

# SCIRE

SPINAL CORD INJURY REHABILITATION EVIDENCE

## Orthostatic Hypotension Following Spinal Cord Injury

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## Key Points

In the management protocol of OH in individuals with spinal cord injury the following recommendations can be made:

- Midodrine hydrochloride should be included.
- There is limited evidence that fludrocortisone is effective.
- There is limited evidence that ergotamine is effective.
- There is little evidence that ephedrine is effective.
- There is limited evidence that droxidopa is effective.
- There is limited evidence that L-NAME is effective.

The benefits of sodium/salt loading have not been sufficiently proven effective in individuals with SCI.

There is insufficient evidence that elastic stockings or abdominal binders have any effect on cardiovascular responses to orthostasis in SCI.

The use of FES is an effective adjunct treatment to minimize cardiovascular changes during changes in position.

Simultaneous arm exercise during a tilt test is not effective for improving orthostatic tolerance.

The benefits of body-weight supported treadmill training for management of OH have not been sufficiently proven in SCI.

There is limited evidence that regular physical activity may improve orthostatic tolerance during a tilt test.

There is limited evidence that active stand training improves the response to orthostatic stress in cervical SCI.

The benefits of body-weight supported treadmill training for management of OH have not been sufficiently proven in SCI.

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## Abbreviations

AB	Abdominal Binder
BP	Blood Pressure
BWSTT	Body Weight Supported Treadmill Training
ELC	External Leg Compression
FES	Functional Electrical Stimulation
FNS	Functional Neuromuscular Stimulation
GCS	Graduated Compression Stockings
HR	Heart Rate
HUT	Head-up Tilt
LBNP	Lower Body Negative Pressure
L-DOPS, Droxidopa	L-threo-3,4-dihydroxyphenylserine
L-NAME	L-arginine-N-methyl-ester
MAP	Mean Arterial Pressure
OH	Orthostatic Hypotension
RATT	Robotic Assisted Tilt-Table
RER	Respiratory Exchange Ratio
WBV	Whole Body Vibration

# Orthostatic Hypotension Following SCI

## 1.0 Executive Summary

### What is orthostatic hypotension?

Orthostatic hypotension (OH) is defined as a decrease in systolic blood pressure of at least 20mmHg, or a reduction in diastolic blood pressure of at least 10mmHg, upon the change in body position from a supine (lying) to an upright position, regardless of the presence of symptoms.<sup>1</sup> Normally, the nervous system automatically constricts or dilates the blood vessels to balance blood pressure. After a SCI, this ability may become compromised, and orthostatic hypotension may be experienced. Several studies have documented the presence of OH following SCI, particularly during the acute period of injury, but it can persist for many years.<sup>2,3,4,5,6,7,8</sup> Sitting or Standing in physiotherapy is reported to trigger blood pressure decreases that are diagnostic of OH in 74% of SCI patients, and cause symptoms of OH (such as light-headedness or dizziness) in 59% of SCI individuals.<sup>9</sup> Thus, this may discourage individuals with SCI from participating in rehabilitation. Management of OH consists of pharmacological and non-pharmacological interventions.

### What are the risk factors of orthostatic hypotension?

Many factors can contribute to OH. The low level of efferent sympathetic nervous activity and the loss of the reflex vasoconstriction following SCI are the two major causes of OH. Decreases in blood pressure (BP) following the change to an upright position in individuals with SCI may be related to excessive pooling of blood in the abdominal viscera and lower extremities.<sup>5,7,10</sup> Additionally, regular movement of muscles pushes against blood vessels which help guide blood back to the heart. Hence, loss of muscle function in the lower extremities can cause blood to accumulate there. These mechanisms lead to a reduction of blood flow back to the heart and the rest of the body and present as orthostatic hypotension.

Other causes of orthostatic hypotension include low blood volume, low sodium levels in the blood, and deconditioning of the heart and blood vessels from extended bedrest.<sup>5,7,9</sup> Those with a traumatic SCI may also be at a greater risk than those with a non-traumatic SCI (McKinley et al. 1999). The prevalence of OH is greater in patients with higher spinal cord lesions, and thus it is more common in tetraplegia.<sup>7,8,11</sup> Some evidence show that nitric oxide, a chemical that widens the blood vessels, is produced more in SCI individuals.<sup>12</sup> This can result in a further decrease in blood pressure.

What are the signs and symptoms of orthostatic hypotension?

Orthostatic hypotension may occur with or without the presence of symptoms. Common signs and symptoms include:

- Temporary loss of consciousness
- Fainting
- Dizziness
- Light-headedness
- Fatigue
- Blurry vision
- Muscle weakness

### How do I manage my patients with OH?

Although a wide array of physical and pharmacological measures are recommended for the general management of OH,<sup>13</sup> very few have been evaluated for use in SCI. The general approach to

management of OH is that the therapeutic interventions should be implemented in stages dependent upon the severity of symptoms.<sup>13</sup> Non-pharmacologic measures alone are often insufficient to prevent symptoms of OH. Pharmacological interventions are often needed, particularly in SCI patients with moderate to severe OH symptoms.

### **Pharmacological Options**

Only Midodrine (a drug that constricts the blood vessels to bring up blood pressure) has some evidence supporting its use. There is evidence that this drug can elevate blood pressure and improve exercise performance.<sup>14,15</sup> Even so, the use of midodrine should be monitored carefully as 2 males reported urinary bladder dysreflexia with its use.<sup>16</sup>

Unfortunately, the number of studies addressing the pharmacological management of OH following SCI is few. It is often difficult to determine the effects of individual medications when they are used in combination therapies.

### **Non-Pharmacological Options**

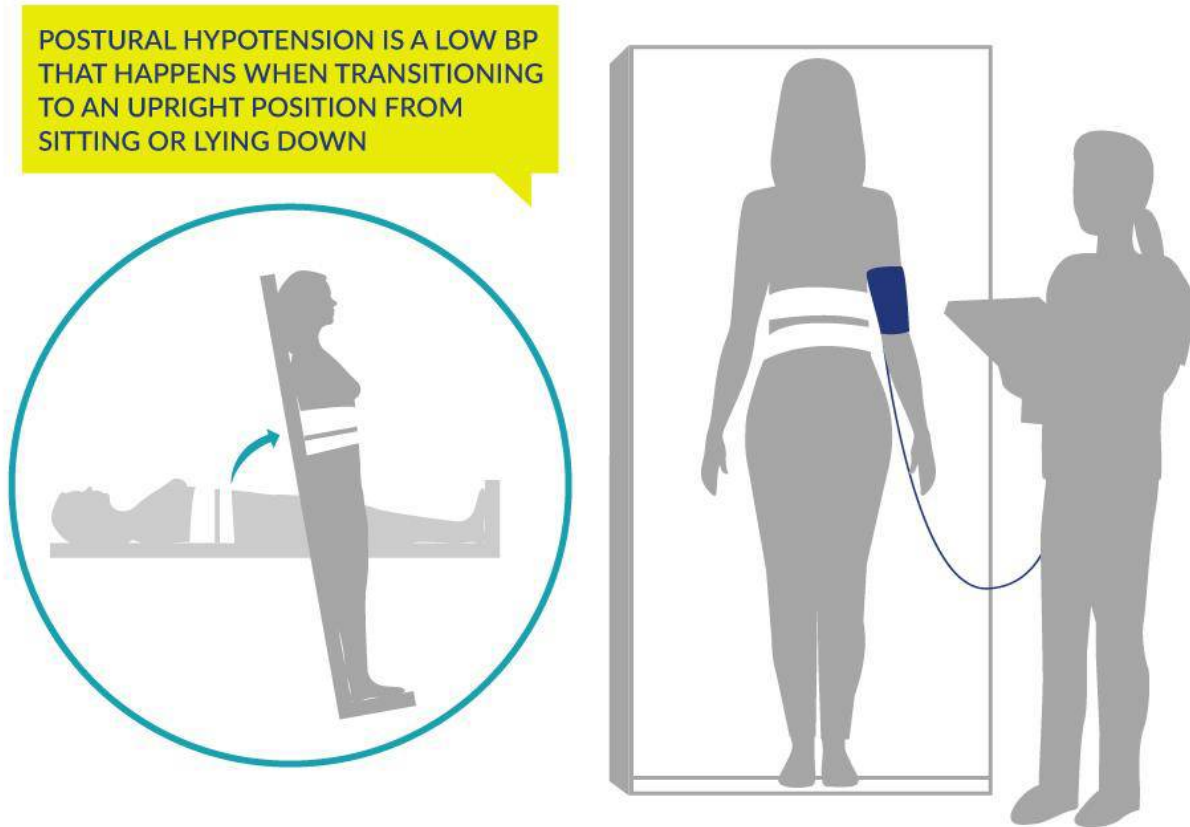
Functional Electrical Stimulation (FES) is one of the only treatments having limited evidence to support efficacy. During functional electrical stimulation, electrical impulses are sent to weak or paralyzed muscles, usually within the legs. This causes muscles to contract and helps move blood back to the heart and around the body. Functional electrical stimulation has been shown to be effective and can be used to supplement other forms of therapy.<sup>17-19</sup> Studies demonstrated that leg muscle contraction by functional electrical stimulation allowed tetraplegics with orthostatic hypotension to stand more often and for longer periods of time.<sup>18-19</sup>

Non-pharmacological options include fluid and salt intake, pressure binders or stockings, whole-body vibration, electrical stimulation, and physical activities. There is currently not enough evidence to support the efficacy of non-pharmacological interventions. Currently, only positive evidence on the effect of fluid and salt intake combined with other pharmacological interventions exist.<sup>8,20</sup>

## **2.0 Introduction**

The Consensus Committee of the American Autonomic Society and the American Academy of Neurology (CCAAS & AAN 1996) defined orthostatic hypotension (OH) as a decrease in systolic blood pressure of at least 20mmHg, or a reduction in diastolic blood pressure of at least 10mmHg, upon the change in body position from a supine to an upright position, regardless of the presence of symptoms. Several studies have documented the presence of OH following SCI (Chelvarajah, 2009, Cariga et al. 2002, Faghri et al. 2001; Mathias 1995). This condition occurs during the acute period of injury and persists in a significant number of individuals for many years (Sidorov et al. 2008; Claydon et al. 2006; Frisbie & Steele 1997). Standard mobilization treatment during physiotherapy (e.g. sitting or standing) is reported to trigger blood pressure decreases that are diagnostic of OH in 74% of SCI patients, and cause symptoms of OH (such as light-headedness or dizziness) in 59% of SCI individuals (Illman et al. 2000). Thus, this may discourage individuals with SCI from participating in rehabilitation. Management of OH consists of pharmacological and non-pharmacological interventions.

