Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Krassioukov et al. 2009 Canada Reviewed published articles from 1950 to July 2008 N=26 n=251 **Level of evidence:** PEDRo Scale - RCTs (9–10: excellent; 6–8: good; 4–5: fair; 0-4: poor) Modified Downs & Black scale - non RCTs (0 to 28) **Type of study:** 2 case reports, 1 case series, 2 observational, 1 pre-post, 1 RCT AMSTAR: 6	**Methods:** 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. **Databases:** PubMed/MEDLINE, CINAHL, EMBASE, PsycINFO.	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). 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. 3. Cardiovascular responses during exercise may be improved with midodrine (level 2) and elastic stockings and abdominal binders (level 2).
Wecht et al. 2020 US RCT Level 1 PEDro = 11 N=41	**Population:** N=41 individuals with SCI ≥ 1 year post-injury and hypotension **Treatment:** Seated sBP, CBFv, and cognitive performance were monitored before and after administration of Midodrine (10mg) or placebo **Outcome Measures:** HR, BP, cerebral blood flow velocity	1. Midodrine increased sBP 18±24 mmHg while the placebo increased sBP 4±13 mmHg ($p < 0.05$). 2. Responses varied widely with midodrine (-15.7 to +68.6 mmHg), suggesting careful clinical monitoring should accompany midodrine administration.

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Wecht et al. 2023 US RCT Level 1 PEDro = 9 N=10	**Population:** N=10 with hypotension or OH **Treatment:** Participants were randomly assigned to received midodrine/placebo or placebo/midodrine, with a 2-week washout period in between, and both the participants and investigators were blinded to randomization order. Study medication was taken 2 or 3 times/day, and BP, and any related symptoms were recorded before and 1 h after each dosage and periodically throughout the day. **Outcome Measures:** BP, symptoms of AD and OH including headache, pounding in the ears, tingling or itching of the scalp, goosebumps, chills, blurry vision, and dizziness, and adverse effects of midodrine including constipation, muscle spasms, urinary urge or increased lower abdominal pressure.	1. Midodrine significantly increased average 30-day SBP (mean increase ~12.6 mmHg, $p < 0.0001$) and DBP (mean increase = 7.7 mmHg, $p < 0.0001$) compared to placebo. 2. The counts of BP recordings that remained below the target range were significantly reduced with midodrine for both SBP (~1.7 times lower, $p = 0.001$) and DBP (~1.5 times lower, $p < 0.001$) compared to placebo. 3. The target ranges were SBP: males: 110–129 mmHg; females: 101–129 mmHg and DBP: 70–89 mmHg. 4. The counts of BP recordings within the pre-defined target range were significantly increased with midodrine for both SBP (~2-times higher, $P < 0.001$) and DBP (~1.5-times higher, $P < 0.001$) compared to placebo. 5. The counts of BP recordings above the target range were significantly increased with midodrine for SBP (~2 times higher, $P = 0.005$) and DBP (~3.4 times higher, $P < 0.001$) compared to placebo.
Nieshoff et al. 2004 USA RCT Level 2 PEDro=6 N=4	**Population:** Chronic motor complete tetraplegia **Treatment:** Midodrine 5mg, 10 mg, or placebo (unmarked capsule), double blind, placebo-controlled cross-over design.	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.

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	Outcome Measures: Measure of cardiovascular parameters during wheelchair ergometer test.	2. Two participants showed reduced perceived exertion and increased VO_2 following midodrine 10 mg. 3. No adverse effects of midodrine were noted.
La Fountaine et al. 2013 USA Prospective controlled trial Level 2 N=27	**Population:** Study 1: 7 individuals with tetraplegia (38±10 years; 2 complete AIS A injury), 6 age-matched neurologically intact controls (32±8 years). Study 2: 7 individuals with tetraplegia (41±9 years; 1 complete AIS A injury), 7 age-matched neurologically intact controls (33±9). **Treatment:** Study 1: open-label trial with intravenous administration of L-NAME at specific doses (0, 1, 2, or 4 $mg \cdot kg^{-1}$) in the supine position. Study 2: orthostatic challenge (head-up tilt) with or without L-NAME (0, 1, or 2 $mg \cdot kg^{-1}$), controls completed a single visit (0 $mg \cdot kg^{-1}$). **Outcomes Measures**: 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.	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 participants with tetraplegia or controls. 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. 3. L-NAME administration does not appear to affect cardiac rate or conduction.
Phillips et al. 2014a Canada Prospective controlled trial Level 2	**Population:** 8 persons with SCI (1 female) and 8 age-and-sex matched able bodied controls Participants with SCI: Mean (SD) age: 30 (11) years	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; β-stiffness index was elevated in SCI when upright (+12%) and relative decrease in

