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Professional

Fatigue Following Spinal Cord Injury

Carlos L. Cano Herrera, PhD
Gita Manhas, MD (Student)
Bob Hoogenes, MD
Matthew Querée, MAppPsych
Elsa Sun, BKin (Student)
Frances Fan, BKin (Student)
E. Ali Bateman, MD
Eldon Loh, MD
Bill Miller, PhD
Ben Mortenson, PhD
Andrea Townson, MD
Janice J. Eng, PhD

Our Partners:

Cano-Herrera CL, Manhas G, Hoogenes B, Querée M, Sun E, Fan F, Bateman EA, Loh E, Miller WC, Mortenson WB, Townson AF, Eng JJ (2024). *Fatigue Following Spinal Cord Injury*. In Eng JJ, Teasell RW, Miller WC, Townson AF, Hsieh JTC, Noonan VK, Loh E, Sproule S, Allison D, Unger J, Bateman EA, Ryan S, Querée M (Eds). Spinal Cord Injury Research Evidence.
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Key Points

- Fatigue has been defined as feelings of tiredness, lack of energy, low motivation, difficulty in concentrating, or an increased perception of effort disproportionate to attempted activities (Anton et al. 2017; Hammell et al. 2009).
- Despite fatigue affecting more than a half of people living with SCI (Fawkes-Kirby et al. 2008), only seven RCTs and ten lower-level quality studies have evaluated the effectiveness of interventions to address fatigue in this population.

Effect of Pharmacological Management of Fatigue

- According to one RCT including only four patients with SCI (Wade et al. 2003), cannabis medicinal extracts (CME) should not be recommended because of the lack of effectiveness in improving fatigue for people with SCI.
- Fatigue did not significantly differ between intrathecal and oral delivery methods of baclofen treatment in people (33% with SCI) after using the medication for one year (McCormick et al. 2016).
- Further research is needed to address whether baclofen and CME provide positive results in fatigue in people with SCI and in the case of baclofen, which delivery method is more effective, accounting also for adverse effects.
- Medical management of fatigue in people with SCI is more likely to include a review of medications that might be causing fatigue.

Effect of Exercise on Fatigue

- Exercise-based interventions may have a positive effect on fatigue in people with chronic SCI; however, there is no consensus on which type of exercise, or the dosage that will be more effective in reducing fatigue in people with SCI.
- Yoga or Tai Chi programs do not seem to provide any effects on fatigue in people with SCI.

Effect of Non-exercise Interventions on Fatigue

- There is conflicting evidence that non-exercise-based interventions, especially massage therapy, could improve fatigue outcomes in people with SCI.

Effect of Self-Management Interventions on Fatigue

- Fatigue self-management and behavioral interventions promoting an active lifestyle does not provide a significant improvement in fatigue in people with SCI. More research is needed.

Table of Contents

1 Executive Summary

1.1 Fatigue Definitions and Consequences

Fatigue is generally defined as feelings of tiredness, lack of energy, low motivation, difficulty in concentrating, or an increased perception of effort disproportionate to attempted activities (Anton et al. 2017; Hammell et al. 2009). It is important to distinguish between peripheral muscle fatigue, that is, fatigue that comes after exercise, and global fatigue (Barat et al. 2006). There is comprehensive research on the pathophysiology of peripheral muscle fatigue (Ibitoye et al. 2016), as well as interventions to reduce muscle tiredness associated with doing specific activities (Hoogenes et al. 2021). However, global fatigue remains an understudied issue in SCI and is often undermentioned and/or underestimated during medical interviews (Anton et al. 2017; Fawkes-Kirby et al. 2008; Jensen et al. 2007). Thus, global fatigue is the focus of this module.

For people with SCI, living with fatigue can be overwhelming, causing a profound negative impact (Wijesuriya et al. 2012). In people with SCI, fatigue has been negatively associated with social integration and productive activity (Wijesuriya et al. 2012), social participation (Kuzu et al. 2022), quality of life (Christofi et al. 2023; Craig et al. 2008), psychological functioning (van Diemen et al. 2016), participation in life activities, mobility, and wheelchair use (Smith et al. 2016; Saunders et al. 2013; McColl et al. 2003). Moreover, fatigue may contribute to functional decline and loss of independence in people with SCI living in the community and in those aging with SCI (Alschuler et al. 2013; Moher et al. 2009).

1.2 Fatigue Measurement

Assessment of fatigue varies greatly given its multidimensional nature (Onate-Figuérez et al. 2023). Measurement of fatigue could be performed via objective methods, such as performing a task repeatedly and measuring the decline in responses, or via subjective measures, like self-reports where a participant describes or rates their fatigue (Onate-Figuérez et al. 2023).

All the studies included in the present module have assessed fatigue through different self-reporting methods. The most common fatigue self-report used was the Fatigue Severity Scale, an outcome measure validated in people with SCI and recently for use in people with stroke (Anton et al. 2008; English et al. 2023). These self-reports are useful to evaluate perceived fatigue intensity or person's view on how much fatigue affects their lives (Onate-Figuérez et al. 2023).

1.3 Fatigue Management

Despite fatigue affecting more than a half of people living with SCI (Fawkes-Kirby et al. 2008), we found only seven RCTs and ten lower-level studies addressing fatigue in this population.

According to the current body of evidence for treating fatigue in people with SCI, exercise-based interventions have stronger quality (and quantity) of evidence. However, there is no consensus on the type or dosage of exercise that will be more effective in reducing fatigue in people with SCI.

Other interventions tested (e.g., medications, massage therapy, self-management, promoting an active lifestyle, and the use of a Segway or exoskeleton) seem not to produce significant effects on fatigue in people with SCI. However, we did find one pre-post study that found significantly large effects on fatigue when pairing manual wheelchair users/people with SCI with a service dog for 9 months.

It should be noted fatigue was not the primary outcome measure for the majority of included studies. Most intervention research we found was attempting to improve pain, spasticity, or physical activity levels in people with SCI and fatigue was a secondary measure. Though many of these studies found positive effects in their primary outcomes that are noted here, our discussions in this module will be focused on fatigue.

1.4 Ideal Fatigue Treatment for People With SCI

Due to the limited literature on fatigue interventions and the multifactorial nature of global fatigue, it is difficult to recommend one ideal treatment protocol in people with SCI. However, some previous research has highlighted certain things that would be useful to address:

- Having a better understanding of which factors are most strongly associated with fatigue is key to designing the best treatments. In a meta-analysis, Onate-Figuérez et al. (2023) found direct associations between fatigue and nine factors (sorted by largest to smallest effect size): self-efficacy, anxiety, stress, depression, pain, participation, analgesic medication, assistive devices, physical activity, lesion level, incomplete SCI, and medication.
- It has been suggested that the management of fatigue in people with neurological disorders like SCI and multiple sclerosis requires a multidisciplinary team and approach (Smith et al. 2016; Hourihan 2015). Health professionals may treat different aspects of fatigue as follows:
    - A physiatrist or family doctor can conduct a thorough physical exam and medical history to determine potential causes of fatigue (e.g., pain, lack of sleep, or medications).
    - Physical therapists and other fitness professionals may work with people with SCI to prescribe exercise, though they should be aware of the person's fatigue status and adjust exercise levels accordingly with gradual increases (Rosenthal et al. 2008; Hourihan 2015; Heine et al. 2015).
    - Psychologists, counsellors, or other mental health therapists can address the stress, anxiety, and depression that has been linked to chronic fatigue. Previous research has suggested that an evidence-based mental health approaches, such as cognitive-behavioral therapy, or the prescription of selective serotonin reuptake inhibitors, such as fluoxetine, paroxetine, or sertraline, could be considered as part of any fatigue treatment in appropriate patients (Craig et al. 2013; Rosenthal et al. 2008; Onate-Figuérez et al. 2023). Researchers have also suggested that cognitive-behavioral therapy could be useful in helping to reduce the effects of chronic pain on depressive moods, and establishing more attributions of self-efficacy to increase feelings of control over one's body and health (Craig et al. 2012; Craig et al. 2013).

1.5 Gaps in the Literature

- Limited number of studies with fatigue as a primary or secondary outcome - perhaps due to its multifactorial nature, or other secondary conditions being perceived as more important, the number of studies focusing on fatigue is extremely low.
- Relationship between sleep factors and fatigue in SCI - none of the included RCTs asked about sleep quality or the presence of sleep disorders in participants.
- Relationship between medications and fatigue in SCI - none of the RCTs included established at baseline what medications participants were taking, despite the fact that multiple medications prescribed for people with SCI may cause fatigue (Lee et al. (2010).

2 Introduction

Spinal cord injury (SCI) is a lesion to the spinal cord that may cause severe neurological impairment and disability (Anton et al. 2017). Consequent sensory, motor, and autonomic dysfunction is also associated with many secondary health conditions, including fatigue, that can cause distressing symptoms and increased disability for people with SCI (Anton et al. 2017).

Fatigue commonly occurs in people with neurological disorders or diseases like fibromyalgia (Overman et al. 2016), Parkinson's disease (Barone et al. 2009), multiple sclerosis (Oliva Ramirez et al. 2021), neuromuscular disease (Lou et al. 2010), spina bifida (Lidal & Larsen 2002) or stroke (Cumming et al. 2016). In people with SCI, fatigue is one of the most common secondary conditions, experienced by approximately 30-78% of the population (Anton et al. 2017; Fawkes-Kirby et al. 2008; Nooijen et al. 2015; Lidal et al. 2013; Hong et al. 2023).

