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Research Articles

Nonpharmacological Treatment, Fludrocortisone, and Domperidone for Orthostatic Hypotension in Parkinson's Disease

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Abstract: There is limited evidence for the treatment of orthostatic hypotension in idiopathic Parkinson's disease. The objective of this study was to determine the efficacy of three treatments (nonpharmacological therapy, fludrocortisone, and domperidone). Phase I assessed the compliance, safety, and efficacy of nonpharmacological measures. Phase II was a double-blind randomized controlled crossover trial of the two medications. Primary outcome measures consisted of the orthostatic domain of the Composite Autonomic Symptom Scale (COMPASS-OD), a clinical global impression of change (CGI), and postural blood pressure testing via bedside sphygmomanometry (Phase I) or tilt table testing (Phase II). For the 17 patients studied, nonpharmacological therapy did not significantly alter any outcome measure. Both medications improved the CGI and COMPASS-OD scores. There was a trend towards reduced blood pressure drop on tilt table testing, with domperidone having a greater effect. © 2007 Movement Disorder Society

Key words: orthostatic hypotension; Parkinson's disease; domperidone; nonpharmacological therapy; fludrocortisone.

Orthostatic hypotension (OH), defined as a decrease of at least 20 mm Hg in systolic blood pressure (SBP) and/or 10 mm Hg in diastolic blood pressure (DBP) during orthostatism or passive tilting, with or without postural symptoms,[1] is the most frequently reported autonomic finding in Idiopathic Parkinson's Disease (IPD), with an estimated prevalence of 20%.[2] Consequences of OH include increased cognitive decline,[3] cardiovascular morbidity,[4,5] and overall mortality.[6]

There is limited evidence supporting the use of any antihypotensive treatments in IPD. Nonpharmacological therapies, such as compression garments, caffeine, exercise, and avoidance of warm weather, hot baths, and strenuous activity, have presumed efficacy by reducing vascular capacitance,[7] while elevation of the bed head reduces nocturia through renin release,[8] and salt and fluid intake increase plasma volume.[9] Medications acting on sympathetic pathways (droxidopa,[10] pyridostigmine),[11] blood volume (erythropoietin),[12] blood vessels (etilefrine,[13] midodrine),[14,15] and for prevention of postprandrial hypotension (octreotide)[16] have been the subject of small series which have included IPD patients. Fludrocortisone is a synthetic mineralocorticoid that elevates blood volume through the renin-aldosterone system, increases norepinephrine release, and sensitizes vascular adrenergic receptors. It is widely used, yet scarcely supported.[17,18] Domperidone antagonizes peripheral D2 receptors, and since presynaptic dopamine receptors on sympathetic nerve endings also modulate noradrenaline release,[19] it has been proposed as a treatment for OH. Evidence for domperidone as a treatment for OH in IPD is limited to patients on dopamine agonists,[20–22] although there is support in other groups with autonomic impairment,

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TABLE 1. *Study population*

Patient no.	Sex	Age	UPDRS	Yr since diagnosis	L (mg/d)	E (mg/d)	C (mg/d)	Max SBP drop	Max DBP drop	Randomization (1st drug)
1	M	51	25	1	150	–	–	20	3	F
2	M	46	6	3	525	–	4	6	5	F
3	M	83	30	2	300	–	–	50	8	Withdrawn
4	F	76	31	4	100	–	–	42	37	D
5	F	74	17	4	250	–	3	63	26	D
6	M	74	70	7	300	–	4	40	10	F
7	M	78	23	3	300	–	–	54	35	F
8	M	73	22	10	900	–	–	20	6	Withdrawn
9	M	63	3	14	0	–	–	19	21	D
10	M	63	23	10	750	–	4	50	20	Withdrawn
11	F	70	14	1	0	–	–	36	14	D
12	M	92	19	10	100	–	–	68	31	F
13	M	69	28	4	450	600	–	12	10	F
14	F	62	38	2	600	–	–	23	20	D
15	M	56	33	16	1250	–	–	23	10	Withdrawn
16	M	76	33	5	300	–	–	15	16	F
17	M	73	25	6	500	200	–	61	24	F

UPDRS, United Parkinson's Disease Rating Scale; F, fludrocortisone; D, domperidone; C, cabergoline; E, entacaptone; L, levodopa. Maximal SBP and DBP drop is the maximum drop detected on the first two BP measurements (baseline sphygnomanometry and tilt table test).

such as diabetics.[23,24] A comparative study between domperidone and fludrocortisone has not be performed to our knowledge.

