Efficacy of pharmacological management of orthostatic hypotension- a systematic review and meta-analysis

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Abstract

Introduction Orthostatic hypotension (OH) is associated with cardiovascular mortality and morbidity. Non-pharmacological and pharmacological therapies are employed in the management of OH. The aim of this systematic review and meta-analysis is to provide an up-to-date review of the efficacy parameters of pharmacological therapies. Methods Medline, Embase, Cochrane Library, and Scopus were searched (inception-July 2021), and published articles with randomized control trials, meeting inclusion and exclusion criteria were quality assessed (Risk of Bias 2 tool). Assessment for trends in patient-related outcome measures and postural blood pressure improvement was undertaken. Studies reporting postural systolic blood pressure (SBP) before and after intervention in comparison to placebo were included in a meta-analysis using inverse -variance in a random-effects model. Results 19 articles were included in the systematic review. The orthostatic symptoms questionnaire (OHQ) was the most common patient-related outcome measure utilized in trials. Six studies included in the meta-analysis demonstrated that pharmacological therapies (pyridostigmine, midodrine, atomoxetine, yohimbine) improved postural SBP compared to placebo, with a mean rise of 12.50 mmHg [95% CI: 6.01, 18.98; p value<0.001, I2 =97%]. Midodrine showed the highest impact on SBP, with a mean SBP of 16.11 mmHg [95% CI: 5.59, 26.63; p=0.003, I2 =99%]. Conclusions Pharmacological treatment can significantly increase postural SBP, however with significant heterogeneity related to trial designs. Further efforts to homogenize outcome measures, incorporating symptom improvement and reduction in the postural drop and testing for a prolonged duration of therapy would strengthen the evidence, and improve the translatability of findings in clinical settings.

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Contributions

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Methods

Medline, Embase, Cochrane Library, and Scopus were searched (inception-July 2021), and published articles with randomized control trials, meeting inclusion and exclusion criteria were quality assessed (Risk of Bias 2 tool). Assessment for trends in patient-related outcome measures and postural blood pressure improvement was undertaken. Studies reporting postural systolic blood pressure (SBP) before and after intervention in comparison to placebo were included in a meta-analysis using inverse -variance in a random-effects model.

Results

19 articles were included in the systematic review. The orthostatic symptoms questionnaire (OHQ) was the most common patient-related outcome measure utilized in trials. Six studies included in the meta-analysis demonstrated that pharmacological therapies (pyridostigmine, midodrine, atomoxetine, yohimbine) improved postural SBP compared to placebo, with a mean rise of 12.50 mmHg [95% CI: 6.01, 18.98; p value$<$0.001, I^2 =97%]. Midodrine showed the highest impact on SBP, with a mean SBP of 16.11 mmHg [95% CI: 5.59, 26.63; p=0.003, I^2 =99%].

Conclusions

Pharmacological treatment can significantly increase postural SBP, however with significant heterogeneity related to trial designs. Further efforts to homogenize outcome measures, incorporating symptom improvement and reduction in the postural drop and testing for a prolonged duration of therapy would strengthen the evidence, and improve the translatability of findings in clinical settings.

1. Introduction

The evolution to bipedalism in humans required development of precisely programmed and complex physiological processes, along with anatomical changes to perform activities while standing. Postural or orthostatic hypotension (OH) is attributed to a failure in physiological systems that help adapt one's blood pressure

(BP) to a change in posture. OH, is defined as a sustained symptomatic drop in systolic blood pressure (SBP) of at least 20 mmHg or diastolic blood pressure (DBP) of at least 10 mmHg within the first three minutes of standing from a supine position (or of tilting the body (head up) to at least a 60-degree angle on a tilt table) (1).

