Table 2 –Characteristics of studies included in the systematic review

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| **Lead author, Year (reference)** | **Journal** | **Total No of participants** | **No. in experimental arm** | **No. in control arm** | **Disease group** | **Study design** | **Duration of Exposure** | **Experimental arm** | **Dose experimental** | **Control medication** | **Mean age (SD)** | **Outcome** |
| Arnold 2014 (15) | Frontier’s physiology | 12 | 12 | 12 | Primary autonomic failure patients | Single blinded, Crossover, RCT | Single dose | Ergotamine and caffeine | 1 and 100mg respectively | Midodrine/ placebo | 64.1 (9.8) | Orthostatic symptom composite score, as well as the light-headedness component of this score were reduced at 60 minutes with intervention, no effect of midodrine or placebo |
| Byun 2017 (16) | American Academy of Neurology | 87 | 29, 29, 29 | 29 | Symptomatic neurogenic orthostatic hypotension | Open label RCT | 3 months | Midodrine, pyridostigmine, midodrine and pyridostigmine in combination | 2.5 mg BD, 30mg BD, and 2.5mg/ 30mg BD | Midodrine | 57.2 (16) | Orthostatic systolic and diastolic BP drops improved significantly at 3 months after treatment in all groups. Orthostatic symptoms were significantly ameliorated during the 3-month treatment |
| Byun 2020 (12) | Annals of clinical and translational neurology | 50 | 25 | 25 | Symptomatic neurogenic orthostatic hypotension | Open label RCT | 1 month | Atomoxetine | 18 mg | Midodrine | 63.1 (9.6) | Both groups showed comparative improvement in the orthostatic BP drop. Only atomoxetine resulted in significant symptomatic improvements at 1 month |
| Hauser 2014 (22) | Journal of Parkinson's disease | 51 | 24 | 27 | Parkinson's disease patients with neurogenic orthostatic hypotension | Double blind RCT | 2 weeks blinded, 8 weeks maintenance | Droxidopa | 100 - 600mg TDS | Placebo | 72.6 (not included) | Dizziness/ light-headedness scores showed numerically greater improvements for droxidopa than for placebo at all time points. But did not reach significance |
| Hauser 2015 (23) | Movement Disorders | 147 | 69 | 78 | Parkinson's disease patients with neurogenic orthostatic hypotension | Double blind RCT | 2 weeks blinded, 8 weeks maintenance | Droxidopa | 100 - 600mg TDS | Placebo | 72.2 (not included) | changes from baseline in OHSA item 1 score and s-SBP favoured droxidopa at weeks 2 through 8, but the differences from placebo were not statistically significant |
| Isaacson 2016 (24) | Journal of Parkinson's disease | 75 | 38 | 37 | Clinical diagnosis of symptomatic nOH associated with primary autonomic failure (PD, MSA, pure autonomic failure), dopamine ß-hydroxylase (DBH) deficiency, or nondiabetic autonomic neuropathy (NDAN) | Open label prior to RCT (open label ignored) Double blinded for RCT | 2 weeks withdrawal post 3 months open label | Droxidopa | 100 - 600mg TDS | Placebo | 65.8 (12.3) | Improvements from baseline in patient-reported nOH symptom severity and impact on daily activities, evaluated using the Orthostatic Hypotension Questionnaire, exceeded 50% and were maintained throughout the 12-month study. Standing systolic and diastolic blood pressures were increased from baseline throughout the study with droxidopa treatment. |
| Jankovic 1993 (17) | The American Journal of Medicine | 97 | 64 (24 - 2.5mg, 24 - 5mg, 26 - 10mg) | 23 | Orthostatic hypotension due to autonomic failure | Double blind RCT | 1 week run in, 4 weeks as RCT | Midodrine | 2.5-10mg TDS | Placebo | 61 (not included) | Symptom improvement for midodrine vs placebo for dizziness or light headedness (5mg), syncope (10mg) and standing time (2.5mg) |
| Kaufmann 2002(18) | Annals of Neurology | 12 | 12 | 12 | Patients with a history of recurrent neurally mediated syncope | Double blind, crossover RCT | 1 off dose | Midodrine | 5mg | Placebo | 42 (4) | 2 (17%) experienced syncope on HUT with midodrine vs 67% on placebo |
| Kaufmann 2003 (25) | Circulation | 19 | 19 | 19 | Patients with severe neurogenic orthostatic hypotension | Double blind, crossover RCT | Single blind dose ranging study ~5 days. Exposure in RCT - 1 day | L-DOPS | 200-2000mg | Placebo | 63.5 (not included) | L-DOPS increased BP in all patients while supine and standing for 1 and 3 minutes (P<0.001 vs placebo) Peak BP at 3.5 hours |
