Orthostatic hypotension (OH) is a common and disabling symptom affecting Parkinson’s disease (PD) patients. We present the effect of the different therapies commonly used to manage PD on this clinical manifestation. For this purpose, we describe the relationship between OH and the current treatments employed in PD, such as L-DOPA, dopaminergic agonists, and continuous dopaminergic stimulation therapies. Additionally, we review the therapeutic measures that could be used to ameliorate OH. There are different approaches to deal with this manifestation, including pharmacological and non-pharmacological treatments, although none of them is specifically aimed for treating OH in PD.

Keywords: treatment, orthostatic hypotension, dopamine agonists, L-DOPA, continuous dopaminergic stimulation, Parkinson’s disease

INTRODUCTION

After the first comprehensive description of the cardinal features of Parkinson’s disease (PD) (Parkinson, 2002) many non-motor features have been recognized (Hughes et al., 1992). One of the most disabling is orthostatic hypotension (OH), which is defined by a sustained reduction of systolic blood pressure (SBP) of at least 20 mmHg or diastolic blood pressure (DBP) of 10 mmHg within 3 min of standing or head-up tilt to at least 60 on a tilt table (Kaufmann, 1996; Freeman et al., 2011).

The presumed pathophysiology of OH is related to the impairment of sympathetic vasomotor neurons due to the neurodegenerative process of PD (Senard et al., 2001; Metzler et al., 2012).

Growing attention has been paid to this non-motor feature of the disease; especially since dopaminergic drugs were introduced [L-DOPA and dopamine agonists (DA)] (Barbeau et al., 1969; Calne et al., 1970; McDowell and Lee, 1970; Duby et al., 1972).

Even in those cross-sectional initial descriptions, the frequency of this symptom has been highlighted, affecting more than 30% of the PD patients (Barbeau, 1969). A similar pooled estimated prevalence has recently been reported in a systematic review (Velsboer et al., 2011). Other inferences have shown higher frequencies [41% (Kaufmann and Goldstein, 2007) and 47% in a community-based study (Allcock et al., 2011)].

Additionally, its consequences are important as it may imply an increased mortality and comorbidity (mainly owing to falls and concomitant vascular disorders) (Fedorowski et al., 2010; Maule et al., 2012).

In the current article, our aim is to review all the therapeutic options available to treat this frequent and incapacitating symptom, focusing on those aspects less studied. We begin describing the influence that common drugs and advanced therapies used in PD may exert on it. Thereafter, we detail non-pharmacological approaches that could be employed to ameliorate this symptom. We end summarizing the existing pharmacological options to treat it.

THE EFFECT OF THE ANTI-PARKINSONIAN THERAPIES ON ORTHOSTATIC HYPOTENSION

One of the initial steps required when assessing a patient who is going to receive any anti-parkinsonian medication/treatment or who needs a dose adjustment is to anticipate the potential effect on his blood pressure, as it is one of the commonly related factors to the appearance of OH (Perez-Lloret et al., 2012).

Several actions could help to improve the detection of this complication, either by the physician or the subject. It seems reasonable to instruct the patient about OH symptoms (lightheadedness or dizziness after standing, fatigue, and others), although many cases go unnoticed (Arbogast et al., 2009). An initial pressor response assessment (blood pressure after standing) could be valuable to have a simple measurement to monitor future changes, as this measurement is one of the easiest ways to appraise OH in various healthcare settings.
Many caveats should be considered prior to establishing the real influence of PD medications on OH. First, there are different diagnostic criteria for defining OH. Additionally, much evidence is based on cross-sectional analyses and other confounding effects, as disease duration or previous autonomous nervous system damage (Awerbuch and Sandyk, 1992; Müller et al., 2011), have not always been considered.

We present the current evidence to estimate the potential role of current PD treatments on OH. The influence of other drugs, such as antidepressants, diuretics, and antihypertensives, is not reviewed here. Nevertheless, they should be considered when dealing with this complication and decreasing the dose or stopping the responsible medication might be advisable.

L-DOPA

Orthostatic hypotension has been documented as a potential side effect of L-DOPA therapy since its early use on PD (Barbeau, 1969). Multiple evidence (Barbeau, 1969; Calne et al., 1970; Keenan, 1970; McDowell and Lee, 1970; Goldberg and Whitsett, 1971; Hoehn, 1975; Camerlingo et al., 1990; Senard et al., 1997; Bouhaddi et al., 2004) has supported this relationship with ranges of decline oscillating from 4.6–20 mmHg in SBP to 2.1–5.0 mmHg in DBP. Other studies failed to show any clear direct relationship (Sachs et al., 1985; Goetz et al., 1986; Haapaniemi et al., 2000; Hoehn, 1975).

The size of the effect in the studies where a decrease on blood pressure was measured is summarized in Table 1. Methodologically limited earlier studies (small sample, not randomized, without blinding) suggested the role of fludrocortisone (0.05–0.2 mg/q.d.) and etilefrine (5 mg/t.i.d.) for treating L-DOPA-associated OH (Miller et al., 1973; Hoehn, 1975).

DOPAMINE AGONISTS

Likewise with L-DOPA, DA use has been commonly reported to produce OH in PD (Guttman, 1997; Senard et al., 1997; Lieberman et al., 1998; Korczyn et al., 1999; Pinter et al., 1999; Kujawa et al., 2000; Brunt et al., 2002; Boehringer Ingelheim Pharmaceuticals, 2003; GlaxoSmithKline, 2003a,b; UCB, Inc, 2003; Poewe et al., 2007), although not always symptomatic (Kujawa et al., 2000); however, in some studies this relationship was not shown (Hubble et al., 1995; Perez-Lloret et al., 2012).

The figures of patients treated with DA having OH are similar to that reported for L-DOPA (Stowe et al., 2008). With active standing, 34% of the DA resulted in OH (Kujawa et al., 2000); nonetheless, OH symptomatic cases listed in clinical trials ranged from 4.6 to 44.0% of the participants (Guttman, 1997; Lieberman et al., 1998; Pinter et al., 1999; Brunt et al., 2002; Boehringer Ingelheim Pharmaceuticals, 2003; GlaxoSmithKline, 2003a,b; UCB, Inc, 2003). The mean decrease of blood pressure was 16.1 mmHg in the SBP and 2.8 mmHg in the DBP (see Table 1) (Haapaniemi et al., 2000).

