SYSTEMATIC REVIEW

Efficacy of treatments for orthostatic hypotension: a systematic review

IAN C. LOGAN1, MILES D. WITHAM1,2

1Medicine for the Elderly, NHS Tayside, Ninewells Hospital, Dundee DD1 9SY, UK
2Division of Medicine, Ageing and Health, Centre for Cardiovascular and Lung Biology, University of Dundee, Ninewells Hospital, Dundee DD1 9SY, UK

Address correspondence to: I. C. Logan. Tel: (+44) 01382 660111. Fax: (+44) 01382 660675. Email: ian.logan@nhs.net

Abstract

Background: orthostatic hypotension (OH) affects up to 30% of adults over 65 and frequently contributes to falls and syncopeal episodes. Current guidelines suggest a wide range of treatments, but systematic reviews of the evidence base for such recommendations are lacking.

Methods: we performed a systematic review to assess the evidence for all non-pharmacological and pharmacological interventions for OH. Our search included the following databases: MEDLINE; EMBASE; CINAHL; and the Cochrane library. We searched grey literature and references from included studies and other reviews. We included randomised, placebo-controlled trials, which measured postural drop as an outcome. Study quality was assessed using pre-specified measures of bias.

Results: overall, 36 trials (21 interventions) were included. We identified a heterogeneous population and a wide variety of study methods, precluding meta-analysis. Most trials were of poor quality with high risk of bias. Changes in postural drop and symptoms were frequently inconsistent. Compression bandages, indomethacin, oxilofrine, potassium chloride and yohimbine improved the postural drop. Several vasoactive drugs—including midodrine and pyridostigmine—improved the standing blood pressure, but overall worsened the postural drop.

Conclusions: many commonly recommended interventions for OH have a limited evidence base supporting their use. High quality, randomised, controlled trials are needed to underpin clinical practice for this condition.

Keywords: orthostatic hypotension, postural hypotension, systematic review, blood pressure, elderly

Introduction

Orthostatic hypotension (OH) is common, affecting up to 30% of the general population over 65 [1], and up to 70% of people living in nursing homes [2]. The following consensus definition of OH was devised by the American Autonomic Society and the American Academy of Neurology, and subsequently endorsed by the European Federation of Autonomic Societies and the World Federation of Neurology: ‘...a sustained reduction of systolic blood pressure of at least 20 mmHg or diastolic blood pressure of 10 mmHg within 3 min of standing or head-up tilt to at least 60° on a tilt table’ [2]. OH is strongly associated with hypertension [3, 4, 5, 6, 7, 8], increasing age [3, 4, 5, 6, 9] and diabetes mellitus [5, 10] as well as conditions causing autonomic failure. In addition to its unpleasant and disabling symptoms, OH is also associated with an increased incidence of cerebrovascular disease [11, 12, 13], myocardial infarction [11], coronary heart disease [3, 6, 13], heart failure [10], cardiovascular mortality [3], all cause mortality [3, 9, 13] and falls [8, 11, 14]. OH has been associated with cognitive impairment in at least one trial [15], but this association was less conclusive in two others [16, 17].

A wide range of non-pharmacological and pharmacological therapies have been used to treat OH. A number of review articles and guidelines have been published offering advice on the optimal management of this complicated condition [18, 19, 20, 21, 22, 23, 24, 25, 26], but rigorous, systematic reviews of the available evidence for treatment of OH are currently lacking. We therefore undertook a systematic review of the efficacy of therapeutic options for managing OH, and set the following objectives: to
systematically review the evidence for pharmacological and non-pharmacological treatments of OH; to quantify the extent of reduction in blood pressure fall by various treatments; and to assess the impact of treatments on standing time, orthostatic symptoms and functional ability.

Methods

Search strategy and selection criteria

We used a pre-specified protocol, on the basis of recommendations set out by the Cochrane Collaboration. The following criteria had to be met for a trial to be considered eligible for inclusion: trials had to be of a randomised, controlled design, and had to compare an intervention with placebo; and could be of either the parallel group or the crossover design. We did not set any language restrictions, but excluded studies involving astronauts and healthy volunteers. We excluded trials that concentrated on post-prandial hypotension and neurally mediated hypotension (‘vasovagal syncope’) as opposed to OH. We considered both pharmacological and non-pharmacological interventions.