In studies including people with SCI, fatigue has been defined as feelings of tiredness, lack of energy, low motivation, difficulty in concentrating, or an increased perception of effort disproportionate to attempted activities (Anton et al. 2017; Hammell et al. 2009). Some definitions have proposed a distinction between peripheral muscle fatigue (i.e., being tired from exercise) and global fatigue (Barat et al. 2006). There is comprehensive research on the pathophysiology of peripheral muscle fatigue (Ibitoye et al. 2016), as well as interventions to reduce muscle tiredness associated with doing specific activities (Hoogenes et al. 2021). However, global fatigue remains an understudied issue in SCI and is often undermentioned and/or underestimated during medical interviews (Anton et al. 2017; Fawkes-Kirby et al. 2008; Jensen et al. 2007). Thus, global fatigue, is the focus of this module.

For people with SCI, living with fatigue can be overwhelming, causing a profound negative impact (Wijesuriya et al. 2012). In people with SCI, fatigue has been associated with poor social integration, less productive activity (Wijesuriya et al. 2012), less participation (Kuzu et al. 2022), lower quality of life (Christofi et al. 2023; Craig et al. 2008), and lower psychological functioning (van Diemen et al. 2016). Fatigue is also negatively associated with mobility and it may have negative effects on SCI rehabilitation (Smith et al. 2016; Saunders et al. 2013; McColl et al. 2003). Moreover, fatigue may contribute to functional decline and loss of independence in people with SCI living in the community and in those aging with SCI (Alschuler et al. 2013; Moher et al. 2009).

3 Fatigue Measurement

Fatigue is generally measured by objective methods, such as performing tasks repeatedly and measuring the decline in responses, or by subjective measures, like self-reports where a participant describes or rates their fatigue (Onate-Figuérez et al. 2023). The studies included in this systematic review measure fatigue using self-reports, with the Fatigue Severity Scale (FSS) being the most common measure. The FSS is a 9-item self-report questionnaire that evaluates the severity of fatigue and its impact on lifestyle and activities in three domains: physical, social, and cognitive effects of fatigue (Curtis et al. 2015; Hewlett et al. 2011). It has high validity and reliability (Cronbach's α=0.89, intraclass correlation coefficient, 0.84; 95% confidence interval [CI] 0.74-0.90) for evaluating fatigue in people with SCI (Anton et al. 2008). More information about the FSS is available on the SCIRE Professional webpage: Fatigue Severity Scale.

Other less commonly used measures included the Chalder Fatigue Scale (CFS), the Multi-Dimensional Fatigue Inventory (MFI-20), the Modified Fatigue Impact Scale (MFIS), the PROMIS Short Form v1.0 Fatigue 8a, and the Fatigue Assessment Scale (FAS). The CFS is a self-rated fatigue scale that provides an overall indicator of chronic fatigue, as well as domains of mental and physical fatigue (Chalder et al. 1993). The MFI-20 covers five dimensions: General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Motivation, and Reduced Activity (Hagelin et al. 2007; Smets et al. 1995). The MFIS is a 21-item shortened version of the 40-item Fatigue Impact scale that examines the perceived impact of fatigue in cognitive functioning, physical functioning and psychosocial functioning (Fisk et al. 1994; Shem et al. 2016; Wong et al. 2023). The PROMIS Short Form v1.0 Fatigue 8a evaluates fatigue based on its frequency, duration, and intensity, as well as its impact on physical, mental, and social activities (Cella et al. 2010; Wong et al. 2023). Lastly, the FAS is a 10-item scale evaluating symptoms of chronic fatigue which treats fatigue as a unidimensional construct and does not separate its measurement into different factors (Shahid et al. 2012).

Although different outcome measures for fatigue have been used in SCI research, the FSS is the only (and most used) outcome measure that has been validated in people with SCI. In addition, the 7-item version of the FSS has been recently recommended as a primary outcome measure in stroke research (English et al. 2023).

4 Pharmacological Management of Fatigue in SCI

Numerous classes of medications (for example, stimulants such as methylphenidate and modafinil, dopaminergic medications such as levodopa, and antidepressants, including selective serotonin reuptake inhibitors, and tricyclic antidepressants) have been studied in other populations with central nervous system disorders and fatigue, such as Parkinson's disease, stroke, or TBI (Levine & Greenwald 2009). However, we found no studies assessing the effects of these medications and fatigue in people with SCI.

It is possible that there are fewer studies on medications and fatigue in SCI because of the increased risks for undesirable side effects, including additional fatigue, difficulty sleeping, anxiety, and headaches (Asano & Finlayson 2014; Levine & Greenwald 2009). In one retrospective chart review, Lee et al. (2010) found that 52% of participants with SCI had clinical levels of fatigue deemed to have been caused by 41/147 medications that they were taking, often anti-spasticity or analgesic medications. Similarly, Fawkes-Kirby et al. (2008) found that people with SCI taking two or more prescriptions from these categories scored significantly worse on the FSS, indicating higher levels of fatigue. According to Fawkes-Kirby et al. (2008), among the medications that people with SCI commonly take, baclofen, benzodiazepines, opioids, tizanidine, gabapentin, amitriptyline, and nortriptyline may induce feelings of fatigue. In addition, people with SCI have commonly reported fatigue as a side-effect after cannabis use (Nabata et al. 2020); however, the therapeutic use of cannabis in SCI is an emerging area of research.

Currently, there are only two medications that have been studied in people with SCI for fatigue improvement purposes: cannabis medicinal extracts (CME) and baclofen.

4.1 Cannabis Medicinal Extracts

Among numerous cannabinoid compounds from plants belonging to the genus *Cannabis*, delta-9-tetrahydrocannabinol (THC) is known to have psychoactive effects while cannabidiol (CBD) is a non-psychoactive component that may have antioxidant and anti-inflammatory properties, as well as the ability to modulate the psychoactive effects of THC (Atakan 2012; Wade et al. 2003; Nabata et al. 2020).

More information about cannabis and SCI can be found in the SCIRE Cannabinoids module.

The use of cannabis medicinal extracts (CME) with SCI-related fatigue has not been widely researched yet. Only one RCT has investigated the use of CME through sublingual delivery and self-titration, its effect on neurological symptoms such as fatigue, and its potential side effects (Wade et al. 2003).

Table 1. Plant-Derived Cannabis Medicinal Extracts

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Wade et al. 2003 UK RCT cross-over Level 1 PEDro=8 N=24	**Objective:** To determine whether plant-derived cannabis medicinal extracts can alleviate neurogenic symptoms unresponsive to standard treatment, and to quantify adverse effects. **Population:** 24 participants with a neurological diagnosis (multiple sclerosis, n=18; SCI, n=4; brachial plexus damage, n=1; and limb amputation due to neurofibromatosis, n=1) 10M, 10F Mean age 48 years **Treatment:** Participants were assigned to each of the following groups for two weeks:	1. No statistically significant difference (p>0.05) between groups (NRS [SD]: placebo=5.0 [2.4], CBD=4.6 [2.4], THC=4.2 [2.2], CBD: THC=5.2 [2.5]).

	• Experimental group 1: Whole-plant extracts of delta-9-tetrahydrocannabinol (THC) • Experimental group 2: Cannabidiol (CBD) • Experimental group 3: 1:1 CBD:THC • Control group: Matched placebo Self-administration by sublingual spray at doses determined by titration against symptom relief or unwanted effects within the range of 2.5–120 mg/24 hours. **Outcome Measures:** Short-oriented memory concentration test, Ashworth, Rivermead Mobility Index, Barthel Activities of Daily Living Index, the General Health Questionnaire, and numeric rating scales (NRS) of fatigue, pain, spasticity and urinary incontinence, measured at baseline and each two weeks.	

Discussion

In an RCT crossover, researchers explored the use of CME and their effect on neurological symptoms including fatigue, spasticity, pain, and bladder incontinence in participants with MS (N=18), SCI (N=4), brachial plexus damage (N=1), and limb amputation due to neurofibromatosis (N=1) (Wade et al. 2003). After two weeks of treatment, no significant differences in fatigue between the CME and placebo groups were observed (Wade et al. 2003). Conversely, all three groups of CME (THC, CBD, and 1:1 THC:CBD) showed significant improvements in spasticity, and both the THC and THC:CBD groups demonstrated significant improvements in muscle spasm frequency (Wade et al. 2003). A systematic review by Nabata et al. (2020) reported two other RCTs using cannabinoids in people with SCI and found improvements in spasticity, unfortunately neither study reported outcomes on fatigue (Hagenbach et al. 2007; Wilsey et al. 2016).

In other clinical populations, such as fibromyalgia, the use of cannabis for fatigue improvement has been understudied as well. Only one RCT showed that THC-rich cannabis oil provides better effects on fatigue scores than a placebo (olive oil) after eight weeks of intervention in 17 women with fibromyalgia (Chaves et al. 2020). In cancer, one follow-up study showed that the self-titration of THC/CBD or THC spray provided a decrease in fatigue, insomnia, or pain (Johnson et al. 2013). Overall, more research is needed to recommend the use of medical cannabis for fatigue in people with SCI.

Conclusions

There is level 1 evidence (from one RCT: Wade et al. 2003) that cannabis medicinal extracts (CME) had no significant effect on fatigue through sublingual delivery in people with neurological conditions, including SCI.

Key Points

According to one RCT which included only four patients with SCI, cannabis medicinal extracts (CME) should not be recommended for the improvement of fatigue in people with SCI. More research is needed in this area before recommendations can be made.

Medical management of fatigue in people with SCI is more likely to include a review of medications that might be causing fatigue.

4.2 Baclofen

Baclofen is a gamma-aminobutyric acid B agonist that is commonly used for the management of spasticity from central nervous system lesions or dysfunction and it is extensively used for SCI, stroke, cerebral palsy and multiple sclerosis (McCormick et al. 2016; Dietz et al. 2023). Baclofen for SCI can be administered orally or intrathecally with implantation of a metered pump (Dietz et al. 2023). Through the oral delivery of baclofen, greater doses than intrathecal delivery may be required for optimal effects, as only a fraction of the medication may pass through the blood-brain barrier (McCormick et al. 2016). However, while the intrathecal delivery of baclofen uses lower doses in comparison, it requires a more invasive approach and commitment to regular maintenance for the surgical placement of an internal pump and a catheter system (McCormick et al. 2016). McCormick et al. (2016) compared these two delivery methods of baclofen treatment and their effects on clinical outcomes such as fatigue.

