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Droxidopa for orthostatic hypotension: A systematic review and meta-analysis

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Abstract

Objective

This systematic review and meta-analysis aims to determine the efficacy and safety of droxidopa in the treatment of orthostatic hypotension (OH), following its recent approvals in the US.

Methods

MEDLINE, EMBASE, PubMed, Cochrane Controlled Trials Register, Web of Science, ProQuest and the WHO Clinical Trials Registry were searched. Studies were included if they randomised adults with OH to droxidopa or to control, and outcomes related to symptoms, daily activity, blood pressure or adverse events. Data was extracted independently by two reviewers. Risk of bias was judged against the Cochrane risk of bias tool and quality of evidence measured using GRADE criteria. A fixed-effects model was used for pooled analysis.

Results

Of 224 identified records, four studies met eligibility, with a pooled sample size of 494. Study duration was between one and eight weeks. Droxidopa was effective at reducing dizziness [mean difference -0.97 (95% confidence interval -1.51, -0.42)], overall symptoms [-0.52 (-0.98, -0.06)] and difficulty with activity [-0.86 (-1.34, -0.38)]. Droxidopa was also effective at improving standing systolic blood pressure [3.9 (0.1, 7.69)]. Rates of adverse events were similar between droxidopa and control groups, including supine hypertension [odds ratio 1.93 (0.87, 4.25)].

Conclusions

Droxidopa is safe and effective at reducing the symptoms associated with neurogenic OH without increasing the risk of supine hypertension.

Registration: PROSPERO ID CRD42015024612

Key Words

Orthostatic hypotension

Droxidopa

Systematic review

Meta-analysis

Introduction

Orthostatic hypotension (OH) is a disabling condition, resulting from a sustained reduction in blood pressure (BP, ≥20 mmHg systolic or ≥10 mmHg diastolic) within 3 minutes of standing [1]. It is highly prevalent in those with chronic disease; affecting approximately 17% of older people with hypertension, 25% of people with type 2 diabetes and up to 60% of people with Parkinson's disease [2-5]. Evidence to support existing treatment options for OH is of poor quality, creating uncertainty in the management of the condition [6-9].

Droxidopa is an oral pharmacological agent which is metabolised both peripherally and centrally into norepinephrine by dopadecarboxylase. It has been used in Japan since 1989 to treat neurogenic OH, but it has not been approved for use in Europe or America [10]. That is until February 2014 when the United States' Food and Drug Administration granted the use of droxidopa for the treatment of symptomatic OH secondary to primary autonomic failure, dopamine β-hydroxylase deficiency (DBHD) or non-diabetic autonomic neuropathy [11]. Early phase studies in the 1980s and 1990s looked promising, particularly in DBHD – a rare genetic disorder in which dopamine cannot be converted into norepinephrine [12-15]. However, the following decade produced larger efficacy studies demonstrating significant improvements in standing BP and orthostatic symptoms in individuals with autonomic neuroapthy [16-18]. In recent years, several large phase 3 clinical trials have been reported, but as yet no systematic review or synthesis of results has been performed. The results of such a review and analysis would be timely and informative both for clinicians and policy makers and are presented here.

Methods

Eligibility criteria

To be eligible for inclusion all studies were required to meet the following criteria:

- Participants: Aged over 18 years, with OH according to international consensus criteria (systolic drop of at least 20 mm Hg or diastolic drop of at least 10 mm Hg within 3 minutes of standing) [1]. Studies relating to healthy participants, astronauts and OH secondary to acute illness (such as haemorrhage) or haemodialysis were excluded.
- Intervention: This review considered the use of droxidopa, administered orally at any dose, when compared to placebo.
- Outcomes: Studies were required to include at least one measure of symptoms, blood pressure, activity of daily living or adverse events (AEs, including supine hypertension).
- Methodology: Only randomised, controlled trials (RCTs) were considered. Randomised, crossover trials were considered if outcomes were presented at the end of phase one (pre-crossover).

Data sources and searches

A search for published articles was performed using MEDLINE (1946 to June Week 3 2015), EMBASE (1974 to 2015 June 25), PubMed (no date limits) and the Cochrane Library (Cochrane Central Register of Controlled Trials, issue 5 of 12, May 2015). To reduce the risk of publication bias, conference proceedings and theses were searched using Web of Science (1970 to 2015) and ProQuest (1970-2015). In addition, reviewers searched the reference lists when reviewing full text articles, to identify additional studies. To identify ongoing and unpublished studies a search of The World Health Organisation International Clinical Trials Registry Platform was performed and Lundbeck, the pharmaceutical company which produced droxidopa, was contacted. All searches were performed on 26th June 2015. A comprehensive list of search terms for each database is included in Supplementary Table 1.

Study selection

All identified studies were collated into Endnote X7 where duplicates were removed. Titles and abstracts of the remaining studies were screened for eligibility by two reviewers (JF, JN); full text was reviewed where there was doubt about eligibility for inclusion. Following the screening process, full text was requested for all identified articles.