Data source and study search

We searched the following databases: MEDLINE; EMBASE; the Cumulative Index to Nursing and Allied Health Literature (CINAHL); the Cochrane Library; Psychinfo; the British Nursing Index; and Current Controlled Trials website. We searched for articles published between 1950 and February 2012. We searched for grey literature using Google, and hand-searched the reference lists of articles we identified, in addition to those in narrative review articles. We utilised the following search terms: [orthostatic hypotension OR postural hypotension] AND [randomised OR randomized OR placebo] AND [interventions as listed below].

Interventions

The interventions examined were derived from previous narrative reviews of OH [18, 19, 20, 21, 22, 23, 24, 25], and included: fluid, hydration, water; salt, sodium chloride; bed tilt, elevating bed; counter manoeuvres/maneuvers; compression stocking/hose/bandage/garment, abdominal compression; antihypertensives (all available classes were listed); fluidrocortisone; erythropoietin; sympathomimetics [midodrine, dihydroxyphenylserine (l-DOPS, d1-DOPS), yohimbine, ephedrine, pseudoephedrine, dihydroergotamine]; acetylcholinesterase inhibition, pyridostigmine; selective serotonin reuptake inhibitor/SSRI; serotonin-norepinephrine reuptake inhibitor/SNRI; vasopressin analogue; methylphenidate; dextroamphetamine; caffeine; dopamine receptor antagonist (metoclopramide, domperidone); and indomethacin.

Outcomes

The primary outcome measures of interest were change in office blood pressure (lying and standing/tilted systolic and diastolic blood pressure, and postural drop) and change in orthostatic symptoms. We extracted data on standing time, functional ability, adverse events and compliance. The following was also recorded: duration of study; source of funding; inclusion and exclusion criteria; sex; age; weight; cause of OH; co-morbidities; medication; method for recording blood pressure; quality of life; functional status; dwelling place; dose, frequency and duration of intervention or placebo; participant flow (numbers that were screened, eligible, assigned to each arm and completed the study); and mortality data. The change in blood pressure and postural drop was calculated (if feasible) for studies not explicitly stating these outcomes.

Data extraction and quality assessment

Data were entered onto a proforma to ensure consistent recording. The first 20 papers were analysed by both authors to ensure consistency, with the remainder analysed by one author. Foreign language articles were translated prior to data extraction. Any discrepancies were resolved by consensus. Studies were also assessed for quality, concentrating on comparability of each arm, strength of randomisation and allocation concealment, effectiveness of patient and staff blinding, detailing of withdrawals and strength of analysis (i.e. use of intention to treat). This was subsequently scored with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, allowing an easily understood quality of evidence ‘rating’ to be given for each intervention. GRADE initially allocates a ‘high’ quality score to randomised controlled trials, with the potential to ‘step down’ the quality of evidence to ‘medium’, ‘low’ or ‘very low’ (dependent on the strength of evidence). The overall grade should be reduced by one level for each of the following criteria found to be present: serious limitations to study design; important inconsistency; indirectness of evidence; imprecise or sparse data; and publication bias. If the limitations of study design are very serious then the quality of evidence may be downgraded by two steps [27].

Data analysis

Meta-analysis could not be undertaken, due to the heterogeneity of participants, study designs, study interventions and reported outcome measures. Instead, results were grouped by intervention in descriptive form.

Results

Trial selection and study demographics

The initial search strategy yielded 1,466 titles, from which 204 abstracts were identified as potentially relevant. Papers that did not meet the inclusion criteria were then
excluded. The main reasons for exclusion were: lack of randomisation and placebo-control; subjects were healthy volunteers or astronauts; or trials were concerned with the management of hypertension. Seventy-eight papers were then obtained and read in detail. Studies were eliminated if they were concerned with syncope for reasons other than OH, or if the lying and the standing blood pressure were not the focus of assessment. A total of 36 studies (37 papers) were finally included, examining 21 different interventions (Figure 1). The results of one trial of yohimbine were published in two separate journals.

