D.3.3 Orthostatic hypotension

Bibliographic reference	Hauser,R.A., Hewitt,L.A., Isaacson,S., 20141014, Droxidopa in patients with neurogenic orthostatic hypotension associated with Parkinson's disease (NOH306A), Journal of Parkinson's Disease Print, 4, 57-65, 2014
Country/ies where the study was carried out	USA
Study type	Intervention, Randomised Controlled Trial
Aim of the study	Determine efficiency and safety of droxidopa in treating Orthostatic Hypotension as a symptom of Parkinson's disease
Study dates	June 2010 - December 2010
Source of funding	Chelsea Therapeutics, Inc.
Sample size	51
Inclusion criteria	• Age >=18 years • PD clinical diagnosis • Symptomatic nOH (Decrease >=20mmHg systolic/>=10mmHg diastolic b.p. within 3 minutes after going from supine to standing) • Patient reported composite score >=3 on Orthostatic Hypotension Questionnaire • Study investigator rating >=3 on Clinical Global Impression-Severity Scale)
Exclusion criteria	• Use of vasoconstrictive agents or long-acting antihypertensive medications • Sustained severe hypertension (>=180/110 mmHg while seated or supine on 3 consecutive measurements over 1h) • Mini-Mental State Examination score <=23
Details	Enrolled patients underwent up to 2 weeks of dosage optimisation by titration in 100mg increments until becoming asymptomatic, reaching the maximum permitted dosage, or experiencing intolerable adverse effects. In the third case, patients were eligible to continue the study under a lower dose if effects occurred at a dosage of more than 100mg twice daily. During study, all PD medications were held stable. Midodrine was disallowed, but fludrocortisone could be continued at a dosage that had been held steady for 2 weeks prior to start of study drug. Primary efficacy measure was mean change in Orthostatic Hypotension Questionnaire from baseline to end of study, recorded on weeks 1, 2, 4 and 8 of treatment Key secondary efficacy variables included dizziness/light-headedness score on OHQ and patient-reported falls from baseline to end of study, which patients were instructed to record by daily entries in an electronic diary, with falls defined as "unexpectedly coming to rest on the ground, floor, or a lower level from where the patient started." Additional secondary effect variables included OHQ symptom and symptom impact composite scores and individual item scores, and hemodynamic efficacy variables such as standing systolic b.p.

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Interventions	Droxidopa: 100, 200, 300, 400, 500 or 600mg twice daily Placebo: placebo twice daily
Results	

	Droxidopa	Placebo
Total assigned	24	27
Discontinued	3	3
Completed Study	21	24

	Droxidopa	Placebo
Patients receiving maximum allowable dosage	6	13
Mean (SD) dosage/mg twice daily	433.3 (155.1)	488.9 (134.0)

	Droxidopa	Placebo
Mean (SD) decrease in OHQ composite week 1	-2.7 (2.6)	-2.1 (2.5)
Mean (SD) decrease in OHQ composite week 2	-2.3 (2.4)	-1.7 (2.2)
Mean (SD) decrease in OHQ composite week 8	-2.2 (2.4)	-2.1 (2.5)
Mean (SD) decrease in dizziness/light-headedness score week 1	-3.1 (3.4)	-1.6 (3.1)
Mean (SD) decrease in dizziness/light-headedness score week 2	-2.3 (3.0)	-1.0 (3.0)
Mean (SD) change in standing systolic bp week 1	+8.4 (17.4)	-4.1 (20.5)
Mean (SD) change in standing systolic bp week 8	+7.0 (18.7)	+7.7 (22.2)

	Droxidopa	Placebo

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# (%) patients recording falls	13 (54)	16 (59)
Repeat fallers	9	13
Total falls	79	192
Mean falls/patient/week	0.4	0.8
Mean (SD) falls/repeat faller/week	1.0 (1.2)	1.9 (2.1)
Number of patients (%) reporting AEs	17 (71)	23 (85)
Fall related injuries	4	8
Most frequently reported AEs	Nausea (3), Headache (3), Skin Laceration (2)	Diarrhoea (4), Nausea (3), Skin Laceration (3)