Data extraction

Data was extracted by two reviewers (JF, VS) onto forms derived from the Cochrane Collaboration (data extraction form version 3, April 2014) which were adapted for this topic review. Data included study design, methodology, duration and funding; participant numbers and characteristics; intervention and control dose, frequency and administration. Outcome measures recorded on scales were only considered for inclusion if they had been previously validated and described in peer-reviewed journals. Scales considered for this review were included in meta-analysis of continuous data if the unit of difference between points on the scale were consistent between points and there were at least 10 points on the scale. Where outcomes were reported at more than one time point, the final data point was extracted. Where possible, a change score was extracted for use in the quantitative analysis. Change in outcome from baseline to end of study are considered more efficient and powerful than final values, because it removes between-person variability from the analysis [19]. Where change values are not presented, the final values were included in the analysis because the difference in mean final values will on average be the same as the difference in mean change scores [19]. Where disagreement or inconsistency arose in data extraction, a third individual (JN) reviewed and selected the data for extraction.

Quality assessment

Three reviewers (JF, VS, MPT) independently assessed the methodological quality of included trials using the criteria described in the Cochrane Handbook for Systematic Reviews of Interventions [19]. This included risk of bias assessment for selection, performance, detection, attrition, reporting and other identified bias. These were classed as high, low or uncertain. When disagreement arose, resolution occurred via arbitration (JN). To explore the possibility of publication bias we planned to construct funnel plots for all analyses of outcomes that contained more than 10 studies.

Data synthesis and analysis

The mean difference (MD) between groups was calculated for continuous outcome data (symptoms and blood pressure). For binary outcome data (adverse events and falls) the odds ratio (OR) and confidence interval (95% CI) was calculated.

Forrest plots were visually inspected to identify obvious heterogeneity. Heterogeneity was quantified using the I^2 statistic; an estimate of 0-40% was considered insignificant, 30-60% as moderate, 50-90% as substantial and 75-100% as considerable [19].

The fixed-effect model was used for all meta-analyses which were performed using Review Manager (version 5.3). As OH is very common and is associated with a variety of chronic diseases, a degree of clinical heterogeneity was expected. In the event of significant heterogeneity, a prospective subgroup analysis was planned in which two reviewers (JF, JN) would identify and remove studies involving OH due to distinctly different pathophysiology, in order to perform sensitivity analysis. If the exclusion of these trials had no effect on the direction of effect or the precision of the effect estimates, they would be included in the analysis.

Quality of evidence was judged independently for each outcome using the GRADE approach (The Grading of Recommendations Assessment, Development and Evaluation) by two reviewers (JF, MPT) [20]. A summary of findings table was created using GradePro software.

Protocol and registration

A protocol of the methodology used for this review was registered and published prospectively, protocol ID CRD42015024612 (http://www.crd.york.ac.uk/prospero/).

Results

Study selection

The number of records identified, screened, excluded and selected are illustrated in Figure 1.

Study characteristics

Four studies meeting the inclusion criteria were identified, the characteristics of which can be seen in Table 1. Both studies by Hauser relate to the same trial but one presents data from an interim analysis [21] and the other presents the larger continued trial [22]. The participants in the interim analysis were not included in the subsequent larger trial.

All included studies were reported in English, were double-blinded and randomised individual participants to droxidopa or placebo. Two of the completed studies were multinational [23 24], the remaining two studies were multicentre within the United States [21 22].

Two studies used an enriched-enrolment design, whereby participants who did not respond to droxidopa were screened out of the study before randomisation [23 24]. Three studies randomised participants to begin placebo or droxidopa, whereas one study randomised participants to continue with droxidopa or to withdraw to placebo [23]. Only one study stated

that analysis would be based on intention to treat [22]. Two studies were eight weeks long [21 22], one was two weeks in duration[23] and one was completed after one week [24]. The mean dose of droxidopa administered across the four included studies (n 245) was 422.2 (±166·1) mg.

Participant characteristics

In the four pooled studies, 494 participants were randomised with a total of 420 (85%) remaining at completion. The commonest reasons for withdrawal were adverse events (n 19), lack of efficacy or treatment failure (n 18) or protocol violation (n 13). The mean age of participants was 66·5 (±13·2) years (range 18 to 92 years) and the reported mean baseline standing systolic BP was 93·7 (±18·2) mmHg across the four studies. All included participants had neurogenic OH (Parkinson's disease 67%, pure autonomic failure 16%, multiple system atrophy 12%, non-diabetic autonomic neuropathy 3%, other 2·3%, dopamine beta-hydroxylase deficiency 0·2%).

Risk of bias

The risk of bias assessment for individual studies is summarised in Table 2.

Effect of interventions

All four studies used the Orthostatic Hypotension Questionnaire (OHQ) as an outcome measure. This validated, self-report questionnaire is divided into two parts, Symptom Assessment (composed of 6 items) and Daily Activity Score (4 items) [25]. Each item is scored from zero to 10 to quantify the severity of the symptom.

Effect of droxidopa on symptoms

All four studies used item one of the OHQ Symptom Assessment as an outcome measure to quantify the symptom of dizziness/light-headedness. Three out of the four studies reported the

change in dizziness score from baseline; for the remaining study the final values reported at the end of the study were included in analysis [24]. In the pooled analysis (4 RCTs, n 439) droxidopa was effective at reducing dizziness [-0·97 (95%CI -1·51, -0·42), p<0·001], with no statistical heterogeneity (I^2 0%), see Figure 2.