Overall, 1,268 patients were included. Their age range was 26–88 years, with a mean age of 58.8 (SD 13.3) years. Twelve of the 36 studies involved subjects with a mean or median age of greater than 65 years, whereas only 4 studies involved patients with a mean or median age of greater than 75 years. Altogether, 11 different populations were identified throughout the 36 studies, with 4 studies inadequately characterising the underlying cause of OH. Fifteen of the 36 trials included a heterogeneous mix of patients, rather than concentrating on one specific disease process. In total, 32 different methods for recording postural drop were identified; variations were predominantly in the timing of the standing blood pressure, with unclear timings in five studies. Eight studies utilised tilt-table testing. Fourteen of the 36 trials used a single dose of therapy only, and in one trial the duration of treatment was unclear. Details are given in Table 1.

Study quality

The quality of study design and reporting was variable; randomisation arms were well balanced in 22/36 (61%) of trials; randomisation was well-described in only 3/36 (8%) and stated in 30/36 (83%) (with a chance of disclosure in 5/30 (17%) of these); patient blinding was effectively described in 12/36 (33%) of trials, and only stated in a further 18/36 (50%); staff blinding was effectively described in only 5/36 (14%) of studies, and stated in a further 23/36 (64%); 13/36 (36%) of trials analysed data on an intention to treat basis, whereas 13/36 (36%) did not, and it was unclear in 10/36 (28%); 12/36 (33%) of studies detailed their withdrawals, whereas 20/36 (56%) made no mention of withdrawals. Table 2 specifies the overall GRADE quality of evidence score for each intervention, and details how each score was reached.

Effect on postural drop

Details and specific figures for the effect of each intervention on the lying and standing blood pressure, and the postural drop, are given in Supplementary data (Appendix 1) available at Age and Ageing online. A single baseline value is given for two or more arms in studies where individual measurements were not available for each arm separately. The overall effect for each intervention is summarised in Table 2.

Clonidine and sleeping head-up produced minor improvements in the postural drop (although the postural drop with clonidine remained very large). The following therapies consistently produced an improvement in postural drop of greater than 10 mmHg: compression bandages; indomethacin; oxilofrine; potassium chloride; and yohimbine. Both midodrine and pyridostigmine displayed an inconsistent trend towards worsening of the postural drop. The following therapies consistently resulted in worsening of the postural drop: amezinium; glypressin; octreotide; and xamoterol. Those interventions that worsened the postural drop tended to do so by raising the lying blood pressure considerably more than the standing blood pressure, with the overall effect of widening the gap between the two.

It is important to acknowledge that many of the included trials are small in size and lack long-term follow-up data. With this in mind, it is difficult to draw strong positive conclusions about any of the interventions examined in this review.

Effect on symptoms

A variety of methods for recording changes in participants’ symptoms were used throughout the included trials, making comparison between interventions difficult. Specific details are given in Supplementary data (Appendix 1) available at Age and Ageing online. This information is also summarised in Table 2. A total of 14 trials either did not examine symptoms or did not publish responses for both arms. The following therapies had insufficient information to comment on their effect on symptoms: fludrocortisone; indomethacin; glypressin; clonidine; nitroglycerine; amezinium; xamoterol; and octreotide. Neither pacing nor sleeping head-up had any impact on symptoms. There was an inconsistent trend towards improvement with the following interventions: midodrine; dihydroxyphenylserine; dihydroergotamine; pindolol; oxilofrine; and camphor-crateagus berry compound. A minor improvement in symptoms was seen in two trials of yohimbine, although another reported worsening of symptoms in both arms. Both compression

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**Figure 1.** Trial selection flow diagram.
Table 1. Participant characteristics and study design by therapy [28–64]