	Droxidopa	Placebo
Mean (SD) decrease MDS-UPDRS total	-19.0 (18.4)	-11.3 (24.9)
Mean (SD) decrease MDS-UPDRS I	-7.3 (7.1)	-5.2 (6.9)
Mean (SD) decrease MDS-UPDRS II	-5.3 (7.7)	-3.1 (6.7)
Mean (SD) decrease MDS-UPDRS III	-4.7 (8.4)	-0.6 (12.9)
Mean (SD) decrease MDS-UPDRS IV	-1.7 (5.3)	-0.7 (4.0)
Mean (SD) decrease H&Y stage	-0.4 (0.9)	0.0 (1.2)

Overall Risk of Bias	Not much information given for method of randomisation, level of blinding present beyond description of study as "randomized, double-blind, placebo-controlled phase 3 trial". However, study groups appear to have been comparable and treated comparably, and results collected would seem to be valid and reasonably connected to the outcomes measured. Overall there is likely high risk of bias.
Other information	1. An appropriate method of randomization was used to allocate pts to treatment groups? not mentioned 2. There was adequate concealment of allocation - not mentioned

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	3. The groups were comparable at baseline, including all major confounding and prognostic factors? approximately similar - possible slight difference in progression of PD, but probably not enough to make much of a difference 4. Comparison groups received same care apart from interventions - yes 5. Pts receiving care were kept blind to tmt allocation - not discussed 6. Individuals administering care were kept blind to tmt allocation - not discussed 7. All groups followed up for an equal length of time - yes, when possible 8. Groups comparable for treatment completion? yes 9. Groups were comparable with respect to availability of outcome data? yes 10. Study had appropriate length of followup - 8 weeks 11. Study used a precise definition of outcome - difference in questionnaire scores, standing Systolic Blood Pressure, number of falls/fall-related injuries sustained, change in H&Y score 12. Valid and reliable method was used to determine the outcome - see above 13. Investigators were kept blind to participants exposure to the intervention - not discussed 14. Investigators were kept blind to other important confounding and prognostic factors - not discussed

Bibliographic reference	Hauser,R.A., Isaacson,S., Lisk,J.P., Hewitt,L.A., Rowse,G., Droxidopa for the Short-Term Treatment of Symptomatic Neurogenic Orthostatic Hypotension in Parkinson's Disease (nOH306B), Movement Disorders.30 (5) (pp 646-654), 2015.Date of Publication: 15 Apr 2015., 646-654, 2015
Country/ies where the study was carried out	USA
Study type	RCT: Intervention
Aim of the study	To determine efficacy and safety of droxidopa as a short term treatment of Orthostatic Hypotension in PD
Study dates	June 2010 - October 2012
Source of funding	Lundbeck NA Ltd.
Sample size	174
Inclusion criteria	• Age >=18 years • Clinical diagnosis of Parkinson's disease