Table 2. Baclofen

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
McCormick et al. 2016 USA Cohort Level 2 N=62	**Objective:** To compare spasticity levels, pain, sleep, fatigue, and quality of life between individuals receiving treatment with intrathecal versus oral baclofen. **Population:** 62 participants who had been treated with intrathecal or oral baclofen for at least one year (SCI, n=38; cerebral palsy, n=10; stroke, n=10; and multiple sclerosis, n=4) Sex: 40M, 22F; Mean age: 45.5 years Level of injury: quadriplegia (n=26), paraplegia (n=12) **Treatment:** Intrathecal Baclofen vs Oral Baclofen **Outcome Measures:** FSS, measured after one year	1. No significant differences in fatigue (FSS) between groups (p=0.80). 2. Sub-analysis of patients with SCI showed no significant differences (p=0.68) between groups with regard to fatigue. 3. Patients receiving intrathecal compared with oral baclofen experienced significantly fewer (1.44 [0.92] versus 2.37 [1.12]) and less severe (1.44 [0.92] versus 2.16 [0.83]) spasms, respectively as measured by the Penn Spasm Frequency Scale (both p<.01).

Discussion

McCormick et al. (2016) compared the two methods of baclofen delivery and how clinical measures of fatigue, spasticity control, pain, sleepiness, and quality of life may be affected by each in participants who have been receiving baclofen for the treatment of spasticity. While the results showed improvements in spasm frequency and severity with intrathecal delivery in comparison to oral delivery, there were no significant differences in fatigue between groups (neither in the whole sample nor in the SCI sample; p=0.68-0.80). In a cross-sectional survey of 24 individuals (nine with SCI) who have been using intrathecal baclofen for more than 10 years, Mathur et al. (2014) reported low levels of pain, moderate levels of life satisfaction, normal levels of sleepiness, low-to-moderate levels of fatigue, infrequent spasms at mild-to-moderate severity, and high levels of satisfaction; however, no pre-post comparison was made (Mathur et al. 2014).

These positive results in spasticity outcomes, favoring intrathecal delivery, were consistent with results obtained in a recent systematic review of 98 studies that assessed the efficacy, dosing, and safety profiles of intrathecal and oral baclofen in treating spasticity after SCI (Dietz et al. 2023). However, this systematic review also found that 43 studies addressed adverse events and reported that muscle weakness and fatigue were the most frequent ones (Dietz et al. 2023). There are no further studies with a specific clinical population assessing the effects of baclofen regarding fatigue as an outcome.

Conclusions

There is level 2 evidence (from one cohort study: McCormick et al. 2016) that intrathecal baclofen resulted in fewer and less severe spasms in people with SCI compared to oral baclofen as measured by the Penn Spasm Frequency Scale. However, there were no significant differences in pain, sleep, fatigue, and quality of life between groups.

Key Points

Fatigue did not significantly differ between intrathecal and oral delivery methods of baclofen treatment.

Further research is needed to address whether baclofen provides positive results in fatigue in people with SCI, which delivery method is more effective, and results in fewer adverse effects.

5 Non-pharmacological Management of Fatigue in SCI

It is possible that people with disabilities are increasingly interested in non-pharmacologic approaches for fatigue management, such as exercise, education, or behavioral management techniques (Su et al. 2020). Contributing factors for this preference may include undesirable side effects of medications, limited efficacy, or inferiority compared with non-pharmacologic interventions (Asano & Finlayson 2014; Levine & Greenwald 2009).

Non-pharmacological interventions that have been studied in people with SCI will be divided in this module into exercise-based interventions, non-exercise-based interventions, self-management interventions, and the provision of assistive devices.

5.1 Exercise-Based Interventions

Several systematic reviews have documented fitness, health, and subjective well-being as benefits of routine physical activity for adults with SCI (Neefkes-Zonneveld et al. 2015; Tomasone et al. 2013; van der Scheer et al. 2017; Martin-Ginis et al. 2009). Exercise guidelines for adults with SCI have been established with levels of activity that are shown to improve cardiorespiratory fitness and muscle strength (Martin-Ginis et al. 2018). However, no systematic reviews about the effects or benefits of physical activity/exercise for fatigue have been done on people with SCI. Individualized and regular exercise and cognitive behavioral therapy are usually recommended for the management of fatigue in the general population (Rosenthal et al. 2008; Dukes et al. 2021).

Table 3. Exercise-Based Interventions

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Jorjafaki et al. 2022 Iran RCT Level 2 PEDro=4 N=45	**Objective:** To compare the effectiveness of virtual reality-based (VR) rehabilitation exercises and reflexology in reducing the fatigue rate of veterans with paraplegia. **Population:** 45 veterans with paraplegia, with a use of a wheelchair for daily work, with a history of exercise for at least the last 6 months, and with a fatigue level of 45.57 Mean age 54.3 years Level of injury: T12-L4 **Treatment:** Participants were randomly assigned to one of three groups: • Experimental condition I (n=15): Upper limb VR games (e.g., Xbox/Kinect boxing). Sessions lasted 50 min, were performed 3 times per week, for 6 weeks. • Experimental condition II (n=15): Reflexology massage therapy. Sessions lasted 30 min (10 min of relaxation techniques and 15 min of reflexology massage), were performed 3 times per week, for 6 weeks. • Control condition (n=15): No details provided.	1. Decrease in fatigue severity in both VR and massage groups ($p \leq 0.001$) compared with control group. 2. No difference in reducing fatigue between massage (28.9 ± 20.65) and VR (27.8 ± 93.97) ($p=0.99$).

	Outcome Measures: Fatigue Severity Scale (FSS) was measured at baseline and after the program (6 weeks).	
Nightingale et al. 2018 UK RCT Level 2 PEDro=5 N=21	**Objective:** To assess the influence of a home-based exercise intervention on indices of health-related quality of life in persons with SCI. **Population:** 21 participants with SCI and non-physically active 15M, 6F Mean (SD) age 47 (8) years Injury level: Below T4 (paraplegia) Mean (SD) time since injury 16 (11) years **Treatment:** Participants were randomly assigned to one of the following two groups: • Experimental group (n=13): Home-based exercise intervention with arm-crank (moderate intensity: 60%-65% VO_2 peak). Sessions lasted 45 min, were performed 4 times per week, for 6 weeks. Control group (n=8): Lifestyle maintenance **Outcome Measures:** FSS and global fatigue (FSS visual analog fatigue scale) were measured at baseline and immediately after the program (6 weeks).	1. The change of the FSS was significantly different between groups (interaction effect; p=0.036), with a significant reduction in the intervention group (p=0.027). 2. Trend for an interaction effect (p=0.084) in global fatigue. 3. These measures of fatigue demonstrated large effect sizes in favor of intervention: • FSS: Cohen's *d* =-0.99 [90% CI=-1.75, -0.22]. • Global fatigue: Cohen's *d*=0.92 [90% CI=0.08, 1.76]
Vestergaard et al. 2022 Denmark Pre-post Level 4 N=8	**Objective:** To assess safety and feasibility of hybrid high-intensity interval training (HIIT) using Functional Electrical Stimulation (FES) leg cycling and arm ski ergometer in people with SCI. **Population:** 8 participants with paraplegia 7M, 1F Mean (SD) age 42.8 (15.11) Etiology: Traumatic or non-traumatic Level of injury: T4 (n=1), T5 (n=1), T7 (n=1), T8 (n=2), T10 (n=1), L1 (n=1), and L2 (n=1) Motor completeness of injury: Complete (n=3), incomplete (n=5) Mean time since injury 14.5 years **Treatment:** Hybrid HIIT protocol, in the form of FES leg cycling combined with arm ski ergometer. Dosage: 4 x 4 min intervals/session, 3 time per week, 8 weeks Intensity: 90% peak watts **Outcome Measure:** MFI-20 was measured at baseline and after the program (8 weeks).	1. There was a decrease in fatigue ranging from: • 15% (for general fatigue). • 26% for physical fatigue. • 42% for reduced activity. • 33% for reduced motivation. • 20% for mental fatigue.

Shem et al. 2016 USA Pre-post Level 4 N=26	**Objective:** To evaluate the feasibility, benefits, and long-term effects of a seated Tai Chi Chih program for people with spinal cord disorder who cannot safely participate in a standing Tai Chi exercise program. **Population:** 26 participants with spinal cord disorder and sufficient arm movement to be able to participate in the Tai Chi program 14M, 12F Mean (SD) age 49.8 (13.0) Etiology: Traumatic and non-traumatic Level of injury: C3 (n=1), C4-C5 (n=1), C5 (n=2), C5-C6 (n=3), C6 (n=1), C6-C7 (n=4), T8 (n=1), T12-L1 (n=1), L3-L4 (n=1), N/A (n=10) Tetraplegia (n=16), paraplegia (n=6), unknown (n=4) AIS: AIS A (n=4), AIS B (n=2), AIS C (n=2), N/A (n=18) Mean (SD) time since Injury 25.1 (18.9) years **Treatment:** Customized seated Tai Chi program (T'ai Chi Chih). Sessions lasted 90 min, were performed once per week and for 12 weeks. **Outcome Measure:** MFIS was measured at baseline, after each session and after the program (12 weeks).	1. There were no detectable changes in MFIS between the first and the last sessions (MFIS average change=2.00, SD=7.57). 2. Only nine participants completed half of the sessions and the long-term surveys.
Curtis et al. 2015 Canada Pre-post Level 4 N=11	**Objective:** To evaluate a modified yoga program for people with SCI, in terms of both participant experiences and also with respect to program satisfaction. **Population:** 11 participants with SCI 1M, 10F Mean (SD) age 48.4 (15.0) years Etiology: Traumatic (n=6), non-traumatic (n=3), and not reported (n=2) Level of injury: Tetraplegia (n=2), paraplegia (n=6), unknown (n=1), not reported (n=2) Motor completeness of injury: Complete (n=3), incomplete (n=6), unknown (n=1), not reported (n=1) Mean (SD) time since injury 157.4 (191.8) months. **Treatment:** Modified Yoga program. Session lasted 25- to 60-min, were performed once a week, and for 8 weeks. **Outcome Measure:** FSS was measured at baseline and after the program (8 weeks).	1. There were not statistically significant differences between baseline and exit scores on fatigue ($p>0.05$).