## ORTHOSTATIC HYPOTENSION

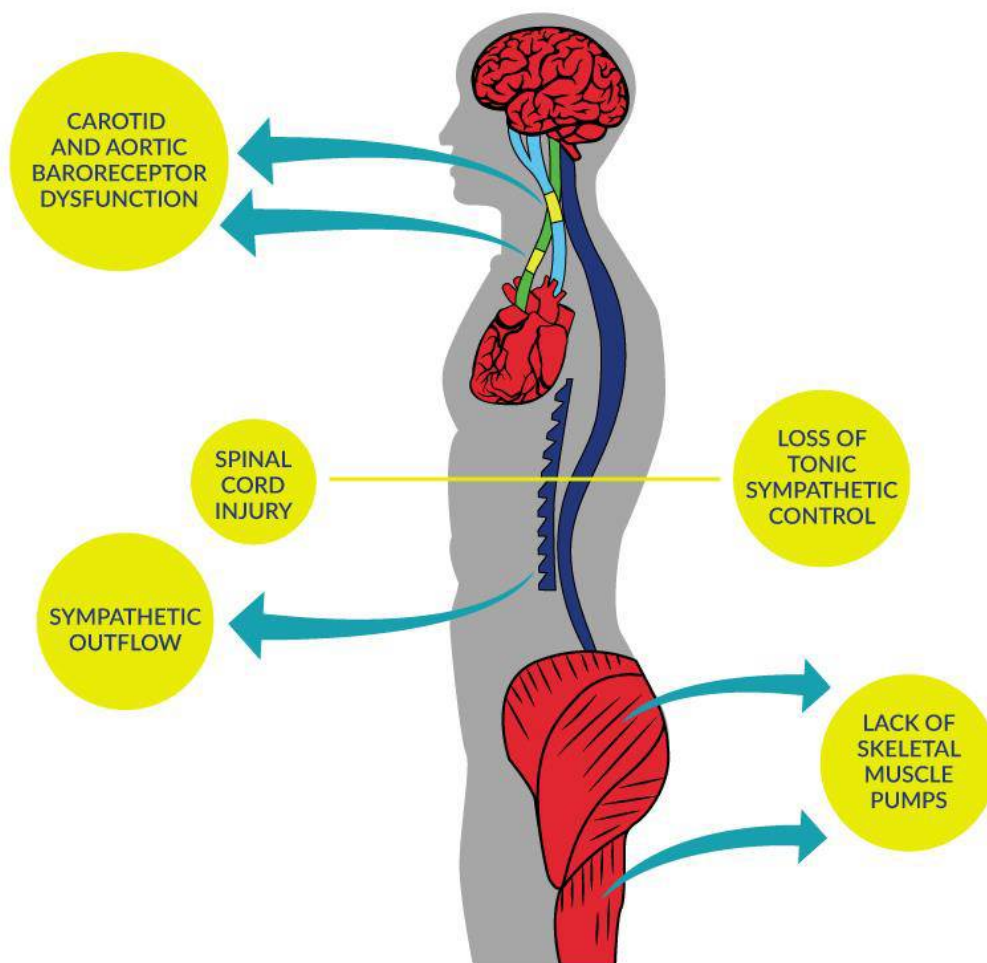


**Figure 1 – Orthostatic Hypotension as generated by Postural Changes**

The low level of efferent sympathetic nervous activity and the loss of the reflex vasoconstriction following SCI are the two major causes of OH (Table 1). Decreases in blood pressure (BP) following the change to an upright position in individuals with SCI may be related to excessive pooling of blood in the abdominal viscera and lower extremities (Krassioukov & Claydon, 2006; Claydon et al. 2006; Mathias 1995). This decrease in BP is compounded by the loss of lower extremity muscle function post SCI that is known to be important in counteracting venous pooling in the upright position. Excessive venous pooling in the lower extremities coupled with reduced blood volume in the intrathoracic veins lead to a decrease in ventricular end-diastolic filling pressure and end-diastolic volume thereby decreasing left ventricular stroke volume (Ten Harkel et al. 1994). Reduced ventricular filling and emptying ultimately lead to a reduction in cardiac output, and thus, arterial pressure (provided the reductions in cardiac output are marked). Unloading of the arterial baroreceptors induces a reflexive reduction in cardiac parasympathetic (vagal) activity. As a result, heart rate increases, although this is usually insufficient to compensate for decreased stroke volume. Therefore, cardiac output is reduced, which in turn, lowers arterial blood pressure. Subsequent pooling of blood in the lower extremities further decreases blood pressure, which may result in reduced cerebral flow, and symptoms of cerebral hypoperfusion (Table 2).

In addition to central causes of OH following SCI, there is also some evidence suggests that peripheral mechanisms also could contribute to orthostatic intolerance following SCI. For example, up-regulation of the potent vasodilator nitric oxide (NO) could potentially contribute to the orthostatic intolerance in this population (Vaziri 2003). In animal studies, it has been shown that NO synthase

expression is dysregulated following SCI (Zhao et al. 2007). Moreover, Wecht and co-investigators found that intravenous infusion of a relatively low dose of the NO synthase inhibitor L-arginine-N-methyl-ester (L-NAME) normalized blood pressure in individuals with SCI (Wecht et al. 2007).



**Figure 2 – Blood Pressure Dysfunction due to SCI**

Several other factors may predispose individuals with SCI to OH, including low plasma volume, hyponatremia, and cardiovascular deconditioning due to prolonged bed-rest (Claydon et al. 2006; Illman et al. 2000; Mathias 1995). The prevalence of OH is greater in patients with higher spinal cord lesions, and thus it is more common in tetraplegia (Claydon et al. 2006; Mathias 2006; Frisbie & Steele 1997). Furthermore, individuals with cervical SCI also experience greater posture-related decreases in blood pressure than those with paraplegia (Claydon et al. 2006; Mathias 1995). There is also an increased risk of OH in individuals who sustain a traumatic SCI versus a non-traumatic injury such as spinal stenosis (McKinley et al. 1999).

**Table 1: Factors Predisposing to OH Following SCI**



- |                                                                                                                                                                                                      |                                                                                                                                                                                                       |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• Multifactorial</li> <li>• Loss of tonic sympathetic control</li> <li>• Altered baroreceptor sensitivity</li> <li>• Lack of skeletal muscle pumps</li> </ul> | <p>Claydon et al. 2006<br/>Houtman et al. 2000; Wallin &amp; Stjernberg 1984<br/>Wecht et al. 2003; Munakata et al. 1997<br/>Faghri &amp; Yount 2002; Raymond et al. 2002; Ten Harkel et al. 1994</p> |
| <ul style="list-style-type: none"> <li>• Cardiovascular deconditioning</li> <li>• Altered salt and water balance</li> </ul>                                                                          | <p>Hopman et al. 2002; Vaziri 2003<br/>Frisbie 2004</p>                                                                                                                                               |

**Table 2: Signs and Symptoms of OH**

- |                                                                                                                                                                                                                                            |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• Light-headedness</li> <li>• Dizziness</li> <li>• Fainting</li> <li>• Blurred vision</li> <li>• Fatigue</li> <li>• Muscle weakness</li> <li>• Syncope (temporary loss of consciousness)</li> </ul> |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

### 3.0 Orthostatic Hypotension Systematic Review

As the body of knowledge is growing in the field of OH management for SCI, it is becoming increasingly important to review the literature and ensure that the information used both in research and clinical practice is current and evidence based. The aim of this section of the OH chapter is to provide an overview of the current systematic reviews available for in areas related to OH management in SCI population.

**Table 3: Orthostatic Hypotension Systematic Review**

<b>Authors; Country</b> <b>Date included in the review</b> <b>Number of articles</b> <b>Level of evidence</b> <b>Type of study</b> <b>Score</b>	<b>Methods</b> <b>Databases</b>	<b>Evidence</b>
Krassioukov et al. 2009; Canada  Reviewed published articles from 1950 to July 2008  N=26 n=251  <b>Level of evidence:</b> PEDRo Scale - RCTs (9–10: excellent; 6–8: good; 4–5: fair; 0-4: poor)  Modified Downs & Black scale - non RCTs (0 to 28)  <b>Type of study:</b>	<b>Methods:</b> Key word literature search for (original) articles, previous practice guidelines, and review articles was conducted to identify literature evaluating the effectiveness of any treatment or therapy for OH in the SCI population.  <b>Databases:</b> PubMed/MEDLINE, CINAHL, EMBASE, PsycINFO.	<ol style="list-style-type: none"> <li>1. There is evidence that OH can be improved with the use of fludrocortisones, ergotamine, ephedrine, L-DOPS, and salt supplementation (level 4 or 5), and salt and fluid regulation, in combination with other pharmacologic interventions (level 5).</li> <li>2. Cardiovascular responses during orthostatic challenges may be improved with FES (level 2), simultaneous upper extremity exercise with paraplegia, but not tetraplegia (level 2), but not 6 months of bodyweight support treadmill training.</li> <li>3. Cardiovascular responses during exercise may be improved with midodrine (level 2) and elastic stockings and abdominal binders (level 2).</li> </ol>

<b>Authors; Country</b> <b>Date included in the review</b> <b>Number of articles</b> <b>Level of evidence</b> <b>Type of study</b> <b>Score</b>	<b>Methods</b> <b>Databases</b>	<b>Evidence</b>
2 case reports, 1 case series, 2 observational, 1 pre-post, 1 RCT  AMSTAR: 6		
Gillis et al. 2008; Belgium  Reviewed published articles from 1966 to April 2007  N=13 n=138  <b>Level of evidence:</b> Downs & Black scale  <b>Type of study:</b> Parallel group, cross-over, quasi-random assignment  AMSTAR: 5	<b>Methods:</b> Key word literature search for non-pharmacological management of OH during early rehab in SCI. <b>Databases:</b> PubMed/MEDLINE, OVID/EMBASE, CENTRAL	<ol style="list-style-type: none"> <li>1. The evidence is inconclusive whether compression/pressure, upper body exercise and biofeedback therapies are able to control OH.</li> <li>2. Upper body exercise may be more relevant to lower-level paraplegia where sympathetic outflow is intact and motor functionality is present.</li> <li>3. FES can attenuate the drop in BP by 8/4 mm Hg during an orthostatic challenge and is promising technology. However, few studies utilized patients in the acute stage.</li> </ol>

## Discussion

We found only one systematic review on OH management for individuals with SCI by Krassioukov et al (2009). Although the authors found that the overall quality of the literature was poor and that higher quality research assessing the treatments for OH in the SCI population is needed, there is level 2 evidence that pressure from elastic stockings and abdominal binders may improve cardiovascular physiologic responses during submaximal upper-extremity exercises. In addition, FES is an important adjunct treatment to minimize cardiovascular changes during postural orthostatic stress and that simultaneous upper-extremity exercises may increase orthostatic tolerance during a progressive tilt exercise in subjects with paraplegia.

### 4.0 Pharmacological Management of OH in SCI

The majority of our knowledge in managing OH has been obtained from patients with neurological causes other than SCI (e.g. diabetic neuropathy, heart disease, multiple system atrophy, pure autonomic failure, Parkinson's disease, dysautonomia). Numerous medications, including midodrine hydrochloride, fludrocortisone, and ephedrine, have been successful in managing OH in these chronic conditions. However, as the mechanisms underlying the development of OH in the SCI population differ from those in these non-SCI populations, it is important to assess the effectiveness of these medications specifically in people with SCI.