| Kaufmann 2014 (41) | Neurology | 162 | 82 | 80 | Patients with symptomatic nOH due to PD, PAF, MSA, nondiabetic autonomic neuropathy, or dopamine-β-hydroxylase deficiency | Double blind RCT | 1 week exposure, following 14 day dose open label dose optimisation | Droxidopa | 100-600mg TDS | Placebo | 56.6 (not included) | Droxidopa increased standing SBP significantly compared to placebo, and also significantly decreased OHQ scores |
| Low 1997 (19) | JAMA | 162 (171 initially but only 162 analysed) | 79 | 83 | Symptomatic neurogenic orthostatic hypotension | Double blind RCT | 1-week single blind run in, 3-week double blind | Midodrine | 10mg TDS | Placebo | 59.5 (1.7) | Standing SBP in the midodrine group improved vs placebo (P<.001) - improved by ~20 mmHg, DBP improved by ~12 mmHg |
| Okamoto 2012 (13) | Hypertension | 12 | 12 | 12 | Patients with severe peripheral autonomic failure | Single blinded, Crossover, RCT | Single day exposures | Yohimbine/ atomoxetine and combined yohimbine atomoxetine | 5.4mg/18mg | Placebo | 64 (11) | Orthostatic burden improved after combination (15.7±17.9 vs. 25.3±16.0, respectively; P=0.013)   Light-headedness was also improved |
| Okamoto 2019 (14) | Hypertension | 10 | 10 | 10 | Patients with severe neurogenic orthostatic hypotension | Single blinded, Crossover, RCT | Single day exposures | Atomoxetine/ pyridostigmine bromide and combined atomoxetine, pyridostigmine bromide | 18mg/60mg | Placebo | 69 (3) | Orthostatic symptom burden after 1 hour had significantly improved for the combination of the two drugs. Atomoxetine alone approached significance |
| Ramirez 2014 (15) | Hypertension | 69 | 69 | 69 | Patients with severe autonomic failure | Single blinded, Crossover, RCT | Single day exposures | Atomoxetine | 18mg | Midodrine/ placebo | 65 (9) | Atomoxetine produced a greater pressor response in upright systolic blood pressure (P=0.03) and upright diastolic blood pressure (P=0.05), compared with midodrine. Atomoxetine, but not midodrine also improved orthostatic hypotension-related symptoms as compared with placebo. |
| Schoffer 2007(30) | Movement disorders | 13 | 13 | 13 | Patients with OH in idiopathic Parkinson’s disease | Double blind crossover RCT | Single exposure | Fludrocortisone | 0.1 mg | Domperidone | 69 (11) | Both medications improved the symptom scores for patients and reduced BP drop was noted on tilt testing with domperidone having a greater effect |
| Senard 1993 (29) | Fundamental Clinical pharmacology | 17 | 17 | 17 | Patients with Parkinson's disease associated OH | Double blind, crossover RCT | 4 weeks | yohimbine | 2mg TDS | Placebo | 69 (5) | Study conducted using ABPM, mean values for SBP, DBP, and HR were not significantly different between the two study groups |
| Shibao 2010 (27) | Hypertension | 31 | 31 | 31 | Patients with severe autonomic failure | Single blinded, Crossover, RCT | Single day exposures | Pyridostigmine | 60mg | Yohimbine (5.4mg)/ placebo | 66 (2) | Yohimbine significantly improved standing DBP as compared to placebo (P <0.001). Pyridostigmine did not increase the standing DBP (P =0.823). Only yohimbine showed a significant improvement in pre-syncopal symptoms. There was no evidence that pyridostigmine and yohimbine, had a synergistic pressor effect |
| Singer 2006 (26) | Archives of Neurology | 58 | 58 | 58 | Patients with neurogenic OH | Double blind, crossover RCT | Single day exposures | Pyridostigmine +/- midodrine | 60mg  60mg +2.5mg  60mg +5mg | Placebo | 59 (11) | the fall in standing diastolic BP was significantly reduced (P = .02) with treatment. Pairwise comparison showed significant reduction by pyridostigmine alone (*P* = .04) and pyridostigmine and 5 mg of midodrine hydrochloride (*P* = .002) |
| Smith 2016 (20) | Clinical Autonomic research | 19 | 19 | 19 | Severe symptomatic orthostatic hypotension | Double blind, crossover RCT | stable dose for at least 3 months, then 1 day washout then randomised to drug or placebo | Midodrine | 2.5-10mg | Placebo | 43.5 (17.9) | The least-squares mean time to syncopal symptoms or near- syncope after tilt-table initiation was significantly longer for midodrine than placebo (p = 0.0131) |
| Wright 1998 (21) | Neurology | 25 | 25 | 25 | Patients with neurogenic OH | Double blind, crossover RCT | 1 day | Midodrine | 2.5-20mg | Placebo | 62 (not included) | The mean scores for the investigator- tor and patient global evaluations of symptoms were significantly higher for midodrine (10 and 20 mg) compared with placebo a t 1 hour after administration of the drug |