Azurdia et al. 2022 USA Pre-post Level 4 N=11	**Objective:** To investigate the effects of using VR during exercise on pain and fatigue in individuals with SCI. **Population:** 11 people with chronic SCI. 5M, 6F Mean age (43.29+–17.5 years) **Treatment:** Three sessions of VR arm ergometer exercise training, 6 minutes each. Exercise intensity was at 60-70% of age-predicted maximum heart rate, or a rating of 11-15 on the Borg's RPE scale. **Outcome Measures:** Heart rate, Blood Pressure, Borg's Rate of Perceived Exertion scale (RPE), Pain Self-Efficacy Questionnaire (PSEQ), Fatigue Severity Scale (FSS), and Fatigue Assessment Scale (FAS).	1. Participants demonstrated significant decreases in all parameters: fatigue (F1, 10=10.487, p<0.009), pain (F1, 10=9.494, p<0.012), heart rate (F1, 10=9.264, p<0.012), and RPE rating (F1, 10=9.046, p<0.013) except for blood pressure (F1, 10=0.025, p<0.878). 2. VR sessions decreased pain by 56% and fatigue by 54%, respectively, as compared with the non-VR exercise sessions.

Discussion

Exercise-based intervention studies that assessed fatigue outcomes in people with SCI included a moderate-intensity arm-crank home exercise program (Nightingale et al. 2018), two virtual reality (VR) exercise programs (Jorjafaki et al. 2022; Azurdia et al. 2022), a hybrid (FES-leg cycling combined with arm ski ergometer) high-intensity interval training (HIIT) protocol (Vestergaard et al. 2022), a seated Tai Chi Chih program (Shem et al. 2016), and a modified Yoga program (Curtis et al. 2015).

Virtual Reality Exercise-Based Interventions

The most recent RCT by Jorjafaki et al. (2022) divided 45 veterans with chronic paraplegia who were experiencing fatigue into an upper limb VR exercise-based program (3x/week for 50 minutes), a reflexology program (3x/week for 30 minutes), or a control group (Jorjafaki et al. 2022). After six weeks, participants in both the VR exercise and the reflexology groups experienced significant reductions in fatigue compared to the control group, but they were not significantly different from each other (Jorjafaki et al. 2022). An additional pre-post study assessed one 6-minute arm ergometry VR exercise session and collected participant responses on pain and fatigue, and found statistically significant reductions in both, though the study only included 11 people with SCI (Azurdia et al. 2022).

We found mixed results for VR exercise programs in other clinical populations. Cho & Sohng (2014) assessed the effects of a VR exercise program, using Nintendo's Wii Fit Plus for 40 minutes, three times a week for eight weeks, versus usual care in patients with hemodialysis and end-stage renal failure. After the program, only the experimental group showed a significant decrease in fatigue and a significant increase in physical fitness and body composition (Cho & Sohng 2014). However, a similar prospective study by Saladino et al. (2023) comparing a 12-week VR exergames program versus usual care in people with MS observed no differences in fatigue between groups.

Home-Based Exercise Intervention at Moderate Intensity

An RCT by Nightingale et al. (2018) divided 21 non-physically-active participants with chronic paraplegia to receive either a home-based arm-crank exercise program at moderate intensity, or to maintain their sedentary behavior. After six weeks of the intervention, fatigue severity (measured by the FSS) was significantly reduced in the intervention group, with a large effect size (Cohen's *d*=-0.99; 90% CI= -1.75, -0.22). Meanwhile global fatigue (measured by the VAS) did not significantly change between or within-groups (Nightingale et al. 2018). Significant positive results were also shown in changes in health-related quality of life outcomes (e.g., physical component scores of the SF-36), exercise self-efficacy, physical activity, and fitness; favoring the intervention group with moderate to large effect sizes (*d*=0.62-1.37) (Nightingale et al. 2018).

Of note, this study was the only one included in this module which provided the exercise program in a home environment (Nightingale et al. 2018). This is of interest, considering that lack of access to gym facilities and exercise equipment, as well as poor information and support, have been identified as key barriers to exercise for adults with SCI (Fekete & Rauch 2012; Stephens et al. 2012; Williams et al. 2014).

The results of the RCT by Nightingale et al. (2018) agree with the recommendations of exercise prescription for patients with multiple sclerosis, where low to moderate-intensity exercise is recommended for the improvement of fatigue (Halabchi et al. 2017) and with the positive results of the implementation of a home exercise program in populations such as men with prostate cancer on androgen deprivation (Alibhai et al. 2024) or systemic sclerosis (Sari et al. 2024).

High-Intensity Exercise Interventions

One pre-post and feasibility study included eight participants with chronic paraplegia who performed a hybrid HIIT protocol, in the form of FES leg cycling combined with arm ski ergometer, three times per week (Vestergaard et al. 2022). After eight weeks, participants reported increased leisure time physical activity and health-related quality of life, and reduced fatigue; however, the nature of this feasibility study did not support statistical analysis (Vestergaard et al. 2022). The study was deemed feasible because of high safety, acceptable attendance rate, and limited drop out (Vestergaard et al. 2022).

The recent systematic review and meta-analysis by Peters et al. (2021) has shown the benefits of HIIT for cardiovascular function in people with SCI (Peak Oxygen Uptake [VO_{2peak}], standardized mean difference [SMD]=0.81; 95% CI 0.23-1.39; $p<0.01$ and Peak Power Output, SMD=0.91; 95% CI 0.32-1.5; $p<0.01$) (Peters et al. 2021). Additionally, different systematic reviews have shown that high-intensity exercise interventions could decrease fatigue in people with cancer (Chen et al. 2023; Wang et al. 2023) or multiple sclerosis (Youssef et al. 2024). Larger and higher quality studies need to be conducted with people with SCI to determine if HIIT has the same positive results in terms of fatigue.

Yoga and Tai Chi Exercise Interventions

Other pre-post studies conducted a modified yoga (Curtis et al. 2015) or a seated Tai Chi (Shem et al. 2016) program for people with chronic SCI. It should be noted that these two studies were the only ones that included participants with tetraplegia and paraplegia. Neither intervention revealed positive results for fatigue (Curtis et al. 2015; Shem et al. 2016).

We found systematic reviews for yoga and for Tai Chi that measured fatigue in similar populations. Positive effects on fatigue were shown in patients with cancer undergoing chemotherapy and/or radiotherapy (Ma et al. 2023), in patients with breast cancer (Hou et al. 2024), and in patients with multiple sclerosis (Shohani et al. 2020). We found one meta-analysis by Xiang et al. (2017) that found Tai Chi improved fatigue in people with cancer (SMD:-0.38, 95% CI: -0.65, -0.11); but not in people with MS (SMD:-0.77, 95% CI: -1.76, 0.22). Overall, the effects of Tai Chi and yoga programs on fatigue require further study.

Relationship Between Fatigue and Physical Activity Level

A previous systematic review and meta-analysis on factors associated with fatigue found that physical activity was inversely associated with fatigue, (r=0.17; 95% CI, 0.28, 0.05; I^2=75.5; p<0.001), and was more often reported in people with SCI who ambulate and/or use their wheelchair less than 50% of the time (Onate-Figuérez et al. 2023). As previously detailed, several systematic reviews have documented fitness, health, quality of life, and subjective well-being benefits of routine physical activity participation for adults with SCI, and are antithetical to feelings of fatigue, though it has not been established in the literature (Neefkes-Zonneveld et al. 2015; Tomasone et al. 2013; van der Scheer et al. 2017).

RCTs assessing the impact of exercise on fatigue are generally effective, however non-RCTs demonstrate mixed results. A cross-sectional study of 49 people with SCI who used manual wheelchairs showed that greater physical activity was associated with fewer secondary complications including fatigue, pain, and depression (Tawashy et al. 2009). When surveying people with SCI about the association between exercise and fatigue, Hammell et al. (2009) found that opinions were divided, with some believing that "exercise made you feel more fatigued" and some believing that "it made you less fatigued".

Exercise Interventions and Fatigue in Other Populations

Overall, fatigue has been more frequently studied in multiple sclerosis than it has in SCI. In a systematic review and meta-analysis on the effectiveness of exercise on fatigue in people with multiple sclerosis, 26 studies were included and found a significant moderate effect of exercise on fatigue, though with significant heterogeneity between studies (SMD=-0.53, 95% CI= -0.73, -0.33; I^2>58%, p<0.01) (Heine et al. 2015). Exercise therapy has also been suggested to be beneficial for reducing fatigue in people with chronic fatigue syndrome (White et al. 2011), people with fibromyalgia (Estévez-López et al. 2021), people who have had a stroke (Zedlitz et al. 2012), and people with or recovering from cancer (Ahlberg et al. 2003).