**Table 4: Pharmacological Management of OH in SCI**

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Nieshoff et al. 2004; USA PEDro=6 RCT N=4	<p><b>Population:</b> Chronic motor complete tetraplegia</p> <p><b>Treatment:</b> Midodrine 5mg, 10 mg, or placebo (unmarked capsule), double blind, placebo-controlled cross-over design.</p> <p><b>Outcome Measures:</b> Measure of cardiovascular parameters during wheelchair ergometer test.</p>	<ol style="list-style-type: none"> <li>1. Midodrine, 10 mg elevated systolic blood pressure during exercise in 3 participants. Peak systolic BPs ranged from 90 to 126 mmHg under baseline and placebo conditions, 114-148 after 5 mg of midodrine, and 104 to 200 mmHg after 10 mg.</li> <li>2. Two participants showed reduced perceived exertion and increased VO<sub>2</sub> following midodrine 10 mg.</li> <li>3. No adverse effects of midodrine were noted.</li> </ol>
Phillips et al. 2014a Canada Prospective controlled trial N=16	<p><b>Population:</b> 8 persons with SCI (1 female) and 8 age-and-sex matched able bodied controls Participants with SCI: Mean (SD) age: 30 (11) years DOI: 7 subjects &lt;1 year post injury, 1 subject &gt;1 year post injury All motor complete cervical spinal cord injuries AIS grade A: 6; AIS grade B: 2</p> <p><b>Treatment:</b> Subjects tested supine and during upright tilt. SCI group had 2 treatment sessions, one with midodrine and one without. AB group had one session without midodrine.</p> <p><b>Outcome Measures:</b> Beat-by-beat BP and HR, common carotid artery (CCA) diameter. Calculated arterial distensibility and arterial stiffness (<math>\beta</math>-stiffness index)</p>	<ol style="list-style-type: none"> <li>1. Systolic BP was lower in SCI while supine vs. AB; BP, CCA diameter and diameter difference were reduced in SCI while upright vs. AB; <math>\beta</math>-stiffness index was elevated in SCI when upright (+12%) and relative decrease in baroreflex sensitivity (BRS) was greater in SCI vs. AB</li> <li>2. Negative relationship between BRS and <math>\beta</math>-stiffness in SCI; no relationship in AB</li> <li>3. Midodrine led to increased BP and decreased HR in both supine and upright positions; no change in BRS or CCA parameters</li> <li>4. Reduced BRS is closely related to increased arterial stiffness in the SCI population</li> </ol>
Phillips et al. 2014b Canada Prospective controlled trial N=20	<p><b>Population:</b> 10 persons with SCI (3 females) and 10 age-and-sex matched able bodied controls Participants with SCI: Mean (SD) age: 29 (10) years DOI: 8 subjects &lt;1 year post injury, 2 subject &gt;1 year post injury 8 cervical injuries, 2 thoracic injuries AIS grade A: 8; AIS grade B: 2</p> <p><b>Treatment:</b> Subjects tested supine and during progressive upright tilt. SCI group had 2 treatment sessions, one with midodrine and one without. AB group had one session without midodrine.</p> <p><b>Outcome Measures:</b> beat-by-beat BP, middle and posterior cerebral artery blood velocity (MCAv, PCAv, respectively)</p>	<ol style="list-style-type: none"> <li>1. Coherence increased in SCI between BP-MCAv and BP-PCAv by 35% and 22% respectively compared to AB.</li> <li>2. SCI BP-PCAv gain was reduced 30% compared to AB.</li> <li>3. The acute (0–30 s after tilt) MCAv and PCAv responses were similar between groups.</li> <li>4. In SCI, midodrine led to improved PCAv responses 30 – 60 s following tilt (10+/- 3% vs. 4+/- 2% decline)</li> <li>5. In SCI, midodrine led to a 59% improvement in orthostatic tolerance</li> </ol>
Phillips et al. 2014c Canada Prospective controlled trial N=20	<p><b>Population:</b> 10 persons with SCI (3 females) and 10 age-and-sex matched able bodied controls Participants with SCI: Mean (SD) age: 29 (10) years DOI: 8 subjects &lt;1 year post injury, 2 subject &gt;1 year post injury</p>	<ol style="list-style-type: none"> <li>1. At rest: mean BP was lower in SCI (70±10 versus 92±14 mm Hg); PCAv conductance was higher in SCI (0.56±0.13 versus 0.39±0.15 cm/second/mm Hg)</li> <li>2. AB had a 20% increase in PCAv during cognition while this response was absent in SCI</li> </ol>

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
	<p>8 cervical injuries, 2 thoracic injuries AIS grade A: 8; AIS grade B: 2</p> <p><b>Treatment:</b> Visual and verbal fluency task to assess neurovascular coupling (NVC). SCI group had 2 sessions, one with midodrine and one without. AB group had one session without midodrine.</p> <p><b>Outcome Measures:</b> beat-by-beat BP, middle and posterior cerebral artery blood velocity (MCAv, PCAv, respectively)</p>	<ol style="list-style-type: none"> <li>3. With midodrine, NVC was improved by 70% in SCI, and cognitive function improved by 13%</li> <li>4. Improvements in BP were related to improvements in cognitive function in those with SCI</li> </ol>
<p>La Fontaine et al. 2013; USA Prospective controlled trial N=27</p>	<p><b>Population:</b> Study 1: 7 tetraplegic subjects (38±10 years; 2 complete AIS A injury), 6 age-matched neurologically intact controls (32±8 years). Study 2: 7 tetraplegic subjects (41±9 years; 1 complete AIS A injury), 7 age-matched neurologically intact controls (33±9).</p> <p><b>Treatment:</b> Study 1: open-label trial with intravenous administration of L-NAME at specific doses (0, 1, 2, or 4 mg·kg<sup>-1</sup>) in the supine position. Study 2: orthostatic challenge (head-up tilt) with or without L-NAME (0, 1, or 2 mg·kg<sup>-1</sup>), controls completed a single visit (0 mg·kg<sup>-1</sup>).</p> <p><b>Outcomes Measures:</b> Study 1: Digital ECGs obtained at baseline, immediately after infusion (60 min) and 1 hour post-infusion (120 min). Study 2: Digital ECGs obtained at baseline, 60 min, and at 2 10 min post-infusion time points after head-up tilt.</p>	<ol style="list-style-type: none"> <li>1. Escalating dose of L-NAME (0.0, 1.0, 2.0, 4.0 mg/kg) did not significantly change heart rate, PQ, QT or QTC (heart-corrected QT) intervals at rest or during head-up tilt in subjects with tetraplegia or controls.</li> <li>2. Escalating dose of L-NAME (0.0, 1.0, 2.0, 4.0 mg/kg) did not significantly change resting heart rate, PQ, QT or QTC intervals in those with tetraplegia or controls.</li> <li>3. L-NAME administration does not appear to affect cardiac rate or conduction.</li> </ol>
<p>Wecht et al. 2013; USA Prospective controlled trial N=10</p>	<p><b>Population:</b> 10 hypotensive subjects with SCI (8M; 2F); 8 tetraplegic, 1 high thoracic (T4) and 1 low thoracic (T10); age: 44±10 years; duration of injury 15±13 years.</p> <p><b>Treatment:</b> Escalating dose of L-Threo-3, 4-dihydroxyphenylserine (droxidopa) (100mg, 200mg, 400mg) given over four lab visits with placebo on first visit. Each visit involved 30 min seated baseline, 30- to 60 min supine, and a 4 hour seated post-drug observation.</p> <p><b>Outcome measures:</b> Blood pressure and heart rate changes from baseline to the post-drug period; orthostatic heart rate and blood pressure responses; reporting of subjective adverse effects.</p>	<ol style="list-style-type: none"> <li>1. Seated blood pressure was significantly elevated with 400mg droxidopa compared with placebo and 100mg droxidopa for 3 hours, and was elevated for 2 hours compared with 200mg droxidopa.</li> <li>2. Increase in supine blood pressure was not worsened following droxidopa.</li> <li>3. Expected fall in blood pressure when transferred from the supine to the seated position was prevented with droxidopa 200mg and 400mg.</li> <li>4. Peak seated blood pressure reached the hypertensive range in 3 study subjects following the 400-mg dose of droxidopa (156/100, 150/94, 149/93 mmHg). These episodes occurred 100 minutes after administration of droxidopa and were resolved within 30 minutes.</li> </ol>
<p>Wecht et al. 2011; USA Prospective controlled trial N=7</p>	<p><b>Population:</b> 5 male and 2 female healthy subjects (26-54 years old, level of injury C4-C7, duration of injury 8-37 years).</p> <p><b>Treatment:</b> Subjects were studied during 3 laboratory visits: no drug, midodrine</p>	<ol style="list-style-type: none"> <li>1. L-NAME and midodrine reduced OH symptoms compared to the no-drug trial.</li> <li>2. L-NAME significantly increased orthostatic MAP compared with the no drug and midodrine trials.</li> <li>3. There was a trend for midodrine to increase MAP</li> </ol>

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
	<p>(10mg; administered orally 30 min before HUT), and L-NAME (1.0 mg/kg; infused over a 60-min period).</p> <p><b>Outcome measures:</b> Heart rate, blood pressure (systolic and diastolic), mean arterial pressure (MAP), cerebral blood flow (CBF), and markers of the renin-angiotensin- aldosterone system (RAAS, plasma renin and serum aldosterone) were measured in the supine position at baseline (BL) and during a 45° HUT manoeuver.</p>	<p>during HUT.</p> <ol style="list-style-type: none"> <li>4. Modest suppression of renin and aldosterone responses to HUT with L-NAME and midodrine.</li> <li>5. There was a significant relationship between change in MAP and change in CBF with HUT among the subjects tested (<math>r^2=0.592</math>).</li> </ol>
<p>Wecht et al. 2010; USA Prospective controlled trial N=10</p>	<p><b>Population:</b> 8 males, 2 females; 43±9 years; duration of injury 22±11 years; SCI C4-C7; AIS A or B</p> <p><b>Treatment:</b> Midodrine (no drug, 5 mg or 10 mg) over 3 testing days.</p> <p><b>Outcome Measures:</b> Blood pressure (BP), heart rate (HR), mean arterial pressure (MAP) and middle cerebral artery mean blood flow velocity (MCA MFV) during supine and head-up tilt (HUT) of 45 min at 45°.</p>	<ol style="list-style-type: none"> <li>1. 10 mg midodrine increased supine diastolic BP and MAP, and increased systolic BP and MAP after tilt test compared to control.</li> <li>2. The significant increase in systolic BP during HUT was due to an augmented response in 2 subjects with little to no change in the 8 other individuals.</li> </ol>
<p>Wecht et al. 2009; USA Prospective controlled trial N=12</p>	<p><b>Population:</b> 5 subjects with chronic tetraplegia (1 AIS A and 4 AIS B); 7 age-, height-, and weight matched able-bodied controls. All subjects were between 19 and 53 years old.</p> <p><b>Treatment:</b> SCI subjects underwent treatment of 1.0 mg/kg of L-NAME, as well as placebo control at supine rest and during head-up tilt (HUT); the control group received only placebo.</p> <p><b>Outcome Measures:</b> Heart rate (continuously monitored by ECG), mean arterial blood pressure (MAP); active plasma renin and serum aldosterone concentrations.</p>	<ol style="list-style-type: none"> <li>1. Supine systolic, diastolic, and mean arterial blood pressure were significantly higher in subjects with SCI after L-NAME infusion compared to placebo</li> <li>2. Orthostatic (45° HUT) MAP was significantly reduced after placebo infusion in SCI compared to controls (66±13 vs. 88±10 mmHg);</li> <li>3. MAP during HUT was comparable to controls (88±10 mmHg) following L-NAME infusion in subjects with SCI (83±3 mmHg).</li> <li>4. Serum aldosterone levels were reduced during HUT after L-NAME infusion (120±45 pg/mL) compared to placebo (259±69 pg/mL; <math>p&lt;0.05</math>) in subjects with SCI.</li> </ol>
<p>Wecht et al. 2008; USA Prospective controlled trial N=14</p>	<p><b>Population:</b> 7 subjects with tetraplegia; age 38±10 years; duration of injury 18±11 years and 7 neurologically intact controls 34±9 years.</p> <p><b>Treatment:</b> Escalating dose of L-NAME (0.0, 1.0, 2.0, 4.0 mg/kg).</p> <p><b>Outcome Measures:</b> Supine heart rate (HR), mean arterial blood pressure (MAP) and plasma norepinephrine (NE) concentrations.</p>	<ol style="list-style-type: none"> <li>1. There was a heightened MAP response to escalating dose of L-NAME in subjects with tetraplegia compared to the controls.</li> <li>2. HR was reduced in a dose dependent manner, and this response did not differ comparing subjects with tetraplegia to the controls.</li> <li>3. Plasma NE was significantly at baseline in subjects with tetraplegia compared to the controls.</li> <li>4. Following L-NAME infusion, plasma NE was reduced in a dose dependent manner in the controls, whereas plasma NE levels were unchanged following L-NAME infusion in subjects with tetraplegia.</li> </ol>