OH, is a topic of concern for physicians for two reasons, the first being its relatively high prevalence in the general population, estimated to be between 6 and 55%, with the higher prevalence rates in older age groups and patients with multiple comorbidities (2-4). Worryingly, more than two thirds of patients in acute geriatric wards may have OH (5). The second reason is the association of OH with an increased risk of ischaemic stroke, coronary events, heart failure and all-cause mortality (6), especially in populations with a higher cardiovascular burden such as patients with hypertension and diabetes mellitus (DM) (4). Hence it is important to identify and manage OH appropriately.

Various aetiologies present with OH as a symptom or a sign and can be further classified into non-neurogenic OH such as secondary to fluid loss, drug induced and vasovagal reflex and neurogenic OH (nOH) such as Parkinson's disease associated pure autonomic failure. Once symptomatic OH is confirmed, nonpharmacological interventions are commonly used as a first step. These may range from medicines rationalisation and deprescribing i.e., stopping contributory medications (such as vasodilators), increasing fluid and salt intake, counterpressure manoeuvres (e.g., sleeping with the bedhead raised), and compression stockings (7).

When non-pharmacological options fail or are ineffective on their own, then pharmacological options are often employed. In the UK, mainly fludrocortisone, midodrine, and pyridostigmine are prescribed, while the FDA approved the short-term use of droxidopa for symptomatic nOH in 2014. Yohimbine, atomoxetine, pyridostigmine, and caffeine have been studied in a few trials. The most commonly used surrogate for OH is the improvement in standing SBP at 1 min. Other commonly utilised trial outcomes include changes in ambulatory BP, head-up tilt (HUT) test and symptom improvement questionnaires in particular Orthostatic Hypotension Questionnaire (OHQ). The OHQ has two components, a six-question symptom assessment ("dizziness, light-headedness, feeling faint or feeling like you might black out" and a four-item daily activity scale (8). The Clinical Global Impressions scale (CGI-S) is the next most frequently used patient related outcome measures (PROM), which consists of two companion measures, the first evaluates the severity of psychopathology from 1 to 7 and the second assesses the change from the initiation of treatment on a similar seven-point scale (9). As reduction in postural BP drop does not always translate into symptomatic benefit, PROM may be considered better markers of efficacy analysis. Midodrine gained FDA approval in 1996 on the basis of a surrogate endpoint of improvement in standing systolic blood pressure at 1 min, though the long-term and real-world evidence for benefit is unclear. In comparison, droxidopa received an accelerated approval in 2014 for nOH for short-term use based on two trials which used improvement in item of orthostatic hypotension symptom assessment., section 1 of the OHQ score, which is considered as a validated PROM tool for nOH. The approval included a box warning for supine hypertension and recommends monitoring, with an agreement that a large post marketing study would be undertaken to show sustained clinical benefit. The existing evidence base for both nonpharmacological and pharmacological treatment options suffer from significant heterogeneity stemming from differing clinical trial designs with extremely short follow ups, and a lack of consensus on appropriate outcome measure acceptable worldwide for this condition. The aim of this systematic review and meta-analysis is to fill the knowledge gap on the exact benefits of pharmacological treatment options for OH by providing an updated review of the literature on efficacy parameters.

2. Methods

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Page et al., 2021).

2.1 Search Strategy and RCT selection

The databases Medline (via Ovid), Embase (via Ovid), Cochrane Library, and Scopus were searched from inception to July 2021, using the search terms outlined in appendix 1. A further search on clinicaltrials.gov for additional completed clinical trials was undertaken in May 2022. All results were limited to English language and human studies using the available limit functions on each database. Inclusion criteria were published studies, randomized control trials (RCT), adults-only ([?]18 years only), pharmacological intervention only. Studies were excluded if they were phase 1 trials, non-RCT/observational design, single-arm trials, participants <18, included animal data, in vitro trials, or had N<10 per arm and if the outcome or impact of the intervention was not clearly presented. The study protocol was not registered. However, the database PROSPERO was searched before starting the review to avoid duplication. Therapy with salt tablets was not treated as pharmacological therapy for the purpose of this review.