There is not an established causal relationship with a specific agonist, as OH has been reported in users of ergot and non-ergotropic compounds (Guttman, 1997; Korczyn et al., 1999; Haapaniemi et al., 2000; Kujawa et al., 2000; Korchounov et al., 2004; Stowe et al., 2008), and in all the current pharmaceutical preparations (conventional, extended release, and patch prescription) (Boehringer Ingelheim Pharmaceuticals, 2003; GlaxoSmithKline, 2003a,b; UCB, Inc, 2003; Poewe et al., 2007). There is no direct comparison between all DA and many clinical trials have not reported this adverse event (Giladi et al., 2007; Pahwa et al., 2007a; Stocchi et al., 2008; Stowe et al., 2008; Poewe et al., 2011; Schapira et al., 2011), so no clear conclusions can be drawn on this issue. Additionally, studies that evaluated different agonists yielded heterogeneous results. In a research involving bromocriptine, ropinirole, selegiline, L-DOPA, and amantadine, an increased frequency of OH was observed when therapies were combined (L-DOPA plus another DA) and with all the DA (a slightly greater increase was found with bromocriptine compared with ropinirole) (Korchounov et al., 2004). In meta-analytic data addressing the profile of adverse events of DA found no differences between L-DOPA (Etminan et al., 2003) and only in another meta-analytic study, an increased risk of OH was suggested for cabergoline (Kulisevsky and Pagonabarraga, 2010). In summary, no clear conclusions can be drawn concerning the risk of OH with a specific DA.

| Table 1 | Lowering effect of PD treatments on blood pressure. |
|---------|-----------------------------------------------|
| **Reference** | **SBP change** | **DBP change** | **Sample size** |
| L-DOPA | Bouhaddi et al. (2004) | 8.1 | 5.0 | 18 |
| | Camerlingo et al. (1990) | 9.21 | 2.11 | 12 |
| | Barbeau et al. (1969) | >202 | Na | 86 |
| | Calne et al. (1970) | 8.7 | 4.4 | 20 |
| Dopamine agonists (excluding apomorphine) | Haapaniemi et al. (2000) | 16.13 | 2.83 | 17 |
| Monoamine Oxidase inhibitors | Chuchyard et al. (1999) | 194 | 54 | 20 |
| | Haapaniemi et al. (2000) | 12.53 | 5.23 | 17 |
| CDS therapies | DBS | Stemper et al. (2006) | 175 | –25 | 14 |
| | Apo | Pathwa et al. (2007b) | 8.76 | Not reported | 56 |
| | CDLI | Pursiainen et al. (2012) | 23.2 | 9.1 | 9 |
| CDS, continuous dopaminergic stimulation; DBS, deep brain stimulation; CDLI, continuous duodenal L-DOPA infusion; Apo, apomorphine pump; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure. *values after tilting in mmHg (positive figures indicate a decrease); 1BP 3 min after tilting and 2 year after starting L-DOPA therapy; 2mean decrease after L-DOPA therapy; 3the blood-pressure reported is immediately after tilting; 4the blood-pressure reported is 2 min after tilting; 5blood-pressure reported after tilting with stimulation on; 620 min after apomorphine injection on standing.
MONOAMINE OXIDASE INHIBITORS

Drugs that inhibit MAO-B selectively, as rasagiline and selegiline, have been also recognized as a potential factor for inducing OH (Churchyard et al., 1997, 1999; Turkka et al., 1997; Haapaniemi et al., 2000; Bhattacharya et al., 2003; Abassi et al., 2004; Rascol et al., 2005; Olanow et al., 2009; Tolosa and Stern, 2012). There have been several studies evaluating the effect of selegiline (Churchyard et al., 1997, 1999; Turkka et al., 1997; Bhattacharya et al., 2003; Korchounov et al., 2004). The percentage of affected individuals ranged from 30% (Churchyard et al., 1999) to 50% (Bhattacharya et al., 2003) and the mean decrease oscillated between 10.4 and 19 mmHg (Churchyard et al., 1999; Bhattacharya et al., 2003) for SBP and five to even an increase of 2 mmHg for DBP (Churchyard et al., 1999; Bhattacharya et al., 2003) for DBP.

Korchounov et al., 2004). The percentage of affected individuals ranged from 30% (Churchyard et al., 1999) to 50% (Bhattacharya et al., 2003) and the mean decrease oscillated between 10.4 and 19 mmHg (Churchyard et al., 1999; Bhattacharya et al., 2003) for SBP and five to even an increase of 2 mmHg for DBP (Churchyard et al., 1999; Bhattacharya et al., 2003) for DBP.

There have been several studies evaluating the effect of selegiline (Churchyard et al., 1997, 1999; Turkka et al., 1997; Bhattacharya et al., 2003; Korchounov et al., 2004). The percentage of affected individuals ranged from 30% (Churchyard et al., 1999) to 50% (Bhattacharya et al., 2003) and the mean decrease oscillated between 10.4 and 19 mmHg (Churchyard et al., 1999; Bhattacharya et al., 2003) for SBP and five to even an increase of 2 mmHg for DBP (Churchyard et al., 1999; Bhattacharya et al., 2003) for DBP. (Table 1). As with the previously reviewed treatments, the hypotensive effect observed with selegiline was not greater than the one occurring with other drugs such as L-DOPA (Bhattacharya et al., 2003) or DA (Haapaniemi et al., 2000) except in one study (Korchounov et al., 2004). There was an initial concern about an increased mortality associated to selegiline, also suggesting a role of its autonomic adverse effects on it, but this has been recently discarded (Lees, 1995; Ives et al., 2004; Turnbull et al., 2005). In addition to OH, hypertensive crises have been reported with selegiline (Rose et al., 2000; Ito et al., 2001).

Rasagiline is a more recent MAO-B widely used in the clinical practice for its potential neuroprotective effect (Abassi et al., 2004; Parkinson Study Group, 2004, 2005; Rascol et al., 2005, 2011; Olanow et al., 2009; Tolosa and Stern, 2012). The percentage of individuals with symptomatic OH was comprised of between 1.5 and 6.5% (Olanow et al., 2009; Tolosa and Stern, 2012). Some of the clinical trials involving rasagiline did not make any comment about the percentage of subjects with OH and the mean decrease on blood pressure was not reported (Parkinson Study Group, 2005).

OTHER COMMON PRESCRIBED AGENTS (L-DOPA METABOLISM INHIBITORS, ANTAGONISTS, AMANTADINE, ACETYLCOLINESTERASE INHIBITORS)

There are descriptions of OH occurring with other medications such as amantadine (Korchounov et al., 2004; Perez-Lloret et al., 2012), and acetylcholinesterase inhibitors (in PD dementia) (Novartis Pharmaceuticals, 2003b). The evidence with anticholinergics is less clear, not increasing OH frequency (Martin et al., 1974), but affecting cardiovascular reflexes (Korchounov et al., 2004). The COMT inhibitors entacapone (Lytinen et al., 2001; Novartis Pharmaceuticals, 2003a; Olanow et al., 2004) and tolcapone (Tolcapone Study Group, 1999; Koller et al., 2001), as well as DOPA-decarboxylase inhibitors, showed no clear influence on OH (Leibowitz and Lieberman, 1975; Rappelli et al., 1978), except in one study where entacapone showed a protective effect (Perez-Lloret et al., 2012).

IS THERE A DOSE-DEPENDENT EFFECT OR AN INFLUENCE OF THERAPIES COMBINATIONS ON OH? WHEN DOES OH OCCUR IN TREATED SUBJECTS?

It seems plausible, based on different observational approaches, that higher doses of dopaminergic medications (Senard et al., 1997; Alcock et al., 2006; Chitsaz et al., 2007) and combined therapies (Korchounov et al., 2004) could also increase the chances of manifesting OH. Also some works have suggested that the main effect of medications could be at the beginning of the therapy developing some tolerance thereafter (Pathak and Senard, 2004).

Based on all these evidence, the possibility of OH should be especially considered, when starting/adding a new drug or increasing its dose as the probability of symptoms could increase.

