cycling exercise in people with longstanding motor complete SCI (> 1 year post-injury) and found no change in muscle size. These non-significant results might be due to the relative insensitivity of the measure of thigh circumference, especially with the short intervention period and the absence of a control group for comparison purposes.

In addition to improving muscle properties, FES-cycling can improve work output and endurance (Crameri et al., 2002; Gerrits et al., 2000). For example, Gerrits et al. (2000) used a short (6 weeks) pre-post trial of FES-assisted cycling intervention in people with motor complete SCI and found an increased resistance to fatigue in the quadriceps muscle and greater work output.

Some mechanistic investigations have been conducted which help to explain some of these adaptations to muscle morphology and function with ongoing electrical stimulation exercise programs. For example, using FES-assisted cycling, Koskinen et al. (2000) demonstrated an increase in total collagen content as well as up- and down-regulation of proteins consistent with muscle-building activity. Others have noted an adaptive response to FES-assisted cycling exercise that serves to limit or alter the shift in the oxidative properties or fibre type composition of muscles that typically occurs following SCI (Crameri et al., 2002).

Conclusion

There is level 2 evidence (Baldi et al., 1998) that FES-assisted cycling exercise prevents and reverses lower limb muscle atrophy in individuals with recent (~10 weeks post-injury) motor complete SCI and to a greater extent than PES.

There is level 4 evidence (Scremin et al., 1999; Crameri et al., 2002) that FES may partially reverse the lower limb muscle atrophy found in individuals with long-standing (>1 year post-injury) motor complete SCI.

There is level 4 evidence (Gerrits et al., 2000) that FES-assisted cycle exercise may increase lower limb muscular endurance.

FES-assisted exercise is beneficial in preventing and restoring lower limb muscle atrophy as well as improving lower limb muscle strength and endurance in SCI.

6.0 Gait Retraining Strategies to Enhance Functional Ambulation

6.1 Overground training

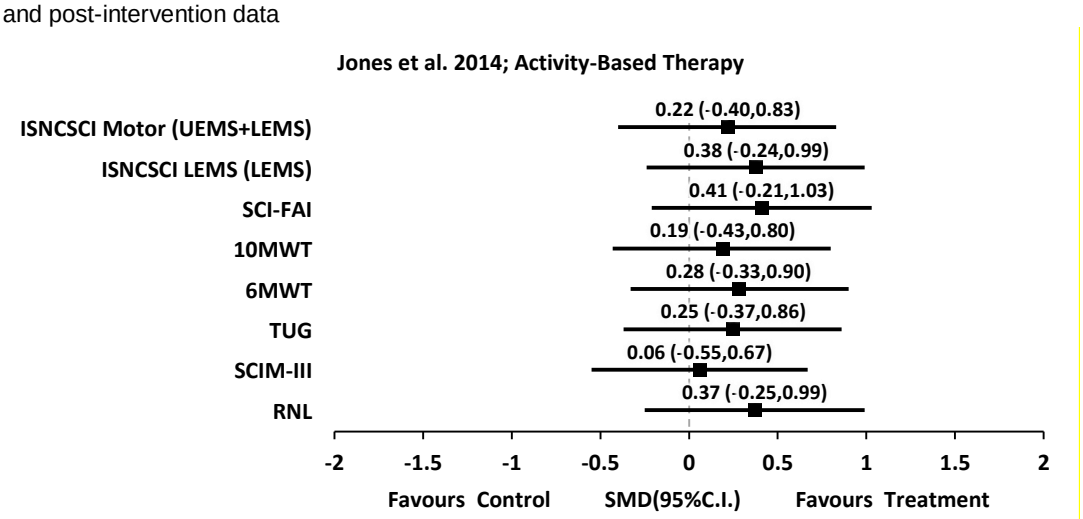
Overground training is usually implemented when there is improved neuromuscular capacity and the person with SCI is ready to learn overground skills to utilize in the home and community. Though overground training is often used as a control group for other types of treatment (e.g., treadmill training) and are described in those respective sections, there is one study that assessed a progressive approach to overground training.

Table 7: Overground Training for Gait Rehabilitation

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
Senthilvelkumar et al. 2015 India RCT PEDro=7 Level 1 N= 16	**Population**: 16 individuals; motor incomplete tetraplegia; 0-2yrs post injury **Treatment**: Participants were randomized to one of two groups: body weight-supported overground training on level ground and body weight-supported treadmill training. Both groups received 30 minutes of gait training per day, five days a week for eight weeks. In addition, both groups received regular rehabilitation which included flexibility, strength, balance, self-care and functional training. **Outcome Measures:** The primary outcome measure was the Walking Index for Spinal Cord Injury (/20 points) and the secondary outcome was the Lower Extremity Muscle Score (/50 points).	1. There was no statistically significant between group differences in the Walking Index for Spinal Cord Injury [mean difference=0.3points; 95% CI (-4.8 to 5.4); p=0.748]. 2. No statistically significant between group differences in the Lower Extremity Muscle Score either [mean difference=0.2 points; 95% CI (-3.8 to 5.1); p=0.749].
Pramodhyakul et al. 2016 Thailand RCT Level 1 PEDro=5 N= 32	**Population**: 32 individuals- 26 males and 10 females; incomplete SCI; 26 AIS D and 10 AIS C; mean age= 41.69 ± 10.90y; months post injury= 35.00 ± 24.40 months **Treatment**: Participants were randomly assigned to the experimental or control groups using stage of injury, severity of SCI, and baseline walking ability as criteria for group arrangement (16 participants per group). The participants were trained to walk over level ground at their fastest safe speed with or without a visuotemporal cue, 30 minutes/day, for 5 consecutive days. **Outcome Measures:** 10 MWT, 6 MWT, Timed up and Go Test (TUG), 5 times sit to stand test	1. The participants demonstrated significant improvement in all functional tests after the 5 days of training. The improvement in the group trained using the visuotemporal cue was significantly better than that trained without using the cue.
Jones et al. 2014 USA RCT PEDro=5 Level 2 N= 38	**Population**: 38 individuals- 27 males and 11 females; chronic, motor incomplete SCI; AIS C or D; age range= 22-63y; years post injury= >12 months **Treatment**: A total of 9h/wk of Activity-based Therapy (ABT) for 24 weeks including developmental sequencing; resistance training; repetitive, patterned motor activity; and task-specific locomotor training. Algorithms were used to guide group allocation, functional electrical stimulation utilization, and locomotor training progression. **Outcome Measures:** Neurologic function (International Standards for Neurological Classification of Spinal Cord Injury), 10-MWT, 6-MWT, and Timed Up and Go test, community participation (Spinal Cord Independence Measure, version III, and Reintegration to Normal Living Index), metabolic function (weight, body mass index, and Quantitative Insulin Sensitivity Check).	1. ABT had a positive effect on neurologic function (International Standards for Neurological Classification of Spinal Cord Injury total motor score and lower extremity motor score.) 2. ABT had a positive effect on 10-meter walk test speed and 6-minute walk test total distance.

<table>
<tr>
<td rowspan="2">Jones et al. 2014
USA
Secondary analysis of results from a randomized controlled trial
PEDro=5
N= 38</td>
<td>Population: 38 individuals- 27 males and 11 females; chronic, motor incomplete SCI; AIS C or D; age range= 22-63y; years post injury= >12 months

Treatment: A total of 9h/wk of Activity-based Therapy (ABT) for 24 weeks including developmental sequencing; resistance training; repetitive, patterned motor activity; and task-specific locomotor training. Algorithms were used to guide group allocation, functional electrical stimulation utilization, and locomotor training progression.

Outcome Measures: Walking speed and endurance (10-meter walk test and 6-minute walk test) and functional ambulation (timed Up and Go test).</td>
<td>1. On the basis of the most conservative estimate, 18%, 26%, and 32% of the participants demonstrated clinically significant improvements on the TUG test, the 10MWT, and the 6MWT, respectively.
2. This secondary analysis identified likely responders to ABT on the basis of injury characteristics: AIS classification, time since injury, and initial walking ability.
3. Training effects were the most clinically significant in AIS grade D participants with injuries <3 years in duration.</td>
</tr>
<tr>
<td colspan="2">Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%C.I.) as calculated from pre- and post-intervention data
 
</td>
</tr>
<tr>
<td>Oh & Park 2013
Korea
Pre-post
Level 4
N=4</td>
<td>Population: 4 participants with incomplete SCI (3M, 1F); 33-63 yrs old; 2 AIS C, 2 AIS D.

Treatment: 4-week training program consisting of 4 stages with different community situations. In each stage, patients underwent 1 hr sessions of community-based ambulation training; 6 times/wk for a 4 week period. During the training period, the level of difficulty was increased weekly with progressive changes in environmental demands.

Outcome Measures: 10MWT; 6MWT; CWT; WAQ; ABC.</td>
<td>1. All outcome measures indicated an improvement in lower limb function from baseline to 4-wk follow-up, as well as from baseline to the 1-yr follow-up:
* values are median (interquartile range)
10MWT: walking speed was 0.58 (0.48-0.78) at baseline; increased to 0.85 (0.66-1.12) at 4-wk follow-up and 0.97 (0.83-1.02) at 1-yr follow-up
6MWT: walking distance was 172.5 (169-198) m at baseline; increased to 259.5 (208.5-337.5) at 4-wk follow-up, 280 (250-323.5) at 1-yr follow-up
CWT: minutes taken to finish the test decreased from 11.86 (9.13-14.24) at baseline to 8.47 (5.98-11.4) at 4-wk follow-up and 7.55 (6.88-8.89) at 1-yr follow-up
WAQ score increased from 38 (27.5-46.5)</td>
</tr>
</table>

Discussion

Overground training can only be undertaken with higher functioning people with incomplete SCI, although the emergence in recent years of robotic exoskeletons has facilitated the opportunity for

overground gait training in motor-complete SCI. However, overground training provides an important mode of exercise for improving walking function, and likely other physical and mental functions (e.g., muscle strength, balance, bone health, cardiovascular function, or depression symptoms) shown to be positively affected by exercise in the general population. In people with motor-incomplete SCI, several studies have indicated the benefits of overground training on functional walking capacity (Forrest et al., 2014; Oh & Park, 2013). Overground training has also been integrated with wider variety of other exercises to provide more comprehensive therapy (Jones et al., 2014) and others have suggested the additive benefits of providing visuotemporal cues during walk training (Pramodhyakul et al., 2016). One Level 1 RCT (Senthilvelkumar et al., 2015) shows no differences between overground vs treadmill-based training. Oh and Park (2013) found that an intensive 6X/week, 4 week training program resulted in effects at 1 year follow-up and demonstrate the positive benefits of exercise.

Conclusion

There is Level 1 evidence (Senthilvelkumar et al., 2015) that overground and treadmill-based training are comparable.

There is level 4 evidence (Oh & Park, 2013) that community-based ambulation training that is progressively challenging may result in long-lasting benefits in incomplete SCI.

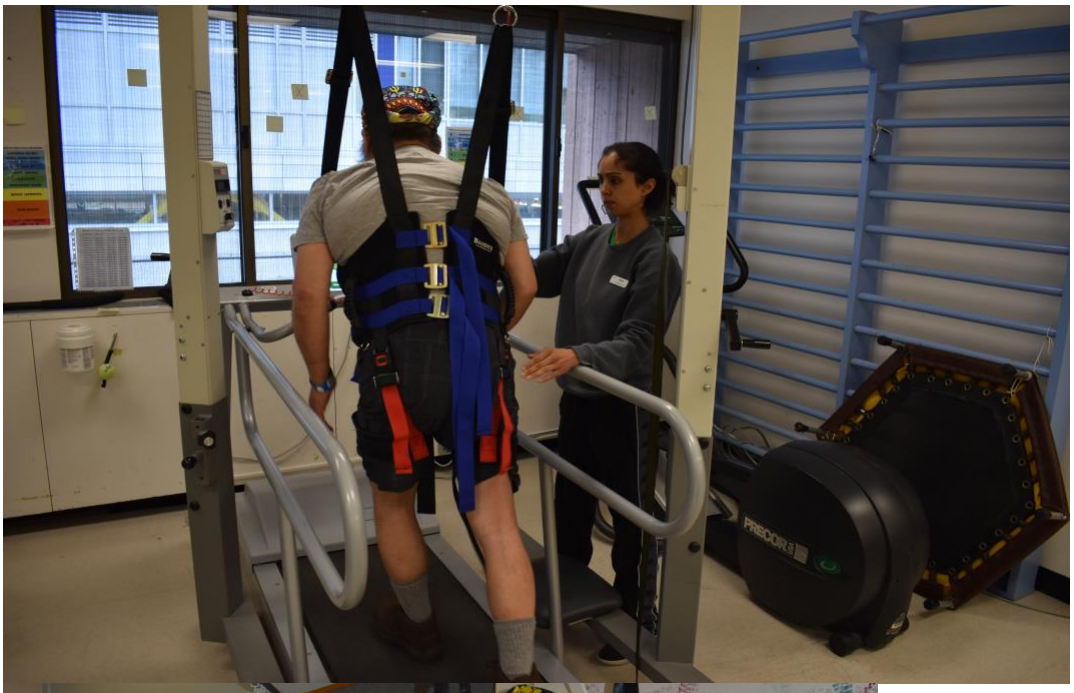
Community-based ambulation training that is progressively challenging may result in long-lasting benefits in incomplete SCI.

6.2 Body-Weight Supported Treadmill Training (BWSTT)

It has been several decades since it was first demonstrated that daily treadmill training can enhance locomotor activity in animals that have a complete spinal cord transection (Edgerton et al., 1991; Barbeau and Rossingnol, 1987). In this approach, partial body weight support is provided by a harness suspended from the ceiling or a frame while limb stepping movements are assisted by a moving treadmill belt. In the ensuing years, BWSTT strategies have been introduced as a promising approach to improve ambulatory function in people with SCI (Barbeau and Blunt, 1991), raising much excitement and interest among rehabilitation specialists and neuroscientists.

In this review, we focus on the BWSTT intervention studies that report functional ambulation outcome measures (such as walking speed or endurance). These studies tend to focus on individuals with motor-incomplete SCI lesions as the recovery of overground functional ambulation has not been shown in people with clinically complete spinal lesions (Waters et al., 1992). Although modulation of muscle (EMG) activity during body weight support treadmill-assisted stepping in individuals with complete SCI lesions has been shown (Dietz and Muller, 2004; Grasso et al., 2004; Wirz et al., 2001; Dietz et al., 1998; Wernig et al., 1995; Dietz et al., 1995; Faist et al., 1994), there has not been any evidence for functional ambulatory gains in this sub-population.

In people with motor-incomplete SCI, much motor recovery already occurs within the first 2 months post-injury; the rate of further recovery then decelerates over the next 3 to 6 months (Burns and Ditunno, 2001). For the purposes of this review, we defined SCI <12 months post-injury as acute/sub-acute and SCI >12 months post-injury as chronic.

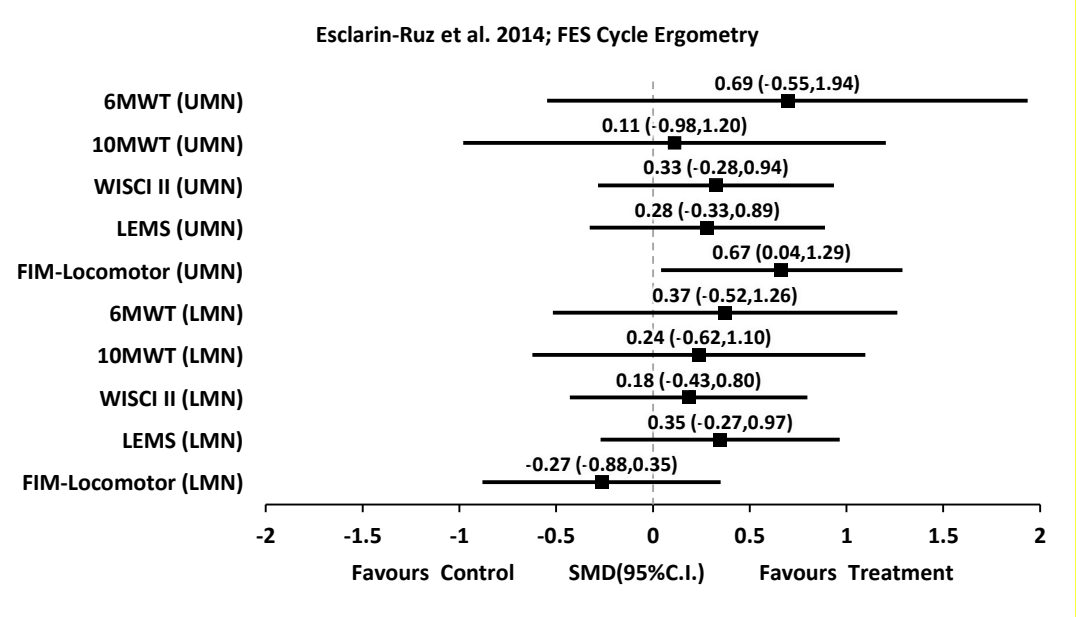

PRECOR

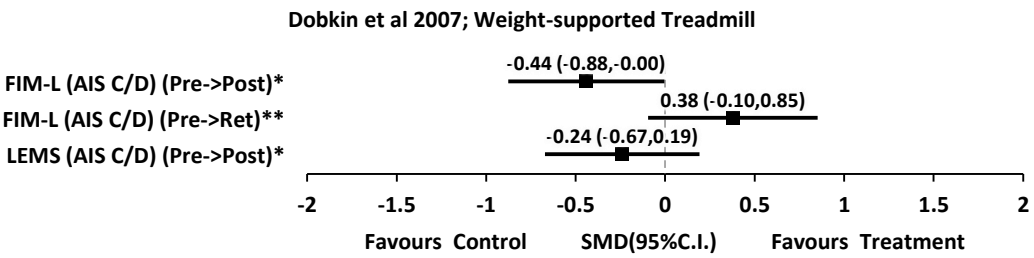

EXIT
BIODEX

6.2.1 BWSTT in Acute/Sub-Acute SCI

Table 8: Studies Using BWSTT in Acute/Subacute in SCI (<12 Months Post-Injury)

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
Alcobendas-Maestro et al. 2012; Spain PEDro=8 Randomized single-blind parallel-group clinical trial Level 1 N=75	**Population:** 75 participants with SCI in total; all <6 months post-injury. For the Lokomat group (N=37), mean (SD) age = 45.2 (15.5); 62%M, 38%F; 68% AIS C, 32% AIS D. For the conventional treatment group (N=38); mean (SD) age= 49.5 (12.8); 63%M, 37%F; 71% AIS C, 29% AIS D. **Treatment:** Randomized to 2 groups: Lokomat and conventional treatment. **Outcome Measures:** 10MWT; WISCI II; 6MWT; walking and stairs tasks of the FIM-L section; LEMS subscale; Ashworth Scale and Visual Analogue Scale for pain.	1. The Lokomat treatment group showed statistically significant differences in favour of Lokomat treatment over conventional treatment in the following outcome measures: WISCI II: Lokomat [16 (8.5-19)], Conventional [9 (8-16)] 6-minute walk test (m): Lokomat [169.4 (69.8-228.1)], Conventional [91.3 (51.4-178.7)] LEMS lower limb strength: Lokomat [40 (35-45.5)], Conventional [35 (29.7-40)] FIM-L: Lokomat [10 (6-12)], Conventional [7 (5-10)] 2. There were no differences between the Lokomat and conventional treatment group in the variables: speed (10MWT), spasticity (Ashworth scale), and pain (Visual Analogue Scale).
Dobkin et al. 2006 USA PEDro=7 RCT Level 1 N=292 (enrolled) N=117 (analyzed)	**Population**: 117 males and females; age 16-69 yrs; AIS B-D; <8 wks post-injury. **Treatment:** BWSTT vs. overground mobility training: 5x/wk, 9-12 wks, 30-45 min/session. **Outcome measures:** FIM-L, walking speed, 6MWT, WISCI at 3 and 6 months	1. No difference in FIM Locomotor Scale (AIS B & C) or walking speed (AIS C & D) between groups. 2. AIS C & D participants in both groups improved walking function. No improvement of functional ambulation in the AIS B participants with either intervention.
Esclarin-Ruz et al. 2014 Spain RCT Level 1 PEDro=7 N= 88	**Population**: 88 individuals; 44 with upper motor neuron SCI and 44 with lower motor neuron SCI; 59 AIS C and 25 AIS D; mean age= 43.6 ± 12; days post injury= 125.6 ± 65.2 **Treatment**: Condition 1: Subgroups A1 and B1 were treated with robotic Locomotor training plus Over ground Therapy (LKOGT) for 60 minutes. Condition 2: Subgroups A2 and B2 received 60 minutes of conventional OGT 5 days per week for 8 weeks. Participants with UMN and LMN were randomized into 2 training groups **Outcome Measures:** Ten-meter walk test and 6-minute walk test (6MWT). Walking Index for Spinal Cord Injury II, lower extremity motor score (LEMS), and the FIM-Locomotor were secondary outcome measures.	1. By using the LKOGT program compared with OGT, we found significant differences in the 6MWT for groups A1 and B1. 2. LKOGT also provided higher scores than did OGT in secondary outcomes such as the LEMS and the FIM-Locomotor.
	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%C.I.) as calculated from pre- and post-intervention data	

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
		
Dobkin et al. 2007 USA and Canada PEDro=5 RCT Level 2 N=112	**Population:** 112 males and females; 29 participants with diagnosis of AIS B, 83 participants with diagnosis of AIS C-D; age 16-70 yrs; mean 4.5 wks post-injury **Treatment:** BWSTT vs. overground mobility training (control): 5x/wk, 9-12 wks, 30-45 min/session. **Outcome measures:** FIM-L (range from 1 (total physical dependence) to 7 (independence to walk > 150 feet)), walking speed, 6MWT, LEMS.	1. At 12 weeks, no differences were found between patients who received BWSTT versus control for FIM-L, walking speed, LEMS, or distance walked in 6 minutes. 2. Combining both interventions, a FIM-L ≥ 4 was achieved in < 10% of AIS B patients, 92% of AIS C patients, and all of AIS D patients; few AIS B and most AIS C and D patients achieved functional walking ability by the end of 12 weeks of BWSTT and control. 3. Time after injury is an important variable for planning interventions to lessen walking disability. Patients who started their rehabilitation sooner (<4 weeks after onset) had better outcomes. This does not imply that an earlier start of rehabilitation for walking led to better outcomes. Rather, entry within 4 weeks allowed some patients to start at a lower level of function. 4. By 6 weeks after entry, most patients who will recover have improved their FIM-L to >3 and are improving in walking speed.
	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%C.I.) as calculated from pre- to post-intervention data and pre-intervention to retention/follow-up data	

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
	 *SD of post-intervention measurements used for calculation *SD of follow-up/retention measurements used for calculation	
Hornby et al. 2005a USA PEDro=5 RCT Level 2 N=30	**Population**: 30 SCI patients (ASIA classification of B, C, or D) Inclusion Criteria: traumatic or ischemic SCI above the T10 spinal cord level experienced between 14 and 180 days prior to study enrollment, partial preservation of voluntary motor control in at least one muscle of the lower extremities **Treatment**: randomly assigned to one of three 8-week training regimens: Robotic-assisted BWSTT, therapist-assisted BWSTT, and overground ambulation with a mobile suspension system **Outcome Measures:** LEMS, WISCI II, FIM	1. Mean changes in all groups improved significantly during the training regimen, with significant changes in FIM locomotor subscores, WISCI scores, and LEMS. 2. Significant difference in the total distance ambulated over ground: mean (SD) distance walked 1282 (606) m vs. both robotic-assisted (2859 (111) m) and therapist-assisted (2759 (215) m) BWSTT groups 3. The number of therapists required to provide gait training on the treadmill or over ground was significantly greater than that required for the robotic-assisted group for the first 5 weeks of training 4. There were no significant differences noted between therapist- and robotic-assisted BWSTT groups for the final 3 weeks of training
Benito-Penalva et al. 2012 Spain Prospective longitudinal study Level 2 N=105	**Population:** 105 participants with SCI. 39 randomized to Lokomat treatment and 66 to Gait Trainer GT I treatment. Mean age for both groups = 45 yrs. For the Lokomat group, 26M 13F and 5 AIS A&B, 18 AIS C, 16 AIS D. For the Gait Trainer GT I group, 45M 21F, and 6 AIS A&B, 26 AIS C, 34 AIS D. Majority of participants were <1 year post-injury. **Treatment:** Patients received locomotor training with one of the electromechanical devices [Lokomat or Gait Trainer GT I System], 5 days/wk for 8 wks. **Outcome Measures:** LEMS, WISCI, 10MWT. Outcomes collected at baseline, midpoint (4wks) and end of program (8 wks).	1. For the total sample, all 3 clinical outcomes showed statistically significant improvement after the use of electromechanical systems: LEMS: pre= 22.07(1.08), post=30.56(1.15) WISCI: pre=3.97(0.49), post=9.16(0.68) 10MWT: pre=0.082(0.01), post=0.26(0.03) 2. Rate of clinical change across the training period was not significantly different between the 2 treatment groups for any of the 3 outcomes. 3. Compared to conventional standard of care from the EM-SCI database, for the LEMS, both ASIA grade C and D patients receiving electromechanical device system gait training had a significantly greater rate of change in motor function when compared to matched patients from EM-SCI group.
Wernig et al. 1995 Germany Case Control	**Population:** Study 1: 12 males and females; 0-4.5 months post injury. Study 2: 85 males and females; 2-30 wks post-injury.	1. Study 1: 9/12 initially wheelchair-bound could walk without assistance after BWSTT. 2. Study 2: 33/36 initially non-ambulatory participants could walk after BWSTT.