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N=16	DOI: 7 participants <1 year post injury, 1 participant >1 year post injury All motor complete cervical spinal cord injuries AIS grade A: 6; AIS grade B: 2 **Treatment:** Participants 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. **Outcome Measures:** Beat-by-beat BP and HR, common carotid artery (CCA) diameter. Calculated arterial distensibility and arterial stiffness (β-stiffness index)	baroreflex sensitivity (BRS) was greater in SCI vs. non-SCI. 2. Negative relationship between BRS and β-stiffness in SCI; no relationship in people without SCI 3. Midodrine led to increased BP and decreased HR in both supine and upright positions; no change in BRS or CCA parameters 4. Reduced BRS is closely related to increased arterial stiffness in the SCI population
Phillips et al. 2014b Canada Prospective controlled trial Level 2 N=20	**Population:** 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 participants <1 year post injury, 2 participants >1 year post injury 8 cervical injuries, 2 thoracic injuries AIS grade A: 8; AIS grade B: 2 **Treatment:** participants 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.	1. Coherence increased in SCI between BP-MCAv and BP-PCAv by 35% and 22% respectively compared to AB. 2. SCI BP-PCAv gain was reduced 30% compared to AB. 3. The acute (0–30 s after tilt) MCAv and PCAv responses were similar between groups. 4. In SCI, midodrine led to improved PCAv responses 30 – 60 s following tilt (10+/- 3% vs. 4+/- 2% decline). 5. In SCI, midodrine led to a 59% improvement in orthostatic tolerance.

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	Outcome Measures: beat-by-beat BP, middle and posterior cerebral artery blood velocity (MCAv, PCAv, respectively)	
Phillips et al. 2014c Canada Prospective controlled trial Level 2 N=20	**Population:** 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 participants <1 year post injury, 2 participants >1 year post injury 8 cervical injuries, 2 thoracic injuries AIS grade A: 8; AIS grade B: 2 **Treatment:** 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. **Outcome Measures:** beat-by-beat BP, middle and posterior cerebral artery blood velocity (MCAv, PCAv, respectively)	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). 2. AB had a 20% increase in PCAv during cognition while this response was absent in SCI. 3. With midodrine, NVC was improved by 70% in SCI, and cognitive function improved by 13%. 4. Improvements in BP were related to improvements in cognitive function in those with SCI.
Wecht et al. 2008 USA Prospective controlled trial Level 2 N=14	**Population**: 7 individuals with tetraplegia; age 38±10 years; duration of injury 18±11 years and 7 neurologically intact controls 34±9 years. **Treatment:** Escalating dose of L-NAME (0.0, 1.0, 2.0, 4.0 mg/kg).	1. There was a heightened MAP response to escalating dose of L-NAME in people with tetraplegia compared to the controls. 2. HR was reduced in a dose dependent manner, and this response did not differ comparing those with tetraplegia to the controls. 3. Plasma NE was significantly at baseline in individuals

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	Outcome Measures: Supine heart rate (HR), mean arterial blood pressure (MAP) and plasma norepinephrine (NE) concentrations.	with tetraplegia compared to the controls. 4. Following L-NAME infusion, plasma NE was reduced in a dose dependent manner in the controls, whereas plasma NE levels were un-changed following L-NAME infusion in people with tetraplegia.
Wecht et al. 2007 USA Prospective controlled trial Level 2 N=14	**Population**: 7 individuals with tetraplegia; age 38±10 years; duration of injury 18±11 years and 7 neurologically intact controls 34±9 years. **Treatment:** Placebo versus L-NAME (1.0 mg/kg). **Outcome Measures:** Supine heart rate (HR), and mean arterial blood pressure (MAP).	1. Supine MAP was significantly reduced in individuals with tetraplegia compared to controls at baseline. 2. Supine HR did not differ between the groups at baseline. 3. MAP was significantly reduced in people with tetraplegia compared to the controls following placebo infusion. 4. Differences in MAP between participants with tetraplegia and controls were no longer evident following L-NAME infusion.
Wecht et al. 2009 USA Prospective controlled trial Level 2 N=12	**Population:** 5 individuals with chronic tetraplegia (1 AIS A and 4 AIS B); 7 age-, height-, and weight matched controls without SCI. All participants were between 19 and 53 years old. **Treatment:** Individuals with SCI 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. **Outcome Measures:** Heart rate (continuously monitored by ECG), mean arterial blood pressure (MAP); active plasma renin and	1. Supine systolic, diastolic, and mean arterial blood pressure were significantly higher in people with SCI after L-NAME infusion compared to placebo. 2. Orthostatic (45° HUT) MAP was significantly reduced after placebo infusion in SCI compared to controls (66±13 vs. 88±10 mmHg). 3. MAP during HUT was comparable to controls (88±10 mmHg) following L-NAME infusion in participants with SCI (83±3 mmHg). 4. Serum aldosterone levels were reduced during HUT after L-NAME infusion (120±45 pg/mL)