CONTINUOUS DOPAMINERGIC STIMULATION THERAPIES

Deep brain stimulation

Cross-sectional studies have suggested a positive effect of subthalamic Deep Brain Stimulation (DBS) on autonomous responses of PD subjects (Stemper et al., 2006; Ludwig et al., 2007). In one of this analysis, including 14 patients, there was a mean general decrease on blood pressure in on and off stimulation status (Table 1), but the baroreflex responses were preserved only when the stimulation was on, suggesting, therefore, a positive influence of the DBS in BP mediated by its influence on central autonomous nervous system pathways (Stemper et al., 2006). In another study comparing subthalamic DBS with a pharmacotherapy-only group, no positive correlation was found between the on-stimulation state and the decrease in blood pressure; but this occurred in the only medicated group. Based on this finding it was suggested that subthalamic DBS did not affect cardiovascular autonomous responses (Ludwig et al., 2007). Noteworthy, in a previous longitudinal study, the initial differences of blood pressure were not found after 1 year’s follow-up, with a similar mean blood-pressure decrease for the subthalamic DBS and the only medicated groups (Holmberg et al., 2005). Additionally, two other studies could not find differences in the cardiovascular responses of the treated subjects (Lipp et al., 2005; Erola et al., 2006).

In summary, subthalamic DBS could exert a neutral/positive influence at the beginning of the therapy because of its direct effects on central pathways, controlling autonomous responses (Benedetti et al., 2004), or the accompanying decrease in medication to subthalamic stimulation (Borgohain et al., 2012). This effect seems to vanish with time (Holmberg et al., 2005). In addition, medial electrode placement in the subthalamus can produce hypertensive crisis (authors experience; unpublished data). As with the common prescribed drugs, further studies will help to clarify the effect of DBS on this disabling symptom.

Apomorphine pump/apomorphine injections

Orthostatic hypotension has been reported since the early use of apomorphine (Duby et al., 1972; Corsini et al., 1979). In these initial descriptions, it was suggested that the peripheral DA receptor, could diminish this complication (Corsini et al., 1979) recommending to pretreat patients 72 h before its administration. A recent report with another peripheral blocker, commercialized in the US, did not show this protective effect and only younger age influenced the development of OH in apomorphine users (Ondo et al., 2012).

The frequency of OH after apomorphine treatment is heterogeneous across the studies. The variability could be influenced, as with the other treatments, by the definitions used (manometric vs.
symptomatic), pressure cutoffs, and subsets of patients evaluated. The figures oscillated between 1.9% (Tyne et al., 2004) and more than 80% of the subjects affected (Duby et al., 1972). In more recent reports, using current diagnostic criteria, a maximum of 17.6% of the subjects receiving 4 mg of apomorphine had OH vs. 14.3% of the orally treated ones (no equivalent levodopa doses reported). No clear differences between the two groups were found (Pahwa et al., 2007b). The main decrease in blood pressure was observed 20–40 min after the injection (Table 1).

**Continued duodenal L-DOPA infusions**

There are different evidences connecting continuous duodenal L-DOPA infusions (CDLI) to OH (Pursiainen et al., 2012; Fernandez et al., 2013). In a recent clinical trial interim analysis (NCT00335513), 8.3% of the subjects had OH as an adverse event related to this therapy (Fernandez et al., 2013). In a longitudinal study involving nine CDLI cases an initial decrease of blood pressure after the therapy instauration was observed (Table 1), but after 2 months the figures rose again, suggesting a compensatory mechanism (Pursiainen et al., 2012).

**Conclusions about the effect of PD therapies on OH**

Many of the common prescribed treatments used for PD could increase the frequency of OH. It seems advisable to monitor blood pressure and this side effect when starting any “conventional medication" or advanced PD therapy and when a dose adjustment is required. If symptoms occur adjunctive therapies should be initiated (see non-pharmacological and pharmacological treatments sections).

Other outcomes, like supine nocturnal hypertension (nocturnal BP means >120/70 mmHg) (Perez-Lloret et al., 2008), should be addressed, as patients taking higher doses of dopaminergic treatment had less decreases in SBP and DBP at night (Berganzo et al., 2013).

Further studies are needed to clarify the adjusted effect of the medication/treatments compared with the one produced by the neurodegenerative process itself.

This will help to draw more specific conclusions for subsets of subjects/treatments and anticipate the risk of OH, granting a more individualized approach when treating PD patients.

---

**Therapeutic measures**

**General considerations**

The common practice nowadays is to manage only the symptomatic cases, as no current therapy has yet evidenced a protective action on the autonomic nervous system impairment and the role of asymptomatic OH is still not defined (Low and Singer, 2008).

It should be stressed that there are not specifically designed therapies for OH in PD subjects. This is linked to the methodological concerns limiting most of the studies presented and making the current evidence insufficient to define clear guidelines for the management of OH in PD. Nevertheless, there are different therapies that might be helpful (Lahrmann et al., 2006; Figueroa et al., 2010; Zesiewicz et al., 2010; Seppi et al., 2011), which we will review after this section.

An additional important feature to consider is that situations of orthostatic stress (early hours of the morning, meals, physical activity among others) may trigger OH that otherwise may go unnoticed (Low and Singer, 2008). Supine hypertension, an inter-related aspect of OH defined as BP means >120/70 mmHg (Perez-Lloret et al., 2008), should be also monitored (Low and Singer, 2008; Berganzo et al., 2013) as treatments used to increase blood pressure, could lead to a worsening of this manifestation. Some authors suggest that supine blood pressure should never exceed 180/110 mmHg (Low and Singer, 2008). In the case of hypertensive patients, short half-life drugs are preferable and evening administration.

Initially, it is also agreed to start with non-pharmacological measures (Lahrmann et al., 2006), because of the lower likelihood of adverse outcomes, the possibility of using them in moments of orthostatic stress (Low and Singer, 2008) and for their simplicity (Seppi et al., 2011).

**Non-pharmacological measures**

In Table 2 there is a description of the main employed strategies.

**Water and salt**

Standing-up implies that 500–700 ml of blood will pool in lower extremities and abdomen (Diedrich and Biaggioni, 2004). This is one of the reasons for trying to increase plasma volume to counter this effect. Many studies have evaluated the influence of drinking water on blood pressure (Jordan et al., 1999a; Senard

---

| Measure                  | Increase on blood pressure (mmHg) | % Compliance<sup>1</sup> | Comment                                                                 |
|-------------------------|-----------------------------------|--------------------------|-------------------------------------------------------------------------|
| Fluid (water) intake    | 15–25                             | 88                       | Recommended daily intake 2–2.5 l                                         |
| Salt Intake             | 10–15                             | 82                       | 150–200 Na+ mmol/day (Salt: 9–12 g/day)                                  |
| Meal frequency          | Unknown                           | 82                       | Multiple smaller meals containing less carbohydrates                    |
| Alcohol consumption     | Unknown                           | 59                       | Avoid its consume throughout the day                                     |
| Night time head-up tilt| 2–11                              | 76                       | Elevated head of the bed (10–15 cm or 12°)                               |
| Stockings/abdominal bandages | 12–26                         | 59                       | Abdominal bandage more effective than stockings alone and may favor compliance |
| Physical countermanoeuvers<sup>2</sup> | 10–15                        | Unknown                  | Leg crossing, squatting, bending-forward, and tiptoeing                 |