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
Level 3 N=97	**Treatment:** Study 1) BWSTT: 30-60 min, 5x/wk, 3-20 wks (median 10.5 wks). Study 2) 45 participants underwent 2-22 wks of BWSTT vs. 40 participants (historical controls) underwent conventional rehabilitation. **Outcome measures:** Wernig Scale of Ambulatory Capacity.	3. 7/9 initially ambulatory participants improved walking distance after BWSTT. 4. 12/24 initially non-ambulatory participants improved to functional ambulation after conventional rehabilitation. 5. Results from the remaining 16 participants (who were initially ambulatory) in historical control group not reported.
Harkema et al. 2012 USA Pre-post (subacute and chronic) Level 4 N=196	**Population**: 196 individuals (148 male, 48 female) with incomplete SCI; mean age 41±15 yrs; YPI- <1 yrs (n=101), 1-3 yrs (n=43), >3 yrs (n=52) **Treatment:** Locomotor training with three components: (1) 1 hour of step training in the body-weight support on a treadmill environment, followed by 30 minutes of (2) overground assessment and (3) community integration **Outcome Measures**: BBS, 6MWT, and 10MWT	1. Scores on the Berg Balance Scale significantly improved by an average of 9.6 points 2. Six-Minute Walk Test distances and 10-Meter Walk Test speeds of all patients significantly improved by an average of 63m and 0.20m/s, respectively 3. 168 (86%) patients (66 of 66 AIS grade C, 102 of 130 AIS grade D) scored lower than 45, the reported threshold for risk for falls for the Berg Balance Scale -Patients with AIS grade C SCI had significantly lower scores at enrollment than those with AIS grade D classification - Patients with AIS grade D SCI walked significantly farther than those with AIS grade C SCI

Discussion

Seven studies (summarized in Table 8) have examined the effect of therapist-assisted (Dobkin et al., 2007; Dobkin et al., 2006; Wernig et al., 1995; Hornby et al., 2005a; Harkema et al., 2012; Alcobendas-Maestro et al., 2012; Benito-Penalva et al., 2012) BWSTT in people who had incurred an incomplete SCI <12 months prior (acute/subacute phase) (aggregate N=566). One study also examined overground training and robotic–assisted treadmill training (Hornby et al. 2005a). Treatment time ranged from 90-300 minutes per week and total treatment duration lasted between 3 and 23 weeks.

Although lower levels of study design (non-randomized, non-blinded) suggest that BWSTT in acute/sub-acute SCI yields better outcomes than conventional rehabilitation (Wernig et al., 1995), there exists strong evidence from a single-blind RCT (Dobkin et al., 2006) (n=117) that there are no differences in effects between matched amounts of BWSTT and overground mobility practice in incomplete SCI during inpatient rehabilitation for the locomotor score of the FIM or overground walking speed. These two variables in both groups improved roughly in parallel over the 12 weeks of therapy (Dobkin et al., 2007). In both groups, improvements in walking function were particularly notable in participants with AIS C (92%) or D (100%). Indeed, as reported by Dobkin et al (2006), the initial AIS classification of participants is an important indicator of locomotor recovery. Among the participants who were initially classified as AIS B, those who improved to AIS C within 8 weeks post-injury showed improved walking function while those who remained as AIS B did not (Dobkin et al., 2006). In addition, participants who entered the trial earlier (< 4 weeks post-injury) had faster walking speeds and endurance post-training. This was particularly the case for participants who improved in their AIS classification within 4 to 6 weeks post-injury. Preliminary analysis from a smaller RCT

(Hornby et al. 2005) (n = 30) had similar results, showing that there were no differences in motor (lower extremity motor scores) or functional recovery (FIM locomotor subscore or WISCI II score) between those that trained overground, with BWSTT, or with robotic assisted treadmill training. All increases from initial to final evaluations were significant. However, the results from a more recent randomized single-blind parallel-group clinical trial from Alcobendas-Maestro et al. (2012) (N=75) suggested that Lokomat-assisted BWSTT may result in better improvements in the WISCI II, 6MWT, LEMS, and FIM-L scores compared to conventional treatment. However, it is unclear whether the conventional treatment group received an equivalent amount of task-specific locomotor practice, so differences in the intensity and/or specificity of training could account for these contrasting results.

Wernig et al. (1995) showed that 86% (49/57) of incomplete SCI participants who underwent BWSTT in the acute phase of injury achieved improvements in functional ambulation. They reported that only 50% of the initially non-ambulatory participants (historical controls) who underwent conventional rehabilitation improved functional ambulation. The results of the remaining 16 historical control participants who were initially ambulatory were not explicitly reported, although it appears from the article's bar graphs that they also improved in functional class. Thus, it is possible that the proportion of participants who improved functional ambulation after Wernig's conventional rehabilitation may actually have been closer to 70% ([16+12]/40).

A contentious issue in field of gait training has been the appropriateness of the control intervention (Wolpaw, 2006). The 'conventional' rehabilitation to which BWSTT was compared was not well defined in Wernig's studies, although it appeared to focus on wheelchair mobility in addition to gait training in parallel bars and using braces (Wernig, 2006a). The control group in the large RCT (Dobkin et al., 2006) underwent task-oriented overground gait retraining of equivalent intensity to the BWSTT group and therefore may not have offered enough of a contrast in treatment modality to detect significant differences. Moreover, based on retrospective analysis from the participating centres, it appeared that significantly enhanced locomotor outcomes were achieved with both treatment and control conditions as compared to what was achieved with "standard practice" in the centres prior to the study – although it is likely that pre-study practice of gait therapy varied to some degree across the study centres. On the other hand, the more recent RCT Alcobendas-Maestro et al. (2012) did not clearly state whether the conventional training group received an equivalent amount of overground therapy for walking compared to the Lokomat training group. Despite these difficulties, the important message from this work is that intensive task-oriented gait retraining, whether implemented by BWSTT or overground practice, facilitates the recovery of functional ambulation especially <12 months post-injury. However, there is no strong evidence that one rehabilitation approach is superior to another.

Conclusion

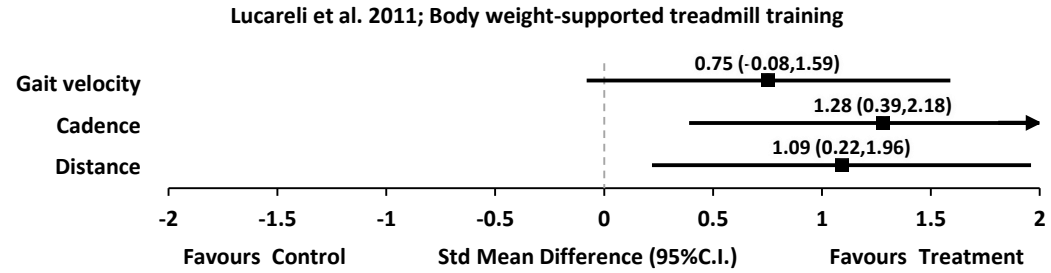
There is level 2 (Alcobendas-Maestro et al., 2012) and level 3 evidence (Wernig et al., 1995) using historical controls that BWSTT is effective in improving ambulatory function. However, two level 2 RCTs (Dobkin et al., 2006; Hornby et al. 2005a) demonstrates that BWSTT has equivalent effects to conventional rehabilitation consisting of an equivalent amount of overground mobility practice for gait outcomes in acute/sub-acute SCI.

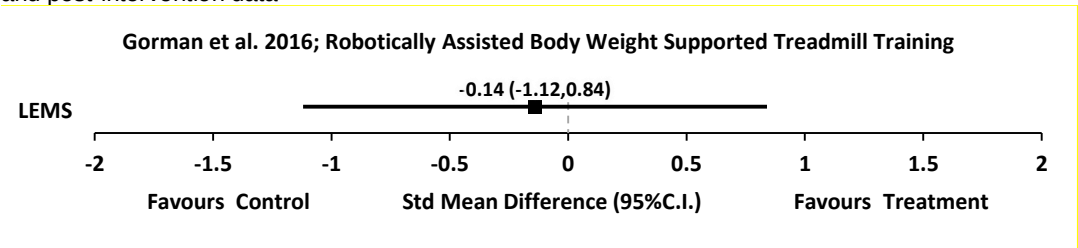
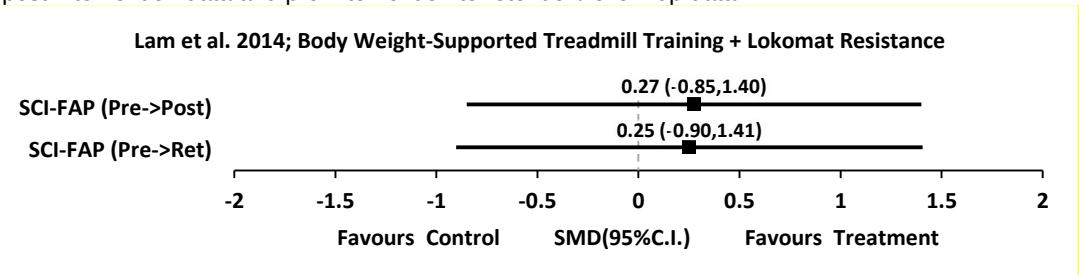
For patients less than 12 months post-SCI, BWSTT may have similar effects on gait outcomes as overground mobility training of similar intensity

6.2.2 BWSTT in Chronic SCI

Table 9: Studies Using Treadmill Training in Chronic SCI (>1 Year Post-Injury)

Author Year; Country Score Research Design Sample Size	Methods	Outcome
Labruyere et al. 2014 Switzerland Randomized cross-over open label clinical pilot study PEDro=6 Level 1 N= 9	**Population**: 9 individuals- 5 males and 4 females; SCI ranging from C4 to T11; mean age= 59 ± 11y; months post injury= 50 ± 56m **Treatment**: Participants with a chronic iSCI were randomized to group 1 or 2. Group 1 received 16 sessions of RAGT (45 min each) within 4 weeks followed by 16 sessions of strength training (45 min each) within 4 weeks. Group 2 received the same interventions in reversed order. Data were collected at baseline, between interventions after 4 weeks, directly after the interventions and at follow-up 6 months after the interventions. Pain was assessed repeatedly throughout the study. **Outcome Measures:** 10 MWT at preferred and maximal speed, walking speed under different conditions, balance, strength, 2 questionnaires that evaluate risk of falling and pain.	1. There were no significant differences in changes in scores between the 2 interventions, except for maximal walking speed (10MWT), which improved significantly more after strength training than after RAGT. 2. Pain reduced after both interventions.
Nooijen et al. 2009 USA PEDro=7 RCT Level 1 N=51	**Population:** All participants had motor-incomplete spinal cord injuries and were at least 1-year post injury; Group 1: mean age = 38.15; T11-C3; Group 2: mean age = 39.47; T9-C4; Group 3: mean age = 41.64; T6-C4; Group 4: mean age = 44.33; L2-C6. **Treatment**: 12-week training period. All BWSTT: Group 1 = treadmill with manual assistance; Group 2 = treadmill with peroneal nerve stimulation; Group 3 = overground with peroneal nerve simulation; Group 4 = treadmill with assistance from Lokomat **Outcome Measures**: Cadence, step length, stride length, symmetry index, intralimb coordination, timing of knee extension onset within the hip cycle; all compared to non-disabled controls.	1. No significant between-SCI group differences. Pooled data were then used to assess the effects of training. 2. Training significantly improved: cadence, step length and stride of both the stronger and weaker legs. 3. After training, participants were able to take more steps per minute 4. There was an interaction effect between step and stride lengths. Post hoc analyses revealed Group 3 had a significantly larger gain compared to group Group 4. 5. No training effects found on symmetry or coordination. 6. After training gait outcome measures were more similar to able-bodied controls than they were before training.
Musselman et al. 2009 Canada PEDro=6 RCT with crossover Level 1 N=4	**Population:** 2 male and 2 female participants, age 24-61, level of injury C5-L1, all AIS-C. **Treatment:** All participants received 3 months of BWSTT, then participants underwent 3 months of BWSTT and 3 months of skill training in random order **Outcome Measures:** mEFAP; 10MWT; 6MWT; BBS; ABC.	1. Improvement of mEFAP with skill training in all participants (average improvement 731.5); improvement also seen with BWSTT in 2 of 4 participants (-1379 and -731 respectively); gains were maintained after training (statistical test for significant was not done) 2. Results for the 10m and 6-min walk tests improved more with skill training (average 0.10m/s) compared to BWSTT (average 0.02m/s); again, tests for significance was not done 3. Minor improvements in Berg Balance Scale (9, 0, 10 and 5 points for participants 1, 2, 3 and 4 respectively), and no improvement for ABC

Field-Fote et al. 2005 USA PEDro=6 RCT Level 1 N= 27	**Population:** 27 males and females; age 21-64 yrs; with incomplete SCI; C3-T10 lesion level; >1 yr post-injury. **Treatment:** Randomized to 4 gait training strategies, 45-50 min, 5X/week, 12 weeks: 1) manual BWSTT (n=7); 2) BWSTT+FES (common peroneal nerve) (n=7); 3) BWS overground + FES (n=7); 4) BWS Lokomat (robotic gait device) (n=6). **Outcome measures:** Walking speed over 6 m (short-bout) and 24.4 m (long bout).	1. No significant differences between pre- and post-intervention walking speed in the manual BWSTT or BWS Lokomat groups. 2. However, there was a tendency for participants with initially slower walking speeds (<0.1 m/s) to have a greater percent increase in walking speed (57% to 80%) compared to those with initially faster walking speeds (-19% to 5%)
Lucareli et al. 2011 Brazil PEDro=7 RCT Level 1 N=30	**Population:** 14 males and 10 females with incomplete SCI; mean age 31.5; mean YPI 9.8 **Treatment:** Group A – treadmill gait training with body weight support + conventional physiotherapy; Group B – conventional physiotherapy; both groups underwent 30 semi-weekly sessions lasting 30 min each **Outcome Measures:** Spatial temporal gait variables and angular gait variables	1. Group B showed no within group differences for spatial-temporal gait measures. Group A showed within group improvements in gait speed (47%), step length (17%), and cadence (16%). 2. There were no statistically significant improvements for Group B for any measure. 3. Group A showed a significantly greater range of motion after intervention compared to Group B for maximum hip extension during stance and maximum plantar flexion during pre-swing. There were no significant group differences after treatment in other angular gait variables.
	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%C.I.) as calculated from pre- and post-intervention data  	
Yang et al. 2014 Canada RCT PEDro=6 Level 1 N= 22	**Population**: 22 participants; 16 males and 6 females; Level of injury between C2 and T12; mean age= 48 ± 13y; years post injury= 5.7 ± 10.5y **Treatment**: Twenty-two participants, ≥7 months post injury, were randomly allocated to start with Precision or Endurance Training. Each phase of training was 5 times per week for 2 months, followed by a 2-month rest. **Outcome Measures:** Walking speed- 10 MWT, distance- 6 MWT, skill, confidence- Activities specific balance confidence scale, depression- Centre for Epidemiologic Studies- Depression Scale (before training and monthly afterwards), WISCI-II, SCI-FAP	1. Both forms of training led to significant improvements in walking, with Endurance Training inducing bigger improvements in walking distance than Precision Training, especially for high-functioning walkers who had initial walking speeds >0.5 m/s. 2. The largest improvements in walking speed and distance occurred in the first month of Endurance Training, with minimal changes in the second month of training. 3. In contrast, improvements in walking skill occurred over both months during both types of training. Retention of over ground walking speed, distance, and skill was excellent for both types of training.
	Population: 18 individuals chronic motor incomplete spinal cord injury between C4 and L2; >1 y post injury	1. The RABWSTT group improved peak VO2 by 12.3% during robotic treadmill walking (20.2 ± 7.4 to 22.7 ± 7.5 ml/kg/min, P = 0.018)

Gorman et al. 2016 USA RCT PEDro=4 N=18	**Treatment**: Participants were randomized to Robotic-Assisted Body-Weight Supported Treadmill Training (RABWSTT) or a home stretching program (HSP) 3 times per week for 3 months. Those in the home stretching group were crossed over to three months of RABWSTT following completion of the initial three-month phase. **Outcome Measures:** Peak VO2 was measured during both robotic treadmill walking and arm cycle ergometry: twice at baseline, once at six weeks (mid-training) and twice at three months (post-training). Peak VO2 values were normalized for body mass.	2. Peak VO2 during robotic treadmill walking and arm ergometry showed statistically significant differences.
	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%C.I.) as calculated from pre- and post-intervention data 	
Lam et al. 2014 Canada RCT Level 1 PEDro=8 N= 15	**Population**: 15 individuals- 9 males and 6 females; chronic motor incomplete SCI; 5 AIS C and 10 AIS D; age range= 26-63y; years post injury> 1y; **Treatment**: Participants were randomly allocated to BWSTT with Lokomat resistance (Loko-R group) or conventional Lokomat-assisted BWSTT (controls). Training sessions were 45 minutes, 3 times/wk for 3 months. **Outcome Measures:** Skilled walking capacity (SCI-FAP), 10 MWT, 6 MWT. Timed Up and Go Test (TUG). All outcome measures were measured at baseline, post=training, and 1 and 6 months follow up.	1. Training was well tolerated by both groups, although participants in Loko-R tended to report higher levels of perceived exertion during training. 2. Participants in the Loko-R group performed significantly better in the SCI-FAP compared with controls at posttraining and in follow-up assessments. 3. Both groups showed improvements in walking speed (10MWT) and distance (6MWT) with training, but there were no between-group differences.
	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%C.I.) as calculated from pre- to post-intervention data and pre-intervention to retention/follow-up data 	
	Population: 40 individuals- 27 males and 13 females; spastic hypertonia in lower extremities	1. The baseline (i.e. pre-training) measures of MVC torque (Td and Tp) could predict the differential treatment response, i.e., participants with high Tp and Td were more likely to have both high

Niu et al. 2014 USA Single centre, unblinded, randomized study PEDro=5 Level 2 N= 40	**Treatment**: Each participant was assigned either to the control or intervention (Lokomat training) group according to a permuted block randomization design. All participants were injured within their cervical or upper thoracic (superior to T10) vertebrae. Each participant received a one-hour training session three times per week for four consecutive weeks; as it took 15-20 mins to set up the participant, the gait training lasted up to 45 mins per session **Outcome Measures:** 10 MWT, 6MWT, Time up and Go (TUG), isometric torque resulting from MVC, Modified Ashworth Score (MAS), EMG, Walking Index for Spinal Cord Injury (WISCI II)	walking capacity and receive significant benefit from Lokomat training. 2. Lokomat training in participants with low walking capacity did not show significant improvements. By contrast, participants with a high walking capacity at baseline presented a consistent linear trend in time for both speed and functional balance over the 4-week training period.
Gorassini et al. 2009 Canada Prospective Controlled Trial Level 2 N=23	**Population:** 17 participants with incomplete SCI, mean (SD) age 43.8(16.5), injury level C3-L1, and 6 AB controls. Participants were divided into 2 groups: those who improved in walking ability (responders, n=9, 4 AIS-C, 5 AIS-D) and those who did not (nonresponders, n=8, 7 AIS-C, 1 AIS-C) **Treatment:** BWSTT, on average for mean (SD) 3.3(1.3) days/week for 14(6) weeks **Outcome Measures:** EMG; WISCI II	1. Responders had an average WISCI II increase of 4.6pts, compared to no increase in the nonresponders. 2. The amount of EMG activity increased significantly after training in responders, whereas no change was observed in nonresponders.
Wu et al. 2012 USA Repeated assessment with crossover PEDro=5 Level 2 N=10	**Population:** 10 participants with chronic SCI (8M 2F); mean (SD) age: 47(7); mean (SD) DOI: 5.8(3.8) yrs; level of injury: C2-T10. **Treatment:** Group 1: BWSTT with 4 wks assistance training, then 4 weeks resistance training. Group 2: BWSTT with 4 wks resistance training, then 4 wks assistance training. Resistance provided by a cable-driven robotic locomotor training system. Sessions were 45 minutes, 3x/wk x 8 weeks **Outcome Measures:** Primary: self-selected and fast walking speed, 6MWT, BBS. Secondary: muscle strength tests, WISCI II, Physical SF-36, Activities-specific Balance Confidence Scale	1. A significant improvement in both walking speed (increased from 0.67(0.20) at baseline to 0.76(0.23) m/s post-intervention) and balance (increased from 42(12) to 45(12)) was observed after robotic treadmill training. 2. Following robotic training, stride length, step length, and cadence during self-selected walking significantly improved. 3. There was no significant difference in walking functional gains after resistance versus assistance training, although resistance training was more effective for higher functioning patients.
Behrman et al. 2012 USA Prospective Cohort Level 2 N=95	**Population:** 95 participants with SCI (75M, 20F); <1 yr (n=47), 1-3 yrs (n=24), ≥3 yrs (n=24) since injury; level of injury: T11 or above; Mean (SD) age: 43(17); median time since injury: 1 year; 31 AIS C, 64 AIS D. **Treatment:** At least 20 sessions of the NRN Locomotor Training Program consisting of manual-facilitated BWS standing and stepping on a treadmill and overground. Training consisted of 1hr of treadmill training, 30 minutes overground assessment, and 15-30 minutes of community reintegration. Frequency: 5 days/wk for non-ambulators, 4 days/wk for ambulators with pronounced assistance, 3 days/wk for independent	1. For those who enrolled in phase 1 and were still classified phase 1 after NRN training, no change was seen in BBS, 6MWT or 10MWT scores. 2. For those who enrolled in phase 1 and were classified phase 2 after NRN training, mean change scores were 1 for BBS, 10 for 6MWT and 0 for 10MWT. 3. For those enrolled at Phase 1 and classified as Phase 3 after NRN training, mean change scores were 38.5 for BBS, 265.5 for MWT and 0.7 for 10MWT. 4. For those enrolled in Phase 2 and classified as Phase 2 after training, mean change scores were 7 for BBS, 46 for 6MWT and 0.1 for 10MWT.

	walkers. Patients split into phases 1-3 depending on level of ability (higher ability = higher phase). **Outcome Measures:** ISNSCI AIS, BBS, 6MWT, 10MWT	5. For those enrolled in Phase 2 and classified as Phase 3 after training, mean change scores were 15 for BBs, 82.3 for 6MWT and 0.3 for 10MWT.
Buehner et al. 2012 USA Prospective cohort Level 2 N=225	**Population:** 225 participants with chronic incomplete SCI (167M, 58F); mean (SD) age=42.5 (15.9); Median DOI=2.45; 57 AIS C, 167 AIS D. **Treatment:** NRN Locomotor Training Program. Training consisted of 1hr of treadmill training, 30 minutes overground assessment, and 15-30 minutes of community reintegration. Frequency: 5 days/wk for non-ambulators, 4 days/wk for ambulators with pronounced assistance, 3 days/wk for independent walkers. **Outcome Measures:** LEMS, pinprick, light touch, 10MWT, 6MWT, BBS	1. Significant gains occurred in LEMS scores (Pretraining: 31.85 (13.98); Posttraining: 38.61 (12.29)) but not in sensory scores. 2. Although 70% of participants showed significantly improved gait speed after locomotor training, only 8% showed AIS category conversion. 3. Significant gains in gait speed (72%), ambulation distance (74%) and balance (43%) occurred after NRN training regardless of initial AIS classification.
Lorenz et al. 2012 USA Longitudinal Level 2 N=337	**Population:** 337 participants with SCI (255M, 82F); mean (SD) age: 40 (17); 99 AIS C, 238 AIS D. **Treatment:** At least 20 sessions of the NRN Locomotor Training Program. Training consisted of 1hr of treadmill training, 30 minutes overground assessment, and 15-30 minutes of community reintegration. Frequency: 5 days/wk for non-ambulators, 4 days/wk for ambulators with pronounced assistance, 3 days/wk for independent walkers. **Outcome Measures:** BBS; 6MWT; 10MWT	1. There was significant improvement on each outcome measure and significant attenuation of improvement over time. 2. Patients varied significantly across groups defined by recovery status and AIS grade at enrollment with respect to baseline performance and rates of change over time. 3. Time since SCI was a significant determinant of the rate of recovery for all measures.
Wernig et al. 1995 Germany Case Control Level 3 N=97	**Population:** Study 1: 44 participants with chronic paraplegia or tetraplegia. Study 2: 53 participants with chronic paraplegia or tetraplegia. **Treatment:** Study 1: BWSTT: 30-60 min, 5x/wk, 3-20 wks (median 10.5 wks). Study 2: 29 participants underwent BWSTT (as in Study 1) versus 24 historical controls that underwent conventional rehabilitation. **Outcome measures:** Wernig Walking Capacity Scale.	1. Study 1: 25/33 initially non-ambulatory could walk after BWSTT. Results of 11 initially ambulatory participants unclear. At 6 months post-training, 18/21 ambulatory patients maintained abilities or improved endurance. 2. Study 2: 14/18 initially non-ambulatory participants could walk after BWSTT. Only 1/14 initially non-ambulatory in the historical controls learned to walk. Other specific improvements in initially ambulatory participants in either the BWSTT or historical control groups were not clearly described.
Benito Penalva et al. 2010 Spain Case control Level 3 N=42	**Population:** 29 motor incomplete SCI patients (24 males, 5 females, mean age 47; Group A < 3 months post-injury (n=16), Group B > 3 months post-injury (n = 13) and 13 healthy volunteers (10 males, 3 females, mean age 32) with pre-test only **Treatment:** Gait training using either the Lokomat or Gait Trainer GT1 (based on availability of the system), 20-45 minutes per	1. After gait training, there was a significant improvement in LEMS, WISCI and 10MWT for both group A and B, with a significantly greater improvement in 10MWT for group A versus group B. 2. After gait training, Group A showed significantly greater H reflex facilitation with TMS at 20 ms than Group B (170.7 + 10.2% vs. 125.3 + 5.6%), with no significant differences at 50 and 80 ms.