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Wecht et al. 2007; USA Prospective controlled trial N=14	<p><b>Population:</b> 7 subjects with tetraplegia; age 38±10 years; duration of injury 18±11 years and 7 neurologically intact controls 34±9 years.</p> <p><b>Treatment:</b> Placebo versus L-NAME (1.0 mg/kg).</p> <p><b>Outcome Measures:</b> Supine heart rate (HR), and mean arterial blood pressure (MAP).</p>	<ol style="list-style-type: none"> <li>1. Supine MAP was significantly reduced in subjects with tetraplegia compared to controls at baseline.</li> <li>2. Supine HR did not differ between the groups at baseline.</li> <li>3. MAP was significantly reduced in subjects with tetraplegia compared to the controls following placebo infusion.</li> <li>4. Differences in MAP between subjects with tetraplegia and controls were no longer evident following L-NAME infusion.</li> </ol>
Frisbie 2004; USA Observational N=4	<p><b>Population:</b> Chronic cervical complete tetraplegia; AIS A.</p> <p><b>Treatment:</b> Evaluation of urinary salt and water output in relation to prescribed dosage of ephedrine (doses range from 0 to 100 mg daily).</p> <p><b>Outcome Measures:</b> Severity of OH, urinary output.</p>	<ol style="list-style-type: none"> <li>1. With decreasing ephedrine dose (and OH severity), there was an increase in mean daily output of urine sodium (from 50 to 181 mEq), water (from 1.5 to 5.3 L), rate of creatinine secretion, rates of water excretion, sodium concentrations, and reduced urine osmolality.</li> </ol>
Mukand et al. 2001; USA Case report N=1	<p><b>Population:</b> 21-year old male with traumatic C6 tetraplegia; AIS C, with symptomatic OH.</p> <p><b>Treatment:</b> Midodrine (2.5 to 15 mg 3X/day).</p> <p><b>Outcome Measures:</b> Blood pressure, symptoms of OH.</p>	<ol style="list-style-type: none"> <li>1. Gradual increase in dose of midodrine from 2.5mg to 10 mg (at 0800, 1200 and 1600 hours) resulted in resolution of symptoms of OH. Patient was able to participate fully in the rehabilitation program.</li> </ol>
Barber et al. 2000; USA Case series N=2	<p><b>Population:</b> 2 cases of acute motor complete tetraplegia.</p> <p><b>Treatment:</b> Fludrocortisone acetate 0.1 mg 4X/day or midodrine 10 mg 3X/day.</p> <p><b>Outcome Measures:</b> Blood pressure, heart rate, and symptoms of OH.</p>	<ol style="list-style-type: none"> <li>1. No effect of fludrocortisone on OH.</li> <li>2. Fludrocortisone in both patients resulted in pitting edema of hands and lower limbs.</li> <li>3. Initiation of midodrine hydrochloride resolved orthostatic symptoms in both individuals without any complications.</li> </ol>
Frisbie & Steele 1997; USA Observational N=231	<p><b>Population:</b> SCI; ephedrine (medically treated for OH) group age, 57±15 years; duration of injury 26±15 years. SCI no ephedrine group: 51±15 years, duration of injury 22±14 years.</p> <p><b>Treatment:</b> Retrospective chart review of use of ephedrine (n=30), salt supplementation (n=6), fludrocortisone (n=3) or physical therapy.</p> <p><b>Outcome Measures:</b> OH symptoms, serum sodium and urine osmolality.</p>	<ol style="list-style-type: none"> <li>1. Single dose of ephedrine usually sufficient to prevent symptoms but observed that some patients failed to recognize need for repeat doses later in day.</li> <li>2. Symptoms of OH were reduced consciousness (100% of subjects), strength (75%), vision (56%) and breath (53%). Precipitating factors were hot weather (77%), bowel care (33%) and meals (30%).</li> <li>3. Low blood sodium found in 54% of the OH patients and 16% of those without.</li> </ol>
Muneta et al. 1992; Japan Case report N=1	<p><b>Population:</b> 72-year old woman with non-traumatic SCI and paroxysmal hypotension.</p> <p><b>Treatment:</b> Several weeks of salt supplement (7 then 15 g/day) was followed by L-threo-3,4-dihydroxyphenylserine (100 mg up to 600 mg/day).</p> <p><b>Outcome Measures:</b> Blood pressure, catecholamines (epinephrine and norepinephrine), plasma renin activity.</p>	<ol style="list-style-type: none"> <li>1. After salt supplement, a marked ↑BP, ↑ norepinephrine and ↓ basal plasma renin activity was observed in response to sitting.</li> <li>2. Addition of L-threo-3,4-dihydroxyphenylserine for 2 weeks, showed elevation in catecholamines about 5 and 10 times without an apparent increase in resting BP.</li> <li>3. Significant improvement in the symptoms of OH and patient was able to participate in rehabilitation program.</li> </ol>

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Senard et al. 1991; France Pre-post N=7	<p><b>Population:</b> 45-year-old subject with chronic complete traumatic paraplegia; 6 non-SCI male controls.</p> <p><b>Treatment:</b> Clonidine (150 µg, 2X/day) and midodrine (specific alpha 1-agonist) (10 mg, 2X daily). Heart rate assessed by blinded tester.</p> <p><b>Outcome Measures:</b> Blood pressure, heart parameters, plasma catecholamine, alpha-adrenoceptor sensitivity.</p>	<ol style="list-style-type: none"> <li>1. The increase in systolic blood pressure induced by midodrine (10 mg) was significantly higher in the tetraplegic patient (change of 56 mmHg) compared to controls (change of 15 mmHg).</li> <li>2. Midodrine and clonidine alone or the two drugs in combination led to an increase in resting BP and decrease severity of OH.</li> </ol>
Groomes & Huang 1991; USA Case report N=1	<p><b>Population:</b> 28-year-old with chronic C5 tetraplegia.</p> <p><b>Treatment:</b> Ergotamine (2 mg), daily combined with fludrocortisone (0.1- .05 mg).</p> <p><b>Outcome Measures:</b> Blood pressure.</p>	<ol style="list-style-type: none"> <li>1. Following 10 days with fludrocortisone patient able to tolerate sitting. Following additional ergotamine, the patient was able to tolerate an upright position without symptoms.</li> </ol>

## Discussion

### Midodrine (ProAmatine)

Midodrine, a selective alpha1 adrenergic agonist, exerts its actions by activating the alpha-adrenergic receptors of the arteriolar and venous vasculature, thus producing an increase in vascular tone and blood pressure. Midodrine has a half-life of approximately 25 minutes. Specifically, plasma levels of Midodrine peak approximately half an hour after oral ingestion, with this amount halved every 25 minutes. However, the primary metabolite reaches peak blood concentrations about 1 to 2 hours after a dose of Midodrine and has a half-life of about 3 to 4 hours. Usual starting dose is 2.5mg two or three times daily. Doses are increased quickly until a response occurs or a maximum recommended dose of 10 mg dose, 2-3 times per day (total 30 mg/day) is attained (Wright et al. 1998). Midodrine does not cross the blood-brain barrier and is not associated with CNS effects. Benefits of Midodrine in the management of OH in individuals with SCI were reported in a level 2 RCT (Nieshoff et al. 2004), in four level 2 prospective controlled trials (Phillips et al. 2014a; Phillips et al. 2014b; Phillips et al. 2014c; Wecht et al. 2010) and three level 4 studies (Mukand et al. 2001; Barber et al. 2000; Senard et al. 1991) and one level 5 study (Mukand et al. 1992). Of note, a recent case report on 2 male subjects demonstrated urinary bladder dysreflexia with the use of midodrine (Vaidyanathan et al. 2007) which suggests Midodrine should be employed cautiously.

Although the only randomized control trial consisted of 4 subjects (Nieshoff et al. 2004), this study used a rigorous double-blind placebo-controlled, randomized, within-subjects cross-over trial. Not only was systolic blood pressure increased during peak exercise in 3 of the 4 subjects tested, but exercise performance was also enhanced. Thus, there is level 2 evidence (Nieshoff et al. 2004) that Midodrine may increase blood pressure and enhance exercise performance in some (75%) individuals with SCI, similar to other clinical populations with cardiovascular autonomic dysfunction. Furthermore, there are four additional prospective controlled trials (n=10-20), which support the positive effect of midodrine on orthostatic tolerance (Phillips et al. 2014a; Phillips et al. 2014b; Phillips et al. 2014c; Wecht et al. 2010). Nevertheless, it would be important to confirm this evidence with a larger trial.

### Fludrocortisone (Florinef)

Fludrocortisone is a mineralocorticoid that induces more sodium to be released into the bloodstream. Because water follows the movement of sodium, fludrocortisone increases blood volume. Furthermore, fludrocortisone may enhance the sensitivity of blood vessels to circulating

catecholamines (Van Lieshout et al. 2000; Schatz 1984). The starting dose is generally 0.1 mg daily. Blood pressure rises gradually over several days with maximum effect at 1-2 weeks. Doses should be adjusted at weekly or biweekly intervals. Adverse effects include hypokalemia (low potassium), which occurs in 50% of individuals, and hypomagnesemia, which occurs in 5%. Both may need to be corrected with supplements. Fludrocortisone should not be used in persons with congestive heart failure due to its effect on sodium retention. Headache is a common side effect. The benefit of Fludrocortisone has not been sufficiently proven in individuals with SCI. One level 4 case series (Barber et al. 2000), one level 5 case report (n=1) (Grooms & Huang 1991), and one level 5 observational (Frisbie & Steele 1997) study have described the use of Fludrocortisone for the management of OH in a SCI population.

Barber et al. (2000) studied two patients and did not observe an effect of fludrocortisone. Frisbie and Steele (1997) combined fludrocortisone with other pharmacological and physical agents in three patients; unfortunately, since outcomes specific to this group were not described, the specific effects of fludrocortisone could not be discerned. Therefore, there is level 4 evidence (Barber et al. 2000) from one case series of two patients that fludrocortisone is not effective for OH in SCI.

#### Dihydroergotamine

Dihydroergotamine, or Ergotamine, is an ergot alkaloid that interacts with alpha adrenergic receptors and has selective vasoconstrictive effects on peripheral and cranial blood vessels. Plasma levels peak around 2 hours after ingestion. One case report combined Ergotamine with fludrocortisone to successfully prevent symptomatic OH in one individual with SCI (Grooms & Huang 1991). Hence, there is level 5 (Grooms & Huang 1991) evidence that Ergotamine, taken daily combined with fludrocortisone, successfully prevents OH in one individual with SCI.

#### Ephedrine

Ephedrine, a non-selective, alpha and beta receptor agonist, acts centrally and peripherally. Its peripheral actions are attributed partly to norepinephrine release and partly to direct effects on receptors. Ephedrine is usually given at a dosage of 12.5-25 mg, administered orally, three times a day. Side effects may include tachycardia, tremor and supine hypertension. Ephedrine raises blood pressure both by increasing cardiac output and inducing peripheral vasoconstriction. Its plasma half-life ranges from 3 to 6 hours (Kobayashi et al. 2003). Systematic review of the literature found level 5 evidence based on one retrospective chart review (Frisbie & Steele 1997) and a cross-sectional observation study (Frisbie 2004). Frisbie (2004) reported that daily urinary output of sodium and fluid was inversely related to the prescribed dose of Ephedrine in 4 patients with OH. While results suggest that Ephedrine resulted in an improvement in hyponatremia, renal conservation of water still exceeded that of sodium in 3 of the 4 cases. Frisbie and Steele (1997) report in their retrospective review of 30 patients taking Ephedrine that one dose in the morning is usually sufficient to reduce symptoms of OH; however, some patients failed to recognize the need for a repeated dose later in the day. Hence, there is level 5 evidence (Frisbie & Steele 1997) that Ephedrine may reduce symptoms of OH.

#### L-threo-3,4-dihydroxyphenylserine (L-DOPS, Droxidopa)

L-DOPS is an exogenous, neutral amino acid that is also a precursor of noradrenalin. Two published studies (Wecht et al. 2013; Muneta et al. 1992) evaluate the effects of L-DOPS on OH. Wecht et al. (2013) in a pre-post study found that the use of increased doses of L-threo-3,4-dihydroxyphenylserine (droxidopa 100 mg, 200 mg, 400 mg) in hypotensive subjects did not cause excessive increases in supine blood pressure. Additionally, the 400-mg dose of droxidopa was found to be effective for increasing seated blood pressure for up to 3 hours in study subjects. The expected fall in blood pressure when transferred to the seated position from supine was prevented with droxidopa 200 and 400mg. There is level 4 evidence based on one pre-post study (Wecht et al. 2013) that L-threo-3,4-dihydroxyphenylserine at the doses tested is safe and moderately effective for the treatment of hypotension and OH.