2.2 Study selection

Two independent investigators (D.J. and S.K.) performed the study selection. Titles and abstracts were screened for duplicates and eligibility. Among the relevant abstracts, full texts were assessed for eligibility.

2.3 Data extraction

Data extraction from the eligible studies was conducted by two independent investigators (D.J. and S.K.). Data were collected for the following domains: authors, journal, publication date, number of participants in experimental and control arms, patient disease group, study design, study duration, experimental medications and doses, control medication and doses, route, duration of follow up, age, sex, and the efficacy parameters as described by the authors not limiting to baseline BP, baseline postural BP drop, post-intervention BP and postural BP drop, symptom improvement.

2.4 Quality assessment

The included studies were quality assessed using the Risk of Bias (ROB) 2 tool from the Cochrane Collaboration (Sterne et al., 2019) for the standard domains including randomization, deviation of intended interventions, missing outcomes, measurement of the outcomes and selection of reported results. The assessment was conducted by two independent investigators (D.J. and S.K.) and any disagreements were resolved with consultation with a third author (F.M.). Studies with a high risk of bias in more than two domains were excluded (Figure 2).

2.5 Data synthesis and analysis

Excel was used to perform summary and descriptive statistics. Where a single study had multiple treatment arms of interest, the arms were assessed separately. Review Manager 5.4 (The Cochrane Collaboration, 2020) was utilized for the meta-analysis of the studies. We used a random-effects model with inverse-variance weighting and heterogeneity of the studies was assessed using the I^2 statistic. Results are presented as the mean differences with 95% confidence intervals (CI) and displayed in forest plots.

3. Results

3.1 Study Selection

Using the aforementioned search strategy, 4,677 studies were identified. 50 other studies were identified from hand-searching previously published reviews. After excluding duplicates, the titles and abstracts were used to screen the 3,174 studies, among which 206 studies were selected for full text review. 19 studies

met the inclusion criteria for the systematic review and six studies (18 treatment arms) could be used for quantitative analysis, as summarised in Figure 1. The updated search using clinicaltrials.gov did not produce any additional studies.

3.2. Risk of Bias 2 Analysis

ROB2 analysis was conducted on the studies and is reported in Figure 2. 13 studies had some concerns of bias, three studies were at a high risk of bias and two studies were low risk for concern.

3.3 Study characteristics

Among the studies that met the eligibility criteria, 19 studies enrolling 806 subjects (range of 12 – 147 participants per study) were included in the systematic review. Table 1 summarises the medications which were evaluated in this review (10, 11). Five studies employed midodrine as the experimental drug, two studies assessed a combination of pyridostigmine and midodrine for the experimental arm, and three studies used midodrine as the control/standard of care. Droxidopa was investigated in four studies, atomoxetine in two studies, one study evaluated atomoxetine in combination with pyridostigmine and one study investigated atomoxetine in combination with yohimbine. One randomised control study each with active arms studying pyridostigmine, yohimbine, and ergometrine and caffeine in combination, were included. Full details of the studies are in Table 2. Notably, there was only one study which examined fludrocortisone that met our inclusion criteria, the reasons for exclusion are discussed below and detailed in table 3.

All included studies were randomised control trials (RCT), two of which used an additional open-label period, and 12 studies used a crossover design. There was extensive heterogeneity between studies in regard to the length of exposure of the study intervention, ranging from a single day of exposure (nine studies) to three months.

All studies included patients with existing OH, with most patients diagnosed with nOH. Within this broad category, aetiological diagnoses varied from Parkinson's disease to primary autonomic failure to patient groups with mixed aetiological diagnosis. Seven studies had primary outcomes focussed on both the OHQ and changes in standing BP. While one study used the OHQ alone, three studies used the OHQ and CGIs, three used standing BP alone and three utilised standing BP in combination with a global symptom assessment (unique for each study). Two studies measured orthostatic tolerance using the HUT test, while another used the mean BP as established by ambulatory BP monitoring (ABPM).