	sessions (5 days a week for 8 weeks). **Outcome Measures:** LEMS, WISCI II, 10MWT, H reflex modulation by TMS	
Fleerkotte et al. 2014 Netherlands Pre-Post Test Level 4 N=10	**Population**: 10 individuals- 4 males and 6 females; motor incomplete chronic SCI; 1 AIS B, 5 AIS C, 4 AIS D; mean age= 48.75 ± 11.3y; months post injury= 46.75 ± 41.03 **Treatment**: Participants participated in an eight-week training program. Participants trained three times per week, for a maximum of 60 minutes per session. The training period was divided in two four-week periods, with one week scheduled for clinical tests in between. During training sessions, rest intervals were introduced if required by the participant or suggested by the therapist. The first training session was used to 1) fit the LOPES to the participant, 2) let participants get used to walking in the device and 3) select their preferred walking speed. **Outcome Measures:** 10-meter walking test (10MWT), the Walking Index for Spinal Cord Injury (WISCI II), the six-meter walking test (6MWT), the Timed Up and Go test (TUG), Lower Extremity Motor Scores (LEMS), spatiotemporal, kinematics measures.	1. Participants experienced significant improvements in walking speed (0.06 m/s, p = 0.008), distance (29 m, p = 0.005), TUG (3.4 s, p = 0.012), LEMS (3.4, p = 0.017) and WISCI after eight weeks of training with LOPES. 2. At the eight-week follow-up, participants retained the improvements measured at the end of the training period. 3. Significant improvements were also found in spatiotemporal measures and hip range of motion.
Stevens et al. 2015 USA Pre-Post Test Level 4 N= 11	**Population**: 7 males and 5 females; average age 47.7y; >1y post injury; AIS C and D **Treatment**: Participants completed 8 weeks (3 × /week) of UTT. Each training session consisted of three walks performed at a personalized speed, with adequate rest between walks. Body weight support remained constant for each participant and ranged from 29 to 47% of land body weight. Increases in walking speed and duration were staggered and imposed in a gradual and systematic fashion. **Outcome Measures:** Lower-extremity strength (LS), balance (BL), preferred and rapid walking speeds (PWS and RWS), 6-minute walk distance (6MWD), and daily step activity (DSA).	1. Participants improved in leg strength (57%), balance (39%), preferred walking speed (34%), rapid walking speed (61%), 6-minute walk distance (82%), and DSA (121%) following UTT.
Aach et al. 2014 Germany Pre-Post Level 4 N=8	**Population**: 6 males and 2 females; mean age 48 ± 9.43 years; years post injury= 97.2 ± 88.4 months; chronic stage of traumatic SCI; incomplete and complete SCI AIS A-D **Treatment**: The participants underwent a BWSTT five times per week using the HAL exoskeleton. **Outcome Measures:** Walking distance, speed, time, 10m walk test (10MWT), timed-up and go test (TUG test), 6-minute walk test (6MWT), the walking index for SCI II (WISCI II), AIS with the	1. Highly significant improvements of HAL-associated walking time, distance, and speed were noticed 2. Significant improvements have been especially shown in the functional abilities without the exoskeleton for over-ground walking obtained in the 6MWT, TUG test, and the 10MWT, including an increase in the WISCI II score of three patients. 3. Muscle strength (LEMS) increased in all patients accompanied by a gain of the lower limb circumferences.

	lower extremity motor score (LEMS), spinal spasticity (Ashworth scale), and the lower extremity circumferences.	
Yen et al. 2013 USA Post Test Level 4 N=12	**Population**: 12 participants; traumatic motor incomplete SCI; ASIA D; injuries ranging from C1-T7; mean age= 48 years; years post injury= 5 years; **Treatment**: Each person participated in one data collection session, about 2.5h long. We recorded each participant's maximum voluntary isometric contraction (MVC). A robotic system provided resistance during the swing phase of gait. The data collection session consisted of three resistance load conditions: light, medium, and heavy. **Outcome Measures:** MVC, EMG, stride length, swing time (with and without robotic system)	1. An increase in the resistance load tended to cause a significant increase in kinematic error size for swing time ($p<.001$) and stride length ($p<.001$) 2. After the robotic system was removed, the aftereffect resulted in a significant increase in stride length for the light ($p=.02$), medium ($p.01$) and heavy loads ($p=.01$) 3. After the robotic system was removed, the aftereffect resulted in an increase in swing time was observed but the increase was not significant ($p>.6$)
Sczesny-Kaiser et al. 2015 Germany Pre-Post Test Level 4 N= 11	**Population**: 11 individuals- 7 males and 4 females; traumatic SCI with incomplete or complete paraplegia; mean age= 46.9 ± 2.7y; years post injury= 8.8 ± 2.1y **Treatment**: Eleven SCI patients took part in HAL® assisted BWSTT for 3 months. Each patient was scheduled for a 30min training session 5 times a week for 12weeks, as previously described by our group. Paired-pulse somatosensory evoked potentials (PpSEP) were conducted before and after this training period, where the amplitude ratios (SEP amplitude following double pulses - SEP amplitude following single pulses) were assessed and compared to eleven healthy control participants. **Outcome Measures:** 10 MWT, 6 MWT Timed up and Go Test (TUG), Lower Extremity Motor Score (LEMS).	1. After training, there was a significant increase in 10MWT speed from 0.25 ± 0.05 m/s to 0.5 ± 0.07 m/s ($p=.001$) and a significant increase in 6MWT from 86 ± 20.86 m to 149.73 ± 20.32 m ($p<.001$).
Varoqui et al. 2014 USA Post-Test Level 4 N= 30	**Population**: 30 individuals; ambulatory chronic incomplete SCI; mean age= 50.80 ± 2.12y; years post injury= 11.80 ± 2.54y **Treatment:** 15 iSCI participants performed twelve 1-hour sessions of Lokomat training over the course of a month. The voluntary movement was qualified by measuring active range of motion, maximal velocity peak and trajectory smoothness for the spastic ankle during a movement from full plantar-flexion (PF) to full dorsi-flexion (DF) at the patient's maximum speed. Dorsi- and plantar-flexor muscle strength was quantified by isometric maximal voluntary contraction (MVC). Clinical assessments were also performed using the Timed Up and Go (TUG), the 10-meter walk (10MWT) and the 6-minute walk (6MWT) tests. All evaluations were performed both before and	1. For the training group, the 10MWT resulted in a significant increase in mean gait speed of 13.4 ± 2.8% after training ($P < 0.05$). 2. For the Control group, there was no significant difference in 10MWT ($P = 0.36$).

	after the training and were compared to a control group of fifteen iSCI patients. **Outcome Measures:** Active range of motion, maximal velocity peak and trajectory smoothness from full plantar-flexion to full dorsi-flexion at patient's maximum speed, maximal voluntary contraction (MVC), Timed up and Go (TUG), 10 MWT, 6 MWT, Modified Ashworth Scale (MAS)	
Knikou 2013 USA Pre-post Level 4 N=14	**Population:** 14 participants with chronic SCI (10M 4F); 21-55 yrs old; 0.5-11 yrs post-injury; 1 AIS A, 1 AIS B, 4 AIS C, 8 AIS D. **Treatment:** All participants received BWS robot-assisted step training with a robotic exoskeleton system (Lokomat). Each participant was trained 1h/day, 5 days/wk. **Outcome Measures:** WISCI II; 6MWT; number of sit-to-stand repetitions completed within 30s; TUG; EMG measurements.	1. BWS robotic-assisted step training reorganized the soleus H-reflex in a functional manner during assisted stepping in people with clinically complete, motor incomplete and motor complete SCI. 2. Training changed the amplitude and onset of muscle activity during stepping, decreased the step duration, and improved gait speed. 3. For the AIS C and AIS D group, distance walked in the 6MWT increased after BWS training but not significantly. For the AIS D group, TUG time decreased after BWS training, but again, not significantly.
Harkema et al. 2012 USA Pre-post (subacute and chronic) Level 4 N=196	**Population**: 96 individuals (148 male, 48 female) with incomplete SCI; mean age 41±15 yrs; YPI- <1 yrs (n=101), 1-3 yrs (n=43), >3 yrs (n=52) **Treatment**: Locomotor training with three components: (1) 1 hour of step training in the body-weight support on a treadmill environment, followed by 30 minutes of (2) overground assessment and (3) community integration **Outcome Measures**: BBS, 6MWT, and 10MWT	1. 168 (86%) patients (66 of 66 AIS grade C, 102 of 130 AIS grade D) scored lower than 45, the reported threshold for risk for falls for the BBS -Patients with AIS grade C SCI had significantly lower scores at enrolment than those with AIS grade D classification - Patients with AIS grade D SCI walked significantly farther than those with AIS grade C SCI 2. Scores on the BBS significantly improved by an average of 9.6 points. 3. 6MWT distances and 10MWT speeds of all patients significantly improved by an average of 63m and 0.20m/s, respectively
Yang et al. 2011 Canada Pre-post Level 4 N=19	**Population:** 14 males, 5 females; mean age 44±13; >7 months post-injury (mean 5.8±8.9 years); AIS C or D **Treatment:** 1 hour/day, 5 days/week of BWSTT until parameters did not progress for 2 weeks (minimum 10 weeks total, mean=18 weeks) **Outcome Measures:** 10MWT, WISCI-II, LEMMT, BBS, EMG measurements (tibialis anterior, soleus, quadriceps, hamstrings), movement at the knee and ankles	1. After training, 17/19 participants improved in duration of walking in a session (mean (SD) 15(11) min), 16/19 improved in treadmill speed (0.14(0.11) m/s), and 16/19 improved in their ability to support their own body weight (18(19)% decrease in body weight support). 2. 13 participants responded to the treatment; 9 showed improvements of >1 m/s (exceeding the smallest real difference in overground walking speed) and 4 showed improvements <1 m/s but greater WISCI-II scores.
Stevens, 2010 USA Pre-post (Dissertation) Level 4 N=11	**Population:** 11 participants with incomplete SCI (7M 4F); 23-64 yrs old; 1-28 years post-injury; 9 AIS C, 2 AIS D; all able to walk at least 10 meters with or without an assistive device. **Treatment:** People participated in an underwater treadmill training exercise program for 8 weeks. Week 1 consisted of 3 5-minute walks, with scheduled increases in walking	1. Repeated-measures ANOVA demonstrated that participants exhibited significant relative improvements in leg strength (57%), balance (39%), preferred walking speed (34%), rapid walking speed (61%), 6-minute walk distance (82%) and daily step activity (121%) following underwater treadmill training. Effect sizes for these 6 variables ranged from 0,50-0.84,

	speed (10% increase biweekly) and duration (up to 8 minute walks) over the following weeks. Each participant completed 24 training sessions in 8 weeks. **Outcome Measures:** lower limb strength (dynamometry); BBS; WISCI II; 10MWT; 6MWT; daily step activity.	indicating that the magnitude of the training effect was large. 2. Prior to training, the average difference in strength between the stronger and lower legs was 33%, whereas after training, a 22% mean difference in strength between the stronger and weaker legs was detected. 3. Relative gains in muscle strength ranged from 32% for the knee flexors to 95% for the hip flexors
Winchester et al. 2009 USA Pre-post Level 4 N=30	**Population:** Mean (SD) age = 38.3(13.6); 22 male; 23 participants with tetraplegia, 7 with paraplegia; mean (SD) time since injury = 16.3(14.8) months. **Treatment:** Locomotor training, including: robotic assisted BWSTT, manually assisted BWSTT, and over ground waking. 3 times per week for 3 months. **Outcome Measures:** WISCI II and 10MWT.	1. 22 participants showed improvement in walking speed; 8 showed no change post-training. 2. Pre-training, 16 participants could not walk. Post-training, 5 remained unable to ambulate, 7 recovered ambulation but needed assistance, and 4 recovered independent ambulation. 3. Step-wise regression analysis showed that time post-injury, voluntary bowel and bladder voiding, functional spasticity, and walking speed before training were the strongest predictors of post-training overground walking speed.
Effing et al. 2006 The Netherlands Pre-post Level 4 N=3	**Population:** 3 males; age 45-51 yrs; participant diagnosis were AIS C and D; C5-C7 lesion level; 29-198 months post-injury **Treatment:** BWSTT: 30 min, 5x/wk,12 wks. **Outcome measures:** Wernig Walking Capacity Scale, gait speed over 7m.	1. Gait improvements in all participants, indicated either by faster gait speed or higher score in Walking Capability Scale.
Hicks et al. 2005 Canada Pre-post Level 4 N=14	**Population:** 14 males and females; age 20-53 yrs; 2 participants with diagnosis of AIS B and 12 participants with diagnosis of AIS C; C4-L1 lesion level; 1.2-24 yrs post-injury. **Treatment:** BWSTT: <45 min, 3x/wk, 144 sessions (12 months). **Outcome measures:** Wernig Walking Capacity Scale.	1. 6/14 participants improved in walking capacity, but only 3 maintained improvements at 8 months post-training. 2. 3/10 initially non-ambulatory participants could walk (with assistance) post-training.
Thomas and Gorassini 2005 Canada Pre-post Level 4 N=6	**Population:** Age 29-78 yrs; 4 participants with diagnosis of AIS C and 2 participants with diagnosis of AIS D; C5-L1 lesion level; 2-28 yrs post-injury **Treatment:** BWSTT: < 60 min, 3-5X/week, 10-23 weeks. **Outcome measures:** 10MWT, 6MWT, WISCI II.	1. 5/6 participants improved WISCI II score. Overall significant improvements in 6MWT and 10MWT and improvements correlated with the increase in corticospinal connectivity.
Wirz et al. 2005 Switzerland Pre-post Level 4 N=20	**Population:** Age range =16-64 yrs; 9 participants with diagnosis of AIS C and 11 participants with diagnosis of AIS D; C3-L1 lesion level; 2-17 yrs post-injury **Treatment:** BWSTT: <45 min, 3-5x/wk, 8 wks.	1. 2/20 participants improved WISCI II scores. 2. Overall increase in 10MWT of mean (SD) 0.11(0.10) m/s (56% improvement). 3. 15/16 participants improved in 6MWT.

	Outcome measures: WISCI II, 10MWT, 6MWT.	
Protas et al. 2001 USA Pre-post Level 4 N=3	**Population:** 3 males; age 34-48 yrs; Participant diagnosis was AIS C and D; T8-T12 lesion level; 2-13 yrs post-injury **Treatment:** BWSTT: 20 min, 5x/wk, for 12 wks. **Outcome measures:** Garrett Scale of Walking, Assistive Device Usage Scale, Orthotic Device Usage Scale, gait speed (5m), gait endurance (5 minutes).	1. All participants showed an increase in gait speed and endurance. 2. All participants showed improvement, indicated by the Garrett Scale of Walking or the type of assistive or orthotic devices used.
Wernig et al. 1998 Germany Pre-post Level 4 N=35	**Population:** 35 males and females; age 19-70 yrs; C4-T12 lesion level; 1-15 yrs post-injury **Treatment:** BWSTT: 30-60 minutes, 5x/wk, 8-20 wks. **Outcome measures:** Wernig Walking Capacity Scale.	1. 20/25 initially non-ambulatory improved to walking with aids. 2. 2/10 ambulatory patients improved functional class, but all improved speed and endurance. 3. At follow-up (0.5-6.5 years later) all ambulatory patients remained ambulatory, with changes only in functional class.

Discussion

As shown in Table 9, there have been 19 pre-post studies, 9 RCT (Musselman et al., 2009; Nooijen et al., 2009; Field-Fote et al., 2005; Field-Fote & Roach, 2011; Lucareli et al., 2011; Gorman et al., 2016; Lam et al., 2014; Labruyere et al., 2014) 5 prospective Controlled Trial (Gorassini et al., 2008) and 2 case-control studies (Wernig et al., 1995; Benito Penalva et al., 2010) that altogether studied 812 persons with complete and incomplete SCI, with chronicity ranging from 1 to 28 years post-injury (although years of chronicity was not specified in Field-Fote et al. 2011 study). Treatment intensity ranged from 45 to 300 minutes per week, and treatment duration lasted between 3 and 48 weeks. Based on the stated primary outcome measure of each study where data was available, about 70% of all participants across these studies showed some improvement following treatment (Musselman et al., 2009; Gorassini et al., 2009; Hicks et al., 2005; Yang et al., 2011; Winchester et al., 2009; Protas et al., 2001; Thomas & Gorassini et al., 2005; Effing et al., 2006; Wernig et al., 1995). In the Harkema et al. 2012 study, 88% of patients had responded to locomotor training treatment, but this study included participants that had been injured less than one year.

All studies generally show improvements in overground walking capacity, whether locomotor training was provided with a treadmill or performed over ground, body-weight support, or involved other variations on walk-based therapies (e.g. over ground training with obstacles, robot-applied resistance. Alternative gait retraining therapies or modified approaches to BWSTT for chronic SCI are being introduced (Musselman et al., 2009; Stevens, 2010; Wu et al., 2012; Lam et al., 2014; Yang et al., 2014). Musselman et al. (2009) and Yang et al (2014) compared BWSTT with over ground 'precision' skilled walking training. The skilled walking training consisted of task-specific practice (without body weight support) of various gait tasks, such as stair climbing, obstacle crossing, and walking along sloped surfaces. BWSTT was better than precision over ground training in improving walking distance. Surprisingly, both training groups were comparable in improving walking skill. Wu et al. (2012) demonstrated a new cable-driven robotic device to apply resistance against leg movements during BWSTT. Participants were randomized (in a cross-over design) to receive robotic resistance or assistance BWSTT. Although there were no significant differences in outcomes between the two modalities, there was some indication that robotic resistance enabled greater gains in over ground walking speed in people who tended to have better initial ambulatory capacity; conversely, robotic

assistance seemed to enable greater gains in walking speed in those who were initially slower walkers. More recently, Lam et al. (2014) showed that training with Lokomat-applied BWSTT with resistance yielded better improvements in skilled walking function that were retained even 6 months post-intervention, vs. Lokomat-assisted BWSTT.

Conclusion

There is level 1b evidence from 1 RCT (Field-Fote & Roach, 2011) that different strategies for implementing body weight support gait retraining all yield improved ambulatory outcomes in people with chronic, incomplete SCI, except for robotic assisted treadmill training which showed little change in walking speed. It is recommended that therapists may choose a body weight support gait retraining strategy based on available resources (Field-Fote & Roach, 2011).

There is level 4 evidence from pre-test/post-test studies (Behrman et al., 2012; Buehner et al., 2012; Harkema et al., 2012; Lorenz et al., 2012; Winchester et al., 2009; Hicks et al., 2005; Wirz et al., 2005; Thomas and Gorassini, 2005; Protas et al., 2001; Wernig et al., 1998) that BWSTT is effective for improving ambulatory function in people with chronic, incomplete SCI.

Body weight-support gait training strategies can improve gait outcomes in chronic, incomplete SCI, but most body weight-support strategies (overground, treadmill, with FES) are equally effective at improving walking speed.

Robotic training was the least effective at improving walking speed, but strategies that provide advanced challenge, such as through practice of skilled walking tasks over-ground or application of resistance against leg movements during walking show promising results.

6.2.3 BWSTT Combined with Spinal Cord Stimulation

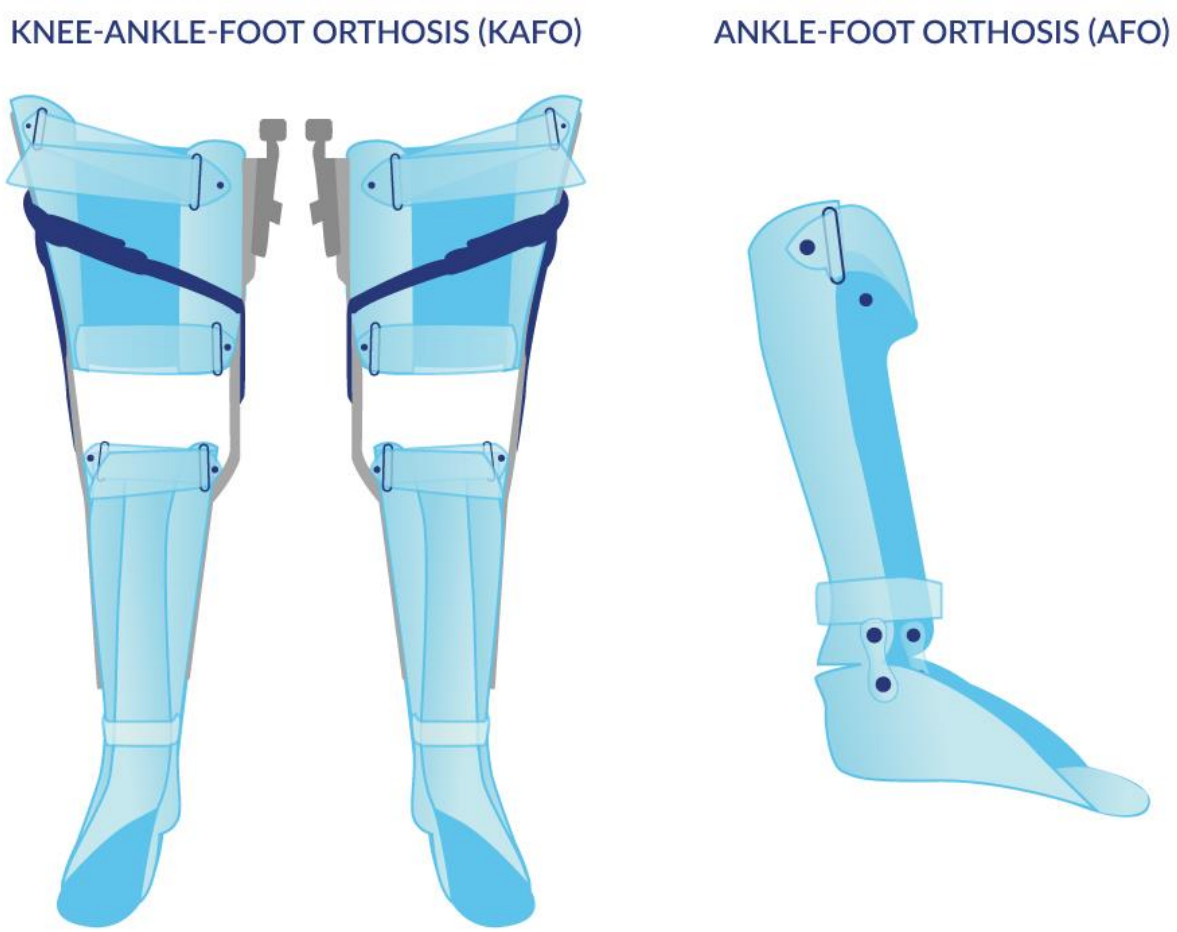
There is heightened interest in the effects of spinal cord stimulation (either via epidural or transcutaneous stimulation). Already almost 20 years ago, Carhart et al. 2004 and Herman et al. 2002 described the effects of epidural spinal cord stimulation combined with gait training in a single participant (male with incomplete tetraplegia, 43 years old, injury level C5-C6, AIS C, 3.5 years post-injury). The participant first underwent 12 weeks of BWSTT that resulted in some significant improvements in treadmill gait parameters although overground ambulation remained limited. Subsequently, the participant underwent surgical implantation of an epidural stimulation system placed over the T10-T12 vertebral level. BWSTT and overground gait training in combination with epidural stimulation commenced after surgical healing. The combination of epidural spinal cord stimulation with gait training resulted in a substantial improvement in treadmill gait parameters as well as in overground ambulation. The participant reported a decreased sense of effort, a doubling in walking speed, and increased walking endurance when assisted by spinal cord stimulation. This was associated with improved community and indoor functional ambulation.