Research evidence measuring the influence of exercise on fatigue is better established in the general population. In a meta-analysis of 81 studies, Wender et al. (2022) found that exercise decreased feelings of fatigue with a small effect size (Hedge's g=–0.374; 95% CI= -0.521, -0.227) and increased feelings of energy by a small-to-moderate effect size (Hedge's g=0.415; 95% CI= 0.252, 0.578). From 12 population-based studies comparing active versus sedentary adults, Puetz (2006) found an odds ratio of 0.61 (95% CI= 0.52, 0.72) between physical activity and a reduced risk of experiencing fatigue. In addition, two reviews stated that individualized and regular exercise therapy or physical activity be recommended as part of the medical management of fatigue in the general population (Dukes et al. 2021; Rosenthal et al. 2008).

Conclusions

There is level 2 evidence (from one RCT: Jorjafaki et al. 2022) that 6 weeks of virtual reality arm-exercise sessions or 6 weeks of reflexology both decreased fatigue severity in veterans with SCI compared to a control group.

There is level 2 evidence (from one RCT: Nightingale et al. 2018) that 6 weeks of home-based, moderate-intensity arm-crank exercise significantly decreased fatigue severity and global fatigue compared to lifestyle maintenance in sedentary people with SCI.

There is level 4 evidence (from one pre-post: Vestergaard et al. 2022) that an 8-week hybrid HIIT program using FES leg cycling and arm ski ergometer, performed 3 times per week, decreased fatigue in people with chronic paraplegia.

There is level 4 evidence (from one pre-post: Shem et al. 2016) that a 12-week customized seated Tai Chi program performed once a week for 90 minutes each session, did not provide any change in fatigue in people with chronic SCI.

There is level 4 evidence (from one pre-post: Curtis et al. 2015) that an 8-week modified yoga program, performed once a week for 25-60 minutes each session, did not change fatigue severity in people with chronic SCI.

Key Points

Exercise-based interventions may have a positive effect on fatigue in people with chronic SCI; however, there is no consensus on which type of exercise, or its effective dosage in reducing fatigue in people with SCI.

Yoga or Tai Chi programs seem to not provide any effects on fatigue in people with SCI.

Exercise-based interventions have generally had a positive effect on fatigue in people with MS and in the general population.

5.2 Non-exercise-Based Interventions

Non-exercise-based interventions that assessed fatigue outcomes in people with SCI were largely different types of massage therapy (such as Swedish massage [Lovas et al. 2017], broad compression massage [Chase et al. 2013], reflexology massage (Jorjafaki et al. 2022]), healing touch (Wardell et al. 2006), and neurofeedback (Jensen et al. 2013).

Table 4. Non-exercise-Based Interventions

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Pourjafari et al. 2022 Iran RCT Level 2 PEDro=4 N=45	**Objective:** To compare the effectiveness of virtual reality-based (VR) rehabilitation exercises and reflexology in reducing the fatigue rate of veterans with paraplegia. **Population:** 45 veterans with paraplegia, with a use of a wheelchair for daily work, with a history of exercise for at least the last 6 months, and with a fatigue level of 45.57 Mean age 54.3 years Level of injury: T12-L4 **Treatment:** Participants were randomly assigned to one of three groups: • Experimental condition I (n=15): Upper limb VR games (e.g., Xbox/Kinect boxing). Sessions lasted 50 min, were performed 3 times per week, for 6 weeks. • Experimental condition II (n=15): Reflexology massage therapy. Sessions lasted 30 min (10 min of relaxation techniques and 15 min of reflexology massage), were performed 3 times per week, for 6 weeks. • Control condition (n=15): No details provided. **Outcome Measures:** FSS was measured at baseline and after the program (6 weeks).	1. Decrease in fatigue severity in both VR and massage groups ($p \leq 0.001$) comparing with control group. 2. No difference in reducing fatigue between massage (28.9 ± 20.65) and VR (27.8 ± 93.97) ($p=0.99$).
Lovas et al. 2017 Australia RCT Level 2 PEDro=4 N=40	**Objective:** To determine the efficacy of massage therapy as a treatment that could be implemented to reduce pain and fatigue in people with chronic SCI. **Population:** 40 participants with SCI 34M, 6F Mean age 45.95 years Etiology: Traumatic (n=30), non-traumatic (n=9), and other (n=1) Level of injury: Paraplegia (n=30), tetraplegia (n=9), and non-reported (n=1) Completeness of injury: Complete injuries (n=20), incomplete injuries (n=19), and NP (n=1) Mean (SD) time since injury 18.4 (12.1) years **Treatment:** Participants were randomly assigned into one of two arms:	1. No significant between-group differences in fatigue scores: $F_{1,38}=0.89$, $p>0.05$, $\eta^2=0.02$ and power=15%. 2. Fatigue scores were reduced significantly over time: $F_{1,38}=18.4$, $p<0.01$, $\eta^2=0.33$ and power=99%, with post-hoc analyses indicating that fatigue scores were reduced significantly in the MT group ($p<0.05$) and in the GI group ($p<0.05$). 3. There was no significant interaction effect

	• Experimental condition (n=20): Swedish massage therapy (MT) on the participant's back, neck and arms in sitting position. • Control condition (n=20): Guided imagery relaxation (GI). All participants received 30 min once a week of either massage or guided imagery over 5 consecutive weeks. **Outcome Measures:** CFS was measured at baseline and after the completion of the five sessions	between groups and intervention over time: $F_{1,38}$=1.49, p>0.05, η^2=0.04, power=22%.
Chase et al. 2013 USA RCT cross-over Level 2 PEDro=5 N=40	**Objective:** To determine the feasibility of conducting a RCT of massage therapy for patients with a new SCI during acute inpatient rehabilitation **Population:** 40 participants with SCI reporting any type of pain 33M, 7F Mean (SD) age 40.24 (13.8) years Etiology: Traumatic (n=36) and non-traumatic (n=4) Level of injury: paraplegia (n=7) and tetraplegia (n=33) AIS A (n=23), AIS B (n=9), AIS C (n=7), and AIS D (n=1) Mean (SD) time since injury 69.35 (31.11) days **Treatment:** Participants were randomized to receive either broad compression massage or light contact touch first, in six 20-min treatment sessions (3 times per week) over 2 weeks, with a 1-week washout period. between the 2-week treatment periods. **Outcome Measures:** FSS was measured at baseline and after the intervention program for each of the two periods.	1. Groups did not significantly differ on fatigue scores (Period 1: FSS change [SD]=1.58 [11.20] [p=0.66]; Period 2: FSS change [SD]=-1.37 [6.97] [p=0.55].
Wardell et al. 2006 USA Prospective controlled trial Level 2 N=12	**Objective:** To determine the feasibility of delivering a healing modality (healing touch and guided progressive relaxation) in a home environment and to determine whether these techniques could influence the pain and coping of veterans with SCI. **Population:** 12 participants with SCI and experiencing chronic neurogenic pain 12M, 0F Mean age 54.35 years Motor completeness of injury: Complete (n=6) and incomplete (n=9) Mean time since injury 257.23 months **Treatment:** Participants were assigned to either healing touch (n=7) or guided	1. No difference in the POMS total score between groups in the trend of change (*F*=0.69, *df*=2, 19, p=0.51) across the study period. 2. In the fatigue scale of the POMS, the experimental group decreased (pre-treatment *M*=17, posttreatment *M*=11.29), but the variation was large (only 4 of the experimental group participants had decreased scores).

	progressive relaxation (n=4) for six weekly home visits **Outcome Measures:** POMS was measured at baseline, after the second session and at posttreatment.	
Jensen et al. 2013 USA Pre-post Level 4 N=13	**Objective:** To address which specific target EEG band-widths in treatment should be recommended, the overall efficacy of neurofeedback treatment, and to assess chronic pain, physical functioning, psychological functioning, and sleep quality) in persons with SCI. **Population:** 13 participants with SCI and experience physical pain on a daily basis 3M, 7F Mean (SD) age 46.1 (12.6) years Mean (SD) time since injury 12.3 (9.0) years. **Treatment:** Participants received four sessions each of three different neurofeedback protocols ([1] reinforce α and suppress β at T3 and T4 [protocol A]; [2] reinforce 10–15 Hz and suppress β and θ at C3–A1 and C4–A2 [protocol B]; and [3] reinforce 10–15 Hz and suppress β and θ at P3–A1 and P4–A2 [protocol C]) assigned in random order for a total of 12 sessions. **Outcome Measures:** FSS was measured at pre- treatment, post-treatment, and at 3-month follow-up.	1. There was a non-significant trend (p=0.053) of increase in fatigue from pre- to post-treatment that continued through the 3-month follow-up.

Discussion

Treatments for fatigue in people with SCI are mainly focused on the management of pain, depression, functionality, muscle strength, and range of motion, while effects on fatigue have mixed results (Chase et al. 2013; Lovas et al. 2017; Norrbrink & Lundeberg 2011; Diego et al. 2002). The RCT by Jorjafaki et al. (2022) reported significant improvement in fatigue severity with reflexology massage performed on the palms for three 30-minute sessions per week for six weeks, in veterans with paraplegia. Conversely, two other RCTs that assessed fatigue after a massage intervention (Swedish massage in the study of Lovas et al. 2017 and broad compression massage in the cross-over of Chase et al. 2013) did not improve fatigue in people with SCI. It is possible that the dose of massage in the included studies (30 minutes once a week over five consecutive weeks [Lovas et al. 2017] and 20 minutes three times a week over two weeks [Chase et al. 2013]) was insufficient to produce desired effects.

Results from larger systematic reviews show that massage therapy has positive effects on fatigue in other populations, such as people with chronic fatigue syndrome (Li et al. 2024), people with kidney failure requiring dialysis (Natale et al. 2023), people with fibromyalgia (Yuan et al. 2015) and people with multiple sclerosis (Salarvand et al. 2021; Zhang et al. 2022). However, fatigue may be different in people from these populations than in those with SCI. It is difficult to properly research fatigue in these populations as the biological bases of fatigue have not been established in MS nor in SCI (Heine et al. 2015).