<table>
<tr><th>Bibliographic reference</th><th>Hauser,R.A., Isaacson,S., Lisk,J.P., Hewitt,L.A., Rowse,G., Droxidopa for the Short-Term Treatment of Symptomatic Neurogenic Orthostatic Hypotension in Parkinson's Disease (nOH306B), Movement Disorders.30 (5) (pp 646-654), 2015.Date of Publication: 15 Apr 2015., 646-654, 2015</th></tr>
<tr><td></td><td>• B.P. decrease >=20mmHg systolic or >=10mmHg diastolic upon standing for up to 3 minutes
• Orthostatic Hypotension Questionnaire score >=3
• Study-investigator Orthostatic Hypotension rating >=3 on clinician reported Clinical Global Impression-Severity scale</td></tr>
<tr><td>Exclusion criteria</td><td>• Use of vasoconstricting agents or long acting antihypertensive medications
• Sustained, sever hypertension (>=180/110 mmHg while seated or supine)
• Mini-Mental State Examination score <=23
• Significant uncontrolled cardiac arrhythmia, unstable angina, congestive heart failure, or a history of myocardial infarction</td></tr>
<tr><td>Details</td><td>Subjects were randomised in a 1:1 ratio to double-blind droxidopa or placebo titration for up to 2 weeks, followed by 8 weeks of double-blind maintenance at the personally optimised dosage
During titration, assigned drug was increased in 100mg increments thrice daily until subject's cCGI-S score fell to 1 or 2, the maximum dosage was reached, subject's blood pressure reached >=180mmHg systolic or >=110mmHg diastolic after ten minutes supine 3 times consecutively over an hour, or subject experienced intolerable adverse effects. If either of the last 2 criteria were met at a dosage of >100mg, subjects were eligible to continue the trial at a lower dosage.
During study, all PD medications were to be held steady; Midodrine was disallowed, but fludrocortisone could be allowed at a dosage that had been kept stable for at least 2 weeks prior to the trial. Bedtime usage of a short-acting antihypertensive was permitted.
An orthostatic standing test, OHQ, cCGI-S and subject reported pCGI-S ratings were completed for each subject at randomisation, and on weeks 1, 2, 4 and 8 of maintenance; patient and clinician reported Clinical Global Impression-Improvement ratings were obtained in weeks 1, 2, 4 and 8; and MDS-UPDRS and PDQ-39 were completed at randomisation and week 8. All assessments were conducted ~3h after the subject's first daily dose, and subjects were instructed to record all falls, defined as "unexpectedly coming to rest on the ground, floor, or a lower level from where the patient started", in a daily electronic diary.</td></tr>
<tr><td>Interventions</td><td>Droxidopa: 100, 200, 300, 400, 500 or 600mg thrice daily
Placebo: placebo thrice daily</td></tr>
<tr><td>Results</td><td><table>
<tr><td></td><td>Droxidopa</td><td>Placebo</td></tr>
<tr><td>N</td><td>89</td><td>85</td></tr>
<tr><td>Treated</td><td>87</td><td>84</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Hauser,R.A., Isaacson,S., Lisk,J.P., Hewitt,L.A., Rowse,G., Droxidopa for the Short-Term Treatment of Symptomatic Neurogenic Orthostatic Hypotension in Parkinson's Disease (nOH306B), Movement Disorders.30 (5) (pp 646-654), 2015.Date of Publication: 15 Apr 2015., 646-654, 2015

Provided week 1 data	69	78
Completed study	62	67
Mean (SD) study drug dosage/mg	436 (163)	468 (165)

Mean (SD) improvement in OHSA item 1 score	Droxidopa	Placebo
To week 1	2.3 (2.95)	1.3 (3.16)
To week 2	1.9 (2.86)	1.6 (2.97)
To week 4	2.0 (3.08)	1.5 (2.74)
To week 8	2.1 (3.03	1.5 (2.91)

Mean (SD) change in OHQ composite score	Droxidopa	Placebo
To week 1	-2.3 (2.12)	-1.9 (2.39)
To week 2	-2.5 (1.98)	-2.0 (2.26)
To week 4	-2.5 (1.93)	-1.9 (2.28)
To week 8	-2.2 (2.29)	-2.0 (2.18)

	Droxidopa	Placebo
Aggregate falls per patient-week	0.38	1.09
Total falls	229	716
Total falls to end of titration	46	232

Bibliographic reference	Hauser,R.A., Isaacson,S., Lisk,J.P., Hewitt,L.A., Rowse,G., Droxidopa for the Short-Term Treatment of Symptomatic Neurogenic Orthostatic Hypotension in Parkinson's Disease (nOH306B), Movement Disorders.30 (5) (pp 646-654), 2015.Date of Publication: 15 Apr 2015., 646-654, 2015