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>n</th>
<th>Study type</th>
<th>Population</th>
<th>Mean age</th>
<th>Sex (% M)</th>
<th>BP recording</th>
<th>Control</th>
<th>Intervention</th>
<th>Duration</th>
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</thead>
<tbody>
<tr>
<td>Amezinium</td>
<td>12</td>
<td>Crossover</td>
<td>‘Orthostatic dizziness’</td>
<td>26-38</td>
<td>17</td>
<td>Tilt table testing</td>
<td>Placebo</td>
<td>Amezinium 30 mg</td>
<td>Once-off</td>
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<td>Belz et al. (1981)</td>
<td>48</td>
<td>Crossover</td>
<td>‘OH’</td>
<td>26-64</td>
<td>39-87</td>
<td>Tilt table testing</td>
<td>Placebo 20 drops</td>
<td>CC: 5 drops or 20 drops or 0 drops</td>
<td>One-off on sugar cube</td>
</tr>
<tr>
<td>Knoll et al. (2005)</td>
<td>38</td>
<td>Parallel group</td>
<td>‘OH’</td>
<td>17-60</td>
<td>63-87</td>
<td>L&amp;S BP</td>
<td>Placebo 25 drops TDS</td>
<td>1/52 each</td>
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<tr>
<td>Clonidine or nitroglycerin</td>
<td>23</td>
<td>Crossover (incomplete)</td>
<td>Primary autonomic failure (MSA/PAF)</td>
<td>66-78</td>
<td>58-78</td>
<td>L&amp;S BP</td>
<td>Placebo tablet or patch</td>
<td>Clonidine 0.3 mg tab or Nitroglycerin 0.1 mg/h patch</td>
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<td>Podolszus et al. (2006)</td>
<td>21</td>
<td>Crossover</td>
<td>Progressive OH (no symptoms first 3 min)</td>
<td>70-80</td>
<td>43-60</td>
<td>Tilt table testing</td>
<td>Sham bandages (5 mmHg ankle and hip for 10 min. Abdo added last 10 min)</td>
<td>Active bandages (40-60 mmHg ankle and 30-40 mmHg hips for 10 min. 20-30 mmHg abdo added last 10 min)</td>
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<tr>
<td>Dihydroergotamine (DHE) and DHE Plus (with etilefrine)</td>
<td>40</td>
<td>Crossover</td>
<td>‘Nursing home residents with OH’</td>
<td>59-88</td>
<td>?</td>
<td>L&amp;S BP</td>
<td>Placebo TDS</td>
<td>DHE: 2 mg TDS</td>
<td></td>
</tr>
<tr>
<td>Math and Jansen (1983)</td>
<td>42</td>
<td>Crossover</td>
<td>‘Old persons’ hospital’</td>
<td>75-85</td>
<td>45-55</td>
<td>Tilt table testing</td>
<td>Placebo TDS</td>
<td>DHE Plus: DHE 2 mg and etilefrine 20 mg TDS</td>
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<tr>
<td>Hamouz and Knappe (1983)</td>
<td>30</td>
<td>Parallel group</td>
<td>Psych inpatients, on neuroleptic therapy</td>
<td>48-78</td>
<td>37-58</td>
<td>L&amp;S BP</td>
<td>Placebo</td>
<td>DHE Plus: DHE 2 mg and etilefrine 20 mg TDS</td>
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<td>38</td>
<td>Parallel group</td>
<td>OH due to DM/alcohol/allopatic</td>
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<td>50-70</td>
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<td>Placebo (sub-cut)</td>
<td>DHE 6.5 mg/kg or 15 mg/kg (sub-cut)</td>
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<td>Thulesius and Berlin (1986)</td>
<td>58</td>
<td>Parallel group</td>
<td>Psych inpatients, on neuroleptic/tri-cycles</td>
<td>55-78</td>
<td>50-70</td>
<td>L&amp;S BP</td>
<td>Placebo BD</td>
<td>DHE 5 mg BD</td>
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<td>Dihydroxyphenylserine (L-DOPS) and D-DOPS</td>
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<td>Crossover</td>
<td>Severe OH (DM/allopatic)</td>
<td>35-81</td>
<td>83</td>