3.3.1 Atomoxetine

Four RCTs studied atomoxetine, three studies assessed impact on standing BP and one assessed impact of BP using HUT test (12-15). Three out of the four studies used a single dose exposure with crossover design, except one study, which assessed orthostatic BP improvement at one month. This study also involved an open label phase lasting for three months designed to assess long term impact; both the atomoxetine and midodrine arms resulted in improvement in orthostatic drop in BP at one month compared to baseline, but only atomoxetine led to significant reduction in orthostatic symptoms at one month (12). In another study, atomoxetine produced a greater increase in standing SBP (mean difference (95% CI): 7.5 (0.6, 14.5) mmHg, p=0.03) and significantly increased standing DBP compared to midodrine, and both atomoxetine and midodrine were superior to placebo (15). In keeping with the earlier study, only atomoxetine showed significant improvement in orthostatic symptoms as compared to placebo. Combination medications of atomoxetine and yohimbine and atomoxetine and pyridostigmine were considered in two studies (13, 14). The combination arms significantly increased the seated SBP and orthostatic tolerance (measured as standing SBP and ability to remain standing), however none of the medications alone significantly improved BP nor symptoms compared to placebo in both studies.

3.3.2 Midodrine

Six studies included midodrine as the primary study intervention arm, three used standing BP measurements, two used HUT testing, and one used standing BP measurements and symptom scores (16-21). Three studies looked at single day exposure in a crossover fashion, while the other three studies involved taking midodrine for a longer duration ranging from 4-12 weeks. Midodrine and pyridostigmine individually and in combination reduced orthostatic drop in BP over three months, however there was no significant differences between groups, but midodrine alone led to improvement in OH-associated symptom scores (12, 16). In this study, OHQ composite score in midodrine arm was reduced by -15 in comparison to pyridostigmine arm where the mean change in score was -9.6 ($p < 0.01$). This trend of a better response with midodrine was seen in all the studies irrespective of trial design and the outcome measurement (17-20) and a summary of the OHQ scores can be found in section 3.3.6. A crossover study demonstrated dose-related impact of midodrine on standing SBP with a peak at one-hour post-administration along with a global improvement of symptoms scores (21).

3.3.3 Droxidopa

Droxidopa was the active intervention in four studies included of which three used the OHQ and one used standing BP and orthostatic tolerance (ability to stand for three minutes) (22-25) as the primary outcome. In a small single-blind, crossover study, L-DOPS (droxidopa) increased both supine mean arterial pressure (MAP) (101±4 to 141±5 mmHg) and standing MAP (60±4 to 100±6 mmHg) along with improved orthostatic tolerance (25). Another early study (n=51) using droxidopa, showed a mean rise in standing SBP of 12.5 mmHg at 1 week in comparison to the placebo arm (p=0.04)(22). This was followed by other studies planned with an intention of gaining marketing approval for this unmet need and the primary outcomes were now measured in terms of OHQ with BP improvement as secondary outcomes as detailed din section 3.3.6. Accordingly, a further larger (n=171) study confirmed improvement in SBP of about 6.4 mmHg (SD:18.9) versus 0.7 mmHg (SD:20.2) in placebo arm (p=0.03)(23). Further a study designed to evaluate efficacy and safety of droxidopa for a longer duration (approximately 12 months) in patients with nOH showed both significant improvement in standing BP and symptoms improvement in the droxidopa arm, however, the improvement was not significantly different in the double blind phase of the trial(24), thus depicting the nature the condition which is prone to a large placebo effect. Interestingly, the open label phases of the study continued to show improvement up to a year.

3.3.4 Pyridostigmine

Two studies focussed on pyridostigmine, both used a crossover design with the primary outcome of change in standing DBP (26, 27). In one of the studies, yohimbine, but not pyridostigmine significantly improved standing DBP and improved pre-syncope symptoms compared to placebo ($p < 0.001$) (27). In contrast, in another crossover trial using pyridostigmine and midodrine, the fall in standing DBP was significantly reduced (p=0.02) with all treatment. Subgroup analysis found that both pyridostigmine alone (p=0.04) and pyridostigmine in combination of 5 mg of midodrine hydrochloride (p=0.002) showed a beneficial impact (26).