Patients experiencing Treatment Emergent Adverse Effects	82%	79.3%
Subjects experiencing fall related AEs	16.9%	25.6%
Severe AEs	8	9
Serious AEs	5	4
AEs leading to discontinuation	11	5
Patients experiencing Supine Hypertension	7	4
Most Common AEs	Headache (12), Dizziness (9), Fatigue (7)	Contusion (10), Excoriation (7), Skin Laceration (7)

Mean (SD) change in lowest standing Systolic Blood Pressure	Droxidopa	Placebo
To week 1	+6.4 (18.85)	+0.7 (20.18)
To week 2	+5.5 (19.34)	-0.6 (20.28)
To week 4	+2.8 (20.23)	+3.0 (19.40)
To week 8	+5.0 (18.52)	+0.9 (18.38)

Overall Risk of Bias	High; most outcomes recorded measured for 1, 2 or 4 weeks, primary outcome altered after futility analysis for part a showed no impact for original primary outcome, no description of randomisation or blinding processes used in study
Other information	1. An appropriate method of randomization was used to allocate pts to treatment groups? method not described 2. There was adequate concealment of allocation - not described 3. The groups were comparable at baseline, including all major confounding and prognostic factors? Yes 4. Comparison groups received same care apart from interventions - pharmacological treatments kept comparable, non-pharmacological treatments not controlled 5. Pts receiving care were kept blind to tmt allocation - not described

Bibliographic reference	Hauser,R.A., Isaacson,S., Lisk,J.P., Hewitt,L.A., Rowse,G., Droxidopa for the Short-Term Treatment of Symptomatic Neurogenic Orthostatic Hypotension in Parkinson's Disease (nOH306B), Movement Disorders.30 (5) (pp 646-654), 2015.Date of Publication: 15 Apr 2015., 646-654, 2015
	6. Individuals administering care were kept blind to tmt allocation - not described 7. All groups followed up for an equal length of time - yes 8. Groups comparable for treatment completion? yes 9. Groups were comparable with respect to availability of outcome data? - yes 10. Study had appropriate length of follow up - 8 weeks from end of dosage titration, most primary and secondary outcomes reported only measured for 1, 2 and 4 weeks 11. Study used a precise definition of outcome - questionnaires as described above, plus blood pressure, number of falls and H&Y stage 12. Valid and reliable method was used to determine the outcome - yes 13. Investigators were kept blind to participants exposure to the intervention - not described 14. Investigators were kept blind to other important confounding and prognostic factors - not described

Bibliographic reference	Schoffer,K.L., Henderson,R.D., O'Maley,K., O'Sullivan,J.D., 20071128, Nonpharmacological treatment, fludrocortisone, and domperidone for orthostatic hypotension in Parkinson's disease, Movement Disorders, 22, 1543-1549, 2007
Country/ies where the study was carried out	Australia
Study type	RCT - Intervention
Aim of the study	Assess the efficacy of nonpharmological therapy, domperidone and fludrocortisone for Orthostatic Hypotension in Parkinson’s Disease
Study dates	January 2005 - November 2005
Source of funding	Not reported
Sample size	17
Inclusion criteria	• Diagnosis of IPD • Sustained response to medications, (held stable through study) • Symptomatic orthostasis
Exclusion criteria	• Acute coronary syndrome