Three RCTs (n 394) reported the change in OH-related symptoms using a composite score for the six symptoms included in the OHQ Symptom Assessment (dizziness/light-headedness, vision disturbance, weakness, fatigue, trouble concentrating, head/neck discomfort) [22-24]. Pooled analysis demonstrated an improvement in symptoms when taking droxidopa (-0·52 (95%CI -0·98, -0·06), p=0·03), with no statistical heterogeneity (I^2 0%), see Figure 2.

Effect of droxidopa on systolic BP

All four RCTs (n 427) reported the change in standing systolic BP. Although the direction of treatment effect was inconsistent, a significant but small effect size was seen in the pooled analysis, with droxidopa increasing the standing systolic BP [3·9 (95%CI 0·1, 7·69), p=0·04]. There was minimal statistical heterogeneity (I^2 10%), see Figure 2.

Effect of droxidopa on activity of daily living

Three RCTs (n 393) used part two of the OHQ as an outcome measure of daily activity [22-24]. Change scores were reported for two studies [22 24] and end-point scores were reported in one [23]. Droxidopa was effective at reducing the impact of OH on daily activity in the pooled analysis [-0·86 (95%CI -1·34, -0·38), p<0·001], with no statistical heterogeneity (I^2 0%), see Figure 2.

Adverse events

The risk of AEs (serious, severe, withdrawal due to adverse event, headache, dizziness, fatigue, nausea and supine hypertension) are summarised in Supplementary Table 2. Event rates for all

AEs were similar between droxidopa and control groups. Pooled analysis included data for those who were randomised, excluding data which arose during dose titration.

Falls were reported differently in the included studies. Two studies reported falls as an AE, reporting the number of participants who had fallen during the study [23 24]. Whereas two studies recorded falls as an outcome measure and reported the number of falls per person per week [21 22], however one of these studies also reported the number of people who had fallen [21]. Including the number of people who had fallen as an outcome measure in a pooled analysis, there was no reduction in risk of falling while taking droxidopa [n=314, OR 0·43 (95%CI 0·18, 1·02), I^2 28%], see Figure 2.

All four studies reported absolute rates of supine hypertension. These were higher in the droxidopa (7·8%) group when compared to the controls (4·2%) but the relative risk was not significantly greater [4 RCTs, n 485, OR 1·93 (95% CI 0·87, 4·25), I^2 0%], see Figure 2. Only one study reported the increase supine BP which was significantly greater in those randomised to droxidopa compared to placebo [7.6 (19.2) mm Hg, 0.8 (14.5) respectively, p <0.001] [24].

Risk of bias across studies

As fewer than 10 studies were included in this review, a funnel plot of reporting bias was precluded [19].

Quality of evidence

Table 3 summarises the quality and findings for each outcome measure, with a grading of the quality of evidence for the effects of droxidopa.

Ongoing studies

One study which completed in February 2015 has not yet reported the results [26]. This is an international, multicentre, randomised, double-blind, placebo-controlled trial of 12 weeks of

droxidopa therapy versus placebo in individuals with symptomatic OH secondary to primary autonomic failure. A further study, currently in progress, is performing a multicentre, randomised, double-blind, placebo-controlled trial of 12 week droxidopa therapy versus placebo in people with OH secondary to multiple system atrophy [27].

Discussion

The results of this systematic review and meta-analysis support the use of droxidopa for the treatment of OH. Pooled analyses demonstrate that droxidopa is effective at reducing the symptom of dizziness, the overall symptom burden and the difficulty with activity. In addition, a beneficial effect on standing systolic BP was seen in those participants randomised to droxidopa. However, the direction of the effect on systolic BP was inconsistent across the four included studies. It is unclear why the effect on symptoms appears to be greater than the effect on systemic BP but there are several possible explanations. Firstly, the OHQ quantifies symptoms experienced over the previous week, in contrast to measures of BP which occur as discrete events, precluding a temporal relationship between symptoms and BP. It is also worth noting that orthostatic BP and symptoms are known to have a poor correlation and this is likely to be explained by varying degrees of cerebral autoregulation [28]. As well as peripheral actions, droxidopa also crosses the blood-brain-barrier, although its effect on cerebral autoregulation are unknown [29]. Given the more objective nature of BP in comparison to symptoms it would be wise to consider these outcomes together when considering the results of this meta-analysis.

In the context of existing evidence for the treatment of OH, droxidopa looks promising for the future. Other commonly used agents such as midodrine and fludrocortisone do not have a robust evidence base and while many other agents have been studied few have generated sufficient benefits and have not translated into practice [6 8 9 30]. Although these results are

encouraging it must be noted that they reflect the short-term effects only. The data presented here are insufficient to consider the longer term clinical benefits of droxidopa therapy.

All four studies used a three times per day schedule for the droxidopa, however only one study provides further details[23], including the rationale for this schedule and a 5pm limit on the final dose to avoid supine hypertension. A previous dose finding study found that droxidopa taken twice per day was effective at reducing symptoms without causing supine hypertension [16].