In this study, we assess the efficacy of nonpharmacological therapy, domperidone, and fludrocortisone for OH in IPD through the use of three primary outcome measures: (1) the orthostatic domain of the Composite Autonomic Symptom Scale (COMPASS-OD); (2) a clinical global impression of change (CGI); and (3) postural blood pressure (BP) testing.

SUBJECTS AND INCLUSION CRITERIA

Subjects

Between January to November of 2005, 17 patients (Table 1) with an established diagnosis of IPD (United Kingdom Parkinson Disease Brain Bank Criteria)[25] were recruited from two Australian movement disorder clinics. At the time of enrolment, none of the patients fulfilled the multiple systems atrophy consensus criteria set forth by Gilman et al.[26] The mean age of patients was 69 ± 11 years, with an average time since diagnosis of 6.0 ± 4.5 years, a daily levodopa dosage of 452 ± 319 mg, and a United Parkinson's Disease Rating Scale (UPDRS) Motor score of 26 ± 15 (recorded at the identical time of the morning after routine medications). One patient (patient 9) had bilateral subthalamic deep brain stimulators.

Inclusion and Exclusion Criteria

Inclusion criteria were (1) diagnosis of IPD; (2) sustained response to medications, held stable throughout the study; and (3) symptomatic orthostasis. All subjects exhibited a postural SBP and or DBP drop at baseline (Table 1), and subjects who had previously fulfilled BP criteria by the definition of OH stated above and who remained symptomatic were not excluded if they did not fulfill the criteria on the single baseline BP recording. Exclusion criteria were (1) an acute coronary syndrome; (2) inability to give consent; (3) another etiology for autonomic failure; and (4) SBP greater than 200 mm Hg or DBP greater than 100 mm Hg.

The study was approved by the Royal Brisbane and Women's Hospital Ethics Committee, and registered through the National Institute of Health.

METHODS

Phase I (Nonpharmacological Treatment)

At Visit I, a clinical evaluation, including UPDRS motor score, was performed. Subjects completed the COMPASS-OD,[27] a series of weighted questions relating specifically to OH and part of the Mayo clinic developed and validated Autonomic Symptom Profile. The OH score has been found to correlate strongly with objective autonomic testing on the Composite Autonomic Scoring Scale (CASS).[28] Patients focused on symptoms over the 3 week period, in order to compare each 3 week treatment allocation upon repeated testing. The maximal score attainable was 16, with a higher score indicating more severe symptoms. BP was measured by a physician (K.S.) using a bedside sphygmomanometer with the patient resting supine for at least 15 min, and then after 1 and 3 min of standing.[1] An instruction sheet for 12

TABLE 2. *Patient compliance with nonpharmacological measures*

Nonpharmacological measure	Reasons for noncompliance	Compliance (%)
Increased dietary salt (10–20 g daily)	Hypertension, dislike of taste	82
Five glasses (250 mL/glass) of water per day	Worsening of nocturia/incontinence	88
Elevated head of bed (10–15 cm)	Inability to lift bed, waterbed, spouse discomfort	76
Thigh-high 30 mm Hg pressure stockings	Difficulty getting on due to tremor, discomfort, leg ulcers, too warm, appearance	59
Frequent small meals (6 per day)	Lack of hunger	82
Coffee/tea in the morning	Dislike of taste	76
No alcohol use	Regular drink in evening	59
Avoid hot weather	Difficult to avoid in summer	65
Avoid strenuous early morning activities.	Work-related activities, caring for children	76
Sit on side of bed 30 s before rising		100
Regular moderate intensity exercise (20 min three times a week)	Unsteady on feet	88
Avoid prolonged standing	Difficult to avoid	82

nonpharmacological measures (Table 2) to be rigorously followed over the subsequent 3 week period was discussed and distributed. Measurements were taken to determine the correct fitting of supplied thigh-high 30 mm Hg pressure stockings. Three weeks later, BP testing, the COMPASS-OD, and a CGI score focusing on orthostatic symptoms (+3 = very much improved, +2 = much improved; +1 minimally improved, 0 = no change, −1 = minimally worse, −2 = much worse; −3 = very much worse), were obtained at Visit 2.