<table>
<tr><th>Bibliographic reference</th><th>Schoffer,K.L., Henderson,R.D., O'Maley,K., O'Sullivan,J.D., 20071128, Nonpharmacological treatment, fludrocortisone, and domperidone for orthostatic hypotension in Parkinson's disease, Movement Disorders, 22, 1543-1549, 2007</th></tr>
<tr><td></td><td>• Inability to give consent
• Alternative etiology for autonomic failure
• SBP>200mg Hg or DBP>100mg Hg</td></tr>
<tr><td>Details</td><td>During first visit, clinical evaluation was performed, focusing on symptoms over 3 week period, including COMPASS-OD score and clinically measured BP after 15 min supine, and after 1 and 3 minutes standing. Patients were instructed to follow series of non-pharmacological treatments for 3 weeks, after which evaluation was repeated.
Patients were randomly allocated to receive one of 2 pharmacological treatments first; this treatment course was followed for 3 weeks, then, after a 1 week washout period, the alternative treatment course was followed for 3 weeks. After each treatment course, a clinical evaluation was performed, including tilt table testing with both a non-invasive finger BP measurement and an automatic sphygmomanometric method, in which the patient lay supine for 15 minutes, and then had heart rate and BP changes recorded over 5 minutes supine, 5 minutes with an 80 degree head up tilt, and a further 5 minutes supine. Non-pharmacological treatments were sustained over both courses of pharmacological treatment.
Patients were asked to choose which, if any, of the 3 treatments they found most beneficial</td></tr>
<tr><td>Interventions</td><td>Instruction sheet of 12 non-pharmacological treatments asked to be followed over entire period
2 treatment courses;
0.1mg fludrocortisone during morning, 2 placebo tablets at lunch and supper
10mg domperidone three times a day</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td></td><td>baseline</td><td>fludrocortisone</td><td>domperidone</td></tr>
<tr><td>COMPASS-OD score (+/-)*</td><td>9 (3)</td><td>6 (3)</td><td>7 (2)</td></tr>
<tr><td>Average CGI score (+/-)</td><td>-</td><td>MC =+0.6 (1.2)</td><td>MC=+0.9 (1.2)</td></tr>
<tr><td>supine SBP/mm Hg</td><td>139</td><td>137 (134 ± 24; 100-165)</td><td>125 (138 ± 27; 107 - 189)</td></tr>
</table>
<table>
<tr><td></td><td>fludrocortisone</td><td>domperidone</td><td>both</td><td>neither</td></tr>
<tr><td>Preference/greater response</td><td>4</td><td>3</td><td>3</td><td>3</td></tr>
</table>
<table>
<tr><td></td><td>fludrocortisone</td><td>domperidone</td></tr>
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</td></tr>
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	<table><tr><td>Patients reporting AEs</td><td>6</td><td>5</td></tr><tr><td>Most common AE</td><td>Nausea</td><td>Nausea</td></tr></table> COMPASS OD = composite autonomic symptom scale -OT component Mean difference scores calculated from mean values and SD's presented in text Supine blood pressure (SBP mm/Hg): fludrocortisone v domperidone: MD= -4 (95%CI: -23.6 to 15.64) COMPASS-OD: fludrocortisone v domperidone: MD = -1 (-2.96 to 0.96)
Overall Risk of Bias	High; very small sample size, with noticeable difference between demographics of treatment groups
Other information	An appropriate method of randomization was used to allocate pts to treatment groups - patients allocated using computerised random number generator program - Research Randomizer There was adequate concealment of allocation - randomisation sequence performed, kept and administered by uninvolved staff member The groups were comparable at baseline, including all major confounding and prognostic factors - all women in trial received domperidone treatment before fludrocortisone, making up 4 of 5 such patients; two fludrocortisone first patients were on Entacapone during study; average UPDRS score seems much higher for fludrocortisone first patients than for domperidone first, though this may be mostly due to a typo in table 1; fludrocortisone first patients receiving 70% more levodopa on average Comparison groups received same care apart from interventions - yes Pts receiving care were kept blind to tmt allocation - yes Individuals administering care were kept blind to tmt allocation - medications identically encapsulated and delivered in unmarked packages All groups followed up for an equal length of time - yes Groups comparable for treatment completion? 3 patients assigned to domperidone and 1 assigned to fludrocortisone withdrawn in first week of pharmacological treatment Groups were comparable with respect to availability of outcome data? yes Study had appropriate length of follow up - 3 weeks on each drug Study used a precise definition of outcome - orthostatic domain of the Composite Autonomic Symptom Scale, clinical global impression of change, and postural blood pressure testing Valid and reliable method was used to determine the outcome - yes Investigators were kept blind to participants exposure to the intervention - not mentioned Investigators were kept blind to other important confounding and prognostic factors - not mentioned