Muneta et al. (1992) conducted a level 5 study involving one person with nontraumatic SCI. They showed that treatment with sodium supplementation in combination with L-threo-3,4-dihydroxyphenylserine, markedly improved the syncope and drowsiness associated with hypotension and increased the patient's daily activity. There is level 5 evidence based on one case study (Muneta et al. 1992) that L-DOPS, in conjunction with sodium supplementation may be effective for reducing OH.

#### Nitro-L-arginine methyl ester (L-NAME)

L-NAME decreases the production of the vasodilator nitric oxide by inhibiting the expression of its enzyme, nitric oxide synthase. Increased nitric oxide release has been associated with orthostatic intolerance after cardiovascular deconditioning and has been proposed to play a role in OH after SCI (Wecht et al. 2007). Three studies (La Fontaine et al. 2013; Wecht et al. 2009; Wecht 2011) examined the use of L-NAME in the treatment of OH following SCI. These studies found that after infusion of 1.0 or 2.0 mg/kg of L-NAME, individuals with tetraplegia had a higher mean arterial pressure in response to orthostatic challenge (a head tilt procedure) compared with those individuals who received a placebo. It should be noted that the increase in mean arterial pressure in the treatment group was not maintained over the entire head tilt procedure for all 3 studies. In La Fontaine et al. (2013), the effect was maintained for 1 additional hour post-infusion. In summary, there is level 2 evidence that L-NAME increases the blood pressure of SCI subjects following a head up tilt procedure.

### **General Discussion**

In summary, the studies addressing the pharmacological management of OH following SCI are limited by a small number of trials with low numbers of subjects and numerous case reports. Furthermore, it is often difficult to determine the effects of individual medications when used as combination therapies. There is sufficient evidence to suggest that Midodrine hydrochloride should be included in the management protocol of OH. Further research needs to quantify the effects of the many pharmacological interventions which have been shown to be effective in conditions other than spinal cord injury.

### **Conclusion**

***There is level 2 evidence (from 1 RCT and 4 prospective controlled trials) (Nieshoff et al. 2004; Wecht 2010; Phillips et al. 2014a; Phillips et al. 2014b; Phillips et al. 2014c) that Midodrine may be effective in reducing OH in individuals with SCI.***

***There is level 2 evidence (from 4 prospective controlled trials) (Wecht et al. 2011, 2009, 2008, 2007) that L-NAME may be effective for reducing OH.***

***There is level 4 evidence (from 1 case series) (Barber et al. 2000) that fludrocortisone is not effective for OH in SCI.***

***There is level 5 evidence (from 1 case report) (Groomes & Huang 1991) that Ergotamine, combined daily with fludrocortisone, may successfully prevent symptomatic OH.***

***There is level 5 evidence (from 1 observational study) (Frisbie & Steele 1997) that Ephedrine may prevent some symptoms of OH.***

***There is level 4 evidence (from 1 pre-pos study) (Wecht et al. 2013) that droxidopa may be effective for reducing OH.***

***There is level 5 evidence (from 1 case report) (Muneta et al. 1992) that L-DOPS, in conjunction with salt supplementation may be effective for reducing OH.***

Midodrine hydrochloride should be included in the management protocol of OH in individuals with spinal cord injury.

There is limited evidence that the following agents are effective for the management of OH in SCI – ergotamine, fludrocortisone, ephedrine, L-DOPS, L-NAME.

## 5.0 Non-pharmacological Management of OH in SCI

Of the non-pharmacological studies, three involved the regulation of fluid and sodium intake while others investigated physical modalities such as abdominal binders, whole-body vibration, physical activities, and electrical muscle stimulation.

### 5.1 Fluid and Sodium Intake in Management of OH in SCI

OH is common among patients with higher levels of SCI, may be present without symptoms, and often coexists with abnormal sodium and fluid metabolism. Increases in fluid intake and a diet high in salt/sodium can expand extracellular fluid volume and improve orthostatic responses. This simple dietary intervention appears to be effective in patients with idiopathic OH without SCI (Claydon & Hainsworth 2004; Davidson et al. 1976).

**Table 5: Fluid and Sodium Intake for Management of OH in SCI**

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Frisbie 2004; USA Observational N=4	<b>Population:</b> Chronic cervical complete tetraplegia; AIS A <b>Treatment:</b> Evaluation of urinary salt and water output in relation to prescribed dosage of ephedrine (doses range from 0 to 100 mg daily) <b>Outcome Measures:</b> Severity of OH, urinary output.	1. With decreasing ephedrine dose (and OH severity), there was a mean increase in daily output of urine sodium (from 50 to 181 mEq), water (from 1.5 to 5.3 L), rate of creatinine secretion sodium concentrations, and rates of water excretion, and a decrease in urine osmolality.
Frisbie & Steele 1997; USA Observational N=231	<b>Population:</b> SCI; Ephedrine (medically treated for OH) group: mean(SD) age 57(15) yrs, mean(SD) duration of paralysis 26(15) yrs; No ephedrine group: mean(SD) age 51(15.2) yrs, mean(SD) YPI 22(13.5). <b>Treatment:</b> Retrospective chart review of use of ephedrine (n=30), sodium/salt supplementation (n=6), fludrocortisone (n=3) or physical therapy. <b>Outcome Measures:</b> OH symptoms, serum sodium and urine osmolality.	1. 3/4 patients on ephedrine who started sodium/salt supplementation with meals became independent of ephedrine use. 2. Symptoms of OH were reduced consciousness (100% of subjects), strength (75%), vision (56%) and breathe (53%). Precipitating factors were hot weather (77%) bowel care (33%) and meals (30%). 3. Low blood sodium found in 54% of the ephedrine (OH) patients and 16% of those without.
Muneta et al. 1992; Japan Case report N=1	<b>Population:</b> 72-year old woman with non-traumatic SCI and paroxysmal hypotension. <b>Treatment:</b> Several weeks of salt/sodium supplement (7 then 15 g/day) was followed by L-threo-3,4-	1. After sodium supplement, a marked increase in BP and norepinephrine were observed in response to sitting, along with a decrease in basal plasma renin activity. 2. Addition of L-threo-3,4-dihydroxyphenylserine for 2 weeks, showed elevation in

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
	dihydroxyphenylserine (100 mg up to 600 mg/day). <b>Outcome Measures:</b> Blood pressure, catecholamines (epinephrine & non-epinephrine), plasma renin activity.	catecholamines about 5 and 10 times without an apparent increase in resting BP level. 3. Significant improvement in the symptoms of the paroxysmal hypotension and patient able to participate in rehabilitation program.

## Discussion

Three out of 4 subjects taking sodium/salt supplementation with meals in Frisbie and Steele's (1997) study became independent of their use of Ephedrine. In 4 patients with OH, Frisbie (2004) demonstrated that the estimated daily intake of sodium and water was inversely related to their Ephedrine requirements and suggested that greater sodium and water intake may lead to a more balanced renal action. Thus, level 5 evidence from two observation studies (Frisbie & Steele 1997; Muneta et al. 1992) suggest that sodium and fluid regulation in conjunction with other pharmacological interventions may reduce symptoms of OH. However, as no evidence exists on the effect of sodium/salt or fluid regulation alone for OH management in SCI, these conclusions should be interpreted with caution. As of now, there are no guidelines suggesting appropriate water and sodium intake specific to individuals with SCI.

## Conclusion

***There is no evidence on the effect of sodium or fluid regulation alone for OH management in SCI. Sodium and fluid regulation was evaluated in combination with other pharmacological interventions and thus, the effects of sodium and fluid regulation cannot be determined.***

The benefits of sodium/salt loading have not been sufficiently proven effective in individuals with SCI.

## 5.2 Blood Pooling Prevention in Management of OH in SCI

The application of external counter pressure through devices such as abdominal binders or pressure stockings is thought to decrease capacitance of the vasculature beds in the legs and abdominal cavity, both major areas of blood pooling during seating or standing.

**Table 6: External Pressure Interventions for Management of OH in SCI**

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Wadsworth et al. 2012; Australia PEDro=4 RCT N=14	<b>Population:</b> 14 adults with recent complete SCI (C3-T1; mean (SD) age: 32(16), range 18-73. <b>Treatment:</b> Abdominal binder (AB) on/off while seated in an upright wheelchair, with three repeated measures at 6 weeks, 3 months, 6 months after commencing daily use of an upright wheelchair. <b>Outcome measures:</b> Forced vital capacity, forced expiratory volume, peak expiratory flow, max inspiratory and	<ol style="list-style-type: none"> <li>1. No statistically significant improvement in mean arterial pressure (MAP) with use of the abdominal binder.</li> <li>2. Variable responses: MAP greater with the AB at the 1<sup>st</sup> and 3<sup>rd</sup> time points; MAP was less with the AB at the 2<sup>nd</sup> time point.</li> <li>3. Measures of supine and seated blood pressure were taken (allowing diagnosis of OH) but this was not a key outcome. 7 occasions of OH found across subjects as indicated by systolic blood pressure changes;</li> </ol>

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
	expiratory pressures, mean arterial pressure (MAP), max sustained vowel time, sound pressure level.	4 had OH regardless of AB application and 3 had OH without the AB only.
Hopman et al. 1998a; The Netherlands PEDro=5 RCT N=9	<b>Population:</b> 9 males, 5 with tetraplegia, 4 with paraplegia; 8 complete, 1 incomplete. <b>Treatment:</b> 5 discontinuous submaximal arm ergometer exercise tests on different days at 20, 40 and 60% of maximum power output while: 1) sitting, 2) supine, 3) sitting plus an anti-G suit, 4) sitting plus stockings and abdominal binder, and 5) sitting plus FES of the leg muscles. <b>Outcome measures:</b> Oxygen uptake (VO <sub>2</sub> ), carbon dioxide output, respiratory parameters, HR, BP, stroke volume, cardiac output.	1. Both FES and anti-G suit increased BP in subjects with tetraplegia whereas binders and stockings reduced HR in those with tetraplegia 2. The interventions did not improve BP responses in subjects with paraplegia however FES and anti-G suit lowered HR.
Hopman et al. 1998b; USA PEDro=4 RCT N=9	<b>Population:</b> same subjects as above study. <b>Treatment:</b> 5 conditions as above except at maximal power output. <b>Outcome Measures:</b> VO <sub>2</sub> , carbon dioxide output, respiratory parameters, HR, BP, stroke volume, cardiac output.	1. The supine posture increased peak VO <sub>2</sub> in subjects with tetraplegia, but reduced HR in subjects with paraplegia compared to sitting. 2. The relatively low pressure generated by stockings and bindings did not improve the venous system or cardiovascular responses during exercise. The positive circulatory benefits from FES and the anti-G suite observed in submaximal exercise (Hopman et al. 1998a) was not found for maximal exercise.
Helmi et al. 2013; The Netherlands Case report N=1	<b>Population:</b> 61-year-old male with C3/C4 traumatic SCI with symptoms of presyncope as a result of severe OH after 60° head-up tilt. <b>Treatment:</b> inflatable external leg compression (ELC); minimal ELC pressure to prevent OH (15 mmHg) found via tolerability test then applied in different positions (supine, 45°, and 60° head-up tilt). <b>Outcome measures:</b> external leg compression (ELC) pressure, mean arterial pressure (MAP), cardiac index, stroke volume index, heart rate, perfusion index (PI), peripheral tissue oxygen saturation (StO).	1. A 28% decrease in MAP when pressure decreased to 7 mmHg, below this level, dizziness rapidly occurred. 2. With the application of ELC 15 mmHg pressure during 45° and 60° head-up tilt: a. stroke volume index and heart rate were maintained with no presyncopal symptoms. b. global and peripheral perfusion parameters improved.
Rimaud et al. 2012; France Pre-post N=9	<b>Population:</b> 9 SCI men (8 were highly-trained athletes who competed regularly at the national or international level); Level of lesion: >T6 (n=4), <T6 (n=5); age in yrs: 34±12 years; range 24-53; duration of injury: 10±10 years; range 2-34. <b>Treatment:</b> Two maximal wheelchair exercise tests with and without graduated compression stockings (GCS). <b>Outcome measures:</b> Heart rate variability (HRV): high frequency (HF), low frequency (LF), and LF/HF ratio; Norepinephrine (NOR) and epinephrine (EPI); BP, heart	1. Increase in sympathetic activity and decrease in parasympathetic activity after maximal exercise in subjects when wearing GCS as shown by the increase in LF and decrease in HF components; results further supported by an enhanced sympathetic activity at rest in SCI, as demonstrated by a significant increase in noradrenergic response when wearing GCS. 2. When wearing GCS: LF increased significantly and HF <sub>post</sub> decreased significantly leading to an enhanced LF/HF ratio and a significant increase in resting NOR.