<td>L&amp;S BP</td>
<td>Placebo TDS</td>
<td>D-DOPS 600 mg or 800 mg</td>
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<tr>
<td>Fireman et al. (1999)</td>
<td>10</td>
<td>Crossover</td>
<td>Severe OH (MSA/PAF)</td>
<td>60-70</td>
<td>70-87</td>
<td>Tilt table testing</td>
<td>Placebo TDS</td>
<td>D-DOPS 1,000 mg</td>
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<tr>
<td>Alizares et al. (2002)</td>
<td>149</td>
<td>Parallel group</td>
<td>Hemodialysis +/-3/week</td>
<td>62-88</td>
<td>48-78</td>
<td>L&amp;S BP post dialysis</td>
<td>Placebo, 30 min pre-HD</td>
<td>D-DOPS 200 mg or 400 mg, 30 min pre-HD</td>
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<tr>
<td>Iida et al. (2002)</td>
<td>86</td>
<td>Parallel group</td>
<td>Hemodialysis +3/week</td>
<td>60-78</td>
<td>51-71</td>
<td>L&amp;S BP post dialysis</td>
<td>Placebo, 30 min pre-HD</td>
<td>D-DOPS 400 mg 30 min pre-HD</td>
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<td>Kaufmann et al. (2003)</td>
<td>19</td>
<td>Crossover</td>
<td>‘Severe OH (MSA/PAF). All on fludrocortisone’</td>
<td>64-78</td>
<td>79-87</td>
<td>L&amp;S BP</td>
<td>Placebo</td>
<td>D-DOPS, variable, mean 1.13 mg</td>
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<td>Fludrocortisone or norfenefrine</td>
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<td>Crossover</td>
<td>DM with autonomic neuropathy</td>
<td>52-100</td>
<td>83-100</td>
<td>L&amp;S BP</td>
<td>Placebo BD</td>
<td>Fludrocortisone 0.1 mg BD</td>
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<td>Volk and Stoll (1970)</td>
<td>13</td>
<td>Parallel group</td>
<td>Psych inpatients, on neuroleptic/tri-cycles</td>
<td>37-78</td>
<td>46-78</td>
<td>L&amp;S BP</td>
<td>Placebo 2 tab/day</td>
<td>Fludrocortisone 0.3 mg/day for 1/52, then 0.2 mg/day for 1/52 (2 tabs each time) or norfenefrine 30 mg/day (2 tabs)</td>
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<td>Glypressin</td>
<td>7</td>
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<td>Parkinsonism with OH</td>
<td>66-78</td>
<td>57-78</td>
<td>L&amp;S BP</td>
<td>Placebo (IV)</td>
<td>Glypressin 5 meg/kg or 7.5 meg/kg or 10 meg/kg (IV)</td>
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<td>Indomethacin</td>
<td>12</td>
<td>Not clear</td>
<td>Idiopathic Parkinsonism with OH ‘Dizziness/fainting due to OH’</td>
<td>72-80</td>
<td>58-78</td>
<td>Not stated</td>
<td>Placebo TDS</td>
<td>Indomethacin 50 mg TDS</td>
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<td>97</td>
<td>Parallel group</td>
<td>Autonomic failure, mixed causes. Mod-to-sev OH</td>
<td>61-97</td>
<td>55-78</td>
<td>L&amp;S BP</td>
<td>Placebo TDS</td>
<td>Midothrine 2.5 mg or 5 mg or 10 mg TDS</td>
<td></td>
</tr>
<tr>
<td>Fouad-Tarazi et al. (1995)</td>
<td>8</td>
<td>Crossover</td>
<td>One MSA, seven idiopathic. No response other therapy</td>
<td>60-88</td>
<td>50-88</td>
<td>L&amp;S BP</td>
<td>Placebo TDS</td>
<td>Midothrine 8.4 mg TDS (ephedrine arm)</td>
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<tr>
<td>Low and Singer (1997)</td>
<td>162</td>
<td>Parallel group</td>
<td>MSA/PD/DM/PAF</td>
<td>59-78</td>
<td>50-78</td>
<td>L&amp;S BP</td>
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<td>Midothrine 10 mg TDS</td>
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<td>Wright et al. (1997)</td>
<td>25</td>