<sup>1</sup>Baased on Schoffer et al. (2007); <sup>2</sup>leg crossing, thigh contraction, or squatting.
et al., 1999; Shannon et al., 2002; Mathias and Young, 2004; Waters et al., 2005; Deguchi et al., 2007; Schoffer et al., 2007). A positive effect has been found in autonomic disorders, including multiple system atrophy or pure autonomic failure (Jordan et al., 1999a; Shannon et al., 2002; Mathias and Young, 2004; Waters et al., 2005; Deguchi et al., 2007). In PD subjects, no difference in BP has been clearly evidenced, but the sample of evaluated individuals was small (Senard et al., 1999; Schoffer et al., 2007). In non-PD-related autonomic failure, blood-pressure augmented once drinking 350–500 ml of water shortly after the ingestion (20–35 min) with a mean increase ranging between 23 and 31 mmHg for SBP and 15–25 in DBP (Shannon et al., 2002; Mathias and Young, 2004; Deguchi et al., 2007). This increase is even comparable to the one obtained with some of the commonly prescribed medications for OH (Ten Harkel et al., 1994) but lasted shortly (1 h) (Jordan et al., 1999a). It has been recommended to apply this strategy in the morning period, where blood pressure is even lower (Omboni et al., 2001; Wieling et al., 2002). The adverse outcomes are said to be mild (Schoffer et al., 2007), i.e., urinary incontinence. No follow-up data for the long-term effect have been presented (Mathias and Young, 2004).

Salt ingestion could also increase plasma volume (Wieling et al., 2002; Waters et al., 2005). One of the reasons to supplement it, is that subjects with autonomic failure are unable to reduce renal sodium excretion during salt restrictions, which could potentially lead to an increase in the blood-pressure drop upon standing (Wieling et al., 2002). The daily dietary average intake of sodium is 150 mmol (Hollenberg, 2006). An increase on blood pressure of 10–15 mmHg could be achieved with a high-salt containing diet (150–200 mmol/day of sodium or 9–12 g/day of common salt), combined with other measures (Wieling et al., 2002). It is necessary to check urine sodium (range between 170 and 260 mmol/day) (Wieling et al., 2002), as well as blood pressure (Hollenberg, 2006), to monitor the positive effects and prevent any deleterious outcomes, as high-salt intake could increase cardiovascular mortality (with urine sodium levels above 300 mmol/day) (O’Donnell et al., 2011). One study including PD cases failed to show this positive influence (Schoffer et al., 2007) after common salt supplements of 10–20 g/day (170–350 mmol/day of sodium). Another aspect yet to be determined is the salt-sensitivity of PD subjects affected by OH, as it is known that is not the same in all individuals (Hollenberg, 2006); further analyses are needed to clarify salt influence on OH in PD.

Physical countermeasures
Several drills aimed to promote venous return and maintain cardiac output have been proposed for different autonomic disorders (Ten Harkel et al., 1992, 1994; Wieling et al., 1993; Bouvette et al., 1996; Tutaj et al., 2006). They include tiptoeing, leg crossing, bending-forward, and squatting (Ten Harkel et al., 1992, 1994; Wieling et al., 1993; Bouvette et al., 1996; Tutaj et al., 2006). The range of increase in blood-pressure fluctuated between 10 and 15 mmHg (Wieling et al., 1993). The importance of these maneuvers is still controversial (Ten Harkel et al., 1994; Bouvette et al., 1996; Tutaj et al., 2006).

Stockings and abdominal bands
Besides the previous active maneuvers, there have been trials to raise the peripheral vascular pressure passively based on studies evaluating antigravity suits (Denq et al., 1997). This was aimed to oppose the mentioned blood pooling upon standing, exerting pressure on different capacitance beds such as the lower extremities and abdomen (Denq et al., 1997). An abdominal band has shown to be more effective and maybe with a better compliance, than the usual recommended stockings (Schoffer et al., 2007). This band could increase the blood pressure as much as 12 mmHg (Denq et al., 1997; Tanaka et al., 1997). In a study including PD patients 30 mmHg pressure stockings failed to show any beneficial effect on OH subjects (Schoffer et al., 2007).

Head-of-bed elevation
There is a physiological drop in blood pressure in the morning, which has been related with night recumbence, although other factors have not been ruled out (Omboni et al., 2001). In patients with PD and autonomic failure, nocturnal hypertension leads to natriuresis and polyuria, which, in turn, may cause severe OH in the morning hours. Raising the head of the bed (10–15 cm or 12°) decreased the nocturnal blood-pressure levels and the release of atrial natriuretic peptide, reducing nocturia, and OH in the early hours of the morning, especially when combined with other measures (Ten Harkel et al., 1992; van Lieshout et al., 2000). The main increase in BP in non-PD cases ranged from 2 to 11 mmHg and symptomatic relief has also been reported (Ten Harkel et al., 1992).

Other proposed measures
Other proposed strategies are based on evidences of different factors, which influence blood pressure in autonomic failure (Lahrmann et al., 2006; Freeman, 2008; Gupta and Nair, 2008; Low and Singer, 2008; Mostile and Jankovic, 2009). Frequent meals with fewer carbohydrates could diminish the postprandial hypotension component (Thomaides et al., 1993). It has been suggested that food could lower blood pressure in autonomic failure through vasodilatation (Thomaides et al., 1993; Chaudhuri et al., 1997) and insulin secretion (Nozaki et al., 1993). Avoiding alcohol during the day has been suggested (Chaudhuri et al., 1995; Narkiewicz et al., 2000). Averting rapid postural changes and warm temperatures and an adequate physical activity have been recommended (Lahrmann et al., 2006; Freeman, 2008; Gupta and Nair, 2008; Mostile and Jankovic, 2009). None of them have shown a favorable influence, when evaluated in PD individuals suffering from OH (Schoffer et al., 2007).

PHARMACOLOGICAL MEASURES
When non-pharmacological therapies are not satisfactory, pharmacological should be considered. Supine hypertension should be always monitored, as some of the pharmacological therapies may worsen it. Additionally, the long-term prognostic implications of OH are not known, so the aim of the therapy focuses on ameliorating the symptoms. The main drugs used to treat OH, not limited to PD, are summarized in Table 3. We describe the most important ones.
Table 3 | Pharmacological therapies.

| Drug        | Dose                        | Posology | Increase on SBP/DBP (mmHg) | Adverse effects                                                                 | Comment                                                                 |
|-------------|-----------------------------|----------|---------------------------|---------------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Pyridostigmine | 30–60 mg                   | b.i.d./t.i.d. | Unknown/8.8               | Abdominal colic, nausea, sialorrhea                                              | No supine hypertension                                                 |
| Fludrocortisone | 0.1–0.2 mg/day              | q.d.     | 9–42/0–16                 | Hypokalemia, edema, congestive heart failure, supine hypertension                | Effect may appear after 1–2 weeks of treatment. Titer slowly           |
| Midodrine   | 2.5–10 mg                   | b.i.d./t.i.d. | 20–22/11–15               | Paresthesia, pruritus, piloerection, supine hypertension                         | Tested in a randomized clinical trial                                 |
| L-DOPS      | 200–400 mg                  | q.d/b.i.d. | 23–28/9–12                | Dizziness, tiredness, visual disturbance, supine hypertension, malignant neuroleptic syndrome | High doses of DOPA-decarboxylase inhibitors could abolish its effect   |
| Octreotide  | 50–100 µg                   | q.d.     | No differences            | Injection-related, abdominal colic, tiredness, headache                          | Useful for postprandial hypotension                                   |
| Yohimbine   | 5 mg                        | q.d.     | 18–33/11–16               | Nausea, tremor, confusion, nervousness                                         | May be useful in postprandial orthostatic hypotension                  |
| Erythropoietin | 25–75 UI/kg                | 3 times/week | 16–19/16–17              | Supine hypertension                                                             | Only if concomitant anemia is present                                 |

SBP, systolic blood pressure; DBP, diastolic blood pressure; 1 values are rounded.