Phase II (Drug Treatment)

Tilt table testing was performed in a quiet room in the morning, with medications taken as usual. Both a continuous noninvasive finger BP measurement and an automatic sphygmomanometric method were used. Patients lay supine for at least 15 min, then quantitative heart rate (HR) and BP changes were recorded during 5 min lying supine, 5 min at an 80° head-up tilt, and 5 min again lying supine. A 5 min tilt was chosen since, by definition, patients with OH should have a drop in BP within 3 min of standing.[1]

Patients were allocated using a computerized random number generator program (Research Randomizer)[29] to receive either fludrocortisone 0.1 mg in the morning and two placebo tablets at lunch and supper, or domperidone 10 mg three times a day. Patients matched to odd numbers received domperidone first, and even numbers received fludrocortisone first. The randomization sequence was performed, kept, and administered by an uninvolved staff member who distributed the identically encapsulated medications in unmarked packages. Patients crossed over to the alternative therapy after 3 weeks with a one-week washout period. Nonpharmacological measures were continued during Phase II, as would normally be done in a clinical setting. At the end of each treatment period (Visit 3 and Visit 4), the COMPASS-OD, CGI, and tilt table testing was repeated. While still blinded, patients chose which, if any, of the three treatments they found beneficial.

STATISTICAL ANALYSIS

A Wilcoxon matched-pairs signed-ranks test was used to compare the change in scoring on the COMPASS-OD and tilt after each intervention. Comparison was made between baseline and nonpharmacological therapy for Phase I, and between nonpharmacological therapy alone, and nonpharmacological therapy plus the designated drug treatment for Phase II. Spearman's rank correlation test assessed associations between responses on the COMPASS-OD, CGI and tilt table testing. A two-tailed *P*-value of less than 0.05 was considered to be significant. Results in the text are expressed as medians (mean ± SD; range). The analysis was performed using *SPSS Version 11.5.0* (SPSS, Chicago, IL, 2002).

RESULTS

Phase I (Nonpharmacological Treatment)

Characteristics of orthostatic symptoms in our patient cohort are listed in Table 3. Dizziness and lightheadedness were the most common presentations, although 16 of 17 patients reported additional symptoms. The mean overall compliance with nonpharmacological measures was 78% (Table 2), and patients were least compliant with compression stockings. At baseline, the maximal changes in SBP or DBP between lying and either the one or three minute blood pressure were −20 (−25 ± 16; −65 to −5) mm Hg and +5 (5 ± 7; −15 to +10) mm Hg respectively. There was no significant change after nonpharmacological therapy. The median score on the COMPASS-OD was 9 (9 ± 2; 4–12) on baseline scoring and 9 (9 ± 3; 5–15) after nonpharmacological treatment. There was no change in the CGI score, with a median

TABLE 3. *Characteristics of orthostatic hypotension in the patient group*

	Number of patients (%)
Orthostatic Symptomatology	
Dizziness	15 (88)
Lightheadedness	14 (82)
Blurring of vision	11 (65)
Concentration Difficulties	8 (47)
Palpitation of the heart	6 (35)
Headache	6 (35)
Nausea	4 (24)
Tremulousness	4 (24)
Profuse perspiration	4 (24)
Chest discomfort	3 (18)
Fainting	2 (18)
Aggravating Factors	
Prolonged Standing	10 (59)
Physical activity	8 (47)
Hot baths.showers	4 (24)
Meals	1 (6)
Frequency of Symptoms	
Rarely	1 (6)
Occasionally	7 (41)
Frequently	6 (35)
Almost Always	3 (18)
Severity of Symptoms	
Mild	5 (29)
Moderate	8 (37)
Severe	4 (24)

score of 0 (0.4 ± 1; −2 to 2). Quantitatively, 7 of 17 patients noted an improvement in their symptoms on nonpharmacological therapy (2 were "much improved" and 5 were "minimally improved"). There was no association between greater compliance and improvement in the CGI or questionnaire scores, and individual conservative measures did not significantly alter the outcome variables. Women followed a median of 11 nonpharmacological measures and men followed a median of 9, with women complying more with stocking use (100% vs. 46%). No correlation was found between compliance and age, years since diagnosis, or UPDRS scoring.