More recently, Harkema et al. (2011) described the effect of epidural spinal stimulation in combination with locomotor training in a single male participant with a *motor complete* spinal cord injury (23 years old, injury level C7-T1, AIS B, 3.4 years post-injury) (Harkema, et al., 2011). Before implantation, the participant underwent 170 locomotor training sessions and was unable to stand or walk independently or voluntarily move his legs. A 16-electrode array was surgically placed on the dura (L1-S1 cord segments). Optimal stimulation parameters for standing and stepping were tested. With stimulation, the participant was able to maintain standing unassisted with full weight-bearing. Locomotor-like muscle activity patterns emerged when epidural stimulation was combined with body weight-

supported treadmill training (but not without stimulation). Interestingly, the participant also was able to regain some ability to voluntarily move the legs (but only in the presence of the epidural stimulation). Further studies have extended these initial findings to other individuals with motor-complete SCI (Angeli et al. 2014; Rejc et al. 2015), and even allowing for recovery of voluntary leg movement and standing without the epidural spinal cord stimulation (Reck and Landmann 2017).

7.0 Orthoses/Braces

There are several available devices used for bracing the legs in order to support standing and walking function, for both complete and incomplete SCI. These range from single-joint bracing (e.g. ankle-foot orthosis), which are usually for individuals with low, incomplete spinal lesions, to whole-leg/long-leg braces that extend from the lower back to the ankle. Reciprocating gait orthosis link the two leg braces together through a trunk/waist component and allow one leg to be flexed (progressed forward) while reciprocal extension is generated in the other leg. Among the most common long-leg braces studied in the literature are the purely mechanical Parawalker (Rose, 1979) or the Reciprocating Gait Orthosis (RGO) (Douglas et al., 1983). The RGO uses the flexion power of one hip to assist with extension of the opposite hip. These devices may also be combined with FES to augment gait function and efficiency (Marsolais et al., 2000; Yang et al., 1996; Nene & Patrick, 1990). These devices must be used with a walking aid (e.g. crutches or walker) for functional ambulation. The braces for higher level complete lesions are costly and can be challenging to take on and off independently. The RGO and Para-step styles are not made to accommodate long periods of sitting so are used only for walking and are therefore are not very functional in everyday life for most people. The power assist or robotic exoskeletons are also emerging in some clinical settings with some indications that they may be applicable to assist with early mobilization of incomplete SCI's. Knee ankle foot orthoses (KAFO) are also used with complete injuries and with these braces you can sit in a wheelchair and get up and down throughout the day without risk of skin issues if they are fitted properly. These can be appropriate for some individuals but there has been poor adherence over the long-term. With these braces people will walk with a swing through or reciprocal stepping style depending on the level of their injury. They require substantial upper body strength to achieve standing. A swing through gait is very tiring on the upper extremities and a reciprocal gait is very slow so most people will opt for a wheelchair when long distances are required.



Pictured: Hinged Ankle-Foot Orthosis (AFO) and a Custom Knee-Ankle-Foot Orthosis (KAFO)

Many styles of AFOs and knee hyperextension braces are used to assist with standing and walking. These can be for joint protection when there is a significant muscle imbalance around a joint such as a knee hyperextension brace (Swedish knee cage or Ossur knee sleeve for example). Depending on an individual's strength, tone and range of motion there are a great deal of AFO's to use ranging from a dynamic small brace to assist with toe clearance like the Dictus to a more rigid custom AFO to stabilize and hold the entire foot and ankle. The more rigid a brace is the more that it will impede "normal" dynamics around the joint although this may be clinically necessary to protect the joints and provide a safe stable base to weight bear on. These braces for the knee and lower leg may require a walking aid like the higher braces but may be able to be used without an aid.

Braces have been advanced with powered actuators to reduce the effort required to advance the limb. Earlier models used actuators in single joints (e.g., ankle or hip), while newer models control multiple lower extremity motions. Some of the newest models utilize an exoskeleton with battery-powered motors to control multiple degrees of freedom and the weight of the device is transferred into the ground by the exoskeleton, alleviating the participant from bearing the weight of the device.

7.1 Ankle Foot Orthosis in SCI

Table 10: Studies of Ankle Foot Orthosis (AFO) in SCI

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
Kim et al. 2004 Canada PEDro=5 RCT Level 2 N=19	**Population:** 19 participants with incomplete SCI who had dropfoot but were able to walk independently **Treatment:** Randomized to conditions of AFO, no AFO, FES and FES and AFO. They walked at their self-selected speed along a flat walkway. **Outcome Measures:** Walking speed and 6MWT	1. Gait speed increased 7.5% from 0.4 m/s (no orthosis) to 0.43 (AFO) 2. 6 Minute Walk Test increased 16% from 138 to 160 m
Arazpour et al. 2013 Iran PEDro=4 RCT Level 2 N=5	**Population:** 5 participants with incomplete SCI (thoracic lesion) **Treatment:** Gait evaluation while walking with 1) no shoe; 2) solid AFO and 3) hinged AFO **Outcome Measure:** Step length, cadence	1. Solid AFO improved step length from 28.5 from 26.3 cm and cadence from 52 to 62 steps/minute. 2. No significance differences between the no shoe and hinged AFO condition.

Discussion

Both these studies (Kim et al., 2004; Arazpour et al., 2013) examined the immediate effects of an ankle-foot-orthosis after randomizing different brace conditions. Positive effects consisted of increased gait speed, step length, cadence and improved performance on the 6 Minute Walk test. These are not typical experimental designs for an RCT as all the conditions were assessed within one single session rather than allowing participants to accommodate to different brace conditions over several weeks or sessions. However, it is generally recognized in the clinical field that effects from an AFO are attained immediately, although it is likely that practice over a few sessions may improve a person's confidence, learning and function.

Conclusion

There is level 1b evidence (Arazpour et al., 2013; Kim et al., 2004) that an ankle-foot-orthosis can enhance walking function in incomplete SCI patients who have drop-foot.

Ankle-foot-orthosis can enhance walking function in incomplete SCI patients who have drop-foot

7.2 Hip-Knee-Ankle-Foot Orthosis in SCI (RGO/HKAFO/KAFO)

Table 11: Studies of Hip-Knee-Ankle-Foot Orthosis in SCI

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
Arazpour et al. 2013 Iran PEDro=4	**Population:** 5 participants with T8-T12 SCI (4M, 1F); had ability to walk with an ARGO for a minimum of 50m	1. Mean MFES score when using the ARGO with solid AFOs (45.8 (9.12)) was significantly higher than when using the dorsiflexion-assisted AFOs (42.8(9.73)).

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
RCT Level 2 N=5	independently; completed a 12-wk gait training rehab program. **Treatment:** Patients were randomized to either an ARGO with solid or dorsiflexion-assist type AFO. They walked at their self-selected speed along a flat walkway. **Outcome Measures:** Walking speed, distance walked, cadence, MFES	2. During static dual-elbow crutch support, there was no significant different between the two types of orthosis in the postural sway in medio-lateral direction, but significant difference between them in the antero-posterior direction. During single crutch support, there was a significant difference in both medio-lateral and antero-posterior directions. 3. Walking speed (7%) and endurance (5%) significantly increased when using the ARGO with dorsiflexion-assisted AFOs compared with solid AFO.
Bani et al. 2013 Iran Pre-post Level 4 N=4	**Population:** 4 participants with SCI (3M 1F); 24-29 yrs old; 12-36 months post-injury; 1 AIS A, 3 AIS B. **Treatment:** Patients completed at least 6 weeks of orthotic gait training using an ARGO with 2 types of AFO. Patients then walked with the orthoses along a 6-m walkway at least 5 times at self-selected walking speed in 2 test conditions: 1) ARGO with dorsiflexion-assisted AFO, 2) ARGO with solid AFO. **Outcome Measure:** Walking speed, endurance, cadence, stride length, kinematic and spatio-temporal parameters of walking	1. Mean walking speed (solid AFO=0.32(0.02); dorsi AFO=0.35(0.01) m/s), cadence (solid AFO=40(2.38), dorsi AFO=42(3.09) steps/min) and stride (solid AFO=94.5(9.25), dorsi AFO=100(9.48) cm) significantly increased for participants using the ARGO fitted with dorsiflexion AFO compared to ARGO fitted with solid AFO. 2. Mean ankle joint ranges of motion were significantly increased when walking with the ARGO with dorsiflexion-assisted AFO (11.63(0.75)^{o}) compared to ARGO with solid AFO (8.05(0.51)^{o}). Knee joint ranges of motion were reduced and hip joint ranges of motion were increased, but not significantly.
Nakazawa et al. 2004 Japan Pre-post Level 4 N=3	**Population:** 3 males; age 22-28 years; all participants had a diagnosis of AIS A; T8 -T12 lesion level; 8-12 months post-injury. **Treatment:** WBCO: 1 hr, 5x/wk, 12 wks **Outcome measures:** Gait velocity	1. All participants showed an increase in gait velocity: 7.7 to 13.2; 11.8 to 21.2, 22.4 to 25m/min
Samadian et al. 2015 Iran Pre-Post Level 4 N= 6	**Population**: 6 individuals- 4 males and 2 females; motor complete SCI ranging from T8 to T12; 2 AIS A and 4 AIS B; mean age= 29y; months post injury= 7 to 35 months **Treatment**: Patients were trained for 12 weeks of gait training after construction of the orthosis that comprised of five sessions per week for a 2-h period with the orthosis. The gait training program also included passive stretching of the lower extremities, upper limb strengthening and balance training with the orthosis while standing and walking. Gait evaluation was performed at baseline and after 4, 8 and 12 weeks.	1. Walking distance increased significantly and also did so during the 8–12-week period.

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
	Walking speed and heart rate were measured to calculate the resulting physiological cost index (PCI). **Outcome Measures:** Walking speed, distance walked, energy consumption, physiological cost index (PCI).	
Scivoletto et al. 2000 Italy Post-test Level 4 N=24	**Population:** 24 males and females; mean (SD) age 33.6(3.2) yrs; AIS A; T1-T12 lesion level; mean (SD) 5.3 (2.1) yrs post-injury **Treatment:** RGO: training, then home-use for 1 year. **Outcome measures***:* gait speed, going up and down stairs, use of walker or crutches, Garrett Score (out of 6; 6 = community ambulation with no limitations; 1=hospital ambulation).	1. No difference between RGO users and RGO nonusers for gait speed, stair climbing, or ambulatory aid. However, RGO users achieved home ambulation with limitations or home ambulation (level 2-3), while nonusers achieved hospital ambulation or home ambulation with limitations (level 1-2). No one reached community ambulation levels.
Massucci et al. 1998 Italy Post-test Level 4 N=6	**Population:** 6 males; age 16-31 yrs; all participants had a diagnosis of Frankel A; T3-T12 lesion level; 12-51 months post-injury. **Treatment:** Rehabilitation training with advanced RGO for 6-8 weeks (including muscle strengthening, standing balance, gait training, stair climbing). **Outcome measures:** Walking speed over 5 m.	1. Participants achieved walking speeds of between 7.8 and 16 m/min with the orthosis.
Franceschini et al. 1997 Italy Post-test Level 4 N=74	**Population**: 74 males and females; mean age 27 yrs; all participants had a diagnosis of Frankel A or B; T1-T12 lesion level; mean 37 yrs post-injury **Treatment:** Orthoses: RGO (n=53), Advanced RGO (RGO with links between mechanical hip joints and hip and knee joints) (n=17), and HGO (n=4). Practice to don/doff device and functional mobility. Follow-up at hospital discharge and 6 months later. **Outcome measures:** Garrett Score, ability to climb up and down 12 steps.	1. At discharge, 28 patients could climb stairs (13 with crutches, 15 with a walker). 2. The ability to climb stairs or Garret score at discharge was associated with continued orthosis use. 31 patients achieved functional gait (Garrett = 2-5) and 9 achieved community ambulation (Garrett=4-5). 19 used orthosis only for exercise (Garrett=1).
Harvey et al. 1997 Australia Post-test Level 4 N=10	**Population:** 10 participants; mean (SD) age 37(8.4) yrs; all participants had a motor complete SCI; T9-T12 lesion level; 4-19 yrs post-injury.	1. No differences between orthoses re: donning/doffing (“independent”), stairs and curbs (“stand-by” or “minimal”), or level gait (“independent” or “stand-by”). 2. Tendency for better performance with IRGO for flat walking, ramp walking, and stairs. Faster gait with IRGO on flat (mean (SD) IRGO=0.34 (0.18) m/s,

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
	Treatment: WO[1] vs. IRGO[1]: training with first orthosis 2-3 hours, 2-3X/week for 6-8 weeks, followed by 3-month home trial period. 2-month wash-out period (no orthosis) followed by other orthosis. **Outcome measures**: functional skills (e.g., curbs, stairs, donning/doffing, sit-stand), Functional Independence Measure, gait speed over flat and inclined surfaces.	mean (SD) WO=0.14 (0.12) m/s) and on inclined surfaces. IRGO allowed more independent gait; WO easier to go from sit-stand and stand-sit. 3. Neither orthosis enabled participants to be fully independent in the key skills necessary for functional ambulation after 8 weeks of training.
Saitoh et al. 1996 Japan Pre-post Level 4 N=5	**Population**: 5 males; age 26-36 yrs; 4 participants had a diagnosis of Frankel A and 1 participant had a diagnosis of Frankel C; T5-L1 lesion level; 8.4-70 mos post-injury. **Treatment:** MSH-KAFO: Long-leg hip-knee-ankle-foot brace with medially-placed single-axis hip joint. Patients were trained to stand and walk using device daily for 2 wks, followed by an exercise program 1-2x/wk. **Outcome measures***:* walking speed and distance.	1. 4 of 5 were able to stand without crutches with MSH-KAFO (1 participant needed parallel bars). 2. 3/5 could climb stairs with crutches and rail. 3. After 3-10 months of therapy, gait speed improved from 0.05-0.2 m/s to 0.17-0.63 m/s and walking distance ranged from 300 to 4000 m.
Lotta et al. 1994 Italy Post-test Level 4 N=28	**Population:** 24 males and 4 females; age 15-48 yrs; all participants had a diagnosis of Frankel A or B; T3-T12 lesion level; 8-312 wks post-injury **Treatment:** 3.5-6 sessions/week, 3-16 weeks training with advanced reciprocating gait orthosis (hip-knee-ankle orthosis) **Outcome Measures:** Garrett Scale for ambulation	1. All patients able to walk at least 30 m with walker or forearm crutches 2. 3 participants attained “community” ambulation levels; 17 attained “home” level; 8 remained as “exercise only” ambulation level 3. Median gait speed with orthosis was 16.6 cm/s
Winchester et al. 1993 USA Post-test Level 4 N=4	**Population:** 4 males; age 24-36 yrs; 2 participants with complete SCI and 2 participants with motor-incomplete SCI; T5-T10 lesion level; 25-58 months post-injury **Treatment:** Gait training with RGO or IRGO: 2 hrs, 2-3x/wk (average total time = 35 ± 7.5 hr). **Outcome measures:** Gait velocity, cadence.	1. Overall, participants achieved overground velocity of mean (SD) 12.7 (1.9) m/min with RGO and 13.5 (2.1) m/min with IRGO; cadence of 30.3 (6.2) steps/min with RGO and 31.3 (7.9) steps/min with IRGO.

[1] Similar model to the MSH-KAFO
[2] Successor model to the RGO (uses a central pivot bar and tie rod arrangement instead of crossed-cable to couple hip flexion/extension). The IRGO is thought to be less fatiguing for participants compared to RGO (Winchester et al 1993).

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
Whittle et al. 1991 UK Post-test Level 4 N=22	**Population:** 22 males and females; age 21-44 yrs; all participants had a SCI diagnosis; T3-T12 lesion level. **Treatment:** HGO (aka Parawalker) + crutches vs. RGO + rollator walker: Practice period + 4-month home use before being switched to the second orthosis. **Outcome measures:** walking speed, cadence, and stride length.	1. No significant differences between orthoses for gait speed, cadence, and stride length 2. Mean walking speed with either orthosis was 0.24 m/s. 3. RGO enabled faster sit-to-stand and stepping up on curbs.

Discussion

The Reciprocating Gait Orthosis (RGO) (or variants of it) is the most common bilateral HKAFO for people with thoracic injuries. In most cases, experimental conditions involving activities without an RGO would not be possible for the participant, and thus, the RGO permits ambulation and in some cases, stairs to be performed.

None of the studies investigating the effectiveness of the braces for upright support and mobility are randomized using a control group without any brace/device, but that is in part due to the ethical dilemma of providing safe and appropriate bracing, and in many cases, participants would not be able to walk safely without the brace. Several studies compare two or more different types of devices, and in some cases (e.g., Arazpour et al. 2013), the conditions were randomized during the testing. Some of the studies did provide a substantial training period (e.g., 5 times/week gait training sessions with braces for at least 2 weeks). Overall, these studies provided level 4 evidence that HKAFOs may help people with subacute or chronic complete paraplegia to stand independently and to achieve some functional ambulation skills, such as stepping up on curbs or climbing stairs with assistive devices. The maximum walking speeds achieved with orthosis use ranged from 0.13 to 0.63 m/s (Nakazawa et al., 2004; Massucci et al., 1998; Harvey et al., 1997; Saitoh et al., 1996; Sykes et al., 1996b; Thoumie et al., 1995; Winchester et al., 1993; Whittle et al., 1991), which is 13 to 57% of the optimal speed (1.1 m/s) required for successful community ambulation (Robinett and Vondran, 1988). In general, however, the use of any of the braces investigated in these studies did not greatly enhance the ability of complete paraplegic participants to be fully independent for functional community ambulation (Scivoletto et al., 2000; Harvey et al., 1997; Hong et al., 1990). In a few studies, some participants demonstrated the ability to climb up and down stairs with the assistance of crutches or walker (Franceschini et al., 1997; Harvey et al., 1997; Whittle et al., 1991). Thus, the greatest benefit derived from orthosis/brace-use is from enhanced home or indoor mobility, for general exercise and health benefits, and psychological benefits from attaining upright posture and standing (Sykes et al., 1996b; Hong et al., 1990; Mikelberg & Reid, 1981).

The successful use of orthoses/braces is also dependent on other more individual and practical factors. It has been recommended that orthoses or braces are best for people who are well-motivated, with complete SCI at T9 or below or incomplete SCI at any level, with good postural control and good level of fitness (Franceschini et al., 1997; Thoumie et al., 1995; Hong et al. 1990). Suzuki et al. (2007) showed that injury level, age, motivation, upper extremity strength, as well as spasticity and contractures were predictive of gait outcomes in long-leg brace users. Medical problems such as limited thoraco-lumbar mobility or mechanical back pain, or any musculoskeletal problems that make standing upright uncomfortable also tend to interfere with successful use of these orthoses/braces (Harvey et al., 1997; Middleton et al., 1997).

The ability for a patient to don/doff the orthosis without difficulty and relatively quickly (e.g. <5 minutes) also appears to enhance the probability of their acceptance (Scivoletto et al., 2000; Franceschini et al., 1997; Harvey et al., 1997; Saitoh et al., 1996; Thoumie et al., 1995; Hong et al., 1990; Mikelberg & Reid, 1981). Frequent reports of technical problems (e.g. mechanical breakdown at the hinges, improper fitting) across many studies (Scivoletto et al., 2000; Harvey et al., 1997; Thoumie et al., 1995; Whittle et al., 1991; Mikelberg & Reid, 1981) suggest that appropriate technical support of these mechanical devices is necessary to enhance ongoing use of these braces (Whittle et al., 1991).

Overall, it appears that most participants feel that the difficulties and inconvenience encountered with orthoses/braces and the modest increase in function do not warrant their acceptance for regular, daily use in functional activities (Harvey et al., 1997; Sykes et al., 1996b; Hong et al., 1990; Mikelberg & Reid, 1981). It has been suggested that the therapeutic benefits of orthosis-use (e.g. health benefits from standing practice) should be stressed to patients rather than setting forth an expectation that they will enhance functional ambulation and be a replacement for wheelchair-use (Franceschini et al., 1997).

Conclusion

There is level 4 evidence (see Table 11) that a reciprocating gait orthosis can enable walking in people with thoracic lesions, although not at speeds sufficient for community ambulation.

RGO can enable slow walking in participants with thoracic lesions, and not at speeds sufficient for community ambulation. The advantages of RGOs appear largely restricted to the general health, well-being and safety benefits related to practice of standing and the ability to ambulate short-distances in the home or indoor settings.

7.3 Powered Gait Orthosis and Robotic Exoskeletons in SCI

Table 12: Studies of Powered Gait Orthosis and Robotic Exoskeletons (with or without Bracing) in SCI

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
Shin et al. 2014 Seoul Prospective, Randomized Clinical Trial PEDro=5 Level 2 N= 53	**Population**: 53 individuals- 34 males and 19 females; 31 with cervical injuries and 22 with thoracic & lumbar injuries; 36 with traumatic SCI and 16 with non-traumatic SCI; mean age= 48.15 ± 11.14y; months post injury= 3.33 ± 2.02 months **Treatment**: Sixty patients with motor incomplete spinal cord injury (SCI) were included in a prospective, randomized clinical trial by comparing Robot-Assisted Gait Training (RAGT) to regular physiotherapy. The RAGT group received RAGT three sessions per week at duration of 40 minutes with regular physiotherapy in 4 weeks. The conventional group underwent regular physiotherapy twice a day, 5 times a week.	1. At the end of rehabilitation, both groups showed significant improvement in LEMS, AMI, SCIM3-M, and WISCI-II. 2. RAGT group members improved their WISCI-II scores.

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
	Outcome Measures: ASIA lower extremity motor score subscale (LEMS), ambulatory motor index (AMI), spinal cord independence measurement III mobility section (SCIM3-M), walking index for spinal cord injury version II (WISCI-II)	
Tanabe et al. 2013 Japan Prospective controlled trial Level 2 N=4	**Population:** 4 participants with complete paraplegia (3M 1F); 30-59 yrs old; 4-20 yrs post-injury. **Treatment:** Participants performed ground-level walking test with both the conventional orthosis (PrimeWalk) and the WPAL orthosis. **Outcome Measures:** Mean duration and distance of consecutive walking; Functional Ambulation Categories scale; PCI; modified Borg CR10 scale; EMG of upper extremities.	1. Activation patterns of the EMG during gait indicate that WPAL needed only intermittent contraction while PrimeWalk demanded persistent contraction. 2. The duration and distance of consecutive walking is higher for the WPAL than the conventional orthosis: for PrimeWalk: 5-12 min, 20-44 m consecutive walking; for WPAL: 7.8-40 min, 40-580m consecutive walking. 3. The PCI, perceived exertion and EMG of upper extremities was lower for the WPAL than the conventional orthosis.
Tanabe et al. 2013b Japan Prospective controlled trial Level 2 N=7	**Population:** 7 participants with motor-complete SCI (6M 1F); 6 AIS A, 1 AIS B; 32-61 yrs old; 6-20 years after injury. **Treatment:** Participants performed ground-level walking test with both the conventional orthosis (PrimeWalk) and the WPAL orthosis. **Outcome Measures:** Mean duration and distance of consecutive walking; Functional Ambulation Categories scale.	1. With the WPAL, all users achieved independent gait on a level floor (Functional Ambulation Categories score of 4). 2. Mean duration and distance of consecutive walking were 14.1(11.4) minutes and 165.6(202.6) m with the WPAL. 3. With the orthosis, duration of walking ranged from 5-8 minutes and distance walked ranged from 20-107m. With the WPAL, duration of consecutive walking ranged from 4.5-40 minutes and distance walked ranged from 30-640m.
Arazpour et al. 2013c; Iran Prospective controlled trial Level 2 N=4	**Population:** 4 participants with thoracic level SCI (2M 2F); 22-29 yrs old; 9-51 months since injury; 3 incomplete 1 complete SCI. **Treatment:** Patients performed orthotic gait training with a Powered Gait Orthosis (PGO) for a min of 6 wks, 1 hr/day for 5 days/wk prior to walking trials. Walking trials with an Isocentric Reciprocal Gait Orthosis (IRGO) and with both separate and synchronized movements with actuated orthotic hip and knee joints in a PGO were conducted. **Outcome Measures:** kinematics and temporal-spatial parameters of walking	1. Using separate and synchronized actuated movement of the hip and knee joints in the PGO increased gait speed and step length, and reduced lateral and vertical compensatory motions when compared to the IRGO, but there were no significant differences in these parameters. 2. Using the new PGO improved knee and hip joint kinematics: Hip flexion (^{o}): IRGO= 9.25(0.95); new PGO=18.75(2.36) Hip extension (^{o}): IRGO=5.5(0.57); new PGO=7.75 (0.95) Knee flexion (^{o}): IRGO = 6.75(0.95); new PGO = 37(1.82)
	Population: 7 males; 2 with tetraplegia and 5 with motor-complete SCI; 3 AIS A, 1 AIS B, and 3 AIS C; median age= 36y; years post injury= 0.5y	1. Walk times ranged from 28 to 94 minutes with average speeds ranging from 0.11 to 0.21 m/s.