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
	rate, max power output, oxygen uptake, stroke volume, cardiac output.	
Rimaud et al. 2008; France Pre-post N=9	<p><b>Population:</b> 9 men with chronic traumatic SCI, were divided into 2 groups: high paraplegia with lesion levels between T4 and T6 (n = 4), and low paraplegia with lesion levels between T10 and L1 (n = 5)</p> <p><b>Treatment:</b> 2 plethysmography tests: with and without graduated compression knee-length stockings (GCS) at rest.</p> <p><b>Outcome Measures:</b> venous capacitance (VC); venous outflow (VO); heart rate; blood pressure.</p>	<ol style="list-style-type: none"> <li>1. No significant difference in HR or BP for either group or either treatment.</li> <li>2. In both groups, VC values were lower with GCS than without.</li> <li>3. VC and VO did not differ significantly with or without GCS.</li> </ol>
Krassioukov & Harkema 2006; Canada Prospective controlled trial N=20	<p><b>Population:</b> 6 subjects with complete tetraplegia; 5 with complete paraplegia; AIS A; 9 able-bodied controls.</p> <p><b>Treatment:</b> With and without harness for locomotor training during supine, sitting and standing (within subject analysis).</p> <p><b>Outcomes measures:</b> BP and HR.</p>	<ol style="list-style-type: none"> <li>1. Orthostatic stress significantly decreased arterial BP only in individuals with cervical SCI.</li> <li>2. Harness application had no effect on cardiovascular parameters in able-bodied individuals, whereas diastolic BP was significantly increased in those with SCI.</li> <li>3. Orthostatic changes in cervical SCI when sitting were ameliorated by harness application. However, while standing with harness, individuals with cervical SCI still developed OH.</li> </ol>
Kerk et al. 1995; USA Prospective controlled trial N=6	<p><b>Population:</b> Chronic complete paraplegia.</p> <p><b>Treatment:</b> Crossover design: with and without an abdominal binder.</p> <p><b>Outcome Measures:</b> BP, HR, VO<sub>2</sub>max, respiratory parameters, and wheelchair propulsion.</p>	<ol style="list-style-type: none"> <li>1. 5/6 subjects demonstrated a mean increase of 31% in forced vital capacity with binder compared to without, which was not significant but this may be because the sixth subject showed an 18% decrease in forced vital capacity when wearing the binder.</li> <li>2. BP, HR, VO<sub>2</sub>max increased significantly with increased exercise intensity and during maximal exercise, but these variables were not significantly affected by the use of the binder.</li> </ol>

## Discussion

The studies examining external pressure interventions generally test different pressure conditions with the same group of individuals (e.g. with and without stockings) either in a randomized order (RCT) (Wadsworth et al. 2012; Hopman et al. 1998a,b) or assigned order (non-RCT) (Helmi et al. 2013; Rimaud et al. 2012, 2008; Krassioukov & Harkema 2006; Kerk et al. 1995).

The application of these interventions must be interpreted with caution, as none of these studies assessed more than the effect of pressure application during acute phase. Whether these effects would persist with chronic use or cause any detrimental effects upon removal after extended use is unknown. Rimaud et al. (2008), after observing a decrease in venous capacitance, suggested that graduated compression stockings worn by individuals with paraplegia may prevent blood pooling in the legs. However, these effects were observed when the subjects were at rest and in the absence of orthostatic stress. Rimaud et al. (2012) found that with the graduated compression stockings, sympathetic activity increased and parasympathetic activity decreased after maximal exercise in men with SCI. Kerk et al. (1995) reported that application of an abdominal binder did not significantly improve cardiovascular or kinematic variables at submaximal or maximal levels of exercise. A single

RCT (n=14) by Wadsworth et al. (2012) found that abdominal binders did not significantly affect mean arterial pressure. In his review, Bhambhani (2002) concluded that the use of abdominal binders does not influence cardiovascular responses. Conversely, in another RCT (Hopman et al. 1998b), demonstrated in a small group of subjects with SCI (n=9) that stockings and an abdominal binder have an effect on cardiovascular responses during submaximal exercises, but not during maximal exercises (Hopman et al. 1998a). Krassioukov & Harkema (2006) found that the use of a harness (which applies abdominal pressure) during locomotor training increased diastolic BP in those with SCI, but not in able-bodied individuals. Therefore, there is level 2 evidence (from 1 RCT) that pressure from elastic stocking and abdominal binders may improve cardiovascular responses during submaximal, but not maximal, arm exercise.

## Conclusion

***There is conflicting evidence based on limited research that elastic stockings/abdominal binders have any effect on cardiovascular responses in individuals with SCI.***

***There is level 2 evidence (Krassioukov & Harkema 2006) that application of a harness in individuals with SCI could alter baseline cardiovascular parameters and orthostatic responses.***

There is insufficient evidence that elastic stockings or abdominal binders have any effect on cardiovascular responses to orthostasis in SCI.

## 5.3 Whole-Body Vibration in Management of OH in SCI

Whole-body vibration (WBV) exercise is performed on a platform that generates vertical sinusoidal vibrations, stimulating muscle spindles and resulting in muscle contractions. The effect of WBV exercise on muscle activity is elicited through reflex muscle activation (Bongiovanni et al. 1990) and muscle twitch potentiation (Cochrane et al. 2010).

**Table 7: Whole-Body Vibration in Management of OH in SCI**

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Yarar-Fisher 2013; USA PEDro=6 RCT (matched) N=21	<p><b>Population:</b> 11 men with SCI (mean age: 49±7 years; C4-T6; AIS A or B; ≥1 year post-injury) and 10 able-bodied men age: 48±8 years.</p> <p><b>Treatment:</b> Randomly assigned to 30, 40 and 50 Hz synchronous-vertical whole body vibration (WBV) with an amplitude (peak to peak) of ≈2 mm on three separate days.</p> <p><b>Outcome measures:</b> Heart rate, mean arterial pressure (MAP), stroke volume, cardiac output, oxygen consumption (VO<sub>2</sub>), relative changes in oxygenated, deoxygenated and total heme groups.</p>	<ol style="list-style-type: none"> <li>1. Both groups demonstrated small but significant increase in VO<sub>2</sub>, oxygenated heme and total heme groups; increases were larger in the SCI compared to the control group.</li> <li>2. Significant decrease in deoxygenated heme in the SCI group.</li> <li>3. No frequency effect was observed.</li> <li>4. WBV responses did not appear sufficient to induce cardiovascular benefits in the SCI group.</li> <li>5. WBV maintained mean arterial pressure levels above the pre-WBV standing values.</li> </ol>

## Discussion

There is one RCT (n=21) by Yarar-Fisher et al. (2013) examined the effect of whole-body vibration (WBV) on blood pressure while standing, and found that lower limb peripheral blood flow improved

post-WBV. However, the clinical application of WBV in preventing orthostatic hypotension has not yet been studied.

## Conclusion

***There is level 1 evidence (Yarar-Fisher et al. 2013) that whole-body vibration increases standing mean arterial pressure in individuals with SCI.***

### 5.4 Effect of Functional Electrical Stimulation (FES) on OH in SCI

The application of FES triggers intermittent muscle contractions that activate the physiologic muscle pump. The physiologic muscle pump facilitates venous return via compression of the superficial and deep veins of the legs.

**Table 8: FES on OH in SCI**

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome												
Faghri & Yount 2002; USA PEDro=2 RCT N=29	<p><b>Population:</b> 7 subjects with paraplegia, 7 with tetraplegia; 4 incomplete and 10 complete injuries; 15 able-bodied controls.</p> <p><b>Treatment:</b> Random order of standing with or without FES (30 mins) for SCI subjects; voluntary tiptoe contractions during 30 minutes standing for able-bodied subjects.</p> <p><b>Outcome Measures:</b> Hemodynamics during supine-sitting-30 min standing.</p>	<ol style="list-style-type: none"> <li>1. Significant reductions (up to 10%) in BP measures for SCI subjects from sitting to passive standing; but minimal changes when moving to FES standing.</li> <li>2. After 30 min of passive standing there was a reduction in stroke volume and cardiac output.</li> <li>3. After 30 min of FES standing, the pre-standing hemodynamics were maintained except for a significant reduction in SV.</li> </ol>												
Elokda et al. 2000; USA PEDro=3 RCT N=5	<p><b>Population:</b> 2 subjects with tetraplegia, 3 with paraplegia; all complete injuries; 2-4 weeks post-injury.</p> <p><b>Treatment:</b> Tilt table - 6 minutes at each tilt angle (0, 15, 30, 45 and 60 degrees), with 4 minutes of recovery between each, with or without bilateral ankle plantar flexor and knee extensor electrical stimulation. Application order or absence of functional neuromuscular stimulation (FNS) was counterbalanced.</p> <p><b>Outcome Measures:</b> HR, BP, perceived exertion.</p>	<ol style="list-style-type: none"> <li>1. At tilt angles of 15, 30, 45 and 60 degrees, systolic BP was significantly lower when FNS was not applied compared to when it was administered, and it was more marked with increasing tilt angles.</li> <li>2. There was a progressive decrease in BP with increasing tilt angle and this increase was less pronounced in the FNS condition.</li> <li>3. Post hoc analysis showed that HR was significantly higher with FNS compared to without FNS at 60 degrees tilt.</li> </ol>												
<p><b>Effect Sizes:</b> Forest plot of standardized mean differences (SMD ± 95% C.I.) as calculated from pre- and post-intervention data</p> <p style="text-align: center;"><b>Elokda et al. 2000; Functional Neuromuscular Stimulation (FNS)</b></p> <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th>Outcome</th> <th>SMD</th> <th>95% C.I.</th> </tr> </thead> <tbody> <tr> <td>SBP</td> <td>3.13</td> <td>(0.97, 5.28)</td> </tr> <tr> <td>DBP</td> <td>1.10</td> <td>(-0.29, 2.48)</td> </tr> <tr> <td>HR</td> <td>-2.98</td> <td>(-5.06, -0.89)</td> </tr> </tbody> </table> <p style="text-align: center;">Favours Control                      Std Mean Difference (95% C.I.)                      Favours Treatment</p>			Outcome	SMD	95% C.I.	SBP	3.13	(0.97, 5.28)	DBP	1.10	(-0.29, 2.48)	HR	-2.98	(-5.06, -0.89)
Outcome	SMD	95% C.I.												
SBP	3.13	(0.97, 5.28)												
DBP	1.10	(-0.29, 2.48)												
HR	-2.98	(-5.06, -0.89)												
Sampson et al.	<b>Population:</b> Motor complete SCI (lesions	1. HR increased for both groups with increasing												