In the short-term there are no safety concerns regarding droxidopa. The rate of adverse events were similar between those randomised to droxidopa or placebo. Supine hypertension has been noted to occur more commonly in people taking existing therapies such as midodrine, but supine hypertension may also be a cardiovascular complication arising from autonomic failure [30 31]. The risk of supine hypertension was greater in those taking droxidopa in all four studies although pooled analysis did not demonstrate a significantly increased risk in comparison to placebo. Only one study reported the change in supine BP during intervention, which demonstrated only a modest increase in supine BP with droxidopa, albeit a significantly greater increase in comparison to those taking placebo [24].

Data concerning falls in those taking droxidopa is inconclusive. The reporting of falls data in the included studies was inconsistent, did not meet recommended methodologies for collecting and analysing falls data and follow-up was of insufficient length of time [32 33]. The true effect of droxidopa on falls therefore remains unknown.

Conflict of interest between study authors and the drug manufacturer were present in all four included studies, with each study including employees of the pharmaceutical company as authors. Regardless of methodological quality, this introduces a significant risk of publication bias, limiting the overall quality of evidence. Furthermore, the enriched-enrolment design of

two studies was judged to introduce a high risk of selection/attrition bias [23 24]. By screening out non-responders before randomisation, studies are determining the effectiveness of an intervention in a cohort of people in whom the intervention is already effective. Although the enriched-enrolment design may increase the sensitivity of study results, which is useful in studies with high attrition rates, the effect size may be inflated and the results are less readily translated into clinical practice [34].

There was inconsistency in the timing of the primary endpoint which can be the result of an underlying reporting bias. This may have been present in one study in which the primary outcome measure and the timing of its measurement changed from week eight to week one [22]. There is no commonly agreed outcome data set for use in trials of OH. While individuals with OH may prioritise symptoms over BP measures, clinicians and academics may prefer the more objective nature of BP [35]. A core set of outcome measures may improve the quality of future clinical trials in OH. It has the potential to reduce reporting bias and improve data synthesis. An additional inconsistency was the reporting of concomitant therapies such as fludrocortisone and non-pharmacological therapies. Two studies mentioned salt and water intake, compression garments and sleeping with the head of the bed elevated, all of which feature in international recommendations but it is unclear how well participants adhered with these therapies [1 36]. However, it is possible that in the context of a clinical trial, participants are more likely to adhere with both the study intervention and other non-pharmacological therapies, which may explain the improvement seen in symptoms and BP in the placebo arm of some of the included studies. While the use of randomisation in the included studies should reduce the impact of concomitant therapy in the study outcomes, these are essential considerations which should be reported.

Limitations of review

To reduce the risk of bias in study selection a range of data sources were searched, including conference proceedings, theses, clinical trials registries and contact with the drug manufacturer. However, the bibliographical databases did not include regional or country-specific databases (e.g. Latin America and the Caribbean LILACS database) which may have identified literature not published elsewhere.

Although four RCTs is greater than the average number of studies in a pooled analysis, it was not possible to make a quantitative analysis of publication bias [37]. It is probable that there is a degree of publication bias given the involvement of the pharmaceutical company (Lundbeck) in all of the included studies. However, it is worth noting that Lundbeck (manufacturer of droxidopa) register all of their clinical trials protocols prospectively on a clinical trials register, which goes some way to reduce the impact of publication bias.

Studies measuring the longer-term efficacy, effectiveness and adverse effects of droxidopa are required. Ideally, to reduce the risk of bias these studies should avoid an enriched-enrolment design and be conducted independently of pharmaceutical companies.

The exclusion of non-randomised clinical trials may have missed important relevant studies, which in the context of rare diseases (such as dopamine-β hydroxylase deficiency, DBHD) may be clinically important. Indeed, in the pooled sample of 494 participants only one had DBHD. A more inclusive, broader review may be more informative for such rare diseases.

Conclusions

There is moderate level of evidence that droxidopa improves both dizziness and general OH-related symptoms in people with neurogenic OH, in the short-term. There is also moderate level of evidence that droxidopa improves difficulty with activity in the short-term.