3.3.5 Other medications

Of the other studies included, one investigated ergometrine and caffeine against midodrine and the other yohimbine vs placebo (28, 29). In a single-blind crossover trial, neither ergometrine and caffeine nor midodrine had a significant effect on orthostatic tolerance; however, ergotamine/caffeine improved presyncope symptoms (p=0.03) (28). A double-blind, crossover study of yohimbine, did not find any differences between baseline, yohimbine or placebo measurements (29).

One study compared domperidone and fludrocortisone treatment with baseline in a cross over fashion. In this

small phase 2 study in patients with OH in Parkinson's disease, comparison was made to baseline BP and between pre and post medication symptoms scores (30). Domperidone performed better than fludrocortisone (fall in SBP reduced by 13 mmHg versus 8 mmHg and DBP reduction improved by 8 mmHg versus 0 mmHg) measured as BP after 5 mins of standing, in this small cohort of OH associated with Parkinson's. The study was however, precluded from further quantitative analysis, due to the lack of placebo or midodrine arms. Further, non-pharmacological treatments were used in head-to head fashion against pharmacological treatment arms in the phase 1 of the study and applied heterogeneously across patients, with reported poor adherence. Other studies employing fludrocortisone included in other systematic reviews and NICE guidance did not meet our inclusion and exclusion criteria. (See table 3) (30-33).

3.3.6 Orthostatic symptom Questionnaires:

Table 4 summarises the findings from studies which used OHQ and other scores as part of study design.

Three studies examined the effect of midodrine on OHQ scores. Two studies demonstrated a statistically significant improvement in the OHQ composite score at three months of midodrine use (12, 16). The third study found that midodrine showed a tendency towards improvement in the total OHQ score, but it did not reach statistical significance (15). In the same study there was no difference between the effect of midodrine and atomoxetine, but atomoxetine did cause a significant decrease in the OHQ composite score as well as OHSA against placebo whereas midodrine decreased OHQ composite score only. A fourth study utilised patient and investigator global evaluations of symptoms and found that scores significantly improved with high dose midodrine (10 and 20 mg) (21).

Four studies used the OHQ to assess atomoxetine. Two studies demonstrated that atomoxetine improves the total OHQ score compared to baseline and placebo respectively (12, 15). In both studies reduction in OHQ composite score and in particular the QH related symptom severity (Q1) was statistically significant in atomoxetine group in comparison to midodrine group. Interestingly, combination therapy of midodrine and atomoxetine did not result in symptom improvement or BP improvement over and above individual therapy. Atomoxetine also had improvement in the scores of the daily activity and depression score. An RCT studying atomoxetine and pyridostigmine found that atomoxetine tended towards symptom improvement but did not reach statistical significance; however, when used in combination with pyridostigmine there was a statistically significant improvement in symptoms (14). In another study atomoxetine or yohimbine alone did not improve OH symptoms but achieved statistical significance when used in combination (13).

Droxidopa was assessed using the OHQ in three studies. In one study, despite droxidopa not showing any significant improvement on the OHQ composite score, fewer falls and fewer fall-related injuries (22) were reported in the droxidopa arm. In a subsequent expansion on the previous study, at one week, the dizziness and light-headedness components of the OHQ score favoured droxidopa over placebo ($p=0.018$), but this effect was not persistent on follow up (23). Another year-long study with three phases (three-month open-label, two-week withdrawal, nine-month open-label) found that during the three-month initial phase, there was a >50% reduction from baseline in the OHQ composite score in the droxidopa arm compared to placebo arm, which was sustained throughout the 12 months of open-label use, and was also reflected in the reduced nOH severity scoring by clinicians and patients using the CGI-S (24). However, the secondary analysis of this expanded dataset did demonstrate that droxidopa significantly improved the symptom aspect of the OHQ (OHSA) vs placebo ($p=0.018$) (23). In a separate study both droxidopa and placebo improved OHQ and CGI scores, however during the double-blind withdrawal aspect of the trial there was no significance between the two groups, but the improvement in the OHQ and CGI scores were maintained (24).