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
2000; USA PEDro=3 RCT N=6	above T6); 3 with recent injury, 3 with long standing injury <b>Treatment:</b> With and without lower-extremity FES while tilted by 10° increments every 3 minutes, from 0-90° with varying intensities of stimulation. <b>Outcome Measures:</b> BP, HR, perceived syncope score.	incline angle. Mean diastolic BP was lower for the recent SCI subjects (105 mmHg) compared with chronic (123 mmHg). 2. Systolic and diastolic BP increased with increasing FES stimulation intensities and BP decreased with increasing incline angle of tilt regardless of the site of stimulation. 3. Subjects tolerated higher angles of incline with FES than without. The higher the intensity of FES, regardless of stimulation site, the greater the tilt incline tolerated.
Craven et al. 2013; UK Cross-sectional N=6	<b>Population:</b> 6 SCI subjects (C3-T9); Lesion grade: 3 complete (cSCI), 3 incomplete (iSCI); 22±4 years; range 18-25), iSCI 50±6; range 44-54); duration of injury: cSCI 18±3 years; range 16-21, iSCI 32±20 years; range 9-46). <b>Treatment:</b> Three experimental sessions (passive, active and FES-assisted) using a Robotic Assisted Tilt-Table (RATT); five phases of testing protocol for each session (phase 1&2: body positioning; phase 3: robotic orthoses with full guidance force; phase 4a: reduced guidance force for robotic orthoses, increased volitional effort; phase 4b: added FES to augment volitional force). <b>Outcome measures:</b> Oxygen uptake, respiratory exchange ratio (RER), minute ventilation, heart rate (HR), mean arterial blood pressure (MAP).	1. Head-up tilt (HUT) tolerated well; no instances of hypotension or autonomic dysreflexia. 2. Incomplete (iSCI) subjects: no change in oxygen uptake, respiratory exchange ratio (RER), minute ventilation, or heart rate (HR) in the first three testing phases; volitional participation in the stepping cycle and addition of functional electrical stimulation (FES) (phase 4a and b) led to significant ↑ in oxygen uptake, Respiratory exchange ratio (RER), minute ventilation, and HR; no significant change in mean arterial pressure (MAP). 3. Complete (cSCI) subjects: small statistically significant ↑ in minute ventilation. 4. iSCI and cSCI subjects: no difference in RER, minute ventilation, or HR response between groups in the first three testing phases. During phase 4b oxygen uptake, minute ventilation, and HR of iSCI subjects was significantly larger than cSCI subjects. MAP was significantly larger across all phases for iSCI subjects.
Yoshida et al. 2013; Canada Cross-sectional N=10	<b>Population:</b> 10 SCI adults (C4-T7); 44±11 years; range 27-59; AIS: A (n=5), B (n=3), C (n=1), D (n=1); duration of injury: 10±9 years; range 2-29. <b>Treatment:</b> During head-up tilt (HUT) subjects underwent four 10 min conditions in random sequence: 1) no intervention 2) passive stepping 3) isometric functional electrical stimulation (FES) of leg muscles 4) FES of leg muscles combined with passive stepping (dynamic FES). <b>Outcome measures:</b> Blood pressure (BP), heart rate, stroke volume, systemic vascular resistance, EMG signals of leg muscles, cross-sectional area of the inferior vena cava.	1. Incidents of OH during tests (based on changes in BP of subjects): 6 during head-up tilt (HUT), 5 during passive stepping, 4 during isometric FES, 3 during dynamic FES. Despite this, no participants reported perceived symptoms of OH during the experiments. 2. FES and passive stepping independently mitigated a ↓ in stroke volume and helped maintain mean BP. 3. Effects of FES on stroke volume and mean BP were greater during passive stepping. FES and passive stepping combined didn't interfere with each other but did not synergistically ↑ stroke volume or mean BP.
Chao & Cheing 2005; China Post-test N=16	<b>Population:</b> Motor complete tetraplegia <b>Treatment:</b> Progressive HUT maneuver with and without the FES to 4 muscle groups. <b>Outcome Measures:</b> BP, HR, perceived presyncope score.	1. Increasing tilt angle without FES significantly reduced systolic and diastolic BP and increased HR. 2. Adding FES to HUT significantly attenuated the drop in systolic BP by 3.7±1.1 mmHg, the drop in diastolic BP by 2.3±0.9 mmHg, and HR



Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
		<p>increased by <math>1.0 \pm 0.5</math> beats/min for every 15 degrees increment in the tilt angle.</p> <p>3. FES increased the overall mean standing time by <math>14.3 \pm 3.9</math> min.</p>
<p>Raymond et al. 2001; Australia Prospective controlled trial N=16</p>	<p><b>Population:</b> 8 male subjects with complete paraplegia, 8 male able-bodied controls. <b>Treatment:</b> Lower-body negative pressure (LBNP) was used to provide the orthostatic challenge. Subjects were evaluated: (1) during supine rest, (2) supine rest with submaximal arm crank exercises (ACE), (3) ACE+LBNP, and (4) ACE+LBNP+leg electrical stimulation (ES). Able-bodied controls participated in the first 3 trial only. <b>Outcome measures:</b> HR, stroke volume, cardiac output.</p>	<ol style="list-style-type: none"> <li>1. ES increased stroke volume from ACE+LBNP to ACE+LBNP+ES condition for SCI group.</li> <li>2. ES did not affect oxygen uptake or cardiac output in the SCI group.</li> </ol>
<p>Faghri et al. 2001; USA Prospective controlled trial N=14</p>	<p><b>Population:</b> 7 subjects with tetraplegia, 7 with paraplegia; 4 incomplete and 10 complete injuries. <b>Treatment:</b> FES augmented standing (active) and non-FES standing (passive), for 30min duration; tests were separated by at least 24 hours. <b>Outcome Measures:</b> Hemodynamics.</p>	<ol style="list-style-type: none"> <li>1. BP changed 8-9% when moving from sitting to passive standing (no FES).</li> <li>2. The augmented FES condition prevented BP change when moving from sitting to standing.</li> </ol>
<p>Faghri et al. 1992; USA Pre-post N=13</p>	<p><b>Population:</b> 6 subjects with paraplegia (T4-T10); 7 subjects with tetraplegia (C4-C7). <b>Treatment:</b> FES-leg cycle ergometer (FES-LCE) training, 3X/week, for about 12 weeks (36 sessions). <b>Outcome Measures:</b> Oxygen uptake, pulmonary ventilation (VE), respiratory exchange ratio (RER), BP, HR, stroke volume (SV) and cardiac output (Q).</p>	<ol style="list-style-type: none"> <li>1. After training, resting HR and systolic BP were increased in subjects with tetraplegia but were reduced in subjects with paraplegia.</li> <li>2. In both groups, HR and BP during submaximal exercise significantly decreased and stroke volume and cardiac output significantly increased after training.</li> <li>3. These results suggest that FES-LCE training improves peripheral muscular and central cardiovascular fitness in SCI subjects.</li> </ol>
<p>Davis et al. 1990; USA Pre-post N=12</p>	<p><b>Population:</b> 12 males subjects with, paraplegia (T5-L2); FES Group, n=6; Non-FES (Control) group, n=6. <b>Treatment:</b> Sub-maximal and maximal arm-crank exercise with or without FES of paralyzed leg muscles. <b>Outcome Measures:</b> Peak <math>VO_2</math>, expired ventilation (<math>V_E</math>), perceived exertion respiratory exchange ratio (RER), BP, HR, resting stroke volume (SV) and cardiac output (Q), total peripheral resistance.</p>	<ol style="list-style-type: none"> <li>1. No significant differences between the FES and Control groups in terms of peak <math>VO_2</math> (2.09 l/min), maximal HR, <math>V_E</math>, respiratory exchange ratio and perceived exertion.</li> <li>2. No differences in power output or <math>VO_2</math> during peripheral FES application but stroke volume and Q were higher during the FES- induced leg contractions on subjects that demonstrated visible isometric contractions. Neither rest nor exercise HR was significantly influenced by lower limb FES. Increase of peripheral and overall ratings of perceived exertion.</li> <li>3. HR, SV and Q were not significantly altered at rest or during hybrid exercise in Control group. Decrease of peripheral and overall ratings of perceived exertion.</li> <li>4. No changes in BP, impedance indexes of myocardial contractility and differentiated subjective ratings of perceived exertion during</li> </ol>

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
		hybrid exercise compared with non-FES conditions.

## Discussion

FES may be an important treatment adjunct to minimize cardiovascular changes during postural orthostatic stress in individuals with SCI. Several studies have suggested that FES-induced contractions of the leg muscles increases cardiac output and stroke volume, which increases venous return (Raymond et al. 2001). Subsequently, this increases ventricular filling and left ventricular end-diastolic volume (i.e., enhanced cardiac preload). According to the Frank-Starling effect, an increase in ventricular preload will lead to greater stretch of the myocytes and a concomitant increase in left ventricular stroke volume. The increased stroke volume may produce greater cardiac output and in turn, greater arterial blood pressure. In this manner, FES-induced contraction of the leg muscles may attenuate the drop in systolic BP in response to an orthostatic challenge.

FES-induced contraction of the leg muscles may also restore the body's ability to redistribute blood from below the level of the lesion back to the heart. In fact, it is through this means that Davis et al. (1990) attributes FES's effectiveness during an orthostatic challenge. In their study, Davis et al. found FES of leg muscles resulted in increased cardiac output and stroke volume in 6 males with paraplegia performing maximal arm-crank exercise. These results suggest that FES of leg muscles could alleviate the lower limb pooling effect during the orthostatic challenge. Chi et al. (2008) suggest that alleviation of the pooling effect could be further enhanced when FES of leg muscles is combined with passive mobilization. The clinical utility of this combination must be examined further in subjects with SCI because subjects in Chi et al. (2008) were able-bodied. A cross-sectional study by Yoshida et al. (2013) compares isometric FES of leg muscles vs. passive stepping vs. isometric FES + passive stepping. They found that both FES and passive stepping increased stroke volume and mean BP and that the highest increase in these two resulted from combined FES + stepping; however, the two interventions did not interact to synergistically increase stroke volume and mean aBP.

FES results in a dose-dependent increase in BP independent of the stimulation site that may be useful in treating OH (Sampson et al. 2000) and may be an important treatment adjunct to minimize cardiovascular changes during postural orthostatic stress in individuals with acute SCI. Three level 2 RCTs (Faghri & Yount 2002; Elokda et al. 2000; Sampson et al. 2000) and five non-randomized controlled trials (Chao & Cheing 2005; Raymond et al. 2001; Faghri et al. 2001; Faghri et al. 1992; Davis et al. 1990) with small sample sizes provide support for use of FES in individuals with SCI. FES of the lower extremity could be used by persons with SCI as an adjunct during standing to prevent OH and circulatory hypokinesia. An FES-induced leg muscle contraction is an effective adjunct treatment to delay OH caused by tilting; it allows people with tetraplegia to stand up more frequently and for longer durations (Elokda et al. 2000; Sampson et al. 2000). This effect may be more beneficial to those with tetraplegia who have a greater degree of decentralized cardiovascular autonomic control and may not be able to adjust their hemodynamics to the change in position (Faghri et al. 2001).

Current protocols predominantly evaluate BP after a single application of FES with a single change in position. The feasibility and practicality of implementing FES to influence orthostatic BP over time needs to be further explored.

## Conclusion

**There is level 2 evidence (from small, lower quality RCTs) (Faghri & Yount 2002; Elokda et al. 2000; Sampson et al. 2000) that FES is an important treatment adjunct to minimize cardiovascular changes during postural orthostatic stress in individuals with SCI.**

The use of FES is an effective adjunct treatment to minimize cardiovascular changes during changes in position.

### 5.5 Effect of Exercise on OH in SCI

Following exercise, individuals with SCI may experience improvements in the autonomic regulation of their cardiovascular system (Lopes et al. 1984). Exercise, or even passive movement of the legs, could potentially attenuate reduced central blood volume in individuals with SCI during an orthostatic challenge. For example, Dela et al. (2003), found a pronounced increase in BP in individuals with tetraplegia when their legs were passively moved on a cycle ergometer. There is also evidence that exercise training may enhance sympathetic outflow in individuals with SCI, as shown by an increase in catecholamine response to maximal arm ergometry exercise (Bloomfield et al. 1994).