Phase II (Drug Treatment)

Because of adverse events (see below), 13 patients participated in Phase II. On a chi square analysis, there was no significant difference between the groups when accounting for variables of age, years since diagnosis, UPDRS score, and mg per day of L-dopa. For this subset, the COMPASS-OD scores were 9 (9 ± 3; 5–15) on nonpharmacological therapy alone, 6 (6 ± 3; 1–10) on fludrocortisone, and 6 (7 ± 2; 3–11) on domperidone. This was statistically significant for both domperidone ($P = 0.04$) and fludrocortisone ($P = 0.02$). The average CGI score improved to 1 (0.6 ± 1.2; −1 to 2) after fludrocortisone, and 1 (0.9 ± 1.2; −2 to 2) after domperidone.

Baseline tilt table testing demonstrated a change in HR of 9 beats per minute (11 ± 9; −2 to 27) at 3 min with a maximal HR change over the 5 min tilt of 19 beats per minute (18 ± 11; 3–38). Ten patients were able to participate in HR responses to deep breathing and valsalva maneuvers, with a mean of 20.5 ± 21.3 and 33.4 ± 11.3 below our laboratories normative values. The drop in SBP was 18 mm Hg (20 ± 19; −15 to 48) at 3 min with a maximal drop during the 5 min tilting period of 28 mm Hg (34 ± 22; 6–68) at an average time of 2.3 min after orthostasis. The drop in DBP was 7 mm Hg (7 ± 7; −4 to 19) at 3 min with a maximal drop of 14 mm Hg (16 ± 10; 3–37). Time to maximal DPB drop after orthostasis was less clear because of minimal or no drop in several patients. All patients except one fulfilled either the SBP or the DBP criteria for OH on tilt table testing. SBP and DBP drop were not statistically associated with age, UPDRS score, or disease duration. There was a

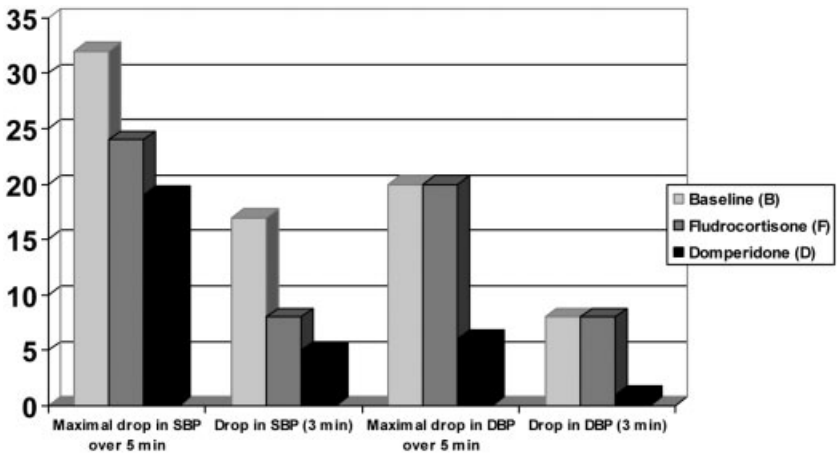

FIG. 1. Tilt table results after each intervention. Maximal SBP drop over 5 min: B = 32 (35 ± 23; 6–68); F= 24 (30 ± 23; −2 to 64); D = 19 (28 ± 21; 5–61); Drop in SBP (3 min): B = 17 (21 ± 20; −15 to 48); F = 8 (18 ± 24; −8 to 64); D = 5 (18 ± 23; −4 to 57); Maximal drop in DBP over 5 min: B = 20 (17 ± 10; 3–37); F = 20 (18 ± 12; 0–35); D = 6 (14 ± 15; −1 to 40); Drop in DBP (3 min): B = 8 (7 ± 7; −4 to 18); F = 8 (8 ± 13; −11 to 33); D= 0 (7 ± 15; −10 to 36).

trend towards improvement on tilt testing for both drugs (Fig. 1), with domperidone showing a greater effect. The supine SBP was 139 mm Hg (138 ± 23; 107–175) prior to drug therapy, 137 mm Hg (134 ± 24; 100–165) with fludrocortisone, and 125 mm Hg (138 ± 27; 107–189) with domperidone, indicating neither drug induced hypertension.