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
Kozlowski et al. 2015 USA Longitudinal Level 2 N= 7	**Treatment**: A convenience sample was enrolled to learn to use the first-generation Ekso powered exoskeleton to walk. Participants were given up to 24 weekly sessions of instruction. Data were collected on assistance level, walking distance and speed, heart rate, perceived exertion, and adverse events. Time and effort was quantified by the number of sessions required for participants to stand up, walk for 30 minutes, and sit down, initially with minimal and subsequently with contact guard assistance. **Outcome Measures:** Primary outcomes: the number of sessions needed to achieve a rating of "minimal assistance", number of sessions required until the rating became "contact guard only" for standing/sitting and for walking; Secondary outcomes: measures of walking tolerance and physical exertion	2. For all participants, heart rate changes and reported perceived exertion were consistent with light to moderate exercise.
Hartigan et al. 2015 USA Pre-Post Level 4 N= 16	**Population**: 16 individuals- 13 males and 3 females; SCI ranging from C5 complete to L1 incomplete; age range= 18-51 years **Treatment**: To assess how quickly each participant could achieve proficiency in walking, each participant was trained in the system for 5 sessions, each session lasting approximately 1.5 hours. Following these 5 sessions, each participant performed a 10MWT and a 6MWT. **Outcome Measures:** 10 MWT, 6MWT, donning and doffing times, ability to walk on various surfaces	1. At the end of 5 sessions (1.5 hours per session), average walking speed was 0.22 m/s for persons with C5-6 motor complete tetraplegia, 0.26 m/s for T1-8 motor complete paraplegia, and 0.45 m/s for T9-L1 paraplegia. 2. Distances covered in 6 minutes averaged 64 meters for those with C5-6, 74 meters for T1-8, and 121 meters for T9-L1. Additionally, all participants were able to walk on both indoor and outdoor surfaces
Yang et al. 2015 USA Post Test Level 4 N= 12	**Population**: 12 individuals- 10 males and 2 females; 9 AIS A, 2 AIS B and 1 AIS C; Level of injury between C8 to T11; age range= 31 to 75 **Treatment**: Twelve individuals with SCI ≥1.5 years who were wheelchair users participated. They wore a powered exoskeleton (ReWalk) with crutches to complete 10-meter (10MWT) and 6-minute (6MWT) walk tests. LOA was defined as modified independence (MI), supervision (S), minimal assistance (Min), and moderate assistance (Mod). Best effort EAW velocity, LOA, and observational gait analysis were recorded **Outcome Measures:** 10 MWT, 6 MWT, level of assistance (LOA), degree of hip flexion, degree of knee flexion, step time	1. 7 of 12 participants ambulated ≥0.40 m/s. 5 participants walked with MI, 3 with S, 3 with Min, and 1 with Mod. Significant inverse relationships were noted between LOA and EAW velocity for both 6MWT and 10MWT. 2. There were 13 episodes of mild skin abrasions. MI and S groups ambulated with 2-point alternating crutch pattern, whereas the Min and Mod groups favored 3-point crutch gait.
Fineberg et al. 2013 USA Pre-post	**Population:** 6 participants with chronic, motor-complete thoracic SCI (5M 1F); 24-61 yrs old; 3 requiring minimal assistance and 3 requiring no assistance. 3 AB controls.	1. Participants in the SCI minimal-assist group demonstrated the lowest vGRF compared with the no-assist and AB controls. The min-assist group had significantly lower area under the curve

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
(with Able-Bodied normative comparisons) Level 4 N=6 participants with SCI (3 control)	**Treatment:** Participants underwent training sessions consisting of 1-2 hours of combined standing and walking 3 times/week for 5-6 months on the ReWalk powered exoskeleton assisted walking system. **Outcome Measures:** magnitude and pattern of mechanical loading via vertical ground reaction force (vGRF): peak stance average (PSA), peak vGRF for heel strike, mid-stance and toe-off.	for gait cycle ($p<0.05$); no significant difference was found for SCI no-assist vs AB control group. 2. SCI min-assist group had statistically slower mean walking velocity than the SCI no-assist group ($P = 0.0148$). 3. Participants with SCI demonstrated mechanical loading magnitudes and patterns similar to able-bodied gait: - SCI no-assist: avg $vGRF_{HS}$=66(8)%, $vGRF_{MS}$=91(12)%, $vGRF_{TO}$=107(7)% - SCI min-assist: avg $vGRF_{HS}$=36(15)%, $vGRF_{MS}$=47(12)%, $vGRF_{TO}$=62(21)% - AB control: avg $vGRF_{HS}$=91(9)%, $vGRF_{MS}$=70(9)%, $vGRF_{TO}$=105(18)%.
Esquenazi et al. 2012 USA Pre-post Level 4 N=12	**Population:** 12 participants with chronic SCI (8M 4F); 18-55 yrs old; all motor-complete cervical and thoracic; >6 months post-injury. **Treatment:** All participants had gait training using the ReWalk powered exoskeleton; participants were trained for up to 24 sessions of 60-90 min duration over approximately 8 weeks. **Outcome Measures:** 6MWT; 10MWT; gait laboratory evaluation; dynamic electromyogram; survey containing questions about comfort and confidence using the ReWalk; assessment of spasticity and pain; physical examination; Short Form-36 v2 Health Survey Questionnaire.	1. By completion of the trial, all participants had walked under their own control without human assistance while using the ReWalk for at least 50-100m continuously and for a period of at least 5-10 minutes. 2. Excluding 2 participants with considerably reduced walking abilities, average distances and average walking speed significantly improved. Average walking speed was 0.25m/s (0.03-0.45m/s). (no significance testing done) 3. 3 participants reported their overall spasticity improved after training. 4. All participants had strong positive comments regarding the emotional/psychosocial benefits of the use of ReWalk. 5. At the 12-month follow-up, general health status as measured by study clinicians did not change.

Discussion

New technology has advanced passive bracing to exoskeletons which are wearable robotic devices that have powered joints and extensive software programming to enable synchronized, functional and safe movement. In addition, the weight of the device can be borne by the exoskeleton and not the patient. While the gait speeds are still relatively slow due to safety issues (to minimize loss of balance and potential falls), the major advance is the reduction of energy that is required to utilize these devices to walk. Patients with primarily thoracic injuries have utilized these devices. With the price continuing to drop for these technologies, this will provide opportunity to evaluate the long-term use as more people acquire them for home-use. Furthermore, newer versions are accommodating the ability to sit or wheel a wheelchair while wearing the device, increasing utility in a clinical setting (assisting with rehabilitation goals).

Conclusion

Studies ranging from level 1b to level 4 evidence show that PGOs can enable safe walking and reduce energy expenditure compared to passive bracing in patients with thoracic injuries, or those with adequate triceps functioning.

PGOs can enable safe walking and reduce energy expenditure compared to passive bracing in patients with thoracic injuries.

8.0 Functional Electrical Stimulation (FES) and Walking

The idea of compensating for paralyzed function using electrical stimulation was introduced as early as the 1960s (Liberson et al., 1961). Functional electrical stimulation of the common peroneal nerve was found to be effective in assisting foot clearance during the swing phase (Liberson et al., 1961). There has also been a report of attempts to stimulate the ankle plantarflexor muscles to assist push-off at the end of stance and enhance the initiation of the swing phase in participants with incomplete SCI (Bajd et al., 1999). Approaches that focus on swing phase activity are more suitable for less severely disabled individuals who have adequate balance to support their stance leg during gait. There are also more complex systems that involve several channels of stimulation that support proper extension as well as foot clearance during swing (e.g. Sigmedics, 2000). These are more suitable for patients who require assistance in standing as well as gait, such as those with neurologically complete SCI. FES systems such as the Parastep or ALT-2 provide stimulation of thigh extensor muscles (quadriceps, gluteal muscles) to support extension and standing, as well as stimulation of the common peroneal nerve to assist with swing phase movements. FES may also be combined with bracing to counter trunk and hip instability (Solomonow et al., 1997). FES to assist with foot clearance during swing (drop-foot) has been studied more extensively in the stroke population (Bosch et al., 2014) and may provide some evidence for individuals with incomplete SCI who present with hemiparesis similar to stroke.

One of the limitations of surface FES is possible skin irritation, discomfort under the electrodes, or difficulties with proper positioning of the electrodes. With improvements in electronics technology, FES systems have become smaller and more practical for everyday use. In addition, some patients have opted for implanted FES systems that may be inserted without surgery. These systems offer a more precise delivery of stimulation, enabling greater muscle selectivity, and the ability to access deeper muscles, such as the hip flexors (Kobetic et al., 1997). Percutaneous electrodes, which are inserted through the skin with a hypodermic needle, offer one possibility to circumvent complications with surface electrodes (Kobetic et al., 1997; Marsolais & Kobetic, 1986). However, there may be complications due to infection or irritation at the site of insertion, and electrode movement or breakage (Agarwal et al., 2003). More recently, there was a case study reporting positive effects with a BION microstimulator in an incomplete tetraplegic participant with drop-foot (Weber et al., 2004). Thus, preliminary reports of the use of such innovative FES technology are promising, but further study is warranted to determine the long-term stability and efficacy of such implanted systems.

8.1 Functional Electrical Stimulation to Improve Locomotor Function

Table 13: Studies Using Functional Electrical Stimulation to Improve Locomotor Function

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
Thrasher et al. 2006 Canada	**Population:** 5 males and females; age 24-72 yrs; all participants had an	1. 4/5 participants significantly increased walking speeds (95% significance level).

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
Pre-post Level 4 N=5	incomplete SCI; C5-T12 lesion level; 2-24 yrs post-injury. **Treatment:** Gait training regimen with FES neuroprosthesis 2-5x/week for 12-18 weeks. First 4-8 sessions consisted of lower limb muscle strengthening performed in 4 sets of 5 min with 5 min rest. Participants then performed walking exercises with the neuroprosthesis for 15-30 min/session (rest as needed) either on a treadmill or overground. **Outcome Measures:** Walking speed, stride length, step frequency	These 4 participants also significantly increased step frequency and stride length (95% significance level).
Ladouceur & Barbeau 2000a Canada Pre-post Level 4 N=14 (enrolled) N=10 (analyzed)	**Population:** 14 participants; age 25-49 yrs; all participants had an incomplete SCI; C3-L1 lesion level; 1.8-19.1 yrs post-injury, **Treatment:** Surface FES: bilateral or unilateral common peroneal nerve, home use as much as possible ~1 year (26 and 56 weeks), 2 participants also had bilateral quadriceps. **Outcome measures***:* temporal gait measures.	1. There were significant increases in mean walking speed (0.10 m/s, p=.007) and mean stride length (0.12 m, p=.065) both with and without FES over the first year of FES use. 2. FES-assisted walking led to minor increases in mean walking speed, but these changes were not significant (p=.543).
Ladouceur & Barbeau 2000b Canada Pre-post Level 4 N=14 (recruited) N=10 (completed)	**Population:** 14 participants; age 25-49 yrs; all participants had an incomplete SCI; C3-L1 lesion level; 1.8-19.1 yrs post-injury **Treatment:** Surface FES: bilateral or unilateral common peroneal nerve, 2 participants also had bilateral quadriceps, home use as much as possible ~1 year. **Outcome measures**: temporal gait measures.	1. 7/14 participants showed improvement based on type of ambulatory device. 2. 13/14 participants improved gait speed with FES. 3. Training/carryover effect after long-term use: increase evident even when FES off in 12/14 participants.
Wieler et al. 1999 Canada Pre-post Level 4 N=31	**Population:** 31 males and females; mean (SD) age 36(2) yrs; all participants had an incomplete SCI; mean(SD) 6(1) yrs post-injury. **Treatment:** Surface FES: common peroneal nerve; some participants also received FES to hamstrings, quadriceps, gluteus medius, duration of FES ranged from 3 months to over 3 years. Each participant was tested at the start and end of the study both with and without FES.	1. There was a significant improvement in gait speed in participants when treated with FES (p<.01) but that improvement in gait speed persisted even when participants walked without FES (p<.01) 2. The slowest quintile of participants increased their walking speed by 70% while the fastest quintile of participants increased their walking speed by 20%. 3. The initial gait speed at the start of study was significantly faster when patients used FES than when no FES was used (p<.05)

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
	Outcome measures: walking speed, stride length, cycle time	
Klose et al. 1997 USA Pre-post Level 4 N=16	**Population:** Mean (SD) age 28.4 (6.6) years; all participants had complete SCI; T4-T11 lesion level; 0.7-9.0 yrs post-injury **Treatment:** Surface FES: Parastep: 6 channels (bilateral common peroneal nerve, quadriceps, glutei); 3X/week, 32 sessions (once participants had sufficient strength to stand). **Outcome measures**: walking distance and speed (with FES).	1. Most participants improved endurance and gait speed. Longest distance walked with FES was between 12 to 1707 m (mean: 334 m; SD 402 m). 2. There were significant differences in distance travelled ($p<.001$) and gait speed ($p<.001$) over the 11 weeks.
Granat et al. 1993 Scotland Pre-post Level 4 N=6	**Population**: 6 males and females; age 20-40 yrs; all participants had diagnosis of Frankel C and D; C3-L1 lesion level; 2 to 18 yrs post-injury **Treatment**: Surface FES: quadriceps, hip abductors, hamstrings, erector spinae, common peroneal nerve, home program >30 min, 5X/week, 3 months. **Outcome measures:** walking speed, stride length, cadence.	1. Significant mean increase in stride length, but not speed or cadence. 2. 3 to 4 participants had significant individual increases in gait speed, stride length and cadence.
Stein et al. 1993 Canada Pre-post Level 4 N=10	**Population:** 10 males and females; age 20-44 yrs; all participants had an incomplete SCI; C2-T10 lesion level; 2.5-10 years post-injury. **Treatment:** Surface, percutaneous, or implanted FES of common peroneal nerve, and sometimes quadriceps, glutei, and psoas. **Outcome measures:** speed, gait parameters.	1. All participants improved gait speed when FES was on (mean change was 4 m/min) 2. Participants with more severe SCI were the most receptive towards the FES treatment
Granat et al. 1992 Scotland Pre-post Level 4 N=6	**Population:** 3 males and 3 females; age 18-40 yrs; all participants had an incomplete SCI; C4-T12 lesion level; 2-10 yrs post-injury. **Treatment:** 12-months of FES to quadriceps for strengthening and gait (specific program not specified). Additional stimulation to hip abductors and erector spinae as needed. **Outcome Measures:** walking speed with FES compared to orthosis.	1. No significant difference in gait speed with FES compared to ambulation with orthosis. 2. Participants were able to use FES for 10-45 minutes. 3. All participants were able to use FES at home for standing and walking; 2 also use FES for outdoor walking. 4. 3 patients eventually discontinued use of FES citing impracticality for regular use

Discussion

To date, there are no randomized controlled or blinded assessments of the training effects of FES to improve mobility after SCI. Furthermore, only three of the studies reviewed here (Thrasher et al., 2006; Granat et al., 1993; Klose et al., 1997) report specific usage parameters for FES during gait rehabilitation, whereby FES was applied for at least 30 minutes, 2 to 5 times/week for up to 4.5 months. In the remainder of the studies, participants were provided with FES systems to use at home "as much as possible" or "as desired" over the course of the study (Ladouceur & Barbeau, 2000a; 2000b; Wieler et al., 1999; Stein et al., 1993). Results from the ten pre-post studies included here show that almost all the participants showed improvements in gait parameters (walking speed or distance) when FES was used (Thrasher et al., 2006; Ladouceur & Barbeau, 2000a; 2000b; Wieler et al., 1999; Klose et al., 1997; Granat et al., 1993; Stein et al., 1993; Granat et al., 1992). This is not surprising, given that the FES could compensate for weakened or paralyzed muscle function during gait. Of greater interest is the finding of carryover effects after FES training. Several investigators have also reported a carryover effect after FES training such that improvements in functional ambulation (e.g. overground walking speed and distance, step length) persisted even when the stimulator was turned off (Ladouceur & Barbeau, 2000b; Wieler et al., 1999). This suggests that neuroplastic changes may have taken place in response to regular use of FES during walking. Indeed, it has been shown in non-disabled human participants that the combination of treadmill walking and FES led to an acute increase in corticospinal excitability that persists even after the cessation of FES (Kido Thompson & Stein, 2004). Improved muscle strength and conditioning after regular use of FES could also contribute to carryover effects in walking function (Granat et al., 1993). The use of FES and weight-bearing also helps to maintain the subtalar and midfoot joint mobility needed for walking (Bittar & Cliquet, 2010).

Although laboratory studies advocate the efficacy of FES systems for improving ambulatory function in patients with SCI, the effectiveness of any technology is only as good as its acceptance by the intended users. Wieler et al. (1999) reported that the majority of their participants found they could use the FES device easily on a regular basis and that they walked better with the FES. Those who reported difficulties reported problems with finding the proper stimulation site or technical difficulties with the leads, switches, or electrodes. There have also been reports of musculoskeletal complications such as ankle sprain, calcaneum fracture, back pain, or falls with FES use (Brissot et al., 2000; Gallien et al., 1995). Some of these complications may have been associated with commencement of upright exercise (gait) after a period of being non-ambulatory. Anecdotal reports found in several studies suggest that most participants mainly use FES indoors or at home, for short distance walking, to prevent complications due to prolonged immobilization, and to enhance physical fitness rather than functional community ambulation (Brissot et al., 2000; Gallien et al., 1995; Klose et al., 1997). Participants who do use FES outdoors for community ambulation tend to be those less severely impaired (Brissot et al., 2000; Granat et al., 1993).

The functional benefits derived from FES are also quite variable. For instance, Stein et al. (1993) report that most participants showed a modest improvement in gait speed (average: 4 m/min), which was more significant for the more severely disabled participants. Higher-functioning participants felt that this small benefit in gait speed did not warrant the daily use of FES. In contrast, Ladouceur and Barbeau (2000b) reported that there was a tendency for the participants with initially faster gait speed to have greater absolute improvements. Thus, outcomes from FES-use also seem to be quite variable in terms of walking speed (Ladouceur & Barbeau, 2000b; Stein et al., 1993) or distance (Klose et al., 1997).

Conclusion

There is level 4 evidence (Thrasher et al., 2006; Ladouceur and Barbeau, 2000a; 2000b; Wieler et al., 1999; Klose et al., 1997; Granat et al., 1993; Stein et al., 1993; Granat et al., 1992) that

FES-assisted walking can enhance walking speed and distance in complete and incomplete SCI.

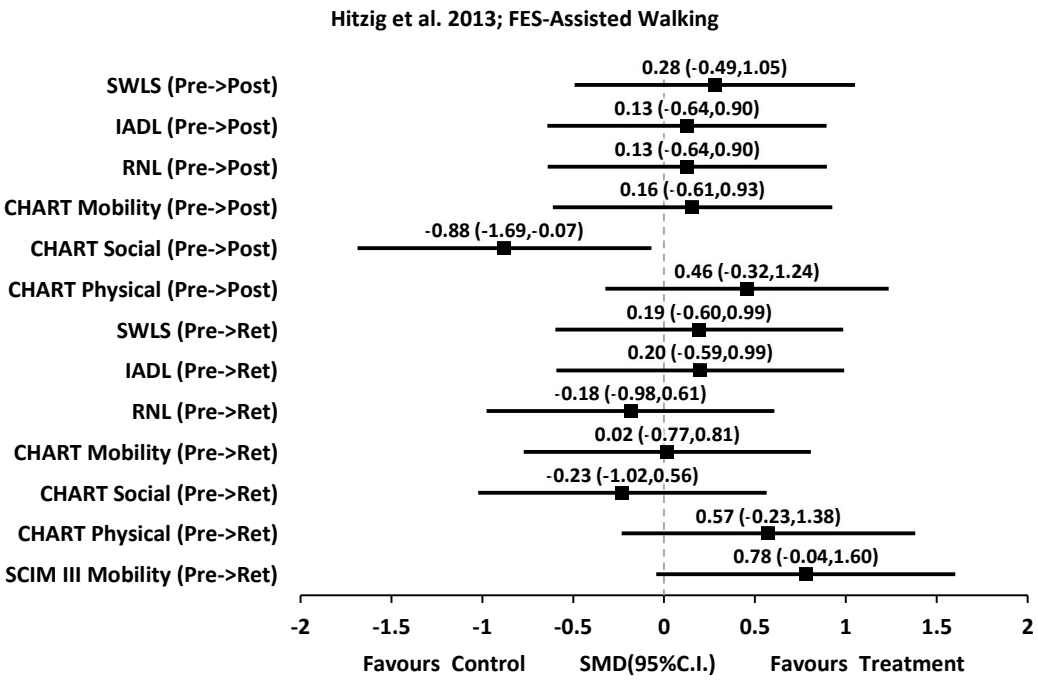
There is level 4 evidence from 2 independent laboratories (Ladouceur and Barbeau, 2000a, 2000b; Wieler et al., 1999) that regular use of FES in gait training or activities of daily living leads to persistent improvement in walking function that is observed even when the stimulator is not in use.

FES-assisted walking can enable walking or enhance walking speed in incomplete SCI or complete (T4-T11) SCI. Regular use of FES in gait training or activities of daily living can lead to improvement in walking even when the stimulator is not in use.

8.2 Functional Electrical Stimulation with Gait Training to Improve Locomotor Function

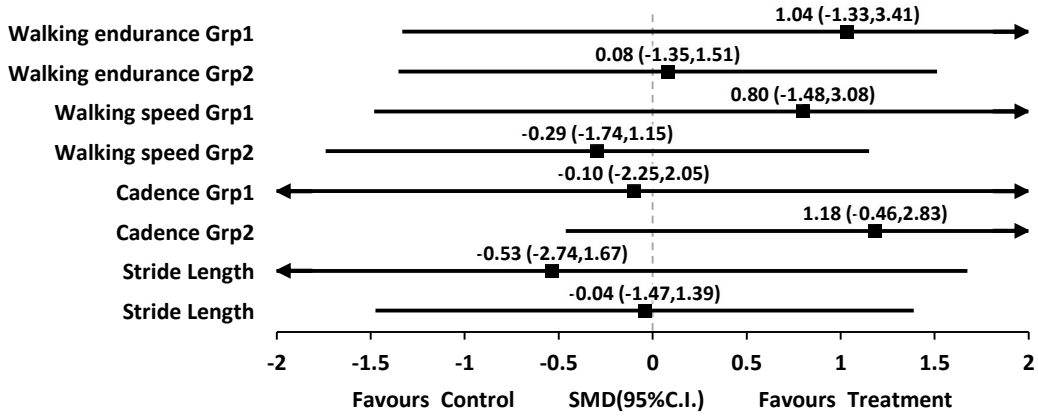
Table 14: Studies Combining Functional Electrical Stimulation with Gait Training to Improve Locomotor Function

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
Field-Fote & Roach 2011 USA PEDro=8 RCT Level 1 N=64	**Population:** Patients with chronic SCI at least 1 year post-injury, mean ages between 38 and 45 of each group; TM group (14 males, 3 females), TS group (14 males, 4 females), OG group (11 males, 4 females), LR group (12 males, 2 females) **Treatment:** Training 5 days/week for 12 weeks with: treadmill-based training with manual assistance (TM), treadmill-based training with stimulation (TS), overground training with stimulation (OG), or treadmill-based training with robotic assistance (LR) **Outcome Measures:** Walking speed (over 10m), distance walked in 2 minutes, LEMS	1. There was a significant time effect of training on walking speed: walking speed significantly increased for the OG group (0.19(0.21) to 0.28(0.28) m/s; Effect Size=0.43), TS group (0.18(0.18) to 0.23(0.18) m/s; ER=0.28). 2. There was a significant time effect of training on walking distance: walking distance significantly increased for the OG group (24.0(35.3) to 38.3(46.1) m; ES=0.40) and the TS group (20.6(23.1) to 24.4(24.3) m; ES=0.16), but not for the TM (22.1(21.4) to 23.0(21.1) m; ES=0.04) or the LR group (16.8(11.3) to 17.9(11.9); ES = 0.11). 3. There was a significant time x group interaction, with the increase in the OG group's walking distance being significantly greater than the TS, TM and LR groups.
Hitzig et al. 2013 Canada PEDro=7 Parallel-group RCT Level 1 N=34	**Population:** 34 participants with SCI. For the FES group (n=17, 14M 3F); mean (SD) age= 56.6(14); DOI = 8.75 (9.7); 6 AIS C, 11 AIS D. For the control group (n=17, 12M 5F); mean (SD) age=54.1(16.5); DOI= 10.3 (11.1); 7 AIS C, 10 AIS D. **Treatment:** Participants were randomized to intervention (FES) or control group. The FES group received FES stimulation while ambulating on a BWS treadmill. Control group exercise program consisted of 20-25 min of resistance and 20-25 min of aerobic training.	1. The FES group had a significant increase on SCIM mobility subscores (mean(SD)=17.27(7.2) to 21.33(7.6)) compared to the exercise group (mean(SD)=19.9(17.1) to 17.36(5.5)) from baseline to 1-yr follow-up. 2. No significant between-group differences were detected for other outcomes. 3. Both FES and control group reported positive gains in wellbeing from trial participation.