<td>Crossover</td>
<td>MSA/PD/DM/PAF</td>
<td>62-78</td>
<td>44-78</td>
<td>L&amp;S BP</td>
<td>Placebo TDS</td>
<td>Midothrine 2.5 or 10 or 20 mg</td>
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<table>
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<th>Treatment</th>
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<th>Design</th>
<th>Disease(s)</th>
<th>Sample Size</th>
<th>Randomization</th>
<th>Comparator(s)</th>
<th>Protocol</th>
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<td>Octreotide</td>
<td>Bordet et al. (1995) [52]</td>
<td>Crossover</td>
<td>MSA</td>
<td>71</td>
<td>Placebo</td>
<td>Octreotide 100 mcg</td>
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<td>Oxilofrine</td>
<td>Pohl and Kriech (1991) [53]</td>
<td>Parallel group</td>
<td>'Orthostatic circulatory disorders'</td>
<td>43</td>
<td>Placebo</td>
<td>Oxilofrine 32 mg TDS</td>
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<td>Pacep</td>
<td>Sahal et al. (2004) [54]</td>
<td>Crossover</td>
<td>Autonomic dysfunction (PD/MSA/PAF/DM)</td>
<td>70</td>
<td>Tilt table</td>
<td>Tilt table testing Unspaced 'wire in situ'</td>
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<td>Pindolol</td>
<td>Cleophas et al. (1986) [55]</td>
<td>Crossover</td>
<td>DM &gt;20 years. Demographics for 11 patients</td>
<td>55</td>
<td>Placebo</td>
<td>Pindolol 5 mg TDS</td>
<td>1/52 each</td>
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<td>Potassium chloride (KCl)</td>
<td>Dejong and Hilard (1980) [56]</td>
<td>Crossover</td>
<td>T1DM with autonomic failure</td>
<td>47</td>
<td>Placebo</td>
<td>Pindolol 5 mg TDS</td>
<td>10/52 each</td>
</tr>
<tr>
<td>Pyridostigmine [NB: two arms with midodrine; yohimbine arm (Shibao et al., 2010) reported below]</td>
<td>Singer et al. (2006) [58]</td>
<td>Crossover</td>
<td>MSA/PAF/IDDM, autonomic, unspecified</td>
<td>59</td>
<td>Placebo</td>
<td>Pyridostigmine 60 mg, alone/with midodrine 2.5 or 5 mg</td>
<td>Once-off</td>
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<td>Crossover</td>
<td>'Severe OH' (PD/MSA/PAF)</td>
<td>66</td>
<td>Placebo</td>
<td>Pyridostigmine 60 mg</td>
<td>Once-off</td>
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<td></td>
<td>Fan et al. (2011) [60]</td>
<td>Parallel group</td>
<td>'Symptomatic OH'</td>
<td>76 (Med)</td>
<td>Placebo</td>
<td>SHU 5° (6 in.) overnight and advice</td>
<td>6/52 each</td>
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<td></td>
<td>Leslie et al. (1991) [61]</td>
<td>Crossover</td>
<td>IDDM, autonomic neuropathy</td>
<td>53</td>
<td>Placebo</td>
<td>Xamoterol 200 mg BD</td>
<td>4/52 each</td>
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<td>Des Lauriers et al. (1980), Lecrubier et al. (1983) [62, 63]</td>
<td>Parallel group</td>
<td>Psych inpatients, on clomipramine</td>
<td>?</td>
<td>?</td>
<td>Psych inpatients, on clomipramine</td>
<td>?</td>
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<td>Laccombe et al. (1989) [64]</td>
<td>Crossover</td>
<td>Psych inpatients, on clomipramine</td>
<td>44</td>
<td>Placebo</td>
<td>Psych inpatients, on clomipramine</td>
<td>3 days and 1 dose each</td>
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<td>Crossover</td>
<td>'Severe OH' (PD/MSA/PAF)</td>
<td>66</td>
<td>Placebo</td>
<td>Yohimbine 5.4 mg</td>
<td>Once-off</td>
</tr>
</tbody>
</table>