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Figure legends

Figure 1. Study selection process

Figure 2. Summary of treatment effects

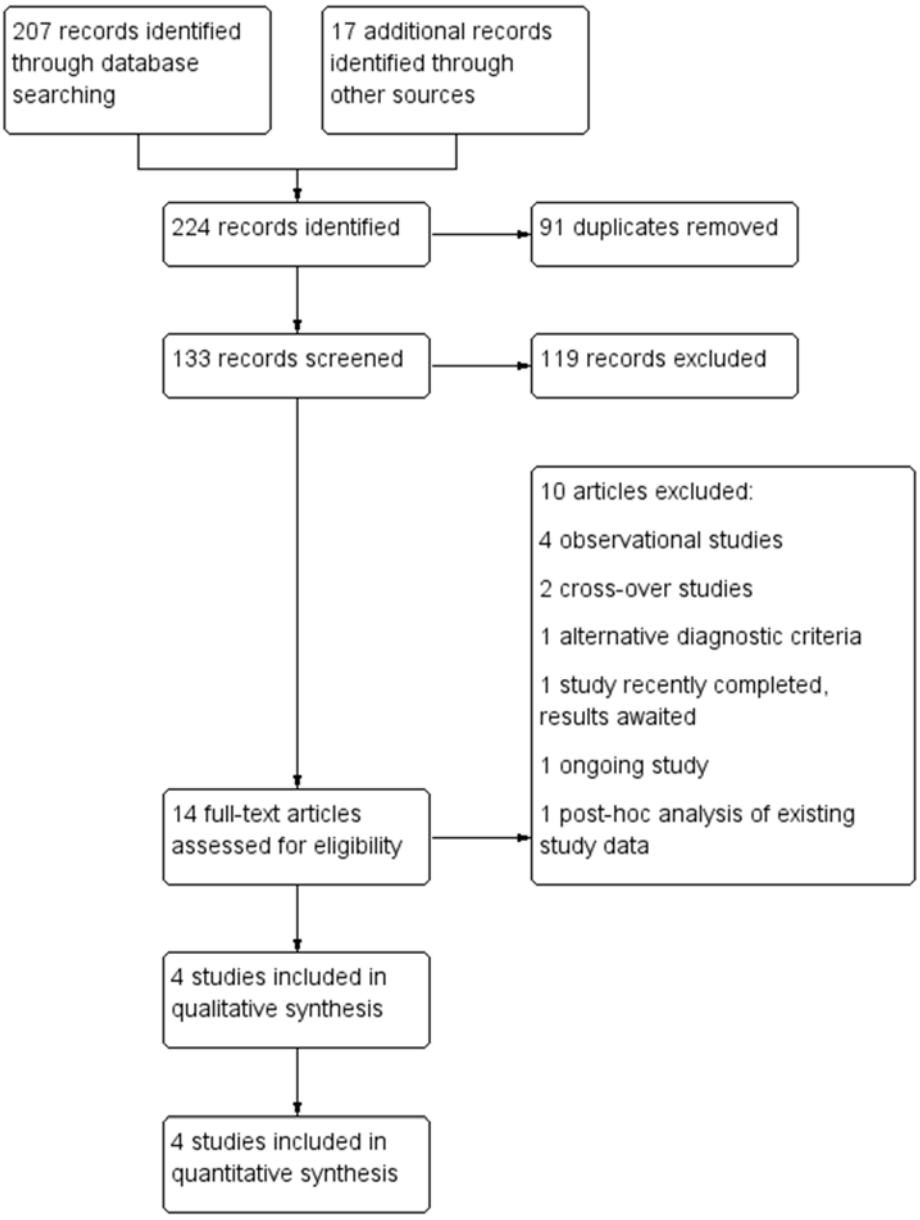

Figure 1. Study selection process

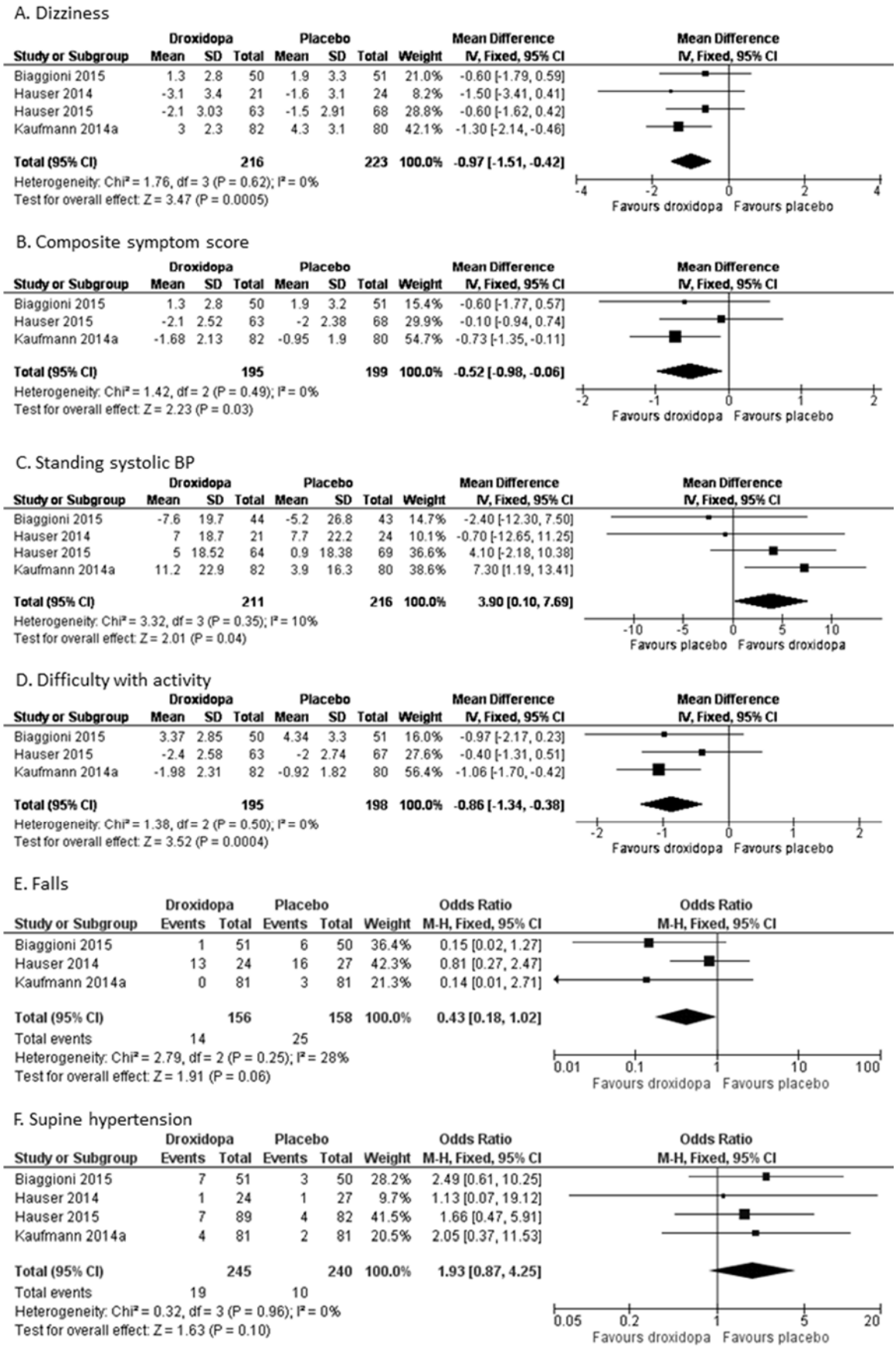

Figure 2. Summary of treatment effects

Table 1. Characteristics of included studies.

Biaggioni 2015	
Methods	Design: enriched enrolment, randomised withdrawal, parallel group, placebo-controlled Allocation: randomised, method not stated Blinding: double blind, no further description Duration: 2 week open label droxidopa dose titration, 1 week open label droxidopa maintenance, 2 week randomised study period Location: Multinational, multicentre, location not specified
Participants	OH: symptomatic (not defined) OH (international consensus criteria) Aetiology: Primary autonomic failure (Parkinson's disease, multisystem atrophy, pure autonomic failure, dopamine beta-hydroxylase deficiency, non-diabetic autonomic neuropathy) N: 181 entered, 101 randomised (50 allocated to droxidopa), 87 completed Female: 40% Age: 63·1 (13·8) years Severity: Standing systolic BP 87 (17·6) mmHg
Interventions	All participants received advice regarding increased salt and water intake, compression garments and sleeping with the head of the bed elevated (although these were not monitored). Other vasoconstricting agents were not permitted to continue. Study medications were administered three times per day, four-hourly during daytime, last dose no later than 5pm: 1. Mean droxidopa dose: 389·6 (180·9) mg. 2. Placebo
Outcomes	Primary: OHQ Symptom Assessment Item 1 (dizziness/light-headedness) Secondary: OHQ Symptom Assessment Composite Score, OHQ Daily Activity Scale Composite Score, Total OHQ Composite Score, OHQ Individual Items (vision, weakness, fatigue, concentration, headache, stand for short time, stand for long time), standing systolic BP, adverse events