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
	Outcome Measures: SCIM; SWLS; IADL; CHART, RNL.	
	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%C.I.) as calculated from pre- to post-intervention data and pre-intervention to retention/follow-up data  	
Kressler et al. 2013 USA PEDro=7 Single-blind RCT Level 1 N=62	**Population:** 62 participants with SCI; AIS C or D; injury at T10 or higher. **Treatment:** Participants trained 5 days/wk for 12 wks. Groups were treadmill-based locomotor training with manual assistance (TM), transcutaneous electrical stimulation (TS), and a driven gait orthosis (DGO) and overground (OG) LT with electrical stimulation. **Outcome Measures:** Oxygen uptake, walking velocity and economy, substrate utilization during subject-selected “slow”, “moderate” and “maximal” walking speeds.	1. All groups increased velocity but to varying degrees: DGO=0.01(0.18) Ln[m/s]; TM=0.07(0.29) Ln[m/s]; TS=0.33(0.45) Ln[m/s]; OG=0.52(0.61) Ln[m/s]. Only the TS and OG groups had significant improvement over DGO (TS: p=.009, OG: p=.001). OG was also significantly higher than TM (p=.015). 2. Changes in walking economy were only significant for TS (0.26(0.33) Ln[L/m], p=.014) and OG (0.44(0.62)Ln[L/m], p=.025).
Field-Fote et al. 2005 USA PEDro=5 RCT Level 2 N = 27	**Population:** 27 males and females; age 21-64 yrs; all participants had an incomplete SCI; C3-T10 lesion level; >1 yr post-injury **Treatment:** Randomized to 4 gait training strategies, 45-50 min, 5x/wk, 12 wks: 1) manual BWSTT (n=7); 2) BWSTT + FES (common peroneal nerve) (n=7); 3) BWS overground + FES (n=7); 4) BWS Lokomat (robotic gait device) (n=6).	1. Significant increases in short-bout walking speed across participants who received BWSTT + FES. 2. Equivalent effects on long-bout gait speed between the 4 groups. 3. Tendency for initially slower walkers (<0.1m/s) to show greater improvement (106%) compared to initially faster walkers (17%).

<table>
<tr><th>Author Year;
Country
Score
Research Design
Sample Size</th><th>Methods</th><th>Outcomes</th></tr>
<tr><td></td><td>Outcome measures: Walking speed over 6 m (short bout) and 24.4 m (long-bout).</td><td></td></tr>
<tr><td rowspan="2">Postans et al.
2004
Scotland
PEDro=3
RCT w/crossover
Level 2
N initial=14
N final=10</td><td>Population: 14 males and females; ages 19-57 yrs; all participants had an incomplete SCI; C4-T9 lesion level; mean 12.2±5.9 weeks post-injury

Treatment: Crossover design: Intervention - Partial weight-bearing (PWB) supported treadmill gait training augmented by FES for up to 25 minutes a day, 5 days a week for 4 weeks; Control - 4-week period of standard physiotherapy. Patients were randomly assigned to either an AB (4 weeks control then 4 weeks intervention) or BA (4 weeks intervention then 4 weeks control) group.

Outcome Measures: Overground and treadmill walking endurance and speed.</td><td>1. Between the intervention and control periods for the BA group, there was a significant difference in walking endurance (in metres; Mean: 60.10, CL: 9.2 to 110.9, P=.030) as well as for walking speed (in m/s; Mean: 0.22, CL: 0.05 to 0.37, P= .019)
2. Between the intervention and control periods for the AB group, there was a significant difference in walking endurance (in metres; Mean: 72.20, CL: 39.8 to 104.6, P= .003) as well as for walking speed (in m/s; Mean: 0.23, CL: 0.13 to 0.33, P=.004).</td></tr>
<tr><td colspan="2">Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%C.I.) as calculated from pre- and post-intervention data
Postans et al. 2004; Partial Weight-Bearing Supported Treadmill Gait Training Augmented by FES
 

*Cross-over study, where participants acted as their own controls. Grp1: control-intervention. Grp 2: intervention-control
**Overground measurements only
***SMD 95%CI calculated from 95%CI of changes in mean outcome values</td></tr>
<tr><td>Triolo et al. 2012
USA
Longitudinal
Level 2
N=15</td><td>Population: 15 participants with thoracic or low cervical level SCI (14M 1F); 10 AIS A, 4 AIS B, 1 AIS C; Mean (SD) DOI: 72.6(71.87) months.

Treatment: Participants received the 8-channel neuroprosthesis and completed rehabilitation with the device. This study follows the patients from discharge to follow-up ranging from 6-19 months after discharge (with exception of 1 participant at 56 months).</td><td>1. Levels of maximum standing time, BWS, knee strength, and knee fatigue index were not statistically different from discharge to follow-up.
2. Neuroprosthesis usage was consistent with participants choosing to use the system on approximately half of the days during each monitoring period. Although the number of hours using the neuroprosthesis remained</td></tr>
</table>

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
	Outcome Measures: Neuroprosthesis usage, maximum standing time, body weight support, knee strength, knee fatigue index, body weight support, electrode stability, and component survivability.	constant, participants shifted their usage to more functional standing versus more maintenance exercise, suggesting that the participants incorporated the neuroprosthesis into their lives. 3. Safety and reliability of the system were demonstrated by electrode stability and a higher component stability rate (>90%).
Hesse et al. 2004 Germany Pre-post Level 4 N=4	**Population:** 3 males; age 45-62 yrs; all participants had a diagnosis of AIS C or AIS D; C5-T8 lesion level; 8-18 months post-injury. **Treatment:** Electromechanical gait trainer + FES to quadriceps and hamstrings: 20-25 min, 5x/wk, 5 wks. **Outcome measures:** Gait velocity and endurance.	1. Gait ability improved in all patients; 3 could walk independently over ground with aids. Overall gait speed and endurance more than doubled. 2. Study made no reports of significance levels or testing of results.
Field-Fote & Tepavac 2002 USA Pre-post Level 4 N=14	**Population**: 14 males and females; age 18-50 yrs; all participants had a diagnosis of AIS C; C4-T7 lesion level. **Treatment:** BWSTT + common peroneal nerve FES: <90 min, 3x/wk, 12 wks. **Outcome measures:** Over ground gait speed.	1. All participants showed an increase in walking speed. 2. Participants with slower walking speeds showed greater improvement. 3. Study made no mention of significance levels or testing of results.
Field-Fote 2001 USA Pre-post Level 4 N=19	**Population:** 19 males and females; mean age 31.7±9.4 yrs; all participants had a diagnosis of AIS C either paraplegia or tetraplegia. **Treatment:** BWSTT + common peroneal nerve FES: <90 min, 3x/wk, 12 wks. **Outcome measures:** Gait speed.	1. Significant increase in walking speed (initial 0.12 ± 0.8m/s; final 0.21 ± 0.15m/s, p = .0008, median change of 77%).

Discussion

Findings from five studies, including three high-quality RCTs (Hitzig et al., 2013; Field-Fote & Roach, 2011; Field-Fote et al., 2005) and three pretest/posttest (Hesse et al., 2004; Field-Fote & Tepavac, 2002; Field-Fote, 2001) studies, demonstrated favourable outcomes when BWSTT was combined with FES in people with chronic, incomplete SCI. There was an overall enhancement of short-distance functional ambulation, as measured by overground gait speed over 6 meters, and walking distance when BWSTT was combined with FES of the common peroneal nerve. Hesse et al. (2004) found that BWSTT combined with FES to the quadriceps and hamstrings muscles enhanced functional ambulation. Hitzig et al. (2013) studied the effects of FES stimulation while ambulating on a BWS treadmill, and found a significant increase on SCIM mobility scores from baseline to 1-year follow-up compared to the control group.

The Kressler et al. (2013) study provides evidence for increased benefit of electrical stimulation over manual assistance and braces (driven gait orthosis). In this study, the transcutaneous electrical

stimulation group and the overground locomotor training with electrical stimulation group had significantly higher walking speeds while the treadmill-training with manual assistance group and driven gait orthosis group had nonsignificant improvements in walking speed.

Triolo et al. (2012) explored use of an 8 channel neuroprosthesis with rehabilitation training and found that there were no statistically significant differences in walking outcomes. However, the safety and reliability of the neuroprosthesis system were supported.

Conclusion

There is level 1b evidence (Field-Fote & Roach, 2011; Field-Fote et al., 2005; Field-Fote & Tepavac, 2002; Field-Fote, 2001) for an overall enhancement of short-distance functional ambulation, as measured by overground gait speed over 6 meters, and walking distance when BWSTT was combined with FES of the common peroneal nerve.

There is level 1b evidence (Kressler et al., 2013) for increased benefit of electrical stimulation over manual assistance and braces (driven gait orthosis).

There is level 1b evidence (Hitzig et al., 2013) for a significant increase in SCIM mobility scores when participants are stimulated with FES while ambulating on a BWS treadmill.

There is level 4 evidence from one pretest/posttest study (Hesse et al., 2004) suggesting that BWSTT combined with FES to the quadriceps and hamstrings muscles enhances functional ambulation.

There is level 4 evidence from one case series study (Triolo et al., 2012) that an 8 channel neuroprosthesis system is safe and reliable, but its use with rehabilitation training shows no statistically significant difference in walking outcomes.

BWSTT combined with FES of the common peroneal nerve can lead to an overall enhancement of short-distance functional ambulation.

Electrical stimulation is shown to be a more effective form of locomotor training than manual assistance and braces.

Stimulation with FES while ambulating on a BWS treadmill can increase SCIM mobility scores.

BWSTT combined with FES to the quadriceps and hamstrings muscles can enhance functional ambulation.

An 8 channel neuroprosthesis system is safe and reliable, but its use with rehabilitation training has shown no statistically significant difference in walking outcomes.

8.3 Bracing Combined with FES in SCI

For people with SCI, walking with braces can be tiring, and thus few people use them. Hybrid systems combine conventional bracing with FES to activate large lower extremity muscles in the hopes of improving the gait pattern and reduce upper extremity exertion. The FES is used to improve trunk and hip stability and to facilitate forward progression.

Table 15: Studies of Bracing Interventions Combined with FES in SCI

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
Marsolais et al. 2000 USA Post-test Level 4 N=6	**Population**: 6 participants; age 22-50 yrs; all participants had a SCI; C7-T12 lesion level; 2.5-20.6 yrs post-injury. **Treatment:** Case-Western Reserve University Hybrid Gait Orthosis (modification of IRGO) combined with FES to various muscles (combination of 8-16 muscles). **Outcome measures:** walking speed and distance.	1. Participants who were unable to use RGO alone could ambulate with hybrid system. 3 participants who were previously ambulatory with either RGO or FES alone showed improvement in walking distance with the hybrid system (from 3-90 m to 200-350 m). 2. Two of the participants were capable of stair-climbing with the hybrid system.
Solomonow et al. 1997 USA Post-test Level 4 N=70	**Population:** 70 participants; age 16-50 yrs; all participants had a SCI; C6-T12 lesion level; 1-10 yrs post-injury **Treatment:** RGO use and gait training 1-3 hr, 3x/wk, 6 wks followed by RGO+FES (bilateral quadriceps and hamstrings) for another 6 wks. **Outcome measures:** Walking ability, 180 m walk.	1. After training, 57 patients could walk at least 180 m (19 could walk > 450 m). 77% of patients could walk independently on different surfaces (grass, ramps, curbs).
Sykes et al. 1996a UK Post-test Level 4 N=5	**Population**: 5 participants; age 24-37 yrs; all participants had a diagnosis of AIS A-C; C2 -T6 lesion level; 8-14 yrs post-injury. **Treatment:** RGO and FES: 20-40 weeks of RGO use at home followed by RGO+FES bilaterally to quadriceps and hamstrings. **Outcome measures:** RGO pedometer measured number of steps over 18 months.	1. Number of steps taken per week varied between 306 and 1879 steps (99-845 m/week). 2. Use of the RGO was low and no increase in use or function after hybrid system supplied. 3. One participant (AIS C) was already a community ambulator and showed most frequent use of RGO but across all participants, RGO-use was variable, intermittent and generally poor.
Sykes et al. 1996b UK Post-test Level 4 N=5	**Population:** 5 participants; age 24-37 yrs; all participants had a diagnosis of AIS A-C; C2-T6 lesion level. **Treatment:** Following conditioning program, RGO+FES bilaterally to quadriceps and hamstrings for home use. **Outcome measures:** Walking speed over 40 m.	1. Without FES, participants' walking speeds ranged from 0.13 to 0.40 m/s. With RGO+FES, speeds ranged from 0.14 to 0.45 m/s, corresponding to changes ranging from -1% to 14%.
Yang et al. 1996 UK Post-test Level 4 N=3	**Population:** 3 participants; age 28-42 yrs; participants had a complete or incomplete SCI; C6 -T8 lesion level; 3-15 yrs post-injury. **Treatment:** RGO ± FES. RGO with and without FES to common peroneal nerve stimulation.	1. RGO + FES: Modest (non-significant) increase in walking speed and stride length compared with RGO without FES. 2. When participants walked with the RGO+FES, average walking speed was 13% faster and stride length was 5% longer.

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
	Outcome measures: walking speed, stride length.	
Thoumie et al. 1995 France Post-test Level 4 N=26	**Population:** 26 participants; age 20-53 yrs; all participants had a complete SCI; C8-T11 lesion level; 9-144 months post-injury **Treatment:** RGO-II orthosis: long-leg brace with reciprocal hip joint combined with FES to the quadriceps and hamstrings. 4-6 weeks of gait training with orthosis alone followed by RGO-II+FES (hybrid) program (total program time: 2-5 months inpatients, 3-14 months outpatients). **Outcome measures**: walking distance and speed with RGO and with RGO+FES.	1. 21/26 completed the training program, 19 were able to stand up alone. Following program, walking distance ranged from 200-1400 m with hybrid orthosis, 150-400 m with RGO II. 2. Maximal walking speed with the hybrid orthosis (mean (SD) 0.32 (0.02) m/s; range 0.21-0.45 m/s) was not significantly different from that with orthosis alone (mean (SD) 0.29 (0.03) m/s; range 0.22-0.41 m/s)

Discussion

We found 6 post-test studies (Marsolais et al., 2000; Solomonow et al., 1997; Sykes et al., 1996a; Sykes et al., 1996b; Yang et al., 1996; Thoumie et al., 1995) that examined the combined effect of lower extremity bracing with FES on functional ambulation in people with complete SCI (aggregate N=115). Most studies found that the combination of long-leg bracing and FES may enable overground ambulation of between 180 and 1400 m at one time (Marsolais et al., 2000; Solomonow et al., 1997; Sykes et al., 1996a; Thoumie et al., 1995). There does not seem to be further benefit in combining FES with orthosis-use in terms of maximal walking speed (Sykes et al., 1996b; Yang et al., 1996; Thoumie et al., 1995), although greater walking distance may be achieved (Marsolais et al., 2000; Thoumie et al., 1995). Three pretest/posttest studies (Marsolais et al., 2000; Yang et al., 1996; Thoumie et al., 1995) and one posttest study (Sykes et al., 1996b) directly compared the effect of bracing+FES with either FES or bracing alone. When participants walked with either braces or FES alone, maximum walking distance ranged from 3 to 400 m. When braces were combined with FES, maximum distance increased to 200 to 1400 m (Marsolais et al., 2000; Sykes et al., 1996b; Thoumie et al., 1995).

Biomechanical studies (*not included in the summary tables if they did not have a training period*) provide some insight into the relative benefits of FES versus bracing. One study that compared FES-alone with bracing-alone found that FES provides a particular advantage in facilitating sit-to-stand movements and donning the system (Bonaroti et al., 1999). However, once standing was achieved, mobility (e.g., walking, stairs) was not found to be different between FES and bracing. For people with incomplete SCI, Kim et al. (2004) found FES produced more benefits in walking speed, and bracing (AFO alone) improved walking distance. However, the combination of AFO with FES improved gait benefits more than either device used alone (Kim et al., 2004).

Conclusion

There is level 4 evidence (Yang et al., 1996) that a combined approach of bracing and FES results in additional benefit to functional ambulation in paraplegic patients with complete SCI. However, in participants who achieve little benefit from bracing alone, the addition of FES

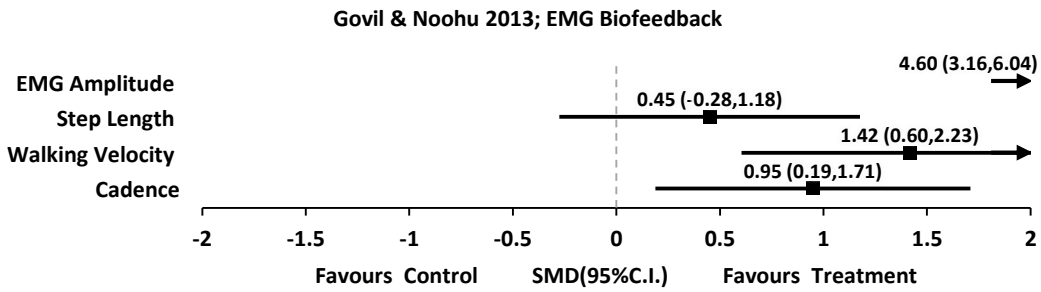
appears to help improve standing or short-distance walking function (Marsolais et al., 2000). In incomplete SCI, however, there is some indication that a combination of bracing and FES provides greater ambulatory function than either approach alone (Kim et al., 2004).

There is limited evidence that a combined approach of bracing and FES results in additional benefit to functional ambulation in paraplegic patients with complete SCI.

8.4 Biofeedback and Gait Rehabilitation

Biofeedback techniques provide information to the patient in order to enhance appropriate responses, specifically gait movements in this chapter. Biofeedback techniques in publications include those based on EMG recordings of muscle activation or position or force sensors that provide feedback on joint motion or functional attributes such as weight-shifting.

Table 16: Biofeedback for Gait Rehabilitation

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
Govil and Noohu 2013 India PEDro=5 RCT Level 2 N=30	**Population:** 30 participants with incomplete SCI; randomized to 2 groups. For Group 1: mean (SD) age = 38.73 (10.75); DOI= 17.87 (8.37). For Group 2: mean (SD) age=38.03 (7.45); DOI = 16.93 (7.10). **Treatment:** Group 1 received EMG biofeedback to the gluteus maximus muscle, as well as traditional rehabilitation and gait training for 5 days/wk for 4 wks. Group 2 received traditional rehabilitation and gait training for 5 days/wk for 4 wks. **Outcome Measures:** Walking speed, step length, cadence, EMG.	1. Significant differences were found between the two groups in: - Walking velocity (m/s): Group 1 pre=0.12(0.11), post=0.27 (0.25); Group 2 pre=0.11(0.08), post=0.12(0.10); (p=0.043) - Cadence: Group 1 pre=22.15(16.18), post=40.40(28.27); Group 2 pre=21.67 (20.71), post=22.04(21.71); (p=0.05). 2. Group 1 showed significant changes for EMG amplitude, step length, walking velocity and cadence pre and post. 3. Group 2 showed significant changes for EMG amplitude, walking velocity and step length, but not cadence pre and post.
	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%C.I.) as calculated from pre- and post-intervention data 	
	Population: 9 SCI individuals- 5 males and 4 females; incomplete SCI; all AIS D; Lesion level between C4 to T12; mean age= 55.1 ± 15.8y; years post injury= 1-5y; 14 healthy individuals	1. The intense VR-augmented training of limb control improved significantly balance, walking speed, ambulation, and muscle strength in patients.

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
Villiger et al. 2015 Switzerland Longitudinal Study Level 2 N= 23	were in the control group - 8 males and 7 females; mean age= 47.1 ± 14.4y **Treatment**: Patients underwent 4 weeks of intensive VR-augmented lower limb training. The patients with iSCI were trained with the VR movement tasks 16–20 times during the 4 weeks (4–5 × 45 min. per week). The training used a VR-augmented therapy system for lower limbs combining action observation, imagination and execution. Before and after the training period a structural volumetric 3D MRI data set was acquired in patients. Retention of the performance improvements was assessed in a 3–4 month follow-up session. **Outcome Measures:** 10 MWT, Berg Balance Scale (BBS), Lower Extremity motor Score (LEMS), Spinal Cord Independence Measure (SCIM mobility)	2. Retention of clinical improvements was confirmed by the 3–4 months follow-up.
Tamburella et al. 2013 Italy Case Control Level 3 N=12	**Population:** 12 participants with SCI; 6 in the vBFB group and 6 in control group (CTRL). vBFB group: mean (SD) age: 52 (11.74); 3M 3F. CTRL group: mean (SD) age: 53.5 (13.21); 3M 3F. **Treatment:** 2 groups: vBFB and Rehab group (control). vFBF and CTRL groups underwent 8 wks of rehab 5 times/wk (CTRL: 60 minutes devoted to Rehab; vBFB: 40 minutes of rehab plus 20 of vBFB). **Outcome Measures:** BBS; WISCI; 6MWT; 10MWT; TUG; balance performance and kinematic spatio-temporal gait parameters.	1. Only the vBFB group experienced a significant improvement in balance and gait: BBS: 26 (10.69) at baseline to 41(7.8) at end of intervention. WISCI: 14.17(1.83) at baseline to 17.15(1.64) at end of intervention 6MWT: 193.18(68.08) at baseline to 259.64(82.84) at end of intervention 2. The improvement in balance and gait for the vBFB group was maintained at follow-up examinations. 3. vBFB participants experienced greater improvements than CTRL participants for all measures, except for one balance measure. 4. vBFB treatment demonstrated a significantly higher level of effectiveness than conventional rehabilitation.
Wall et al. 2015 USA Pre-Post Level 4 N= 5	**Population**: 5 males; incomplete SCI; mean age= 58.6y; years post injury >1y **Treatment**: An interrupted time series design with three pre-tests over three weeks, a post-test within one week of the intervention, and a four-week follow up. Intervention consisted of one-hour sessions with varied games using the Nintendo Wii Fit twice per week for seven weeks. Survey data was also collected at post-test. **Outcome Measures:** Gait speed, Timed up and Go (TUG), Forward Functional Reach Test (FFRT), Lateral Functional Reach Test (LFRT), RAND SF-36	1. There were statistically significant changes found in gait speed and functional reach. 2. The changes were also maintained at the four-week follow up post-test. 3. Survey reports suggested improvements in balance, endurance, and mobility with daily tasks at home.

Discussion

In the study by Govil & Noohu (2013), biofeedback was provided in the form of EMG from the gluteus maximus muscle. Participants (N=30) were randomized into 2 groups either receiving biofeedback and gait rehabilitation or just gait rehabilitation. Both groups significantly improved from baseline in EMG amplitude, walking velocity and step length but the group receiving biofeedback improved by more. The biofeedback group also had significantly higher walking cadence. In the Tamburella et al. (2013) study, the visual biofeedback group experienced significant improvement in balance and gait measures which were maintained at follow-up.

Conclusion

There is level 2 evidence (Govil & Noohu, 2013) that EMG biofeedback may improve gait outcomes in patients with SCI.

There is Level 2 evidence that lower limb training augmented by biofeedback of ankle and knee movements can improve gait, balance, and muscle strength (Villiger et al., 2015).

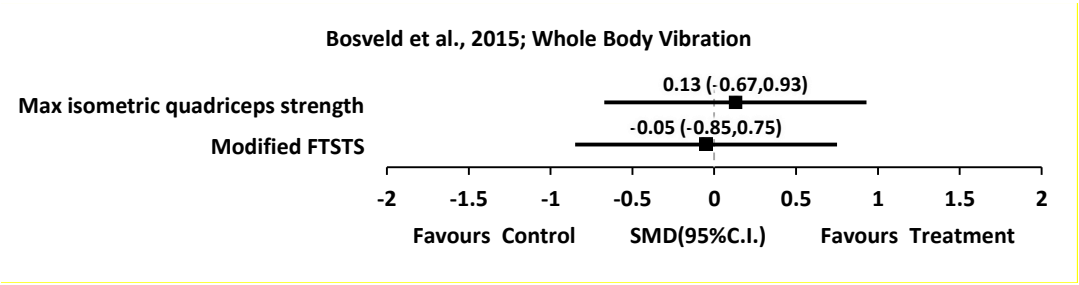
There is level 4 evidence that virtual games (i.e., Nintendo Wii Fit) can enhance gait speed and functional reach and that these gains can be maintained at a 4 week follow-up (Wall et al., 2015).