**Fludrocortisone**

Several studies have evaluated the effects of fludrocortisone on OH based on its volume expanding (by means of enhancing renal sodium reabsorption) and α-adrenoreceptor sensitizing activities (Hoehn, 1975; Ten Harkel et al., 1992; Schoffer et al., 2007). The common prescribed dosages range between 0.1 and 0.2 mg/day (Low and Singer, 2008). Supine hypertension could worsen under this treatment and other adverse outcomes like hypokalemia and peripheral edema should be considered (Low and Singer, 2008). The combining action with other non-pharmacological measures like salt ingestion and head-up tilt has proved to be more effective on increasing blood pressure (Ten Harkel et al., 1992).

**Pyridostigmine**

Pyridostigmine acts mainly improving ganglionic cholinergic transmissions through cholinesterase inhibition. It favors normal physiologic responses upon standing, without worsening supine hypertension (Singer et al., 2006; Low and Singer, 2008). The pressor effect was modest (a 6.4 mmHg increase in DBP) (Singer et al., 2006), so it is recommended for initial treatment or mild cases (Low and Singer, 2008). Doses are started at 30 mg b.i.d. or t.i.d. and could be increased to 60 mg b.i.d. or t.i.d (Singer et al., 2006). Adverse outcomes include diarrhea and nausea, among other cholinergic symptoms (Singer et al., 2006; Low and Singer, 2008).

**Midodrine**

This drug is a α1-agonist with a short duration effect (2–4 h). Its main action is to augment vascular resistance and therefore blood pressure. In addition to the anti-OH effect, it can also enhance supine hypertension, so close monitoring of recumbent blood pressure and avoiding evening administration are required (Jankovic et al., 1993; Low and Singer, 2008). Doses range between 2.5 and 10 mg b.i.d or t.i.d (Jankovic et al., 1993; Low et al., 1997). Along with hypertension, other common adverse events are piloerection, paresthesia, and itching (characteristically in the scalp) (Jankovic et al., 1993; Low et al., 1997).

**L-DOPS**

L-Threo-dihydroxyphenylserine or droxidopa is a pro-drug converted by DOPA decarboxylase into norepinephrine. Doses between 100 and 900 mg have been used in PD and other autonomic disorders, improving the drop in blood pressure in OH significantly (Kaufmann, 2008; Mathias, 2008). Side effects were mild, but supine hypertension should be monitored (Kaufmann, 2008). Noteworthy, DOPA-decarboxylase inhibitors used in high doses (200 mg) could block this therapeutic effect (Kaufmann, 2008), but the current combinations employed with L-DOPA (25–50 mg of inhibitor) do not produce this interference (Kaufmann, 2008). Recently, promising results suggesting a positive influence on symptoms and OH related outcomes (falls and fall related injuries) have been presented by Isaacson et al. (2013), American Academy of Neurology, San Diego, CA, USA.

**Other drugs**

Many other medicaments have been attempted to correct the effects of OH. The evidence in which they are based is weak, mostly because of the small samples sizes and the designs used. We describe some, but this is not intended to be an exhaustive review of them.

Octreotide has been used mainly to correct postprandial hypotension linked to OH (Hoeldtke and Israel, 1989), as it could counter the release of vasoactive peptides secreted with food/alcohol ingestion (Bordet et al., 1995; Chaudhuri et al., 1995; Hoeldtke et al., 1998). Its combination with midodrine was more effective than when it was given alone (Hoeldtke and Israel, 1989).
The doses range from 50 to 100 µg/kg (subcutaneous injection). In some studies, no clear change of blood pressure could be evidenced, but symptomatic relief was reported (Bordet et al., 1995).

Yohimbine is an alpha-2 adrenergic receptor antagonist, which enhances the residual sympathetic tone (Omor et al., 1987; Shibao et al., 2010). Some reports, including PD cases, have suggested a positive role and even better results on raising blood pressure than pyridostigmine (Shibao et al., 2010).

Erythropoietin has been useful in correcting a drop in blood pressure in patients with concommitant anemia and autonomic failure (Hoeldtke and Streeten, 1993; Perera et al., 1995).

Desmopressin studies have suggested a positive influence on orthostatic tolerance (Mathias et al., 1986; Larina et al., 2009). Desmopressin reduced nocturnal polyuria, raised supine blood pressure, and reduced the postural fall, especially in the morning, when patients were often at their worst (Mathias et al., 1986; Larina et al., 2009).

Caffeine has been studied alone or in combination with ergotamine to treat OH and postprandial hypotension in subjects with PD and other conditions causing autonomic failure (Lipsit et al., 1994; Dewey et al., 1998). Caffeine has been studied alone or in combination with ergotamine to treat OH and postprandial hypotension in subjects with PD and other conditions causing autonomic failure (Lipsit et al., 1994; Dewey et al., 1998).

Domperidone (30 mg t.i.d.), a dopaminergic antagonist, has also shown beneficial effects on OH (Montastruc et al., 1985; Lang, 2001; Schoffer et al., 2007). It has also been recommended to treat autonomic symptoms related to apomorphine (see above).

Ephedrine is an indirect sympathomimetic agent that has also been used in OH (Brooks et al., 1989), but due to its central nervous system actions, midodrine, that does not cross the blood-brain barrier, may be preferred. Supine hypertension is also related to its use (Brooks et al., 1989).

Etilefrine (5–10 mg) was used in 15 PD patients to increase blood pressure upon standing (mean increase of 4.3%) reporting only headaches as adverse outcomes (Miller et al., 1973).

Fluoxetine (20 mg) was used in a pilot study including 14 PD patients, reducing the drop in blood pressure in 11 mmHg and improving orthostatic symptoms (Montastruc et al., 1998).

For treating supine hypertension, it has been recommended to use nitroglycerine patches (0.025–0.2 mg/h) (Jordan et al., 1999b), or clonidine (0.1 mg) (Shibao et al., 2006), but further studies are needed to measure the impact of this drugs on PD cases.

OVERALL SUMMARY
Orthostatic hypotension is a common and challenging symptom affecting PD patients. The neurodegenerative process is responsible for damaging the autonomous nervous system, but anti-parkinsonian treatments could enhance the symptoms derived from it. Current therapeutic strategies include non-pharmacological and pharmacological measures aimed to favor baroreceptor responses or to increase blood volume. There is insufficient evidence to recommend any specific treatment for the PD-related autonomic failure. Therefore, it should be individualized for the individual patient. Studies addressing the underscored questions related to OH in PD are needed.