Other alternative non-exercise approaches, such as neurofeedback (Jensen et al. 2013) or healing touch (Wardell et al. 2006) have been studied with lower-quality studies in people with SCI and have provided non-positive results in the management of fatigue.

Conclusions

There is level 2 evidence (from one RCT: Pourjafari et al. 2022) that 30-minute reflexology massage sessions or 50-min upper limb virtual reality exercise sessions, decreased fatigue severity (FSS) in veterans with paraplegia when performed 3 times per week for 6 weeks compared to the control condition.

There is level 2 evidence (from one RCT: Lovas et al. 2017) that 5 weeks of weekly 30-min Swedish massage sessions or guided imagery relaxation sessions decreased fatigue in people with chronic SCI.

There is level 2 evidence (from one RCT: Chase et al. 2013) that neither broad compression massage nor light contact touch sessions improved fatigue severity for people with acute SCI reporting pain.

There is level 2 evidence (from one prospective controlled trial: Wardell et al. 2006) that 6 weeks of healing touch sessions once a week decreased (with a large variation) fatigue scores on the POMS and chronic neurogenic pain compared to guided progressive relaxation sessions in people with SCI.

Key Points

There is conflicting evidence that non-exercise-based interventions, like massage therapy, improve fatigue outcomes in people with SCI.

5.3 Self-Management Interventions

Although several taxonomies have been proposed (McIntyre et al. 2020), self-management has been defined by Barlow et al. (2002) as "the individual's ability to manage the symptoms, treatment, physical and psychosocial consequences, and lifestyle changes inherent in living with a chronic condition."

SCI is increasingly being viewed as a chronic disease, like diabetes, placing greater emphasis on the role of self-management as a means for improving long-term outcomes (Dobkin et al. 2016). It has been shown that self-management approaches are increasing in popularity for addressing a range of issues post SCI, including secondary health conditions (e.g., pain management, pressure ulcer prevention), health promotion (e.g., physical activity, weight loss), emotional well-being and coping, and community living (McIntyre et al. 2020). Specifically, effective self-management is associated with more physical activity in people with SCI (Arbour-Nicitopoulos et al. 2009;

Froehlich-Grobe et al. 2014; Nooijen et al. 2016a; Warms et al. 2004) and in people with chronic conditions other than SCI (Cramp et al. 2013; Ferrier et al. 2011; Taylor et al. 2012).

However, there is no gold standard on what constitutes self-management in SCI, and studies often use different tools, formats, and resources to implement their programs (McIntyre et al. 2020). Current studies include methods of behavioral intervention (Kooijmans et al. 2017; Nooijen et al. 2016b), and text messaging (Wong et al. 2023).

Table 5. Self-Management Interventions

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Kooijmans et al. 2017 Netherlands RCT Level 1 PEDro=6 N=64	**Objective:** To evaluate the effectiveness of a structured self-management intervention to promote an active lifestyle in inactive persons with long-term SCI. **Population:** 64 participants with SCI, able to use a hand-rim wheelchair, and physically inactive 45M, 19F Mean age 48.5 years Level of injury: Paraplegia (n=33), tetraplegia (n=21) Completeness of injury: Complete (n=50), incomplete (n=14) Mean time since injury: 22 years **Treatment:** Participants were randomized to: • Self-management intervention (n=33) consisting of group meetings (5 sessions) and individual counseling (1 home visit and 5 individual sessions) and a book. • Control intervention (n=31), consisting in only receiving information about active lifestyle by one group meeting and a book. Both interventions lasted 16 weeks. **Outcome Measures:** FSS was collected at baseline (T0) and at 16 weeks (T1) and 42 weeks (T2) after baseline.	1. No significant differences in fatigue (p=0.62) were observed.
Nooijen et al. 2016b Netherlands RCT Level 1 PEDro=6 N=39	**Objective:** To assess the mediating effects of physical and psychosocial factors on the intervention effect on physical activity in order to unravel the working mechanisms that underlie the effectiveness of a behavioural intervention promoting physical activity in persons with subacute SCI. **Population:** 39 participants with SCI, dependent on a manual wheelchair for their daily mobility, and able to handcycle 33M, 6F	1. No direct intervention effect on fatigue was found (B=0.03, p=0.93; B represents the overall between-group difference, adjusted for baseline levels, rehabilitation centre, sex and age).

	Mean (SD) age 44 (15) years Etiology: Traumatic (n=26) and not reported (n=26) Injury level: Tetraplegia (n=13) and paraplegia (n=26) Completeness of injury: Complete injury (n=24) and incomplete (n=15) Mean time since injury: 150 days **Treatment:** Participants were randomly assigned to one of two groups: • Experimental condition (n=20): Behavioral intervention promoting an active lifestyle, based on motivational interviewing. Participants received 13 face-to-face sessions, with a maximum 1 hour per session, for 8 months. • Control group (n=19). **Outcome Measures:** FSS was assessed at T1 (prior to the start of the interventions at 2 months before discharge from inpatient rehabilitation), T2 (before discharge from inpatient rehabilitation [< 2 weeks before]), T3 (after completion of the behavioural intervention at 6 months after discharge from inpatient rehabilitation), and T4 (1 year after discharge from inpatient rehabilitation).	
Wong et al. 2023 USA Pre-post Level 4 N=27	**Objective:** To evaluate the acceptability, feasibility, and participant engagement with a Short Message Service (SMS) text messaging intervention for fatigue self-management and to explore the pre- and post-score health changes in people with disabilities. **Population:** 27 participants with disability (multiple sclerosis, n=9; stroke, n=9; and SCI, n=9) and fatigue in their daily lives; 10M, 17F; Mean (SD) age 29.7 (12.3) years; Initial patient activation level (PAM-13): Level 1 (n=2), Level 2 (n=5), Level 3 (n=5), Level 4 (n=15). **Treatment:** For 12 weeks, participants received text messages based on their baseline patient activation level: • Participants in levels 1 or 2 received a set of 48 text messages focusing on informing and educating them about fatigue and activities in their daily life that may affect their fatigue. • Participants in levels 3 or 4 received another set of 48 messages focusing on providing strategies for implementing changes into daily life that may help manage their fatigue. **Outcome Measures:** MFIS and PROMIS Fatigue were measured at baseline and post-intervention.	1. The two fatigue measures showed moderate effect sizes of reducing fatigue (MFIS: η^2=0.06 and PROMIS Fatigue: η^2=0.12).

Discussion

The present systematic review has only shown three self-management interventions promoting an active and healthy lifestyle that assessed fatigue outcomes in people with SCI: (1) the implementation of a self-management program (Kooijmans et al. 2017), (2) a motivational interviewing program (Nooijen et al. 2016b), and (3) a text messaging intervention (Wong et al. 2023). This number of self-management interventions for fatigue is quite small compared to the results of the recent scoping review of McIntyre et al. (2020) where 112 studies were included representing 102 unique self-management programs for people with SCI.

The self-management program (Healthy Active Behavioral Intervention in SCI [HABITS]) in the RCT by Kooijmans et al. (2013) aimed to evaluate the effectiveness of a structured self-management intervention measuring physical activity, perceived behavior control, stages of exercise change, attitude, effects on perceived behavioral control (exercise self-efficacy, proactive coping), stages of change concerning exercise, and attitude toward exercise. Overall, there were no significant differences observed between the HABITS intervention and control groups on the outcome measures, and thus the study did not support the effectiveness of the self-management intervention (Kooijmans et al. 2017).

In a similar series of RCTs, 45 participants with SCI were randomly assigned to receive a behavioral intervention based on 13 motivational interview sessions for promoting an active lifestyle, or no-intervention (Nooijen et al 2016a; Nooijen et al. 2016b; Nooijen et al. 2017). In this case, the behavioral intervention increased physical activity levels at the time of discharge and at 12 months after discharge (Nooijen et al 2016a), and elicited a behavioral change toward a more active lifestyle (Nooijen et al. 2016b). They found that proactive coping, exercise self-efficacy, pain disability, and helplessness (but not fatigue) were shown to be mediating effects of the increase in physical activity after this intervention (Nooijen et al. 2017). However, the differences in the results of physical activity levels of these studies may be related to the sample included. Participants of the study by Kooijmans et al. had chronic SCI (mean time since injury 22 years) and were physically inactive, whereas the series of RCTs (Nooijen et al 2016a; Nooijen et al. 2016b; Nooijen et al. 2017) included participants with subacute SCI (mean time since injury 150 days) and were receiving regular rehabilitation, including handcycle training.

The lower-level study (pre-post) by Wong et al. (2023) found a moderate (but not significant) effect of a 12-week text messaging intervention on fatigue, sleep, and satisfaction with participation in social roles. However, there was no effect on patient activation (participation health management), nor for fatigue self-management in people with neurological conditions, including SCI (33%). This feasibility study did however show that this intervention had high acceptability, adherence, and satisfaction.

Self-Management Interventions in Other Clinical Populations

RCTs that test behavioral interventions on fatigue have been conducted in other clinical populations, such as multiple sclerosis. Bombardier et al. (2008) studied a motivational interviewing-based telephone counseling service in 130 people with multiple sclerosis; the treatment group showed significantly greater improvement in fatigue impact versus the wait-list control group. Additionally, more clinically measurable improvements for fatigue were observed in participants who received telephone counselling (33.3% reduction) compared to those who received self-directed physical activity education (18.3% reduction) (Turner et al. 2016).

Pöttgen et al. (2018) also found that a self-management intervention significantly reduced fatigue in people with multiple sclerosis at week 12 (between-group mean difference 2.74 points; 95% CI, 1.16, 4.32; p=0.0007; effect size d=0.53) and sustained those improvements at week 24 (between-group mean difference 2.19 points; 95% CI, 0.57, 3.82; p=0.0080). However, the mechanisms behind self-monitoring or self-management interventions for fatigue in people with multiple sclerosis or SCI remain unclear; they are likely grounded in broader behavioral principles such as self-efficacy (Bandura 1977; Lorig & Holman 2003). This notion is partially supported by Wang et al. (2022) who found in a multiple regression analysis that behavioral variables such as outcome expectations (β=0.287) and self-efficacy (β=0.153) explained approximately 41% of the variance in predicting fatigue self-management in people with multiple sclerosis.