Pyridostigmine was assessed in two studies, one of which found that pyridostigmine improved OHQ scores at three months of usage but was less effective than midodrine (16). On the contrary, the other study found that pyridostigmine did not improve OH associated symptoms, except when used in combination with atomoxetine (14).

A quantitative analysis of the OHQ composite or OHSA scores could not be undertaken further due to

heterogeneity in reporting methods, trial design and small number of studies.

4. Meta-analysis

Five studies comparing medications to placebo using mean SBP measurements before and after dosing were chosen for meta-analysis. Mean SBP differences and the pooled standard deviation (SD) values were calculated (Table 5). Studies were excluded from meta-analysis if data were not reported for baseline values, if there were unclear datasets or if they used symptoms and questionnaires as their primary outcome, as opposed to absolute BP changes. The differences in measures taken and reported from the questionnaires made further analysis impossible. Analysis of droxidopa could not be completed either due to the main outcomes being symptom change and/or lack of baseline BP data and/or missing standard deviations. Atomoxetine and yohimbine could not be further assessed individually vs placebo due to fewer studies comparing them with placebo, or their concurrent use in combination with another medication.

Our meta-analysis showed that pharmacotherapy (pyridostigmine, atomoxetine, midodrine, yohimbine and combinations) lead to rises in postural SBP which was higher in the experimental arm compared to placebo, with a pooled rise in SBP of 12.50 mmHg [95% CI, 6.01 to 18.98; p<0.001]] (heterogeneity: I^2 = 97%, p<0.001) (Figure 3).

On subgroup analysis of single medication versus placebo, there was a mean difference [95% CI] of 12.96 mmHg [4.69, 21.23 p = 0.02] in favour of the experimental medication (heterogeneity: I^2 = 98%, p < 0.001). There was a moderately higher mean difference in combined medications vs placebo, 13.81 mmHg [2.68, 24.94, p = 0.02] (heterogeneity: I^2 = 81%, p = 0.002), although the difference between combined and single medications did not reach significance on an unpaired t test (p=0.66) (Figure 3).

In the analysis of midodrine vs placebo the mean rise in postural SBP was higher in the experimental midodrine arm, with an overall effect size of 16.11 mmHg [95% CI: 5.59, 26.63], p=0.003 (heterogeneity: I^2 =99%, p<0.01) (Figure 4).

Subgroup analysis based on improvement in SBP data comparing experimental medications (pyridostigmine, midodrine and pyridostigmine, and atomoxetine) vs midodrine, demonstrated that overall midodrine was favoured, but that this did not reach significance with an effect size (95% CI) of -0.50 (-2.96, 4.32), p = 0.47) (12, 16).

Funnel plots were produced for each subgroup analysis (Supplementary - Figures 1-3). While asymmetry of the plots was noted and could potentially be caused by selection bias, the cylindrical shape of the plots may be due to the heterogeneity of the studies as evident by a high I^2 values which could be accounted by several factors mentioned before.

5. Discussion

In our meta-analysis, we demonstrated statistically significant effects of pharmacological intervention on standing SBP compared to placebo treatment, which was especially apparent at higher dose ranges of midodrine and improvement in OHQ composite square especially apparent for atomoxetine and droxidopa. The meta-analysis also demonstrated a lack of effect of pyridostigmine alone at improving SBP, suggesting that it may not be a suitable single intervention for individuals with nOH. Whether this impact would be sufficient in mild to moderate non-neurogenic OH, with or without additional therapy is difficult to assess using available data. There have not been enough studies of atomoxetine vs placebo or atomoxetine vs midodrine to make valid conclusions, but the data suggest that either alone or in combination with yohimbine or pyridostigmine, atomoxetine could be a useful pharmacological intervention for OH. Atomoxetine also seems to have more sustained impact with improvement in symptoms lasting at 3 months (12). Atomoxetine improves depression scores and that is indeed strength in its own right as most patients with OH tend to be elderly with multimorbidity including mental health illness. Additive improvement in SBP or symptoms was not demonstrated with combination of midodrine and atomoxetine, which probably is due to similar