Hauser 2014	
Methods	Design: parallel group, placebo controlled Allocation: randomised, method not stated Blinding: double-blind, no further description Duration: 2 week dose titration, 8 week randomised study period

	Location: Multicentre, location not specified
Participants	OH: Symptomatic (OHQ score ≥3 and clinician reported CGI-severity score ≥3) OH (international consensus criteria) Aetiology: Parkinson's disease N: 51 enrolled, 51 randomised (24 allocated to droxidopa), 45 completed Female: 42% Age: 72·2 (7·3) years Severity: standing systolic BP 99·2 (15·9) mmHg
Interventions	Advice regarding non-drug therapies is not reported. Fludrocortisone use continued in 3 participants in the droxidopa arm and 8 participants in the placebo arm. Other vasoconstricting agents were not permitted to continue. The following interventions were administered three times per day (no further details reported by authors): 1. Mean droxidopa dose 433·3 (155·1) mg 2. Mean placebo dose 488·9 (134) mg
Outcomes	Primary: Total OHQ Composite Score Secondary: OHQ Item 1 (dizziness/light-headedness) at week 1 and week 2, OHQ Symptom Assessment Composite Score, OHQ Daily Activity Composite Score, Falls, standing systolic BP, adverse events Unusable: OHQ Item 1 (dizziness/light-headedness) at week 8 - presented as figure without values
Hauser 2015	
Methods	Design: parallel group, placebo controlled Allocation: randomised, method not stated Blinding: double-blind, no further description Duration: 2 week dose titration, 8 week randomised study period Location: Multicentre, location not specified
Participants	OH: Symptomatic (OHQ score ≥3 and clinician reported CGI-severity score ≥3) OH (international consensus criteria) Aetiology: Parkinson's disease N: 174 randomised (89 allocated to droxidopa), 129 completed Female: 35% Age: 72·5 (8) years Severity: Standing systolic BP 94·7 (21·5) mmHg