During the domperidone arm, there was a significant correlation between the changes in the CGI and the COMPASS-OD (rho = −0.730; $P = 0.005$), the 3 min SBP drop and both the COMPASS-OD (rho = 0.760; $P = 0.007$) and CGI (rho = −0.879; $P < 0.001$), and the maximal SBP drop and both the COMPASS-OD (rho = 0.740; $P = 0.009$) and CGI (rho = −0.764; $P = 0.006$). There was a similar trend during the fludrocortisone arm, indicating a strong relationship among all of the primary endpoint variables.

When asked for preferences following the study, 3 patients preferred domperidone, 4 preferred fludrocortisone, 3 responded to both drugs equally, and 3 had no response to either drug. Of the 6 patients who preferred domperidone, 3 were on a dopamine agonist, 2 were on L-dopa alone, while 1 patient was unmedicated.

Adverse Events and Patient Compliance

Nine of 17 patients were randomly assigned to receive fludrocortisone first and 8 of 17 to receive domperidone first. However, 4 patients (3 randomly assigned to domperidone and 1 to fludrocortisone) were withdrawn in the first week of Phase II. Patient 3 became confused due to hyponatremia from drinking excessive water, patient 8 suffered a hip fracture due to a fall, patient 10 developed malignant hypertension during the domperidone arm, and patient 15 had recurrence of a prior bowel disturbance. Since all 4 patients were withdrawn within less than a week of the first drug treatment, analyses of Phase II was done as per protocol on the remaining 13 patients.

Two patients (Patients 6 and 13) had severe tremor which obscured BP recordings during the baseline and post-treatment tilt table testing. This persisted despite binding of the limb, attempted use of the less tremulous limb, and sensory stimulation. COMPASS-OD and CGI data were included for these 2 patients as per intention to treat analysis, but their data could not be used in comparing tilt table changes.

Five patients reported side effects while on domperidone, and these included two reports of nausea, and single reports of chest pain, abdominal pain, palpitations, and headache. Six patients reported side effects while on fludrocortisone, including two reports of nausea, and single reports of chest discomfort, morning headache, lightheadedness, and dizziness. On the basis of unused medication in returned pill bottles, compliance with medication was excellent, with an average missed dosage of one tablet of fludrocortisone, and three tablets of domperidone.

DISCUSSION

Our study highlights several important points in the treatment of OH in IPD. From a diagnostic point of view, the diversity of symptomatology in our cohort emphasizes that simply asking about lightheadedness may overlook those who experience other features. Bedside BP and tilt table testing can be challenging because of tremor interference and daytime variability. Significant BP changes may be missed on a single assessment, as demonstrated by our subjects who had nonsignificant BP changes on initial assessment (which occurred at any time of the day), but a significant drop in BP on the fasting morning tilt table test. Hence, a detailed patient history remains most important.

In our study, nonpharmacological measures did not significantly change any outcome measure. However, quantitatively, almost half (7 of 17) of our patients noted an improvement in their CGI scoring, suggesting a larger study may be required to further assess this. A key finding in our study was the surprisingly high level of adverse effects in IPD patients. Elevated fluid intake aggravated urinary incontinence and led to hyponatremia in 1 patient. Dietary salt was a concern in elderly patients with hypertension, and was difficult to quantify in those with mild cognitive impairment. On the basis of our experiences, the close monitoring of the serum and 24 h urinary sodium (patients with a normal volume will excrete >170 mmol Na^+/24 h)[30] would be helpful during implementation of nonpharmacological measures in this frail patient group. Compression stockings were particularly problematic due to bradykinesia and tremor. A Jobst "stocking donner" was helpful in 1 patient. In retrospect, abdominal binders, which provide about two thirds of the benefits of stockings,[31] and physical countermaneuvers, such as toe-raising and leg crossing[32] may have been simpler options for this patient group.