mechanism of action on the post ganglionic neurons. As such further studies are warranted to validate these findings.

Droxidopa gained popularity for treating OH and seemed to result in both SBP improvement and symptom improvement. Unfortunately, we were unable to analyse it specifically due to the lack of data on the change in SBP from baseline. Despite the relatively common usage of fludrocortisone in practice for decades and its approval by NICE (31) (but not approved by FDA), there is a lack of strong evidence base for its use. There were 4 RCTs which we considered further for inclusion in this review (table 3). However, these studies did not meet our inclusion on the basis of number of participants, or by including patients with orthostatic intolerance as opposed to OH, the former is encompassing OH, however the causes of OH pathophysiological are different to other causes of orthostatic intolerance such as postural orthostatic tachycardia and as such should be studied separately.

Of particular note, some studies demonstrated that improvements in standing SBP were not associated with symptom improvement, highlighting the need to re-consider the primary outcomes and trial designs for future studies assessing medications for OH (16). It is possible that there is an element of high "placebo effect" in treating this condition. Symptom improvement may be postulated to lead to a greater increase in the quality of life of the patient, and as such the OHQ or CGI scores could be used in conjunction with BP readings in clinical practice and future pharmacotherapy trials after clinical validation. The downside is the subjective nature of the scoring, which makes extrapolation of results to large populations problematic. Long term studies may help validate these patient related outcome measurements.

This study intended to provide an updated, robust assessment of the evidence for pharmacological intervention in treating OH, as demonstrated in RCTs. Previously published reviews have generally focussed on single medications (34-36), pharmacotherapy and included non-RCT studies and do not include the newer medications such as droxidopa (37) and atomoxetine(38). Additionally, compared to previously published reviews we included studies which used symptom questionnaires in order to broaden the perspective of a successful treatment for OH. Our inclusion criteria were also more stringent in regard to participants per arm and exclusion of head-to-head comparison of pharmacological and non-pharmacological treatments as active arms.

Though data from RCTs is considered more robust, the RCTs included in this meta-analysis have included small numbers of patients belonging to particular phenotypes, hence it can be argued that real world data could fare better in this condition. As such non-inclusion of non RCTs in this study may be perceived as a limitation and this certainly is the case for medications such as fludrocortisone, as shown in this recent systematic review (39). It is prudent to re-visit and possibly study long term effects of the older approved medications prospectively in phase 4 trials such as NCT04128137 and trials such as CONFORM-OH (40) and/or in registries.

Our study was limited by the inability to perform extensive subgroup analyses, an inadequacy of data showing impact on DBP and the significant heterogeneity in study design and reporting. Further, we did not assess adverse effects, which is a principal element of prescribing and continued adherence. We also excluded non-English languages studies and hence it is possible we missed some useful studies published in other languages.

Conclusion and future

Though there is sufficient evidence that pharmacological treatment for OH significantly increases standing SBP, especially for midodrine, the newer medications need further evidence for establishing both reduction in postural BP, symptom improvement and sustained impact. There is a further need for delineating the adverse effects of these medications. The lack of consensus on the most appropriate patient reported outcome measures, the heterogeneity in trial designs and outcome reporting reduce the ability to directly compare different medications and their impact. Further research and efforts to develop guidance on the outcome measures incorporating both symptoms and/or improvement in the postural drop and supine hypertension

especially more consistent use of the symptom scores both clinically and in trial settings could aid testing novel medications appropriately.

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