EMG Biofeedback may improve gait, balance, and lower limb muscle strength in incomplete SCI

8.5 Whole-Body Vibration and Lower Limb Motor Output

Table 17: Whole-Body Vibration on Lower Limb Motor Output

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
Bosveld et al. 2015 USA RCT PEDro=8 Level 1 N= 25	**Population**: 25 individuals; chronic SCI; age =49.7 ± 12.5 years; years post injury= >1y **Treatment**: Participants were randomized into two groups. Group 1 (*n* = 13) received whole-body vibration treatment (frequency: 50 Hz, amplitude: 2 mm) comprising of four 45-second bouts with 1-minute rest periods after each bout. Group 2 (*n* = 12) received sham electrical stimulation. Maximal voluntary isometric quadriceps force was measured with a fixed dynamometer. A modified Five-Time-Sit-To-Stand (FTSTS) test was used to assess functional lower extremity strength. Measures were made at pre-test, immediate post-test, and delayed post-test 20 minutes later. **Outcome Measures:** Maximal voluntary isometric quadriceps force, modified Five-Time-Sit-To-Stand (FTSTS) test.	1. When comparing the pre-test and immediate post-test data, the difference in mean quadriceps strength between the two groups approached significance (P = 0.10). However, between the pre-test and delayed post-test, there were no significant difference between groups (P = 0.82). 2. The within-group change for the WBV group was significant with a moderate effect size (P = 0.05; ES = 0.60) 3. Between the pre-test and immediate post-test, the time from sit to stand between the two groups approached significance (P = 0.10). Between the pre-test and delayed post-test, there was no significant difference between groups (P = 0.32).
	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%C.I.) as calculated from pre- and post-intervention data	

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
		
Alizadeh-Meghrazi et al. 2015 Canada Pre-Post Level 4 N= 10	**Population**: 10 males; 6 healthy, 4 with chronic SCI; 1 AIS A and 3 AIS C; age= 28.83 ± 7.78y; years post injury > 1y **Treatment**: Testing was performed on 2 days, where the participants were randomly allocated to exposure to either the WAVE® or Juvent™ platform each day. All participants were provided with the same shoes to eliminate footwear variability. In the case of the WAVE® platform, all combinations of the following parameters were used: (1) vibration frequencies of 25, 35, and 45 Hz; (2) two vibration amplitude settings and (3) knee angles of 140°, 160°, and 180°. In the case of the Juvent™ platform, all combinations of the following parameters were used: (1) vibration frequencies of 25, 35, and 45 Hz; (2) constant power setting of 28; and (3) knee angles of 140°, 160°, and 180°. **Outcome Measures:** EMG	1. WBV can elicit EMG activity among participants with chronic SCI, if appropriate vibration parameters are employed. 2. The participants' knee angle had no significant impact on lower extremity EMG activity. 3. The vibration frequency had a significant impact on EMG activation in all lower extremity muscles except VL while the amplitude of vibration had a significant impact on EMG activation on the GM and RF muscles only.
Ness & Field-Fote 2009 USA Pre-Post N=17	**Population:** 3 women, 14 men; aged 28-65 years; all participants had a motor-incomplete SCI; C3-T8 lesion level; ≥1 year duration. **Treatment:** WBV 3 days/week for 4 weeks with four 45 second bouts of 50 Hz frequency and 2-4mm intensity each session, while standing on a vibration platform and 1 minute seated rest in between. **Outcome Measures:** 3-D motion capture system used to measure walking function (walking speed; step length; cadence (steps/min); hip-knee intralimb coordination).	1. Walking speed significantly increased by mean (SD) 0.062 (0.011) m/s. 2. Speed continued to improve 1 week post final intervention; only one participant tested. 3. Cadence, weak side step length, and strong side step length all significantly increased following 12 sessions of WBV. 4. Increased walking speed was significantly related to increased cadence.

Discussion

A recent report demonstrated the potential benefits of WBV administered for 3 minutes a day for 12 sessions over a 4-week period (Ness & Field-Fote, 2009). Following this training period, the authors reported a mean improvement in walking speed of 0.062 m/s, which although statistically significant, was considered a small effect size. Training was also associated with an increase in cadence and hip-knee inter-joint coordination. Although whole-body vibration has been introduced for other neurological disorders such as Parkinson's disease, this is the first report to demonstrate the potential benefits of whole-body vibration in the SCI population. Another study has since shown the potential

benefits of WBV through improvements in muscle force output and sit-to-stand function (Bosveld & Field-Fote, 2015).

Another study investigated the physiological effects of whole-body vibration in persons with SCI (Herrero et al., 2010), suggesting possible mechanisms of how WBV could be beneficial for lower limb function (not presented in table due to lack of functional or behavioural results). The authors showed that peak blood flow in the femoral artery increased with higher vibration frequencies (20 or 30 Hz), and that muscle activity increased regardless of frequency. This suggests that incorporating whole body vibration to rehabilitation programs could benefit persons with SCI by promoting circulation in the legs and increasing muscle activation.

Conclusion

There is Level 1 evidence that WBV improves muscle force output and Sit to Stand test scores (Bosveld & Field-Fote, 2015) though neither of these differences was significant.

> There is limited evidence that whole body vibration improves walking function in incomplete SCI but stronger evidence that it could improve muscle force output.

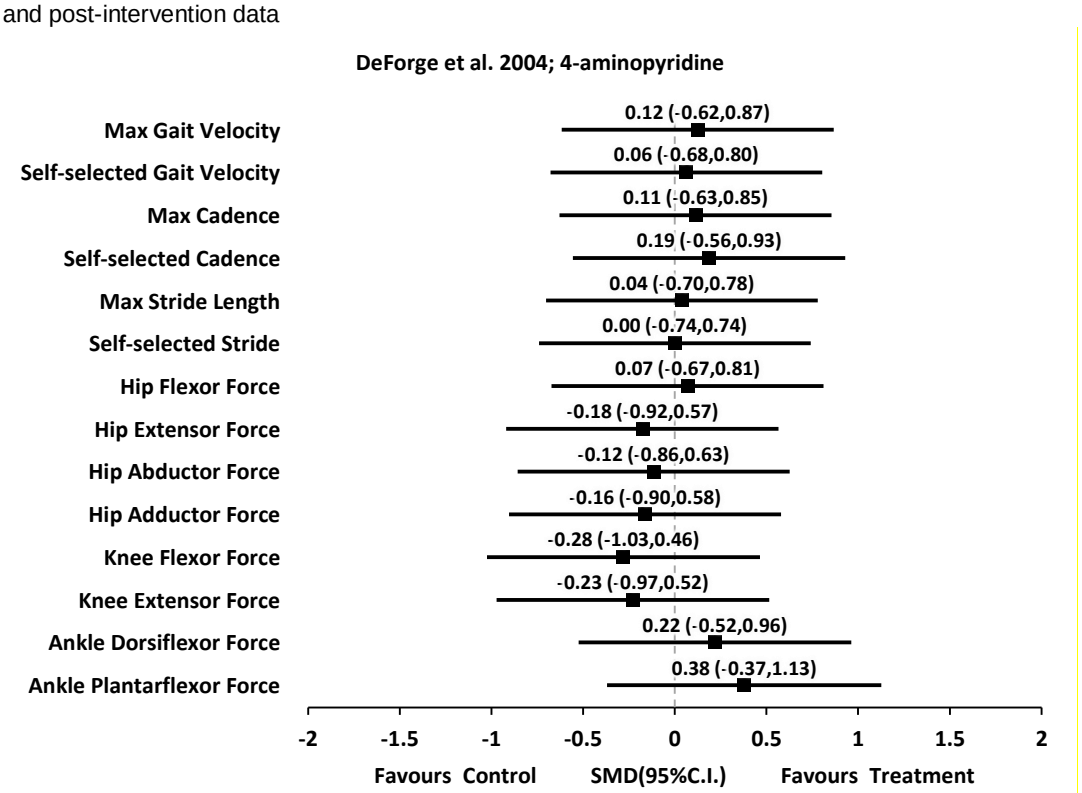
9.0 Pharmacological interventions to augment Gait/ambulation

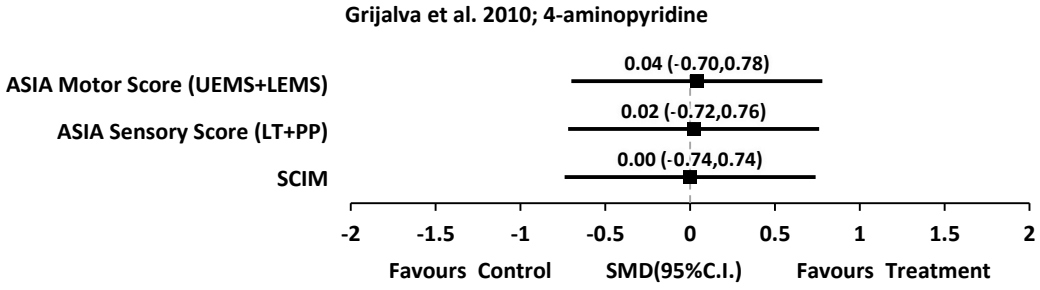
9.1 Combined Gait Training and Pharmacological Interventions

Drugs such as clonidine (a noradrenergic agonist), cyproheptadine (a serotonergic antagonist), baclofen (GABA agonist), GM-1 ganglioside, L-Dopa and 4-aminopyridine have been used in association with attempts to improve ambulation in individuals with SCI. The results from animal studies indicate that some of these drugs may act on the receptors in the spinal cord which facilitate interaction with a locomotor central pattern generator (spinal circuits which produce coordinated locomotor movement) (Chau et al., 1998; Rossignol et al., 1996; Barbeau & Rossignol, 1990). Although not conclusive, there is some evidence that similar "central pattern generator" circuits exist in humans (Bussel et al., 1996; Illis, 1995; Calancie et al., 1994; Bussel et al., 1989; Bussel et al., 1988) and provide the rationale for clinical use of these drugs.

Table 18: Studies of Pharmacological Interventions effects on gait outcomes

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
DeForge et al. 2004 Canada PEDro=10 RCT N=15 N SCI=11	**Population:** 11 participants with SCI; Age 22-70 yrs; all participants with diagnosis of AIS D; C3-T12 lesion level; 1-20 post-injury. **Treatment**: Double-blind, placebo-controlled, crossover design; 4-Aminopyridine (4-AP): up-titration to 10 mg 4x/day stable dosing of 4-AP (n=15) versus Placebo (n=14), 2 weeks each condition **Outcome measures**: Isometric muscle force, gait analysis.	1. Some positive effects for both placebo and 4-AP treatment when compared to baseline, but no changes between groups were significant.

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%C.I.) as calculated from pre- and post-intervention data  ***Forces measured using dynamometer**	
Duffell et al. 2015 USA RCT PEDro=7 Level 1 N= 48	**Population**: 26 individuals in locomotor treadmill training group (LTT)- 19 males and 7 females; mean age= 46.6 ± 12.6y; years post injury= 9.3 ± 8.9y; 22 individuals in combined LTT and tizanidine group- 15 males and 7 females; mean age= 46.5 ± 11.9y; years post injury= 10.2 ± 10.4y; Level of injury 30 C and 15 T **Treatment**: Participants were randomly assigned into one of two intervention groups; LTT alone (LTT; n = 26) or combined LTT and Tizanidine (TizLTT; n = 22). Participants assigned to the TizLTT group, were initially provided with Tizanidine alone for a period of 4 weeks, and results for that period have been presented elsewhere, together with the LTT group clinical outcomes. Outcomes were measured at 0, 1, 2 and 4 weeks from the start of LTT for both groups **Outcome Measures:** Timed up and go (TUG), 10MWT, 6MWT, MAS, Maximum voluntary isometric contractions (MVIC), active range of motion (AROM), Peak isokinetic velocity (Vp)	1. Both LTT and TizLTT improved in walking speed and dorsiflexion maximum strength, with no significant differences between them, using group-averaging analysis at 0, 1, 2 and 4 weeks from the start of LTT for both groups. 2. A higher proportion of participants in the TizLTT group achieved the MID for walking speed (40%) compared with LTT alone (13%) 3. Those that achieved the MID for walking speed were significantly higher functioning at baseline than those that did not in the TizLTT group, and the change in walking speed was associated with the change in dorsiflexion peak velocity.

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
van der Bruggen 2001 The Netherlands PEDro=10 RCT Level 1 N=20	**Population**: Age 25-70 yrs; all participants had an incomplete SCI; C2-L3 lesion level; 3-56 yrs post-injury. **Treatment**: Double-blind, placebo-controlled, crossover design: up-titration to maximum of 15-45 mg, immediate-release 4-Aminopyridine capsules or Placebo, 4 weeks each condition. 2 week washout between conditions. **Outcome measure**: comfortable and maximum walking speed.	1. No statistically significant functional benefits were found.
Grijalva et al. 2010 Mexico PEDro=9 RCT Level 1 N=14	**Population:** 10 males, 4 females; mean age 29; average YPI 6.2; 8 cervical SCI, 6 thoracic **Treatment:** Phase 1: protocol found in Grijalva et al., 2003 Phase 2 (3 months): Administration of 10mg/day of 4-AP the first week, 20 mg/day the second week, 30 mg/day the third week, and 10mg increase per day every 2-3 months if patients were not experiencing any adverse reactions. **Outcome Measures:** AIS motor and sensory scale, SCIM, SEPs	1. There were no significant differences between placebo and 4-AP in phase one. 2. There were no significant differences comparing pretreatment and highest 4-AP doses evaluations in phase 2. 3. Two patients experienced adverse reactions severe enough to cause drop out; one of them had epileptic seizures and the other persistent anxiety and insomnia.
	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%C.I.) as calculated from pre- and post-intervention data 	
Maric et al. 2008 Switzerland PEDro=8 RCT with crossover Level 1 N = 12	**Population:** 12 participants with incomplete SCI, 4 female, 8 male, ages 31-75. **Treatment:** Double-blind, placebo-controlled crossover study design: Participants were randomly divided into two groups. Group 1 first received 6 weeks of treatment of 200mg L-Dopa and 50mg dopa decarboxylase inhibitor with physiotherapy for 30-45min 1-4hrs after L-dopa intake. Group 1 then received then 6 weeks of treatment with placebo. Group 2 first received 6 weeks of placebo and then 6 weeks of treatment with 200mg L-Dopa and 50mg dopa decarboxylase inhibitor with physiotherapy.	1. There was no effect of L-Dopa and physiotherapy on the outcomes. 2. The treatment group had greater improvement than control in AMS (+7.8 in treatment, vs. +6.6 in control) and SCIM (+16.6 vs. +11.7), but the difference was not significant (p=0.49 for AMS, p=0.31 for SCIM). 3. The control showed greater average improvement than treatment group in WISCI II score (+2.9 in treatment, vs. +3.4 in control) but the difference was not significant.

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
	Outcome Measures: Asia motor score (AMS); WISCI II; SCIM II.	
Walker & Harris 1993 USA PEDro=6 RCT Level 1 N=9	**Population:** Age 21-44 yrs; all participants incomplete SCI; C5-L1 lesion level; 1-13 yrs post-injury **Treatment:** Double-blind, placebo-controlled crossover study design: Intravenous GM-1 ganglioside (Sygen ®) or placebo + 2 hr PT (gait training) 6x/wk for 2 months, followed by switch of drug administration (total 4 months). All participants given 6 months of PT before trial. **Outcome measures:** Motor score, walking distance, and velocity.	1. GM-1 + PT resulted in increase in motor scores, walking distance, and walking velocity. 2. *Note: Klose and Calancie (1994) wrote a critique of this article, re-calculated data, and came up with different results.
Stewart et al. 1991 Canada PEDro=6 Crossover Design Level 1 N = 9	**Population:** 6 participants with paraplegia, 3 participants were paretic; age 19-57 yrs; AIS A-D; C7-T10 lesion level; 1-10 yrs post-injury. **Treatment:** Double-blind, placebo-controlled, crossover design: Two periods of 4 weeks of medication (Clonidine (up to 0.1-0.5 mg daily) or Placebo, randomly assigned) separated by a 2 week washout period. **Outcome measures:** Kinematic measures during body weight support gait, spasticity, adverse effects.	1. No group differences were presented or analyzed in this study. 2. Clonidine did not elicit locomotor activity in the paraplegic patients, but there were reductions in stretch reactions and clonus during assisted locomotion. 3. Side effects were experienced by 8 of 9 patients during dosage increases, although for most patients these symptoms were transient. Dryness of the eyes and mouth were the most common, though other participants experienced lethargy, mild hypotension and constipation.
Duffel et al. 2015 USA RCT PEDro=4 Level 2 N= 83	**Population**: 29 individuals in control group- 9 males and 10 females; mean age= 47.8 ± 13.1y; years post injury= 8.1 ± 8.1y; 27 individuals in lokomat group- 19 males and 8 females; mean age= 46.6 ± 12.6y; years post injury= 9.3 ± 8.9y; 27 individuals in tizanidine group- 19 males and 8 females; mean age= 47.4 ± 11.6y years post injury= 10.9 ± 10.8y; motor incomplete SCI, AIS C or D **Treatment**: Participants were assigned to 3 groups: no intervention, Lokomat, or tizanidine. For the Lok group, locomotor training was provided using a robot-assisted locomotor training device. This device provides bodyweight- supported gait assistance. For the Tiz group, 0.03 mg/kg of tizanidine was administered 4 times a day for 4 weeks. **Outcome Measures:** Timed up and go (TUG), 10MWT, 6MWT, MAS	1. There was no difference between interventions, though overall walking speed and endurance did improve. 2. Only a small number of participants achieved the MID. Both MID and GMM-RCR analyses revealed that tizanidine improved endurance in high-functioning participants. 3. GMMRCR classification also showed that speed and mobility improved after locomotor training.
Remy-Neris et al. 1999 France	**Population:** 9 males, 2 females; ages 25-66 yrs, mean age 40 years.	1. No significance testing was conducted in this study. 2. Three participants improved their gait velocity after clonidine administration;

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
Prospective study Level 2 N = 11	**Treatment**: Each patient received 3 doses of 15-90 µg clonidine and a placebo by lumbar puncture. Each injection separated by a minimum of 3 days. **Outcome measures:** Spatiotemporal gait data, Ashworth scores, soleus H-reflex, and polysynaptic flexion reflexes recorded before and every hour for 4-6 hours after injection.	one (S6) increased his stride amplitude; the two others decreased their cycle durations. 3. 3 of 8 ambulatory participants had greater maximum overground walking speed with clonidine. These participants were more severely impaired and had shorter times post-injury.
Wainberg et al. 1990 Canada Prospective controlled trial Level 2 N = 8	**Population:** 8 participants with spinal spastic paresis; 7 male, 1 female, 2 wheelchair-bound, 6 can walk with aids; age 23-56 years; C4-T11 lesion level; 1-15 yrs post-injury **Treatment:** 6 of the 8 participants were included in double-blind, placebo controlled, crossover design: Two periods of 3 weeks of medication (2-8 mg 3x daily Cyproheptadine or Placebo, randomly assigned) separated by a 1-week washout period. Four participants continued in an open label, long term trial (>6 months) **Outcome measures:** Temporal measures, EMG, joint angles, spasticity, comfortable walking speed. No statistical analysis.	1. No significant differences between groups were reported in this study. 2. Maximum comfortable walking speed increased in ambulatory participants, with a decrease in cycle duration and double support duration. 3. Two patients that required body weight support during placebo could walk with full weight bearing during cyproheptadine therapy. Muscle coordination improved, and clonus was reduced.
Leech et al. 2014 USA Randomized Cross Over Design Level 2 N= 10	**Population**: 10 individuals; level of injury ranging from C2 to C7; months post injury= 12 – 301 months; **Treatment**: Participants were involved in a double-blinded, randomized, cross-over design to assess the effects of acute pharmacological manipulation of 5HT transmission on various measures of locomotor performance. The agents used were overencapsulated, orally administered doses of a selective serotonin reuptake inhibitor (SSRI): 10 mg of escitalopramoxalate and a 5HT antagonist: 8 mg of cyproheptadin. Participants participated in 2 days of testing separated by at least 1week. Before initial locomotor testing, a licensed physical therapist assessed standardized measures of strength, spastic motor activity, and walking ability. **Outcome Measures:** AIS Lower Extremity Motor Scores, Spinal Cord Assessment Tool for Spastic Reflexes, Modified Ashworth Scale, The Walking Index for Spinal Cord Injury II, EMG, O2 consumption	1. Neither medication led to improvements in locomotion, with a significant decrease in peak overground gait speed observed after 5HT antagonists. 2. Additionally, 5-HT medications had differential effects on EMG activity, with 5HT antagonists decreasing extensor activity and SSRIs increasing flexor activity
Norman et al. 1998 Canada Pre-post Level 4	**Population:** 12 males recruited, 7 completed evaluations; age 19-35 yrs; participants had diagnosis of AIS C-D; C4-T12 lesion level; 1.1-5.3 yrs post-injury **Treatment**: 3 different oral tablets in order of convenience: Clonidine (≤0.25 mg/day) or	1. No significance testing was completed in this study. 2. 7/12 participants had evaluations of all 3 drugs; adverse effects for 4/5 participants prevented completion of all conditions. The greatest effects in more severely disabled participants.

Author Year; Country Score Research Design Sample Size	Methods	Outcomes
N (enrolled) = 12 N (completed) =7	Cyproheptadine (≤24 mg/day) or Baclofen (≤80mg/day): each drug trial had incremental increase to maximum dose and stable dosing over 3 weeks followed by incremental decrease from maximum dose and washout over 2 weeks. **Outcome measures:** Surface EMG and kinematic gait analysis during treadmill walking. *Note: No statistical analysis was done.	3. Cyprohyeptadine resulted in decreased need for assistance, an increase in maximum treadmill speed and decreased clonus. 4. Clonidine resulted in an increase in maximal treadmill speed and a generally more upright posture. 5. Baclofen resulted in minor changes in walking. Maximal treadmill speed increases and other changes were often retained following washout of drugs.
Segal and Brunnemann 1998 USA Pre-post Level 4 N=9	**Population:** 9 males; age 28-60 yrs; participants had diagnosis of AIS C-D; C2-L4 lesion level; 4-28 yrs post-injury **Treatment:** 4-AP (single 10mg immediate-release capsule). Comparison of means at baseline and at intervals over 24-hour follow-up. **Outcome measures:** Ambulation parameters.	1. Significant improvements in gait velocity (increased by 36% from 24.1(16.5) m/min to 32.7 (22.9) m/min ($p \leq 0.04$) and in stride length (increased from 0.9 (0.3) meters to 1.0 (0.3) meters) ($p \leq 0.02$). 2. There was also no increase in cadence ($p=0.06$) and no decrease in gait cycle duration ($p=0.1$). 3. Gait changes began 6 hours after drug administered and persisted after the 24-hour follow-up.
Azouvi et al. 1996 France Pre-post Level 4 N = 18	**Population:** 18 patients with severe and disabling spinal spasticity, 12 of 18 participants with thoracic or low cervical lesion (Frankel A-D); age 21-59; C4-T11 lesion level; 0.5-27 years post-injury. **Treatment:** Implanted intrathecal baclofen pump. 17 patients had an electronically driven programmable pump filled with 18 cc of 500 or 2000 ug/cc baclofen delivered by continuous infusion or by intermittent bolus. One patient had a manually operated pump delivering a bolus of 50 ug. Follow up assessment was 6-72 months after implantation. **Outcome Measures:** Ashworth scale, spasm frequency scores, FIM. No statistical analysis on FIM walking score.	1. Average motor FIM score for the 18 patients was 39.9 _+ 18.1 before treatment, 58.5 _+ 28.7 at 6 months (Wilcoxon $Z = -3.62$, $p < .001$) 2. In 5 patients, walking ability improved (average initial FIM walking score: 3.6 ± .87, 6-month score: 5.8 ± .2), and 2 of these patients acquired the ability to climb stairs. 3. Severe side effects were observed in 2 patients and one patient's treatment interrupted after 9 months due to severe side effects.

Discussion

The interactions of these pharmacological interventions are complex and appear to have limited effects on walking ability in people with SCI. Multiple RCTs and some prospective and pre-post studies using clonidine (oral or intrathecal), cyproheptadine and baclofen demonstrate some improvements in various aspects of gait (i.e., walking speed, posture, spasticity), but no significant improvements to functional changes in walking. Only one pre-post study found significant improvements in gait velocity and stride length (Segal and Brunneman, 1998). Norman et al. (1998) found the greatest improvements in more severely disabled participants and the effects were generally retained following washout of clonidine. Bradycardia and hypotension, common side-effects of oral clonidine can be ameliorated with intrathecal injection of clonidine (150-450µg) (Filos et al.,

1994). The combined effect of different drugs has not been well explored. One very small study (not tabled due to its small sample size, Fung et al., 1990) showed that a combination of clonidine, cyproheptadine and treadmill training improved SCI locomotion in its 2 participants.

Conflicting evidence exists on the use of GM-1 ganglioside for neurologic recovery for walking in SCI. A large scale multicenter RCT (n=760) (Geisler et al., 2001) suggested that although GM-1 treatment may have accelerated initial SCI recovery (at 8 weeks), it did not improve the final extent of recovery (26 weeks). However, walking ability was not assessed.

Immediate release, 4-AP capsules have been shown to have no benefit to ambulation as indicated by 2 RCTs (van der Bruggen et al. (2001), n=20; DeForge et al. (2004), n=15). However, the study of van der Bruggen et al. (2001) was not directed solely at exploring the effects on walking and therefore the heterogenous nature of the participant groups may have confounded the ambulation results. Furthermore, differences in intervention (i.e. up-titration to 15-45mg/day over 4 weeks in van der Bruggen et al. (2001) vs. up to 10mg 4X/day for 2 weeks in DeForge et al, (2004)) and the lack of consistent clinically relevant outcome measures complicates the interpretation of the available evidence.

Two of the studies noted above used a combination of pharmacological and physical therapy gait training interventions. One small RCT (Walker & Harris, 1993) (N=9) provided some evidence that a combination of physical therapy (including gait training) and GM-1 ganglioside improved motor scores, walking distance, and walking speed in chronic SCI participants compared to physical therapy plus placebo (though Klose and Calancie (1994) posted a critique and re-calculated their results with different conclusions). Other results from the pre-test/post-test study conducted by Fung et al. (1990) provide level 5 evidence that clonidine and cyproheptadine in conjunction with BWSTT may be effective in enabling nonambulatory incomplete SCI patients to achieve overground ambulation with assistive devices.