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	serum aldosterone concentrations.	compared to placebo (259±69 pg/mL; p<0.05) in individuals with SCI.
Wecht et al. 2013 USA Prospective controlled trial Level 2 N=10	**Population:** 10 hypotensive individuals 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. **Treatment:** 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. **Outcome measures:** 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.	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. 2. Increase in supine blood pressure was not worsened following droxidopa. 3. Expected fall in blood pressure when transferred from the supine to the seated position was prevented with droxidopa 200mg and 400mg. 4. Peak seated blood pressure reached the hypertensive range in 3 study participants 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.
Wecht et al. 2010 USA Prospective controlled trial Level 2 N=10	**Population:** 8 males, 2 females; 43±9 years; duration of injury 22±11 years; SCI C4-C7; AIS A or B **Treatment:** Midodrine (no drug, 5 mg or 10 mg) over 3 testing days. **Outcome Measures:** 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°.	1. 10 mg midodrine increased supine diastolic BP and MAP, and increased systolic BP and MAP after tilt test compared to control. 2. The significant increase in systolic BP during HUT was due to an augmented response in 2 participants with little to no change in the 8 other individuals.

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Wecht et al. 2011 USA Prospective controlled trial Level 2 N=7	**Population:** 5 male and 2 female healthy participants (26-54 years old, level of injury C4-C7, duration of injury 8-37 years). **Treatment:** Participants were studied during 3 laboratory visits: no drug, midodrine (10mg; administered orally 30 min before HUT), and L-NAME (1.0 mg/kg; infused over a 60-min period). **Outcome measures:** 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.	1. L-NAME and midodrine reduced OH symptoms compared to the no-drug trial. 2. L-NAME significantly increased orthostatic MAP compared with the no drug and midodrine trials. 3. There was a trend for midodrine to increase MAP during HUT. 4. Modest suppression of renin and aldosterone responses to HUT with L-NAME and midodrine. 5. There was a significant relationship between change in MAP and change in CBF with HUT among the participants tested (r^2=0.592).
Senard et al. 1991 France Case-control Level 3 N=7	**Population:** A 45-year-old participant with chronic complete traumatic paraplegia; 6 non-SCI male controls. **Treatment:** Clonidine (150 µg, 2X/day) and midodrine (specific alpha 1-agonist) (10 mg, 2X daily). Heart rate assessed by blinded tester. **Outcome Measures**: Blood pressure, heart parameters, plasma catecholamine, alpha-adrenoceptor sensitivity.	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). 2. Midodrine and clonidine alone or the two drugs in combination led to an increase in resting BP and decrease severity of OH.
Barber et al. 2000 USA Case series	**Population:** 2 cases of acute motor complete tetraplegia.	1. No effect of fludrocortisone on OH. 2. Fludrocortisone in both patients resulted in pitting

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Level 4 N=2	**Treatment:** Fludrocortisone acetate 0.1 mg 4X/day or midodrine 10 mg 3X/day. **Outcome Measures***:* Blood pressure, heart rate, and symptoms of OH.	edema of hands and lower limbs. 3. Initiation of midodrine hydrochloride resolved orthostatic symptoms in both individuals without any complications.
Frisbie & Steele 1997 USA Retrospective chart review and survey Level 3/5 N=231	**Population:** N=231 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. **Treatment:** Retrospective chart review of use of ephedrine (n=30), salt supplementation (n=6), fludrocortisone (n=3) or physical therapy. **Outcome Measures**: OH symptoms, serum sodium and urine osmolality.	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. 2. Symptoms of OH were reduced consciousness (100% of participants), strength (75%), vision (56%) and breath (53%). Precipitating factors were hot weather (77%), bowel care (33%) and meals (30%). 3. Low blood sodium found in 54% of the OH patients and 16% of those without.
Frisbie, 2004 USA Observational Level 5 N=4	**Population:** Chronic cervical complete tetraplegia; AIS A. **Treatment:** Evaluation of urinary salt and water output in relation to prescribed dosage of ephedrine (doses range from 0 to 100 mg daily). **Outcome Measures**: Severity of OH, urinary output.	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.