**Table 9: Exercise on OH in SCI**

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Lopes et al. 1984; USA PEDro=2 RCT N=12	<b>Population:</b> 5 tetraplegia, 1 paraplegia; 6 control subjects. <b>Treatment:</b> Random assignment to active exercise (60 bilateral forearm flexion and extension movements per minute during the first and third minute of each tilt angle) versus no upper limb exercises during tilt from 0-70 degrees by 10 degrees increments at five-minute intervals until BP dropped below 70/40. <b>Outcome measures:</b> BP, hypotensive symptoms.	1. No significant difference between the active upper extremity exercise group versus the non-exercise group with reference to orthostatic tolerance to progressive vertical tilt.
Otsuka et al. 2008; Japan Prospective controlled trial N=30	<b>Population:</b> 10 men with tetraplegia, age: 29±6 years who were on a wheelchair basketball team and had physical training for at least 2hr/day, 2 days/week, for 2 years; 10 untrained men with tetraplegia, age 32±6 years and 10 able-bodied sedentary men, age 23±2 years were included as controls. <b>Treatment:</b> regular physical activity training <b>Outcome Measures:</b> HR, BP; electrocardiogram; autonomic nervous system activity in supine and 60° sitting position.	1. During supine rest, trained subjects with tetraplegia had significantly lower HR than the able-bodied controls. 2. Increase in HR from supine to sitting position in trained and untrained subjects with tetraplegia. 3. Untrained subjects with tetraplegia, but not trained subjects with tetraplegia demonstrated significant orthostatic responses (increased sympathetic activity and reduced vagal activity).
Ditor et al. 2005; Canada Pre-post N=8	<b>Population:</b> Sensory incomplete (AIS B-C) cervical SCI (C4-C5). <b>Treatment:</b> 6 months of body weight-supported treadmill training (BWSTT). <b>Outcomes measures:</b> HR, BP, and orthostatic responses, heart-rate variability.	1. Resting HR was reduced but no change in resting BP after BWSTT. 2. BWSTT did not improve BP or HR during head-up tilt (HUT).

## Discussion

Only three exercise studies have attempted to assess the effect of exercise on orthostatic tolerance in subjects with SCI and protocol differed in each. Lopes et al. (1984) found no effects on orthostatic tolerance with the addition of upper extremity exercises during a progressive head-up tilt (HUT) protocol. Such findings are not surprising given the small muscle mass involved in the upper limbs and the fact that venous pooling occurs primarily in the lower limbs. Ditor et al. (2005) demonstrated that individuals with incomplete tetraplegia retain the ability to make positive changes in cardiovascular autonomic regulation with BWSTT. However, six months of BWSTT did not adversely affect the orthostatic tolerance in subjects with SCI. The authors found this encouraging as it suggests that orthostatic tolerance is retained after exercise training, even though this intervention probably reduced peripheral vascular resistance. Otsuka et al. (2008) found that individuals with complete tetraplegia who were involved in regular physical activity training (2 hrs/day, 2 days/wk,  $\geq 2$  yrs) demonstrated greater orthostatic tolerance than inactive individuals with SCI (<30 mins/wk).

## Conclusion

***There is level 2 evidence (from 1 RCT) (Lopes et al. 1984) that simultaneous upper extremity exercises does not improve orthostatic tolerance during a progressive tilt exercise.***

***There is level 4 evidence (from 1 pre-post study) (Ditor et al. 2005) that 6 months of BWSTT does not significantly improve orthostatic tolerance during a tilt test.***

***There is level 4 evidence (from 1 post-test study) (Otsuka et al. 2008) that regular physical activity (2hrs/day, 2x/wk,  $\geq 2$  yrs) may improve orthostatic tolerance during a tilt test.***

Simultaneous arm exercise during a tilt test is not effective for improving orthostatic tolerance.

The benefits of body-weight supported treadmill training for management of OH have not been sufficiently proven in SCI.

There is limited evidence that regular physical activity may improve orthostatic tolerance during a tilt test.

## 5.6 Effect of Standing on OH in SCI

Active stand training that emphasizes weight bearing is thought to stimulate the neuromuscular system below the level of injury in individuals with SCI and may affect the response to orthostatic stress by increasing venous return (Harkema et al. 2008).

**Table 10: Standing on OH in SCI**

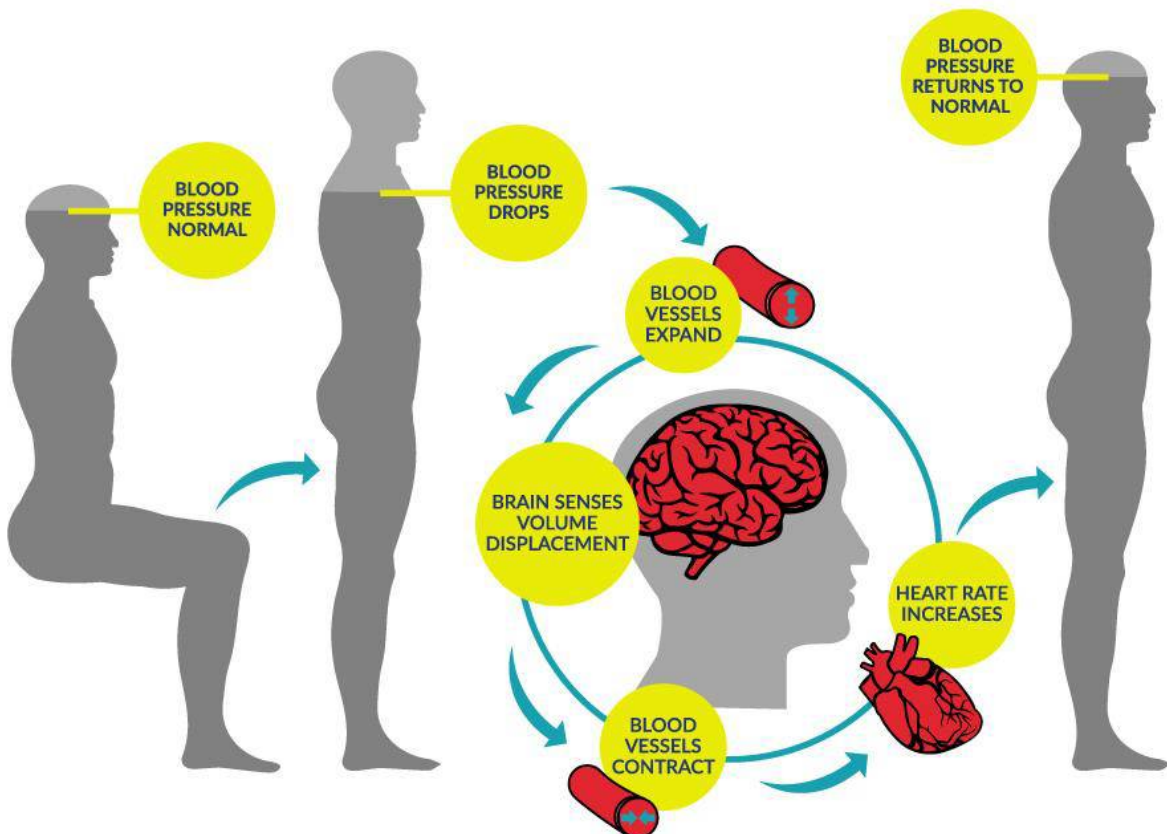
Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
-----------------------------------------------------------------------	---------	---------

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Harkema et al. 2008; USA Pre-post N=8	<p><b>Population:</b> 8 SCI subjects, all AIS grade A (4 cervical, 4 thoracic), with no cardiopulmonary disease, aged between 21-55, mean(SD) 33.8(12.6) yrs.</p> <p><b>Treatment:</b> Stand locomotor training (stand LT), for 60 minutes, five times per week.</p> <p><b>Outcome Measures:</b> BP and HR, measured while seated, seated with a harness, and standing with a harness; weight bearing load on legs; measurements taken before training, after 40 sessions, and after 80 sessions of training.</p>	<ol style="list-style-type: none"> <li>1. OH present prior to training was not evident after 80 sessions of stand LT.</li> <li>2. Significant improvements in cardiovascular response to standing in cervical SCI subjects.</li> <li>3. Resting arterial BP increased significantly in cervical SCI subjects after 80 sessions.</li> <li>4. Hemodynamic parameters showed no significant difference pre- and post-training in thoracic SCI subjects.</li> <li>5. All subjects were able to bear more weight on legs after training.</li> </ol>

### Discussion

Only one study examined the effect of active stand training using the body weight support treadmill system on cardiovascular function among individuals with complete SCI. Harkema et al. (2008) found that after 80 sessions (60 minutes/session; 5x/week) of active stand training, individuals with complete cervical SCI demonstrated increased resting blood pressure and improvements in the cardiovascular responses to standing.

### NORMAL CARDIOVASCULAR RESPONSE TO CHANGE IN POSITION (E.G. SITTING TO STANDING)



### Figure 3 – Normal Cardiovascular Response to Change in Position (e.g., Sitting to Standing)

#### Conclusion

***There is level 4 evidence (from 1 pre-post study) (Harkema et al. 2008) that 80 sessions of active stand training improves cardiovascular control such as response to orthostatic stress after cervical SCI.***

There is limited evidence that active stand training improves the response to orthostatic stress in cervical SCI.

#### 5.7 General Discussion

The major part of our present understanding of pathophysiology and management of incapacitating symptoms of OH is derived from the management of this condition in individuals with both central autonomic neurodegenerative disorders, such as multiple system atrophy and Parkinson's disease, and peripheral autonomic disorders, such as the autonomic peripheral neuropathies and pure autonomic failure (Freeman 2003; Mathias 1995). From previous studies in non-SCI individuals it is well established that combining patient education with the use of pharmacological and non-pharmacological modalities could lead to successful management of OH. Earlier literature suggested that the therapeutic goal for management of OH is not to normalize BP values but rather to ameliorate symptoms while avoiding side effects (Kaufmann et al. 2006). However, evidence in the general medical literature supports associations between chronic asymptomatic hypotension and increased reporting of tiredness, malaise, fatigue and depression (Wessely et al. 1990; Pilgrim et al. 1992; Rosengren et al. 1993; Barrett-Connor et al. 1994) as well as deficits in cognitive performance (Costa et al. 1998; Morris et al. 2002; Weisz et al. 2002; Duschek et al. 2003). In fact asymptomatic hypotensive individuals with SCI performed significantly more poorly on tasks of memory and attention processing compared to a matched (i.e., for level of injury, self-reported incidence of traumatic brain injury and IQ) cohort of normotensive individuals with SCI (Jegade et al. 2010). In addition, asymptomatic OH is associated with adverse changes in mood and cognition (Czajkowska et al. 2010) as well as increased morbidity and mortality (Benvenuto et al 2011; Fedorowski et al. 2010) and a diastolic blood pressure below 70 mmHg was recently found to be associated with increased all-cause mortality (Tringali et al. 2013).

The general approach to management of OH is that the therapeutic interventions should be implemented in stages dependent upon the severity of symptoms (Kaufmann et al. 2006). It is also well known from previous studies in non-SCI population that non-pharmacologic measures alone are often insufficient to prevent symptoms of OH. Pharmacological interventions are needed, particularly in SCI patients with moderate to severe OH symptoms.

Although a wide array of physical and pharmacological measures are recommended for the general management of OH (Kaufman et al. 2006), very few have been evaluated for use in SCI. Of the pharmacological interventions, only midodrine has some evidence supporting its use and FES is one of the only non-pharmacological interventions having limited evidence to support efficacy. Furthermore, the number of studies addressing the pharmacological management of OH following SCI are few. It is often difficult to determine the effects of individual medications when they are used in combination therapies. Nonetheless, Midodrine hydrochloride should be included in the management protocol of OH in individuals with SCI while further research is needed to quantify the effects of the many pharmacological interventions which have been shown to be effective in other conditions of neurogenic OH.

## 6.0 References

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