Interventions	Participants' use of non-pharmacological therapy was not monitored. Other vasoconstricting medication was not permitted; fludrocortisone was continued in 30 participants in the droxidopa arm and 16 in the placebo arm. The study interventions were administered three times per day (no further details provided): 1. Mean droxidopa dose 436 (163) mg 2. Mean placebo dose 468 (165) mg
Outcomes	Primary: OHQ Item 1 (dizziness/light-headedness) at week 1 Secondary: OHQ Item 1 at week 2, 4 and 8; Total OHQ Composite Score at week 8; standing systolic BP; patient and clinician reported CGI severity and improvement scores; adverse events; falls
Kaufmann 2014	
Methods	Design: parallel group, placebo controlled, enriched enrolment Allocation: centralised, computerised, 1:1 randomisation Blinding: double blind, no further description Duration: 2 week open label dose titration, 1 week washout, 1 week randomised study period Location: US, Canada, Europe (not specified)
Participants	OH: Symptomatic (not defined) OH (international consensus criteria) Aetiology: Primary autonomic failure (Parkinson's disease, multisystem atrophy, pure autonomic failure, dopamine beta-hydroxylase deficiency, non-diabetic autonomic neuropathy, other) N: 263 enrolled, 168 randomised, 82 allocated to droxidopa of which 82 completed Female: 49% Age: 57·4 (16·9) years Severity: standing systolic BP 90·8 (15·6) mmHg
Interventions	Participants received advice regarding salt and water intake, physical activity and elevating the head of the bed. The use of these non-pharmacological measures were not monitored. Other vasoconstricting agents were not permitted. Concomitant use of fludrocortisone is not reported. Study interventions were administered three times per day (no further details provided): 1. Mean droxidopa dose 430 (163) mg 2. Mean placebo dose 381 (144) mg
Outcomes	Primary: Total OHQ Composite Score:

	Secondary: OHQ Symptom Assessment Composite Score, OHQ Daily Activity Composite Score, OHQ individual items, standing BP, supine BP, adverse events

Table 2. Risk of bias for included studies

	Selection bias		Performance bias		Attrition bias	Reporting bias	Other bias
	Randomisation	**Allocation**	**Participant & personnel blinding**	**Blinding of outcome assessment**			
Biaggioni 2015	Unclear *	Unclear †	Unclear ‡	Low	High §	Unclear ‖	High ¶
Hauser 2014	Unclear *	Unclear †	Low	Low	Low	Low	High ¶
Hauser 2015	Unclear *	Unclear †	Low	Low	Low	Low	High ¶
Kaufmann 2014	Low	Low	Unclear ‡	Low	High §	Low	High ¶

* Method of randomisation is not specified

† Method of allocation is not specified

‡ Participants received open-label droxidopa before randomisation, increasing the risk that participants would recognise the change from droxidopa to placebo

§ Enriched-enrolment design screened out non-responders before randomisation

‖ Sample size was based on an empirical clinically meaningful value. The authors refer to a detailed explanation in an online supplement, but the explanation is not present

¶ The study sponsor was the drug manufacturer and were involved in the preparation of the manuscript

Table 3. Quality of evidence summary for the effects of droxidopa

Number of studies (number of participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Quality of evidence
Dizziness/light-headedness						
4 (439)	Not serious	Not serious	Not serious	Not serious	Strongly suspected *	⊕⊕⊕ MODERATE
OH related symptoms						
3 (394)	Not serious	Not serious	Not serious	Not serious	Strongly suspected *	⊕⊕⊕ MODERATE
Difficulty with daily activity						
3 (393)	Not serious	Not serious	Not serious	Not serious	Strongly suspected *	⊕⊕⊕ MODERATE
Standing Systolic BP						
4 (427)	Not serious	Not serious	Not serious	Serious †	Strongly suspected *	⊕⊕ LOW
Falls						
3 (314)	Serious ‡	Not serious	Not serious	Serious †	Strongly suspected *	⊕ VERY LOW
Supine hypertension						
4 (485)	Not serious	Not serious	Not serious	Serious †	Strongly suspected *	⊕⊕ LOW

* Authors' conflict of interest with drug company sponsor

† The direction of the effect is variable or confidence intervals are wide

‡ Methodologically inadequate data collection and analysis for falls outcome data

Supplementary Table 1. Comprehensive list of search terms used in systematic review

Database	Search strategy
MEDLINE	1. randomized controlled trial.pt.
1946 to June Week	2. controlled clinical trial.pt.
3 2015	3. randomized.ab.
	4. placebo.ab.
	5. drug therapy.fs.
	6. randomly.ab.
	7. trial.ab.
	8. groups.ab.
	9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
	10. exp animals/ not humans.sh.
	11. 9 not 10
	12. hypotension, orthostatic.sh.
	13. orthostatic intolerance.sh.
	14. postural hypotension.mp.
	15. 12 or 13 or 14
	16. droxidopa.sh.
	17. DL-threo-3,4-Dihydroxyphenylserine.mp.
	18. 3,4-Dihydroxyphenylserine.mp.
	19. 3,4-threo-DOPS.mp.
	20. erythro-3,4-Dihydroxyphenylserine.mp.
	21. threo-DOPS.mp.
	22. 16 or 17 or 18 or 19 or 20 or 21