L&S BP, lying and standing blood pressure; OH, orthostatic hypotension; MSA, multiple system atrophy; PAF, pure autonomic failure; PD, Parkinson's disease; DM, diabetes mellitus; T1DM, type 1 diabetes mellitus; IDDM, insulin dependent diabetes mellitus (distinction not always made between these three); 1/7, 1 day; 2/52, 2 weeks.
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bandages and potassium chloride resulted in a significant improvement in symptoms. One trial of pyridostigmine reported a worsening of symptoms with intervention, whereas another was unclear—the changes in symptoms were given at only 1 h post-dose. No trials commented on functional ability and few used validated tools for assessing changes in quality of life.

**Side effects and adverse events**
The majority of studies (22 of the 36) either did not comment on side effects and adverse events, or commented on only the active arm. The trials that did comment often gave results that conflicted with each other. Details are given in Supplementary data (Appendix 1) available at Age and Ageing online.

**Discussion**

**Key findings**
This systematic review demonstrates that several common treatments for OH have not been examined in randomised, placebo-controlled trials. These include: drinking water;
increasing salt intake; and discontinuing antihypertensives. In addition, a number of interventions that frequently appear in guidelines have either no effect on the postural fall in blood pressure, or even worsen the fall in blood pressure. Changes in postural fall in blood pressure (whether an improvement or deterioration) are frequently not associated with a corresponding change in symptoms. There are very few data on how treatments affect functional ability, and few trials examine quality of life.

**Strengths and weaknesses**

As with any systematic review, it is possible that not all relevant published or unpublished studies were identified by the search strategy. However, we were able to obtain all papers that were deemed appropriate for the review, including those published in non-English languages (eight non-English articles were included in the final review). The strength of our findings is limited by small study size, variable quality of study design, and heterogeneity of participants, interventions and measured outcomes. Any positive results should therefore be interpreted with caution, particularly when information on symptom change, quality of life and functional ability is lacking. The considerable age of many of the studies made it impractical for us to obtain further information not available in the printed papers. Additionally, using results from trials of once-off intervention to influence routine clinical practice is problematic, particularly in relation to symptoms. More positively, we investigated a wide range of interventions, and did not exclude foreign language studies, thus allowing us to capture as much of the available literature as possible. For this review, we have concentrated on changes in the postural drop (given that this is the measure used to make the diagnosis of OH), but it may be that other outcome measures are equally valid; further research is needed to establish which measure best correlates with symptoms and quality of life in OH.

**Study findings in context**

The range of patient groups studied in the included papers confirms that OH is not a single disease process, but rather a symptom or sign to be found in a variety of different illnesses and age groups. Few trials have concentrated on participants without autonomic failure, which may limit the generalisability of any results to the large number of sufferers who do not have autonomic failure, e.g. older adults with generalised vascular disease [20, 65, 66]. It may be that these individuals require a different approach to managing their condition, and perhaps measures to improve cardiovascular health and function merit investigation.

This review should highlight to clinicians that many of the commonly recommended therapeutic interventions for OH do not have a large, high-quality evidence base to support their use. Additionally, the evidence base from which current guidelines are written is of poor quality. It may be that doctors with an interest in looking after older people with OH would wish to re-evaluate their own practise in view of the findings of this review. It is difficult for the authors to make any strong recommendations in light of the findings of the review.

The paucity of large, high-quality RCTs confirms that OH remains very much an underinvestigated condition. We would recommend that clinicians who look after patients with OH should actively try to enrol their patients in trials that seek to better understand the nature of this complex condition, and how best it should be managed.

**Conclusion**

There is a lack of good quality, randomised, placebo-controlled trials to give firm guidance on how best to manage OH. Several commonly recommended treatments have not been subjected to rigorous investigation, and of those that have, some may actually worsen the postural fall in blood pressure. There is also limited information on how therapies affect symptoms.

Large, well-designed, randomised, placebo-controlled trials that focus on changes in lying and standing blood pressure, postural drop, symptoms, quality of life and functional ability are required. There is a need to establish whether currently accepted treatments are effective, as well as testing novel approaches. Until this work is undertaken, it remains unclear how best to treat those individuals affected by this complex and unpleasant condition.

**Key points**

- Many trials of treatments for OH are of low quality and limited clinical utility.
- Several vasoactive interventions, as recommended by narrative review articles, may worsen the postural drop in blood pressure.
- There is limited evidence on how treatments for OH affect symptoms, functional ability and quality of life.
- Well-designed, randomised, placebo-controlled trials of treatments for OH (focusing on symptoms and quality of life) are needed.

**Conflicts of interest**

None declared.

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Supplementary data

Supplementary data mentioned in the text is available to subscribers in Age and Ageing online.

References

The very long list of references supporting this review has meant that only the most important are listed here, and are represented by bold type throughout the text. The full list of references is given in Supplementary data (Appendix 2) available at Age and Ageing online.


5. Fagard RH, De Cort P. Orthostatic hypotension is a more robust predictor of cardiovascular events than nighttime reverse dipping in elderly. Hypertension 2010; 56: 56–61.