Conclusions

There is level 1 (from RCT: Kooijmans et al. 2017) that a 16-week self-management intervention to promote an active lifestyle (providing group meetings, individual counseling, and a book) shows a non-significant improvement in fatigue severity (FSS) in comparison with only providing information about active lifestyle by one group meeting and a book, in people physically inactive with chronic SCI.

There is level 1 (from one RCT: Nooijen et al. 2016) that 8-months of 13 face-to-face sessions of behavioral intervention promoting an active lifestyle (based on motivational interviewing) did not provide a direct effect on fatigue severity (FSS) in people with subacute SCI and manual wheelchair-dependency.

There is level 4 (from one pre-post: Wong et al. 2023) that a 12-week self-management text messaging intervention, based on the baseline activation level of each participant, non-significantly decreases fatigue (MFIS and PROMIS Fatigue) in people with disabilities (33% SCI).

Key Points

Preliminary research shows that self-management and behavioral interventions promoting an active lifestyle provided small or non-significant improvements in fatigue in people with SCI.

5.4 Assistive Device Interventions

Assistive technologies (ATs) and supports enable people with disabilities to live healthy, productive, independent, and dignified lives, and to participate in education, the labour market, and civic life (GOV.UK: Assistive technology: definition and safe use). They are commonly implemented providing a great opportunity to support people with different types of disabilities (Morone et al. 2023; Lenker et al. 2013; Ripat & Woodgate 2012).

The provision of assistance dogs is an example of a support intervention that aims to address the participation needs of people with disabilities. A recent scoping review by Futeran et al. (2022)

including 38 studies (11 of them being performed on patients with SCI) showed how assistance dog partnerships can positively impact participation, a key factor in promoting quality of life. Another recent systematic review has shown that despite the purpose of assistance dogs usually being for physical tasks, positive outcomes were noted in psychological, social, quality of life, and vitality domains; but none on psychosocial health or wellbeing (Rodriguez et al. 2020).

The Segway Personal Transporter is a self-balancing, electric-powered personal transporter and a popular mobility device among non-SCI controls (Boutilier et al. 2012; Sadeghi et al. 2016). They could be used by an individual with SCI, with or without long leg braces depending upon their level of injury (Sadeghi et al. 2016). Previous research investigating whether the Segway could be used as a mobility device for people with disabilities and limited mobility has shown that very little strength, flexibility, and coordination was needed to operate the Segway, making it a good alternative to existing equipment (Sawatzky et al. 2007; Sawatzky et al. 2009).

Over the last years, overground-powered lower limb exoskeletons have emerged as practical devices for rehabilitative or substitutional interventions (Tamburella et al. 2022). The feasibility of these devices has been demonstrated and research into clinical benefits suggests possible improvements in bladder and bowel function, pain, spasticity, bone density, lean body mass, muscle tone, and improved walking speed (Postol et al. 2021).

Table 6. Assistive Device Interventions

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Mobility Service Dogs		
Vincent et al. 2019 Canada Pre-post Level 4 N=17	**Objective:** To assess the effects of a mobility service dog on pain, fatigue, wheelchair-related functional tasks, participation and satisfaction among manual wheelchair users over a nine-month period. **Population:** 17 (SCI, n=14; spastic diplegia, n=1; traumatic leg amputation, n=1; cerebral palsy, n=1) manual wheelchair users 9M, 8F Mean (SD) age 41.9 (15.3) years Level of injury (participants with SCI): Paraplegia (n=10), tetraplegia (n=4) **Treatment:** Each participant was partnered with a mobility service dog for nine months. **Outcome Measures:** RPE Scale and the vitality subscale of the SF-36 were	1. Significant and favorable decreases (p=0.005) in the RPE were observed at three months (-5.0 ± 1.4 to 3.8 ± 1.5) and nine months after the intervention (-3.3 ± 1.9). 2. Participants reported having more pep (p=0.039) but no difference to be less worn out (p=0.068) and have more energy (p=0.066). 3. Significant changes in vitality were perceived three months after the intervention (more pep: p=0.008; more energy: *p*=0.008) and were no longer present at six months (more pep: p=0.454; more energy: p=0.963) and at nine months

	assessed at baseline and three times more until the last one which was set at the end of the intervention (9 months).	(more pep: p=0.305; more energy: p=0.281). 4. Moderate to strong effect sizes (Glass delta) were confirmed for fatigue despite a relatively small sample size: • RPE scale: T1=-0.85; T2=-0.71; T3=-1.21 • Vitality (SF-36) – Did you feel full of pep? T1=0.74; T2=-; T3=- • Vitality (SF-36) – Did you have a lot of energy? T1=0.79; T2=-; T3=- • Vitality (SF-36) – Did you feel worn out? T1=-0.69; T2=-0.93; T3=-0.79
Segway Personal Transporter		
Boutilier et al. 2012 Canada Pre-post Level 4 N=8	**Objective:** To determine whether a dynamic standing program using the Segway Personal Transporter results in any measurable physiological effects in participants with SCI using both qualitative and quantitative measures of spasticity, pain and fatigue. **Population:** 8 participants with SCI, with the ability to stand with or without external support, and having a history of pain and spasticity 7M, 1F Mean (SD) age 44.13 (8.90) years Level of injury: C5 (n=4), C6 (n=1), T5 (n=1), T6 (n=1), T11 (n=1) AIS: AIS A (n=1), AIS B (n=1), AIS C (n=3), AIS C/D (n=2), AIS D (n=1) Mean (SD) time since injury 13.75 (9.29) years. **Treatment:** Participants performed a 4-week dynamic standing program using a Segway (navigating around different places [indoor/outdoor] with some obstacles). Sessions lasted 30 min and were performed three times per week. **Outcome Measures:** FSS was measured at baseline, at the sixth session (Mid test), and twelfth session (Final test).	1. For fatigue, the difference between initial and final visits was not significant, however, the fatigue scores did improve from a mean of 4.2 (±0.47) at initial visit to a final level of 3.7 (±0.54).
Free-standing Exoskeleton		

Postol et al. 2021 Australia Pre-post Level 4 N=3	**Objective:** To evaluate the feasibility of therapy with a free-standing exoskeleton in people with SCI, and to determine the potential health-related benefits of this intervention. **Population:** 3 participants with SCI and severe mobility impairment and reliant on wheelchair, mobility aid, or the assistance of others for standing activities 1M, 2F Mean age 36 years Etiology: Traumatic (n=2), non-traumatic (n=1) Level of injury: C5 (n=1), C6 (n=1), L3 (n=1) AIS: AIS A (n=1), AIS B (n=1), AIS C (n=1) **Treatment:** Participants received exercise therapy sessions in a free-standing lower limb robotic exoskeleton (REX, Rex Bionics). Each session lasted 30 min, were performed twice a week, and for 12 weeks. **Outcome Measures:** FAS was measured upon enrolment (week 0), prior to the commencement of the intervention (week 12), mid-way through the intervention phase (week 18), at the end of the 12-week intervention (week 24), and then again 12 weeks after the intervention had been completed (week 36).	1. Only three of 41 potential participants being eligible completed this study. 2. Changes in fatigue were inconsistent between and within P1 and P2. 3. Trends towards improvement over time in fatigue were evident for P3 (scores at week: 0=31, 12=29, 18=26, 24=23, 36=21).

Discussion

Mobility Service Dogs

The pre-post study by Vincent et al. (2019) was the only study included in the present systematic review that assessed fatigue in manual wheelchair users with SCI during nine months of partnering each participant with a mobility service dog. They found that end-of-day fatigue significantly decreased, with moderate to strong effect sizes, along with positive results in shoulder and wrist pain, wheelchair-related functional tasks, participation, and satisfaction with the psychosocial aspects and technical dimensions of their animal technical assistance over time (Vincent et al. 2019).

These results are in line with those obtained by Hubert et al. (2013) which showed reduced perceived exertion and shoulder pain, and increased endurance in 11 manual wheelchair users with SCI after seven months of training with a service dog. However, these positive effects need to be considered with caution as different systematic reviews with service dogs for people with disabilities have several methodological weaknesses in the original studies assessed (Winkle et al. 2012; Rodriguez et al. 2020).

Segway Personal Transporter

The pre-post study by Boutiller et al. (2012) found that a 4-week dynamic standing program using the Segway Personal Transporter improved fatigue scores in eight participants with SCI, though not to a level of significance (n=8, p>0.05). On the other hand, spasticity improved considerably immediately after the first session with the Segway, but the improvements were not significant after the 4-week program, contrary to pain which dropped significantly over time (Boutilier et al. 2012). These results raised the question as to whether the use of a Segway has additional benefits for managing spasticity over purely static standing (Sadeghi et al. 2016). The same research group performed a crossover trial in 10 participants with chronic SCI and spasticity who performed one 20-minute static standing session and one 20-minute dynamic standing session (one week apart) with the Segway (Sadeghi et al. 2016). Although in this project, fatigue was not assessed; spasticity decreased after both conditions, but without a difference between sessions (n.s. Sadeghi et al. 2016). To the author's knowledge, no new studies have been carried out with respect to this assistive technology in populations with disabilities such as SCI, stroke, or multiple sclerosis.