ACKNOWLEDGMENTS
The author thank Mrs. Lavinia Abel for her help in the edition of this manuscript

REFERENCES
Abasi, Z. A., Sinah, O., and Youdim, M. B. (2004). Cardiovascular activity of rasagiline, a selective and potent inhibitor of mitochondrial monoamine oxidase B: comparison with selegiline. Br. J. Pharmacol. 143, 571–578. doi:10.1038/sj.bjp.0705962
Aloccon, L. M., Kenny, R. A., and Burn, D. J. (2006). Clinical phenotype of subjects with Parkinson’s disease and orthostatic hypotension: autonomic symptom and demographic comparison. Mov. Disord. 21, 1851–1855. doi:10.1002/mds.20996
Aloccon, L. M., Ulbyart, K., Kenny, R. A., and Burn, D. J. (2004). Frequency of orthostatic hypotension in a community based cohort of patients with Parkinson’s disease. J. Neurol. Neurosurg. Psychiatr. 75, 1470–1471. doi:10.1136/jnnp.2003.029413
Arboagast, S. D., Alshekhlee, A., Hussain, Z., McNeeley, K., and Chelimsky, T. C. (2009). Hypotension unawareness in profound orthostatic hypotension. Am. J. Med. 122, 574–580. doi:10.1016/j.amjmed.2008.10.040
Awerbuch, G. L. and Sandyk, R. (1992). Autonomic functions in the early stages of Parkinson’s disease. Int. J. Neurosci. 64, 7–14. doi:10.3109/00207249209000530
Barbeau, A. (1969). L-dopa therapy in Parkinson’s disease: a critical review of nine years’ experience. Can. Med. Assoc. J. 101, 59–68.
Barbeau, A., Gillo-Joffroy, L., Boucher, R., Nowaczynski, W., and Genest, J. (1969). Renin-aldosterone system in Parkinson’s disease. Science 165, 291–292. doi:10.1126/science.165.3896.291
Benedetti, F., Colloca, L., Lanotte, M., Bergamasco, B., Torre, E., and Lopiano, L. (2004). Autonomic and emotional responses to open and hidden stimulations of the human subthalamic region. Brain Res. Bull. 63, 203–211. doi:10.1016/j.brainresbull.2004.01.010
Bergano, K., Diez-Atrosla, B., Tijero, B., Somme, J., Lescano, E., Llorens, V., et al. (2013). Nocturnal hypertension and dysautonmia in patients with Parkinson’s disease: are they related? J. Neurol. doi:10.1007/s00415-013-6859-5 [Epub ahead of print].
Bhattacharya, K. F., Nouri, S., Olanow, C. W., Yahy, M. D., and Kaufmann, H. (2003). Selegeline in the treatment of Parkinson’s disease: its impact on orthostatic hypotension. Parkinsonism Relat. Disord. 9, 221–224. doi:10.1016/S1353-8020(02)00053-6
Boehringer Ingelheim Pharmaceuticals. (2003). “A 12-week study of pramipexole ER in patients with Parkinson’s disease, followed by a 52-week long-term treatment period.” in ClinicalTrials.gov (Bethesda, MD: US National Library of Medicine). Available at: http://www.clinicaltrials.gov/ ct2/show/results/NCT00560508 [accessed February 22, 2013].
Bordet, R., Benhadjali, J., Destee, A., Belabbas, A., and Libersa, C. (1995). Octreotide effects on orthostatic hypotension in patients with multiple system atrophy: a controlled study of acute administration. Clin. Neuroradiol. 15, 83–89. doi:10.1007/978-3-7091-9950-2_00012
Bordehuis, R., Kandadai, R. M., Jabeen, A., and Kannikannan, M. A. (2012). Nonmotor outcomes in Parkinson’s disease: is deep brain stimulation better than dopamine replacement therapy? Ther. Adv. Neurol. Disord. 5, 23–41. doi:10.1177/1756285611423412
Bouhaddi, M., Vuiller, F., Fortrat, J. O., Cappelle, S., Henriet, M. T., Rambach, L., et al. (2004). Impaired cardiovascular autonomic control in newly and long-term treated patients with Parkinson’s disease: involvement of L-dopa therapy. Auton. Neurosci. 116, 30–38. doi:10.1016/j.autneu.2004.06.009
Bouvette, C. M., McPhee, B. R., Opper-Gehrking, T. L., and Low, P. A. (1996). Role of physical countermeasures in the management of orthostatic hypotension: efficacy and biofeedback augmentation. Mayo Clin. Proc. 71, 847–853. doi:10.4065/71.9.847
Brooks, D. I., Redmond, S., Mathias, C. J., Bannister, R., and Symon, L. (1989). The effect of orthostatic hypotension on cerebral blood flow and middle cerebral artery velocity in autonomic failure, with observations on the action of ephedrine. J. Neurol. Neurosurg. Psychiatry. 52, 962–966. doi:10.1136/jnnp.52.8.962
Orthostatic hypotension treatment in PD

Sánchez-Ferro et al.  