A more recent study examined the effects of combining L-Dopa (dopamine precursor) with gait retraining in a group of individuals with acute/sub-acute incomplete SCI (Maric et al., 2008). Unlike the promising effects of L-Dopa on motor recovery following stroke (Scheidtmann et al., 2001), there was no added benefit in this SCI group. Although spinal neural circuits can certainly undergo plastic changes, the results of this study suggest that dopaminergic neurons may not have been sufficiently stimulated by the dosage used here, or that they may not contribute to motor recovery associated with gait retraining.

There is limited evidence that oral Baclofen may improve walking after SCI from two Level 5 pre-post studies that examined the effects of Baclofen on gait (total N = 21, 0.5-27 years post-injury (Azouvi et al., 1996; Norman et al., 1998). Avouzi et al. (1996) showed increases in the Functional Independence Measure (FIM™) walking scores in 5 of 18 patients, and 2 people acquired the ability to climb stairs following Baclofen administration. Participants in the Norman et al. (1998) study only showed minor changes in walking when using this drug.

Conclusion

There are nine Level 1 and 2 studies (DeForge et al. 2004; Duffell et al. 2015 (2); Leech et al. 2014; van der Bruggen 2001; Grijalva 2010; Maric 2008 ; Stewart et al. 1991; Wainberg et al. 1990) that found no significant differences of the effects of medication on walking ability.

There is level 1 evidence (Walker & Harris, 1993), limited by a small sample size, that GM-1 ganglioside combined with physical therapy improves walking ability in chronic incomplete SCI patients (though Klose and Calancie (1994) posted a critique and re-calculated their results with different conclusions).

There are two level 4 studies (Azouvi et al. 1996; Segal and Brunnemann 1998) that found significant differences in aspects of gait after baclofen administration.

There is limited evidence for the benefits of combining the use of certain pharmacological agents with gait training on ambulation in individuals with SCI.

10.0 Emerging experimental approaches

Greater understanding of the mechanisms underlying locomotor pattern generation, neuroplasticity, and motor recovery naturally leads to the development of new experimental approaches for improving locomotor function following spinal cord injury. In this section, we highlight these innovative emerging experimental approaches.

10.1 Conditioning Reflex Protocols

Traditional tenets about the hard-wired nervous system have long been dispelled with mounting evidence for activity-dependent plasticity throughout the CNS. Fascinating results from animal, and more recently, human studies have shown that even the "simplest" spinal cord reflex, the stretch reflex pathway or its electrical analog, the H-reflex, can be altered to increase or decrease in size through operant conditioning (Wolpaw, 2010). In animals, a reward is provided whenever the H-reflex amplitude is above or below a threshold value. Through modulation of descending influence, the animal can gradually learn to maintain its H-reflex amplitude at a certain level. Humans can also learn to increase or decrease the size of the soleus H-reflex (Thompson et al., 2009). Some gait impairments following SCI could be associated with hyperreflexia and abnormal reflex responses in the ankle plantarflexors (Dietz & Sinkjaer, 2007). The possibility that H-reflex amplitude could be down-conditioned raises the compelling question of whether such protocols may benefit individuals with SCI who present with spastic gait disorder.

This idea was recently tested in a group of 13 individual with chronic (>8 months) motor-incomplete SCI who all were ambulatory and presented with spasticity (e.g. ≥1 on Modified Ashworth Scale) and weak ankle dorsiflexion (Thompson et al., 2013). Participants were randomly assigned at a 2:1 ratio to the down-conditioning (DC) group (n=9) or the unconditioned (UC) group (n=4). Each participant completed 6 baseline sessions followed by 30 sessions (3 sessions/week) of control (UC group) or conditioning (DC group). Visual feedback was provided to the DC group to inform them of whether they were successful in reducing their H-reflex amplitude to within the target range. In the UC group, each session involved H-reflex recordings without any visual feedback or instructions about H-reflex amplitude. Note that in this study, no locomotor training was provided; training sessions consisted of only the H-reflex down-conditioning (or control protocol).

Table 19: Study Using Conditioning Reflex Protocols

Author Year; Country Score Research Design Sample Size	Methods	Outcome
Thompson et al. 2013; USA PEDro=7 RCT Level 1 N=13	**Population:** 13 ambulatory participants with SCI (9M 4F); mean(SD) age: 48.4 (13.9) yrs; DOI ranging from 8 months to 50 yrs. **Treatment:** Participants randomly assigned at a 2:1 ratio to the down-	1. Success (average conditioned H-reflexes significantly less for session 25-30 than baseline) rate for participants with SCI = 67%, which is slightly, but not significantly, less than that for neurologically normal participants (89%).

Author Year; Country Score Research Design Sample Size	Methods	Outcome
	conditioning (DC) group (6M 3F) or the unconditioned (UC) group (3M 1F). Each participant completed 6 baseline sessions and 30 control (UC participants) or conditioning (DC participants) sessions at a rate of 3 sessions/week. Electrical stimulation of the soleus H-reflex was elicited by a 1ms square pulse stimulus. **Outcome Measures:** Locomotion (participant asked to walk 10 m at comfortable speed 3 times; average walking time determined); locomotor symmetry; EMG activity; H-reflex modulation.	2. Conditioned H-reflex for UC group as a whole showed a slight by significant increase (to (mean[SE]) 116(7)%). Down-conditioning was achieved in 6 of 9 participants. 3. Over the 30 conditioning or control sessions, the participants' 10m walking speeds increased by 0-123%. The increase was significant in the 6 DC participants in whom the H-reflex decreased. For the 7 participants in whom H-reflex did not decrease, walking speed increased less and not significantly. 4. For DC participants with decreased H-reflex (n=6), locomotion became faster and more symmetrical and the modulation of EMG activity across the step cycle increased bilaterally.

Discussion

Among the 9 participants in the DC group, 6 were able to successfully down-condition their H-reflex amplitude by the last 5 training sessions. There was no reduction in H-reflex amplitude in the UC group. Across the 6 participants who could successful down-condition their soleus H-reflex amplitude, there was a significant increase in their 10MWT speeds of 59% (range: 0-123%) along with a significant improvement in gait symmetry. For the 7 participants in whom H-reflex did not decrease, walking speed increased less and not significantly.

Conditioning reflex protocols have been published many years ago for the upper extremity in SCI (Segal & Wolf, 1994) to reduce spasticity and are an important neuroscience observation. However, they have not been accepted into practice likely due to the variable results and laborious number of sessions to get a small effect. This one small RCT for the lower extremity shows similar findings as the upper extremity – that soleus spinal reflexes can be down-conditioned in about 2/3 of the participants, although a few of these participants did demonstrate large improvements in gait speed. The success rate of down-conditioning in the SCI participants was comparable to previous studies in able-bodied participants. Unfortunately, absolute values were not reported here, making the clinical significance of these results difficult to ascertain. Furthermore, the complexity of this approach may make it inaccessible for most clinicians. Nevertheless, these results are very intriguing and point towards another potential approach of directly manipulating spinal cord plasticity to enhance functional recovery.

Conclusion

There is level 1b evidence from one RCT (Thompson et al., 2013) that down-conditioning reflex protocols of the soleus could facilitate gait outcomes.

Down-conditioning (DC) reflex protocols of the soleus could facilitate gait outcomes.

10.3 Repetitive Transcranial Magnetic Stimulation

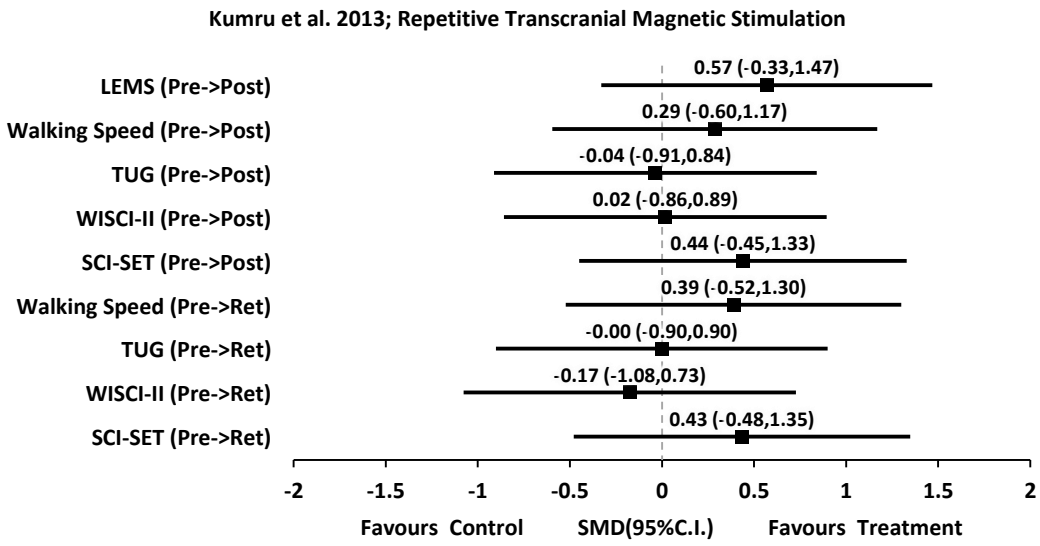
Repetitive transcranial magnetic stimulation (rTMS) has been widely explored as a tool for treating a variety of disorders, including depression (Martin et al., 2003; Couturier et al., 2005), pain (Lima & Fregni, 2008), and motor disorders following Parkinson's disease (Elahi et al., 2009) and stroke (Corti et al., 2011). Experimental studies in humans have shown that low frequency rTMS (<1 Hz) can reduce the excitability of the motor cortex whereas high frequency rTMS (>1 Hz) causes an increase

in motor cortical excitability (Kobayashi & Pascual-Leone, 2003). Given the ability for rTMS to modulate cortical excitability, there has been much interest in exploring its potential to facilitate supraspinal connectivity or restore the balance of interhemispheric inhibition (in stroke) as a means to promote motor recovery and function.

The recovery of functional ambulation following motor-incomplete SCI has been shown to be associated with enhanced excitability of motor cortical areas (Winchester et al., 2005) and corticospinal connectivity to the lower limb (Thomas & Gorassini, 2005). Recently, Kumru et al. (2013) explored the potential efficacy of combining rTMS with locomotor training on gait outcomes in people with sub-acute (<12 months) motor-incomplete SCI (ASIA D). Seventeen participants were randomized to either a control group with sham stimulation, or the rTMS group. Stimulation (sham or rTMS) was delivered while participants lay supine, 5 times/week for 3 weeks. All participants also received daily overground gait training for 1 hour for 3 weeks. The gait training session was performed within 30 minutes of the stimulation session. There was an additional 2 weeks of overground gait training only as a follow-up.

Table 20: Repetitive Transcranial Magnetic Stimulation

Author Year; Country Score Research Design Sample Size	**Methods**	**Outcome**
Kumru et al. 2013; Spain PEDro=8 Randomized sham-controlled trial Level 1 N=17	**Population:** 17 participants with SCI (13M, 4F); 19-60 yrs old; all AIS D. **Treatment:** Patients were randomized to 2 groups: an active repetitive transcranial magnetic stimulation (rTMS) group and a sham group. 3 participants who began in the sham group were crossed over to the active rTMS group after a washout period of more than 3 weeks. **Outcome Measures:** Lower Extremity Motor Score (LEMS); 10 Meter Walk Test (10MWT); Timed Up and Go (TUG); Walking Index for Spinal Cord Injury (WISCI); Modified Ashworth Scale (MAS); Spinal Cord Injury Spasticity Evaluation Tool (SCI-SET).	1. A significant improvement was observed after the last rTMS session in the active group for LEMS, walking speed, and spasticity. Improvement in walking speed was maintained during the follow-up period. 2. Sham stimulation did not induce any improvement in LEMS, gait assessment, and spasticity after the last session and neither during follow up.
	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%C.I.) as calculated from pre- to post-intervention data and pre-intervention to retention/follow-up data	

Author Year; Country Score Research Design Sample Size	Methods	Outcome
		
Benito et al. 2012 USA Cohort Study Level 2 N= 17	**Population**: 17 individuals- 13 males and 4 females; incomplete SCi; all AIS D; level of injury: C4 – T12; age range= 18 – 60y **Treatment**: Patients were randomized to active rTMS or sham stimulation. Three patients from the initial group of 10 randomized to sham stimulation entered the active rTMS group after a 3-week washout period. Therefore, a total of 10 patients completed each study condition. Both groups were homogeneous for age, gender, time since injury, etiology, and ASIA scale. Active rTMS consisted of 15 days of daily sessions of 20 trains of 40 pulses at 20 Hz and an intensity of 90% of resting motor threshold. rTMS was applied with a double cone coil to the leg motor area. **Outcome Measures:** Lower extremities motor score (LEMS), Modified Ashworth Scale (MAS), Walking Index for SCI (WISCI II), 10 MWT, Step length and cadence (assessed during 10 MWT), Timed Up and Go (TUG)	1. There was a significant improvement in LEMS in the active group but not in the sham group. 2. The active group also showed significant improvements in the MAS, 10MWT, cadence, step length, and TUG, and these improvements were maintained 2 weeks later. 3. Following sham stimulation, significant improvement was found only for step length and TUG.
Guzman-Lopez et al. 2014 UK Pre-Post Level 4 N= 12	**Population**: 12 healthy individuals- 6 males and 6 females; mean age= 34y; **Treatment**: The experiment included four different conditions in two positions: We examined participants lying supine at rest, which was considered the control condition (rest), and while maintaining a steady ankle tonic plantar flexion (pf), dorsiflexion (df) or standing still (ss) of about 30 % of their maximum voluntary contraction (MVC). **Outcome Measures:** H-Reflex, EMG	1. During pf, there was an increase in the facilitation of the H reflex at ISIs 0–20 ms. 2. During ss, there was inhibition at ISIs 40–60 ms.

Discussion

Few studies have investigated the effects of rTMS on gait-related outcomes (Kumru et al., 2013; Benito et al., 2012). The authors report significant improvements in LEMS and 10MWT in the rTMS group, but not the sham stimulation group.

Conclusion

There is level 1b evidence from one RCT (Kumru et al., 2013) that rTMS combined with overground locomotor training may not afford further benefits over overground locomotor training alone (with sham stimulation).

rTMS combined with overground locomotor training may not afford further benefits over overground locomotor training alone.

10.4 Cellular Transplantation Therapies to Augment Strength and Walking Function

Experimental animal research utilizing stems cells and other cells or tissue to treat severe spinal cord injury is now being translated to human clinical studies. Recent reports have explored the feasibility of using cellular transplantation therapies (autologous bone marrow MSCs or OMA) to help increase function and reduce impairments in people with chronic SCI, but further studies are needed to determine safety, dosage, and timing before these treatments should be offered to patients.

Table 21: Cellular Transplantation Therapies to Augment Strength and Walking Function

Author Year; Country Score Research Design ample Size	Methods	Outcomes
Kishk et al. 2010 Egypt Case Control Level 3 N=64	**Population:** Treated Group – 36 males, 7 females; mean (SD) age 31.7(10.4); 12 complete, 31 incomplete SCI Control Group – 15 males, 5 females; mean (SD) age 33.8(11.8); 3 complete, 17 incomplete SCI **Treatment:** Monthly intrathecal injection of autologous bone marrow MSCs for 6 months, all participants received 3 rehabilitation therapies per week. **Outcome Measures:** Trunk muscle assessment, MASS, Functional Ambulation Categories, AIS sensorimotor, motor and sensory scores, lower-limb somatosensory evoked potentials (SSEPS)	1. A significantly greater proportion of the treatment group showed improved motor scores, but this is not clinically relevant as it was only by 1-2 points in 18/44 participants (48.7(9.1) to 49.3(9.2)). 2. There were no significant differences between-groups for trunk support, Functional Ambulatory Categories, sensory exam (pin prick), scores, tone, bladder control questionnaire, bowel control, and AIS changes. 3. 1 patient dropped out due to adverse reactions (acute disseminated encephalomyelitis)
Lima et al. 2010 Portugal Pre-post Level 4 N=20	**Population:** 17 males, 3 females; mean (SD) age 30.2(5.7); 15 patients AIS grade A, 5 patients AIS grad B; all > 1 YPI **Treatment:** OMA into the area of the SCI a mean of 49 months after injury, with pre-operative rehabilitation (mean (SD) 31.8(6.8) hours/week for 34.7(30) weeks) and post-operative rehabilitation (mean (SD) 32.7(5.2) hours/week for 92(37.6) weeks) with BIONT or robotic BWSTT.	1. Estimated mean change in all ASIA neurological measures (pink prick, light touch, motor arms, motor legs) was statistically significant. ASIA motor legs score improved from 0 to 4.95(7.1) post intervention. 2. 11 patients improved their AIS grades (6 by 2 grades), and 1 patient's score deteriorated and suffered ARs (aseptic meningitis, spinal cord edema) 3. 9 of the patients with an AIS score of 0 at baseline improved from 4 to 22 at last evaluation.

Author Year; Country Score Research Design ample Size	Methods	Outcomes
	Outcome Measures: AIS score and AIS grade, FIM, WISCI	4. Of the 13 patients assessed for functional studies, all had improvements on FIM scores (mean (SD) 71(23) to 85(28)) and WISCI scores (0.2(0.4) to 7.4(2.6)). 5. Patients at facilities focusing on BIONT showed better motor recovery compared with those at facilities focusing on BWSTT. 6. Voluntary motor potentials of the lower limb muscles were found in 11/20 patients.

Discussion

One case control study investigated the effects of monthly intrathecal injections of MSCs in combination with 6 months of rehabilitation therapies on muscle strength and function (Kishk et al., 2010). There were no differences between groups for functional ambulation, but motor scores were slightly (but significantly) greater in the treatment group. Several patients experienced side effects, including increased spasticity, neuropathic pain, excessive sweating and transient hypertension. One patient withdrew from the study for severe adverse reactions to the treatment. Further studies are needed to establish safety, and controlled studies are needed to determine timing, dose and duration of this intervention.

In a pre-post study, OMA were transplanted into the site of injury in persons with chronic complete or motor-complete SCI (Lima et al., 2010). Patients then underwent locomotor training (either robotic assisted treadmill training or assisted overground walking training). Functional Independence Measure and Walking Index for Spinal Cord Injury scores improved in 13 participants tested, and this improvement correlated with increases in leg strength. Five of twenty patients experienced adverse events, where one patient developed aseptic meningitis and another developed irritable bowel syndrome. Other adverse events were easily treated or resolved on their own. Randomized controlled trials are necessary to further show efficacy of this treatment.

10.5 Case Report: Nutrient Supplement to Augment Walking Distance

The potential benefits of a nutrient supplement ingested after fatiguing ambulation on gait parameters over a 2-week period were described by Nash et al. (2007). Participants were randomized to receive either a blended drink containing whey protein and carbohydrate or a placebo control consisting of soy protein in the first 2 weeks of training. Following a 2-week washout period, participants returned to receive the other supplement. After 2-weeks of ingesting the whey protein and carbohydrate supplement post-exercise, participants were able to walk longer and farther than if they ingested the placebo control. Whey protein and carbohydrate supplements are commonly used to facilitate recovery following intense exercise in the able-bodied population. This is the first report to demonstrate the potential benefits of such nutrient supplementation in the SCI population.

Table 22: Nutrient Supplement to Augment Walking Distance

Author Year; Country Score Research Design ample Size	Methods	Outcomes
Nash et al. 2007 USA PEDro=6 RCT w/crossover Level 1 N=3	**Population:** 3 females and males; age 34-43 yrs; all participants had an incomplete SCI; C5-T4 lesion level; mean 11.3 yrs post-injury **Treatment:** Blended drink containing 48 g of vanilla-flavored whey and 1g/kg of body weight maltodextrin. **Outcome Measures:** Distance walked	1. Ambulation time to fatigue was 17.8% longer (32.0 min vs 27.1 min) and distance walked to fatigue was 37.9% longer (470m vs 341m) with the whey and maltodextrin supplement than with the placebo soy drink.

Gap: Lower limb edema after SCI

Source of evidence: http://sci.washington.edu/info/newsletters/articles/15_spr_edema.asp

While there are no studies on lower limb edema after SCI, there are recommendations based on general leg edema management from cardiovascular and diabetic populations, as well as clinical consensus from SCI practitioners.

Recognizing lower limb edema

Lower limb edema is common after SCI. Lower limb edema may require treatment if there is substantial edema, edema with pitting, edema which impacts shoe fitting or cellulitis (infection of the skin due to pooling), edema can even affect bladder management.

Management

Elevation

Elevating the feet above the hip (heart) can help counter the effects of gravity and drain the fluid back to the heart. This can be done at night or intermittently through the day. Studies in non-SCI populations have shown that elevating at least 30 degrees for 15 minutes can reduce some edema.

Compression stockings

Compression stockings (typically 20-30 mm Hg) can be prescribed by a physician and purchased at standard medical supply stores, lighter compression 15-20 mm Hg can be purchased without a prescription. Stockings can be difficult to put on, especially for those with less hand function and a number of assistive devices can help with donning. Custom stockings may be required for severe cases of swelling or wrapping with therapeutic compression bandages until transition to standard compression stockings. It is important to ensure that the stockings are applied without wrinkles and to check skin daily after stocking use. Stocking to be applied in the morning and removed when going to bed.

Medication

If edema cannot be controlled with conservative treatments, diuretic medication prescribed from a physician may be necessary to reduce body fluid and then transition the patient to more conservative methods. Diuretics should not be used for routine use, as they have side effects including lowering blood pressure and they can affect bladder management.

Gap: Footcare after SCI

Source of evidence:

Although ingrown toenails are cited in the Autonomic Dysreflexia literature as an aggravating stimulus there are no SCI specific studies on more global footcare and its management after SCI. There are recommendations based however on footcare for individuals with diabetes drafted by the Canadian Association of Wound Care (CAWC - http://cawc.net/en/index.php/public/feet/) as well clinical consensus from SCI practitioners.

Recognizing footcare issues:

Individuals with SCI have numerous issues that can arise to their feet that can lead to significant secondary complications if not addressed and prevented. These include: nail care and ingrown toenails, wounds, fungal infections, dermatitis and burns, mechanical trauma

Management

Daily skin checks to ensure no open areas, no deep tissue trauma, no fungal or dermatitis evident

Edema management including compression socks if indicated. Ensure proper fitting shoes including purchasing them at time of day when edema is at its greatest

Increase skin checks to feet when shoes are new (every 2 hours)

May need to purchase shoes 1 size larger for easier application – consider Velcro to fasten

Closed toed shoes best to prevent trauma

Wear shoes in and outside the house (ambulatory or not)

Inspect shoes for abnormalities and shake out before applying

Consultation of a podiatrist or foot care nurse to manage nails if unable to do independently

Change socks daily

Do not smoke as this affects circulation

Dry feet well and between the toes

Moisturize dry skin as needed

11.0 References

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Abbreviations

4-AP	4-Aminopyridine
6MWT	6 Minute Walk Test
10MWT	10 Meter Walk Test
ABC	Activity-specific Balance Confidence Scale
AFO	Ankle Foot Orthosis
AMS	ASIA Motor Score
ARGO	Advanced Reciprocating Gait Orthosis
BBS	Berg Balance Scale
BIONT	Brain-Initiated Overground Nonrobotic/nonweight Supported Training

BWS	Body Weight Support
BWSTT	Body Weight Supported Treadmill Training
CHART	Craig Handicap and Assessment Reporting Technique
CK	Creatine Kinase
CWT	Community Walk Test
ES	Electrical Stimulation
FES	Functional Electrical Stimulation
FIM-L	Functional Independence Measure-Locomotor
HKAFO	Hip Knee Ankle Foot Orthosis
IADL	Instrumental Activities of Daily Living
IRGO	Isocentric Reciprocal Gait Orthosis
KAFO	Knee Ankle Foot Orthosis
LCE	Leg Cycle Ergometry
LEMMT	Lower Extremity Manual Muscle Test
LEMS	Lower Extremity Motor Score
MASS	Modified Ashworth Spasticity Scale
mEFAP	Modified Emory Functional Ambulation Profile
MFES	Modified Falls Efficacy Scale
MSCs	Mesenchymal Stem Cells
NMES	Neuromuscular Electrical Stimulation
OMA	Olfactory Mucosal Autografts
PCI	Physiological Cost Index
PES	Patterned Electrical Stimulation
PGO	Powered Gait Orthosis
PRT	Progressive Resistance Training
PSA	Peak Stance Average
RET	Resistance Exercise Training
RGO	Reciprocating Gait Orthosis
RNL	Reintegration to Normal Living Index
rTMS	repetitive Transcranial Magnetic Stimulation
SCIM	Spinal Cord Independence Measure
SEPs	Somatosensory Evoked Potentials
SWLS	Satisfaction With Life Scale
TUG	Timed Up and Go test
vBFB	visual Biofeedback task-specific Balance Training
vGRF	visual Ground Reaction Force
WAQ	Walking Ability Questionnaire
WBCO	Weight Bearing Control Orthosis
WBV	Whole-Body Vibration
WISCI	Walking Index for Spinal Cord Injury
WO	Walkabout Orthosis
WPAL	Wearable Power-Assist Locomotor