Both fludrocortisone and domperidone showed a statistically significant improvement in two outcome measures (the COMPASS-OD and CGI), and a strong trend on tilt table testing. Somewhat surprisingly, domperidone appeared to have a greater effect on tilt table testing, and was preferred by all patients on dopamine agonists as well as 3 not on agonists. The exact mechanism of domperidone is unknown. Prior studies have shown no effects on renin, aldosterone, or sodium levels.[23] Inhibition of splanchnic dilation, which is modified by D1 receptors, seems unlikely considering domperi-

done's D2 antagonism. Since underlying postganglionic autonomic impairment and exogenous dopamine may reduce noradrenaline release, domperidone may serve to enhance it via dopaminergic blockage. Studies have not demonstrated significant changes in orthostatic noradrenaline levels with domperidone treatment, however.[23] Hence, more detailed study is required to further elucidate its mechanism, with consideration to the fact that efficacy appears not to be limited to patients on dopamine agonists.

Limitations of this study include our small study population, and a relatively high drop-out rate, although this is perhaps reflective of the high risk of complications in IPD patients. We used single doses of medications, and thus cannot comment on their effectiveness if used at higher or lower dosages. Bedside BP testing was used for the first part of the study, and tilt table testing for the second. It was felt that performing more than three autonomic tests performed as part of the study would be too rigorous for participants. Future assessment with continuous BP monitoring might give further information of variations over the course of the day. For example, our patients had a drop in supine BP when on domperidone. It would be of interest to see if this BP fluctuated over the day and night, since previous studies have demonstrated an increased BP with domperidone therapy particularly during the day.[33] Finally, while there are no specific scales developed for IPD patients with OH, the COMPASS-OD score had a close correlation with our other outcome measures, supporting its use in this population.

In conclusion, this study has assessed in a practical way the use of nonpharmacological treatments, domperidone, and fludrocortisone in the treatment of OH in IPD. We found supportive evidence for the efficacy and safety of both medications, and suggest caution when implementing nonpharmacological therapies, since they may not be as benign as it is commonly presumed. Future directions would include a larger study to confirm these findings as well as further delineate if particular characteristics, such as concurrent use of dopaminergic medications, could be used to predict response to a particular treatment.