Frontiers in Neurology | Movement Disorders  
June 2013 | Volume 4 | Article 64 | 8
Kaufmann, H., and Goldstein, D. (1996). Neurogenic orthostatic hypotension: a double-blind, placebo-controlled study with midodrine. Am. J. Med. 95, 38–48. doi:10.1002/0002-9343(96)90230-M
Jordan, J., Shannon, J. R., Gro- gani, E., Biaggiioni, L., and Robert- son, D. (1999a). A potent pressor response elicited by drinking water. Lancet 353, 723. doi:10.1016/S0140-6736(99)90451-5
Jordan, J., Shannon, J. R., Pobar, H., Parana- je, S. Y., Robertson, D., Robertson, R. M., et al. (1999b). Contrasting effects of vasodilators on blood pressure and sodium balance in the hypotension of autonomic failure. J. Am. Soc. Nephrol. 10, 35–42.
Kaufmann, H. (1996). Consensus state- ment on the definition of ortho- static hypotension, pure autonomic failure and multiple system atrophy. Clin. Auton. Res. 6, 125–126. doi:10.1007/BF02291236
Kaufmann, H. (2008). L- dihydroyphenylserine (Drox- idopa): a new therapy for neurogenic orthostatic hypotension: the US experience. Clin. Auton. Res. 18(Suppl. 1), 19–24. doi:10.1007/BF02291236
Kaufmann, H., and Goldstein, D. S. (2007). Autonomic dysfunc- tion in Parkinson’s disease. Handb. Clin. Neurol. 83, 343–363. doi:10.1016/S0072-9757(07)38014-4
Kean, R. E. (1970). The Eaton Col- laborative Study of levodopa therapy in Parkinsonism: a summary. Neurology 20, 46–59. doi:10.1212/WNL.20.12_Part_2.46
Koller, W., Lees, A., Dodor, M., and Hely, M. (2001). Randomized trial of tol- midrine vs placebo in neurogenic orthostatic hypotension: a ran- domized, double-blind multicen- ter study. Midodrine Study Group. JAMA 277, 1046–1051. doi:10.1001/jama.1997.07340307063003
Low, P. A., and Singer, W. (2008). Management of neurogenic orthostatic hypotension: an update. Lancet Neu- rol. 7, 451–458. doi:10.1016/S1474-4223(08)70088-7
Ludwig, J., Remien, P., Gobella, C., Binder, A., Binder, S., Schattni- der, J., et al. (2007). Effects of subthalamic nucleus stim- ulation and levodopa on the autonomic nervous system in Parkinson’s disease. J. Neurol. Neurosurg. Psychiatr. 78, 742–745. doi:10.1136/jnnp.2006.103739
Lyttinen, J., Sovijärvi, A., Kaakkola, S., Gordin, A., and Teravainen, H. (2001). The efficacy of catechol-O- methyltransferase inhibition with entacapone on cardiovascular auto- nomic responses in L-Dopa-treated patients with Parkinson’s disease. Clin. Neuropharmacol. 24, 50–57. doi:10.1097/00002826-200101000-00009
Martin, W. E., Loewenson, R. B., Resch, J. A., and Baker, A. B. (1974). A controlled study comparing trihexyphenidyl hydrochloride plus levodopa with placebo plus levodopa in patients with Parkin- son’s disease. Neurology 24, 912–919. doi:10.1212/WNL.24.10.912
Mathias, C. J., and Young, T. M. (2004). Water drinking in the manage- ment of orthostatic intolerance due to orthostatic hypotension, vaso- vagal syncope and the postural tachycardia syndrome. Eur. J. Neu- rol. 11, 613–619. doi:10.1111/j.1468-1331.2004.00840.x
Maule, S., Milevoz, V., Maule, M. D., Di Stefano, C., Milan, A., and Veglio, F. (2012). Mortality and prognosis in patients with neurogenic orthosta- tic hypotension. Funct. Neurol. 27, 101–106.
McDowell, F. H., and Lee, J. E. (1976). Levodopa, Parkin- son’s disease, and hypertension. Ann. Intern. Med. 72, 751–752. doi:10.7326/0003-4819-72-5-751
Metzler, M., Duer, S., Granata, R., Kri- mmer, R., Robertson, D., and Wenning, G. K. (2012). Neurogenic orthostatic hypotension: pathophysiology, evalua- tion, and management. J. Neurol. Neurol. 10. doi:10.1007/s00415-012-6736-7. [Epub ahead of print].
Miller, E., Wiener, L., and Bloom- field, D. (1973). Etdeline in the treatment of levodopa- induced orthostatic hypotension. Arch. Neurol. 29, 99–103. doi:10.1001/archneur.1973.0041028.0030010
Montastruc, J. L., Chavantin, B., Senard, J. M., and Rascol, A. (1985). Dopemider in the manage- ment of orthostatic hypotension. Clin. Neuropharmacol. 8, 191–192. doi:10.1097/00002826-198506000- 00010
Montastruc, J. L., Pelat, M., Ver- waerde, P., Brefel-Courbon, C., Tran, M. A., Blin, O., et al. (1998). Fluoxetine in orthostatic hypotension of Parkinson’s dis- ease: a clinical and experimental pilot study. Fundam. Clin. Pharma- col. 12, 398–402. doi:10.1046/j.1472-1828.1998.tb00653.x
Mottile, G., and Jankovic, J. (2009). Treatment of dysautonomia associated with Parkinson’s dis- ease. Parkinsonism Relat. Disord. 15(Suppl. 3), S224–S232. doi:10.1016/S1353-8028(09)70820-X
Müller, B., Larsen, J. P., Wentzel-Larsen, T., Skeie, G. O., and Tynes, O. B. (2011). Autonomic and sensory symptoms and signs in incident, untreated Parkinson’s disease: frequent but mild. Mov. Disord. 26, 65–72. doi:10.1002/mds.23387
Narkiewicz, K., Kooley, R. L., and Somers, V. K. (2000). Alcohol potentiates orthostatic hypotension: implications for alcohol-related syncope. Circulation 101, 398–402. doi:10.1161/01.CIR.1.10.398

Orthostatic hypotension treatment in PD

Sánchez-Ferro et al.

www.frontiersin.org
Novartis Pharmaceuticals. (2003a). “Efficacy and safety of carbidopa/levodopa/entacapone in patients with Parkinson’s disease requiring initiation of levodopa therapy (STRIDE-PD),” in ClinicalTrials.gov (Bethesda, MD: US National Library of Medicine). Available at: http://www.clinicaltrials.gov/ct2/show/results/NCT00099268 [accessed February 22, 2013].

Novartis Pharmaceuticals. (2003b). “Long-term safety of rivastigmine capsule and patch in patients with mild to moderately-severe dementia associated with Parkinson’s disease (PDD),” in ClinicalTrials.gov (Bethesda, MD: US National Library of Medicine). Available at: http://www.clinicaltrials.gov/ct2/show/results/NCT00623103 [accessed February 22, 2013].

Nozaki, S., Kang, J., Miyai, I., and Novartis Pharmaceuticals. (2003b). “Orthostatic hypotension treatment in PD Sánchez-Ferro et al. Olanow, C. W., Rascol, O., Hauser, R. A., Mizuno, Y., Haaksma, M., et al. (2011). Extended-release pramipexole in early Parkinson disease: a 33-week randomized controlled trial. Neurology 77, 759–766. doi:10.1212/WNL.0b013e31822af6db

Poewe, W., Rascol, O., Barone, P., Hauser, R. A., Mizuno, Y., Hauksma, M., et al. (2011). Extended-release pramipexole in early Parkinson disease: a randomized controlled trial. Neurology 77, 767–774. doi:10.1212/WNL.0b013e31822af6db

Schapira, A. H., Barone, P., Hauser, R. A., Mizuno, Y., Rascol, O., Busse, M., et al. (2011). Extended-release pramipexole in advanced Parkinson disease: a randomized controlled trial. Neurology 77, 767–774. doi:10.1212/WNL.0b013e31822af6db

Schöffer, K. L., Henderson, R. D., O’Maley, K., and O’Sullivan, J. D. (2007). Nonpharmacological treatment, fludrocortisone, and domperidone for orthostatic hypotension in Parkinson’s disease. Mov. Disord. 22, 1543–1549. doi:10.1002/mds.21428

Senard, J. M., Brefel, C., Carel, C., Tran, M. A., and Montastruc, J. L. (1999). Water drinking and the heart. Lancet 353, 1971–1972. doi:10.1016/S0140-6736(05)67183-X

Senard, J. M., Brefel-Courbon, C., Rascol, O., and Montastruc, J. L. (2001). Orthostatic hypotension in patients with Parkinson’s disease: pathophysiology and management. Drugs Aging 18, 495–505. doi:10.2165/00002512-200118070-00003

Senard, J. M., Rai, S., Lapeyre-Mestre, M., Brefel, C., Rascol, O., Rascol, A., et al. (1997). Prevalence of orthostatic hypotension in Parkinson’s disease. J. Neurol. Neuropsychiatry. 63, 584–589. doi:10.1136/jnnp.63.5.584