Figure 1. Segway use in the study of (Boutilier et al. 2012). Image downloaded from YouTube (https://www.youtube.com/watch?v=9W6XB8Nzmec&t=188s)

Free-Standing Exoskeleton

A small (but recent) feasibility study by Postol et al. (2021) evaluated the efficacy of a 12-week intervention program using a free-standing exoskeleton for weightbearing exercises in three participants with severe mobility impairment. Findings were inconsistent between the three study participants in terms of fatigue.

Exoskeleton technology is a rapidly developing field that, with long-term rehabilitation therapy, could improve cardiovascular fitness, increase bone mineral density and lean body mass, lower spasticity, optimize bowel function, enhance neuromuscular and musculoskeletal function, improve gait function, promote neuroplasticity, improve the quality of life and physical discomfort, enable active participation in social and community activities, engage in employment opportunities, and pursue recreational pursuits (Pinelli et al. 2023). Fatigue represents an interesting topic to study as people with SCI who use robotic locomotor exoskeletons have cited that increased fatigue, spasticity, and spasms (among other factors) are a barrier to using exoskeletons; however, no larger studies assessing fatigue as an outcome have been conducted in this area (Kinnet-Hopkins et al. 2020).

Conclusions

There is level 4 evidence (from one pre-post: Postol et al. 2021) that 12 weeks of exercise therapy sessions in a free-standing lower limb robotic exoskeleton, performed twice a week for 30 minute each session, does not provide consistent changes in fatigue in the three participants with SCI.

There is level 4 (from one pre-post: Vincent et al. 2019) that a 9-month partnership with a mobility service dog provides significant improvements in fatigue (RPE) and vitality (vitality subscale of the SF-36) with moderate to strong effect sizes in manual wheelchair users (82% with SCI).

There is level 4 evidence (from one pre-post: Boutilier et al. 2012) that a 4-week dynamic standing program using a Segway, performed three times per week for 30 minute each session, provides a non-significant improvement in fatigue severity (FSS) in people with SCI and a history of pain and spasticity.

Key Points

Partnerships with mobility service dogs seem to be beneficial for the improvement of fatigue in people with SCI.

There is conflicting preliminary evidence to support the use of exoskeletons or Segways to improve fatigue in people with SCI.

6 Ideal Fatigue Interventions for People With SCI Based on What We Know

Because of the limited literature on interventions and the multifactorial nature of global fatigue, it is difficult to recommend one ideal treatment protocol for fatigue in people with SCI; however, some previous research has highlighted certain things that would be useful to address.

Having a better understanding of which factors are most strongly associated with fatigue is key to establishing preventive and therapeutic interventions. Onate-Figuérez et al. (2023) conducted a systematic review including 29 studies, and a meta-analysis including 23 studies, investigating the association between fatigue and clinical and demographic variables in people with SCI. A direct association was found between fatigue and 9 factors: self-efficacy (r=-0.63; 95% CI, 0.81 to 0.35), anxiety (r=0.57; 95% CI, 0.29-0.75), stress (r=0.54; 95% CI, 0.26-0.74), depression (r=0.47; 95% CI, 0.44-0.50), pain (r=0.34; 95% CI, 0.16-0.50), participation (r=-0.32; 95% CI, 0.58 to 0.001), analgesic medication (r=0.32; 95% CI, 0.28-0.36), assistive devices (r=0.23; 95% CI, 0.17-0.29), physical activity (r=-0.17; 95% CI, 0.28 to 0.05), lesion level (r=0.15; 95% CI, 0.07-0.23), incomplete SCI (r=0.13; 95% CI, 0.05-0.22), and medication (r=0.12; 95% CI, 0.01-0.23) (Onate-Figuérez et al. 2023). No association was found with age, sex, educational level, time since injury, or spasticity (Onate-Figuérez et al. 2023). These results should be considered when designing intervention approaches to improve fatigue in people with SCI.

It has been suggested that the management of fatigue in people with neurological disorders like SCI and multiple sclerosis requires a multidisciplinary team and approach (Hourihan, 2015; Smith et al. 2016). A physiatrist or family doctor can conduct a thorough physical and medical history to determine potential causes of fatigue (such as pain, sleep, or medications). Physicians should review whether medications that may contribute to fatigue can safely be replaced, decreased, or discontinued (Rosenthal et al. 2008; Dukes et al. 2021). It is important to ask about and address pain, as it is one of the most common co-occurrences with fatigue in people with SCI (Onate-Figuérez et al. 2023). Laboratory testing may also uncover any contributing factors to fatigue like anemia or thyroid disorders (Hourihan 2015). Sleep quality should be reviewed to ensure that treatable secondary causes of sleep dysfunction—such as obstructive or central sleep apnea—are not contributing to fatigue. Structured physical activity and/or exercise is indicated to treat fatigue in people with SCI, multiple sclerosis, and in the general population; physical therapists or other professionals prescribing exercise should be aware of the person's fatigue status and levels of exercise should be moderate and increased gradually (Rosenthal et al. 2008; Hourihan 2015; Heine et al. 2015). To ensure that any regimens that are put into place to manage fatigue, it has been suggested that follow-up visits are regularly scheduled (Rosenthal et al. 2008).

Previous research has identified that psychological factors like stress, anxiety, and depression contribute substantially to fatigue in people with SCI, suggesting that an evidence-based mental health therapy such as cognitive-behavioral therapy or the prescription of selective serotonin reuptake inhibitors, such as fluoxetine, paroxetine, or sertraline, could be considered as part of any fatigue treatment in appropriate patients (Craig et al. 2013; Onate-Figuérez et al. 2023; Rosenthal et al. 2008). Researchers have posited that cognitive-behavioral therapy could be useful in helping people lessen the effects of chronic pain on depressive moods, and might help in establishing more attributions of self-efficacy, in that the person with SCI has some control over their body and their health (Craig et al. 2012; Craig et al. 2013). In an interview study with people with SCI, family members, care assistants, and occupational therapists, Hammell et al. (2009) found that interviewees suggested an ideal fatigue management program would address achieving greater participation in their everyday lives; providing a sense of enhanced control, reduced pain and helplessness; and enhancing relationships strained by fatigue. Notably, these goals align with the intended achievements of cognitive-behavioral therapy as well as with the self-management interventions found in two of the RCTs included in this review.

7 Gaps in the Evidence

- Limited number of studies with fatigue as a primary or secondary outcome: Perhaps due to other secondary conditions being perceived as more important, the number of studies focusing on fatigue is extremely low. More research where fatigue is a primary or secondary outcome should be completed in people with SCI.
- The amount of covariance between factors in fatigue also makes it difficult to study. For example, in a multiple regression analysis, Craig et al. (2013) found that people with SCI who had high levels of pain were nine times more likely to have elevated fatigue ($p<0.001$), and that all of their participants who had depressive mood also suffered from fatigue whereas none of the participants with low levels of fatigue suffered from depressive mood ($p<0.001$). Furthermore, Craig et al. (2013) also found that pain and depressive mood contributed, significantly and independently, almost 20% and 10% of the variance to chronic fatigue presentation in their participants with SCI ($R=0.82$, $R^2=0.67$; pain $\beta=0.52$, 95% CI=0. 34, 0.69, t (67)=6.1, sr=0.43, $sr^2=18,5\%$, $p<0.001$; depressive mood $\beta=0.40$, 95% CI=0.22, 0.58, t (67)=4.7, sr=0.33, $sr^2=10.9\%$, $p<0.001$) (Craig et al. 2013). Researchers will need to account and control for the covariance between multiple factors when studying fatigue in people with SCI.
- Relationship between sleep and fatigue in SCI: None of the included RCTs investigated or measured sleep quality or presence of sleep disorders in participants. It is well-known that sleep-disordered breathing occurs more frequently in people with SCI, particularly in those with higher-level injuries; prevalence estimates are that sleep-disordered breathing is present in 60% of people with motor complete tetraplegia (Chiodo et al. 2016; Proserpio et al. 2015). If the included studies had asked participants about their sleep quality or the presence of sleep-disordered breathing, it could have been accounted for as a factor, analyzed to assess any differences between the randomized groups at baseline or post-intervention, or to help differentiate between primary and secondary fatigue. Primary fatigue more commonly describes fatigue that is resolved by a proper night's sleep, whereas secondary fatigue, typically experienced by those with neurological disorders, is not accompanied by a desire to sleep, symptoms are not resolved by sleeping, and the fatigue is caused by an underlying medical condition generally lasting longer than one month (Levine & Greenwald 2009; Rosenthal et al. 2008).
- Relationship between medications and fatigue in SCI: None of the RCTs included discussed the effects of medications or established what baseline at baseline participants were currently taking. Sedating medications are frequently prescribed to people with SCI to help manage spasticity, mental health issues, or pain; among the medications that may induce feelings of fatigue that people with SCI commonly take include baclofen, benzodiazepines, opioids, tizanidine, gabapentin, amitriptyline, and nortriptyline (Fawkes-Kirby et al. 2008). In a retrospective chart review, Lee et al. (2010) found that 52% of participants with SCI had clinical levels of fatigue, 41/147 medications that they were taking were identified to be causing fatigue, and the medications were usually antispasticity or analgesic medications. Similarly, Fawkes-Kirby et al. (2008) found that people with SCI taking two or more prescriptions from these categories scored significantly worse on the FSS, indicating higher levels of fatigue. Future studies should consider documenting the current medications their participants are currently taking so that effects can be factored in and/or accounted for.

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Abbreviations

CBD	cannabidiol
CI	confidence interval
CFS	Chalder Fatigue Scale
CME	cannabis medicinal extracts
FAS	fatigue assessment scale
FES	functional electrical stimulation
HIIT	high-intensity interval training
MFI-20	Multi-Dimensional Fatigue Inventory
MFIS	Modified Fatigue Impact Scale
VO_{2peak}	Peak Oxygen Uptake
POMS	Profile of Moods States
RCT	randomized controlled trial
SCI	spinal cord injury
SMD	standardized mean difference
THC	delta-9-tetrahydrocannabinol