	23. 11 and 15 and 22
EMBASE	1 random:.tw.
1974 to 2015 June	2 clinical trial.mp.
25	3 exp health care quality
	4 1 or 2 or 3
	5 orthostatic hypotension.sh.
	6 postural hypotension.mp.
	7 orthostatic intolerance.sh.
	8 orthostatic stress.sh.
	9 standing.sh.
	10 5 or 6 or 7 or 8 or 9
	11 droxidopa.sh.
	12 northera.mp.
	13 DL-threo-3,4-Dihydroxyphenylserine.mp.
	14 3,4-Dihydroxyphenylserine.sh.
	15 3,4-threo-DOPS.mp.
	16 erythro-3,4-Dihydroxyphenylserine.mp.
	17 threo-DOPS.mp.
	18 11 or 12 or 13 or 14 or 15 or 16 or 17
	19 4 and 10 and 18
PUBMED	#1. randomized controlled trial [pt]
No date	#2. controlled clinical trial [pt]
restriction	#3. randomized [tiab]
	#4. placebo [tiab]
	#5. drug therapy [sh]

	#6. randomly [tiab] #7. trial [tiab] #8. groups [tiab] #9. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 #10. animals [mh] NOT humans [mh] #11. #9 NOT #10 #12. hypotension, orthostatic [mesh] #13. orthostatic intolerance [mesh] #14. #12 OR #13 #15. droxidopa [mesh] #16. #11 AND #14 AND #15
The Cochrane library Cochrane Central Register of Controlled Trials, issue 6 of 12, May 2015	#1. orthostatic hypotension #2. MeSH descriptor: [hypotension, orthostatic] explode all trees #3. orthostatic intolerance #4. MeSH descriptor: [orthostatic intolerance] explode all trees #5. #1 or #2 or #3 or #4 #6. droxidopa #7. MeSH descriptor: [Droxidopa] explode all trees #8. #6 or #7 #9. #5 and #8
Web Of Science 1970 to 2015	#1. TS=(orthostatic hypotension) #2. TS=(orthostatic intolerance) #3. TS=(postural hypotension) #4. #1 OR #2 OR #3 #5. TS=(droxidopa)

	#6. TS=(random*) #7. TS=(clinical trial) #8. TS=(placebo) #9. #6 OR #7 OR #8 #10. #4 AND #5 AND #9
ProQuest 1970-2015	(MESH(hypotension, orthostatic) OR MESH(orthostatic intolerance) OR MESH(Posture) OR AB,TI,DISKW,FT(orthostatic)) AND (MESH(Droxidopa) OR MESH(Droxidopa, (DL-Tyr) -Isomer) OR AB,TI,DISKW,FT(Droxidopa)) AND YR(1970-2015) AND (MESH(Treatment Outcome) OR MESH(Clinical Trial) OR TI,AB,DISKW,FT(random*))
The World Health Organisation International Clinical Trials Registry Platform	Droxidopa

Appendix Table 2. Adverse events (AEs)

	Droxidopa	**Placebo**	**Risk (odds ratio with 95% CI)**
Severe AE	8/245	11/240	0·66 (0·26, 1·68)
Biaggioni	0/51	2/50	
Kaufmann	0/81	0/81	
Hauser 2015	8/89	9/82	
Hauser 2014	0/24	0/27	
Serious AE	5/245	5/240	0·93 (0·28, 3·12)
Biaggioni	0/51	1/50	
Kaufmann	0/81	0/81	
Hauser 2015	5/89	4/82	
Hauser 2014	0/24	0/27	
Discontinued due to AE	11/221	7/213	1·47 (0·57, 3·82)
Biaggioni	0/51	2/50	
Kaufmann	0/81	0/81	
Hauser 2015	11/89	5/82	
Hauser 2014	not reported	not reported	
Headache	23/245	12/240	1·91 (0·94, 3·92)
Biagionni	2/51	4/50	
Kaufmann	6/81	0/81	
Hauser 2015	12/89	6/82	
Hauser 2014	3/24	2/27	
Dizziness	16/245	7/240	2·32 (0·93, 5·77)

Biagionni	2/51	1/50	
Kaufmann	3/81	1/81	
Hauser 2015	9/89	4/82	
Hauser 2014	2/24	1/27	
Fatigue	9/221	8/213	1·06 (0·41, 2·74)
Biagionni	0/51	1/50	
Kaufmann	2/81	2/81	
Hauser 2015	7/89	5/82	
Hauser 2014	not reported	not reported	
Nausea	12/245	7/240	1·67 (0·67, 4·16)
Biagionni	0/51	2/50	
Kaufmann	2/81	0/81	
Hauser 2015	7/89	2/82	
Hauser 2014	3/24	3/27	
Supine hypertension	19/245	10/240	1·93 (0·87 to 4·25)
Biagionni (not defined)	7/51	3/50	
Kaufmann (systolic BP >180)	4/81	2/81	
Hauser 2015 (systolic BP >180)	7/89	4/82	
Hauser 2014 (systolic BP >180)	1/24	1/27	