Seppi, K., Weintraub, D., Coelho, M., Perez-Lloret, S., Fox, S. H., Katzmeschler, R., et al. (2011). The movement disorder society evidence-based medicine review update: treatments for the non-motor symptoms of Parkinson’s disease. Mov. Disord. 26(suppl. 3), S42–S80. doi:10.1002/mds.23884

Shannon, J. R., Diedrich, A., Biaggio, I., Tank, J., Robertson, R. M., Robertson, D., et al. (2002). Water drinking as a treatment for orthostatic hypotension syndromes. Am. J. Med. 112, 355–360. doi:10.1016/S0002-9345(02)01025-2

Shibahara, S., Okamoto, E. E., Gamboa, A., Yu, C., Diedrich, A., Raj, S. R., et al. (2002). Clonidine for the treatment of supine hypertension and presyncope in patients with autonomic failure. Hypertension 47, 522–526. doi:10.1161/01.HYP.0000199982.71858.11

Shibahara, C., Okamoto, E. E., Gamboa, A., Yu, C., Diedrich, A., Raj, S. R., et
Stocchi, F., Hersh, B. P., Scott, B. L., Nausieda, P. A., and Giorgi, L. (2008). Ropinirole 24-hour prolonged release and ropinirole immediate release in early Parkinson's disease: a randomized, double-blind, non-inferiority crossover study. *Curr. Med. Res. Opin.* 24, 2883–2895. doi:10.1185/030079908X2387130

Stowe, R., Ives, N., Clarke, C. E., van Helden, I., Ferreira, J., Hawker, R. J., et al. (2008). Dopamine agonist therapy in early Parkinson's disease. *Cochrane Database Syst. Rev.* 2008:CD006564. doi:10.1002/14651858.CD006564.pub2

Tanaka, H., Yamaguchi, H., and Tamai, H. (1997). Treatment of orthostatic intolerance with inflatable abdominal band. *Lancer* 349, 175. doi:10.1016/S0140-6736(97)02403-1

Ten Harkel, A. D., Van Lieshout, J. J., and Wieling, W. (1992). Treatment of orthostatic hypotension with sleeping in the head-up tilt position, alone and in combination with fludrocortisone. *J. Intern. Med.* 232, 139–145. doi:10.1111/j.1365-2796.1992.tb00563.x

Ten Harkel, A. D., Van Lieshout, J. J., and Wieling, W. (1994). Effects of leg muscle pumping and tensing on orthostatic arterial pressure: a study in normal subjects and patients with autonomic failure. *Clin. Sci. 87, 553–558.*

Thomaides, T., Blesiadale-Barr, K., Chaudhuri, K. R., Pavitt, D., Marsden, C. D., and Mathias, C. J. (1993). Cardiovascular and hormonal responses to liquid food challenge in idiopathic Parkinson's disease, multiple system atrophy, and pure autonomic failure. *Neurology* 43, 900–904. doi:10.1212/WNL.43.5.900

Tolcapone Study Group. (1999). Efficacy and tolerability of tolcapone compared with bromocriptine in levodopa-treated parkinsonian patients. *Mov. Disorder* 14, 38–44.

Tolosa, E., and Stern, M. B. (2012). Efficacy, safety and tolerability of rasagiline as adjunctive therapy in elderly patients with Parkinson's disease. *Eur. J. Neurol.* 19, 258–264. doi:10.1111/j.1468-1331.2011.03484.x

Turkkia, J., Suominen, K., Tolonen, U., Sotaniemi, K., and Myllyla, V. V. (1997). Selegiline diminishes cardiovascular autonomic responses in Parkinson's disease. *Neurology* 46, 662–667. doi:10.1212/WNL.46.3.662

Turnbull, K., Caskade, R., MacLeod, A., Ives, N., Stowe, R., Counsell, C. (2005). Monoamine oxidase B inhibitors for early Parkinson's disease. *Cochrane Database Syst. Rev.* 2005:CD004898. doi:10.1002/14651858.CD004898.pub2

Tutaj, M., Marthol, H., Berlin, D., Brown, C. M., Axelow, F. B., and Hiltz, M. J. (2006). Effect of physical countermaneuvers on orthostatic hypotension in familial dysautonomia. *J. Neurol.* 253, 65–72. doi:10.1007/s00415-005-0928-3

Tyne, H. L., Parsons, J., Sinnott, A., Fox, S. H., Fletcher, N. A., and Steiger, M. J. (2004). A 10 year retrospective audit of long-term apomorphine use in Parkinson's disease. *J. Neurol.* 251, 1370–1374. doi:10.1002/14651858.AE000168

UCB, Inc. (2003). "An open-label extension trial to assess the safety of long-term treatment of rotigotine in advanced-stage Parkinson's disease," in ClinicalTrials.gov (Bethesda, MD: US National Library of Medicine). Available at: http://www.clinicaltrials.gov/ct2/show/results/NCT00301969 [accessed February 22, 2013].

van Lieshout, J. J., ten Harkel, A. D., and Wieling, W. (2000). Fludrocortisone and sleeping in the head-up position limit the postural decrease in cardiac output in autonomic failure. *Clin. Auton. Res.* 10, 35–42. doi:10.1071/WR02291.388

Velseboer, D. C., de Haan, R. J., Wieling, W., Goldstein, D. S., and de Bie, R. M. (2011). Prevalence of orthostatic hypotension in Parkinson's disease: a systematic review and meta-analysis. *Parkinsonism Relat. Disord.* 17, 724–729. doi:10.1016/j.parkreldis.2011.04.016

Waters, W. W., Platts, S. H., Mitchell, B. M., Whitson, P. A., and Meck, J. V. (2005). Plasma volume restoration with salt tablets and water after bed rest prevents orthostatic hypotension and changes in supine hemodynamic and endocrine variables. *Am. J. Physiol. Heart Circ. Physiol.* 288, H839–H847. doi:10.1152/ajpheart.00220.2004

Wieling, W., Van Lieshout, J. J., and Hainsworth, R. (2002). Extracellular fluid volume expansion in patients with posturally related syncope. *Clin. Auton. Res.* 12, 242–249. doi:10.1007/s10286-002-0024-x

Wieling, W., van Lieshout, J. J., and van Leeuwen, A. M. (1993). Physical manoeuvres that reduce postural hypotension in autonomic failure. *Clin. Auton. Res.* 3, 57–65. doi:10.1007/BF01819146

Zesiewicz, T. A., Sullivan, K. L., Arnulf, I., Chaudhuri, K. R., Morgan, J. C., Gronseth, G. S., et al. (2010). Practice parameter: treatment of non-motor symptoms of Parkinson disease: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 74, 924–931. doi:10.1212/WNL.0b013e3181d55f24

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 21 March 2013; paper pending published: 08 April 2013; accepted: 19 May 2013; published online: 10 June 2013.

Citation: Sánchez-Ferro Á, Benito-León J and Gómez-Esteban JC (2013) The management of orthostatic hypotension in Parkinson’s disease. *Front. Neurosci.* 7:64. doi: 10.3389/fneur.2013.00064

This article was submitted to Frontiers in Movement Disorders, a specialty of Frontiers in Neurology.

Copyright © 2013 Sánchez-Ferro, Benito-León and Gómez-Esteban. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original authors and source are credited and subject to any copyright notices concerning any third-party graphics etc.