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REFERENCES

1. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. J Neurol Sci 1996;144:218–219.
2. Senard JM, Rai S, Lapeyre-Mestre M, et al. Prevalence of orthostatic hypotension in Parkinson's disease. J Neurol Neurosurg Psychiatry 1997;63:584–589.
3. Elmstahl S, Rosen I. Postural hypotension and EEG variables predict cognitive decline: results from a 5-year follow-up of healthy elderly women. Dement Geriatr Cogn Disord 1997;8:180–187.
4. Eigenbrodt ML, Rose KM, Couper DJ, Arnett DK, Smith R, Jones D. Orthostatic hypotension as a risk factor for stroke: the atherosclerosis risk in communities (ARIC) study, 1987–1996. Stroke 2000;31:2307–2313.
5. Rose JM, Tyroler HA, Narndo CJ, et al. Orthostatic hypotension and the incidence of coronary heart disease: the Atherosclerosis Risk in Communities Study. Am J Hypertens 2000;13:571–578.
6. Masaki KH, Schatz IJ, Burchfiel CM, et al. Orthostatic hypotension predicts mortality in elderly men: the Honolulu Heart Program. Circulation 1998;98:2290–2295.
7. Denq JC, Opfer-Gehrking TL, Giuliani M, Felten J, Convertino VA, Low PA. Efficacy of compression of different capacitance beds in the amelioration of orthostatic hypotension. Clin Auton Res 1997;7:321–326.
8. Van Lieshout JJ, Ten Harkel AD, Wieling W. Fludrocortisone and sleeping in the head-up position limit the postural decrease in cardiac output in autonomic failure. Clin Auton Res 2000;10:35–42.
9. Jordan J, Shannon JR, Black BK, et al. The pressor response to water drinking in humans : a sympathetic reflex? Circulation 2000;101:504–509.
10. Freeman R, Landsberg L, Young J. The treatment of neurogenic orthostatic hypotension with 3,4-DL-threo-dihydroxyphenylserine: a randomized, placebo-controlled, crossover trial. Neurology 1999; 53:2151–2157.
11. Singer W, Opfer-Gehrking TL, McPhee BR, Hilz MJ, Bharucha AE, Low PA. Acetylcholinesterase inhibition: a novel approach in the treatment of neurogenic orthostatic hypotension. J Neurol Neurosurg Psychiatry 2003;74:1294–1298.
12. Nair B, Leitch J. Erythropoietin treatment for postural hypotension from autonomic dysfunction. Aust N Z J Med 1996;26:859–860.
13. Miller E, Wiener L, Bloomfield D. Etilefrine in the treatment of L-dopa-induced orthostatic hypotension. Arch Neurol 1973;29:99–103.
14. Jankovic J, Gilden JL, Hiner BC, et al. Neurogenic orthostatic hypotension: a double-blind placebo-controlled study with midodrine. Am J Med 1993;95:38–48.
15. Low PA, Gilden JL, Freeman R, et al. Efficacy of midodrine vs. placebo in neurogenic orthostatic hypotension. JAMA 1997;277: 1046–1051.
16. Bordet R, Benhadjali J, Libersa C, Destee A. Octreotide in the management of orthostatic hypotension in multiple system atrophy: pilot trial of chronic administration. J Clin Neuropharmacol 1994;17:380–383.
17. Hoehn MM. L-Dopa-induced postural hypotension. Treatment with fludrocortisone. Arch Neurol 1975;32:50–51.
18. Hakamaki T, Rajala T, Lehtonen A. Ambulatory 24-hour blood pressure recordings in patients with Parkinson's disease with or without fludrocortisone. Int J Clin Pharmacol Ther 1998;36:367–369.
19. Senard JM, Brefel-Courbon C, Rascol O, Montastruc JL. Orthostatic hypotension in patients with Parkinson's disease: pathophysiology and management. Drugs Aging 2001;18:495–505.
20. Lang AE. Acute orthostatic hypotension when starting dopamine agonist therapy in parkinson disease: the role of domperidone therapy. Arch Neurol 2001;58:835.
21. Capria A, Attanasio A, Quatrana M, et al. Cardiovascular effects of lisuride continuous intravenous infusion in fluctuating Parkinson's disease. Clin Neuropharmacol 1989;12:331–338.
22. Merello M, Pirtosek Z, Bishop S, Lees AJ. Cardiovascular reflexes in Parkinson's disease: effect of domperidone and apomorphine. Clin Auton Res 1992;2:215–219.

23. Lopes de Faria SR, Zanella MT, Andriolo A, Ribeiro AB, Chacra AR. Peripheral dopaminergic blockade for the treatment of diabetic orthostatic hypotension. Clin Pharmacol Ther 1988;44:670–674.
24. Destee A, Leys D, Delisse B, Warot P. Orthostatic hypotension due to diabetic autonomic neuropathy? Treatment with domperidone. Arch Neurol. 1987;44:11.
25. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181–184.
26. Gilman S, Low P, Quinn N, et al. Consensus statement on the diagnosis of multiple system atrophy. J Neurol Sci 1999;163:94–98.
27. Suarez GA, Opfer-Gehrking TL, Offord KP, Atkinson EJ, O'Brien PC, Low PA. The autonomic symptom profile: a new instrument to assess autonomic symptoms. Neurology 1999;52:523–528.
28. Low PA. Composite autonomic scoring scale for laboratory quantification of generalized autonomic failure. Mayo Clin Proc 1993; 68:748–752.
29. Urbaniak GC, Plous S. http://www.randomizer.org. 1997–2005.
30. El-Sayed H, Hainsworth R. Salt supplement increases plasma volume and orhostatic intolerance in patients with unexplained syncope. Heart 1996;75:134–140.
31. Smit AA, Wieling W, Fujimura J, et al. Use of lower abdominal compression to combat orthostatic hypotension in patients with autonomic dysfunction. Clin Auton Res 2004;14:167–175.
32. Bouvette CM, McPhee BR, Opfer-Gehrking TL, Low PA. Role of physical countermaneuvers in the management of orthostatic hypotension: efficacy and biofeedback augmentation. Mayo Clin Proc 1996;71:847–853.
33. Sigurdardottir GR, Nilsson C, Odin P, Grabowski M. Cardiovascular effects of domperidone in patients with Parkinson's disease treated with apomorphine. Acta Neurol Scand 2001; 104:92–96.