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Emerging drugs for autonomic dysfunction in Parkinson's Disease.

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Abstract.

Introduction: Autonomic dysfunction, including orthostatic hypotension, sialorrhea, sexual dysfunction, urinary dysfunction and constipation is a common feature of PD. Even though its treatment has been recognized as a major unmet need in PD, there is a paucity of clinical trials to assess their treatment.

Areas covered: Evidence about the efficacy and safety of available treatments for autonomic dysfunction is summarized. Potential targets for upcoming therapies are then discussed in light of what is currently known about the physiopathology of each disorder in PD. Proof-of-concept trials and circumstantial evidence about treatments for autonomic dysfunction as well as upcoming clinical trials are discussed. Finally, critical aspects of clinical trials design are considered.

Expert opinion: Botulinum Toxin or glycopirrolate might be used for sialorrhea whereas macrogol could be useful in constipation. There is preliminary evidence suggesting that fludrocortisone, domperidone, droxidopa or fipamezole may be effective for the treatment of orthostatic hypotension. Tropicamide, clonidine or radiotherapy are under development for sialorrhea. Sildenafil may be effective for the treatment of erectile dysfunction; Botulinum toxin or behavioral therapy for urinary incontinence and lubiprostone and probiotics for constipation. Sound clinical trials are needed in order to allow firm evidence-based recommendations about these treatments.

Keywords: Parkinson’s disease; Non-motor symptoms; orthostatic hypotension, sialorrhea, urinary dysfunction; incontinence; sexual dysfunction; erectile dysfunction; constipation; clinical trials design; botulinum toxin; muscarinic antagonists; macrogol; droxidopa, fludrocortisone, domperidone, fipamezole; solifenacin; probiotics; lubiprostone.

- **Background**

Autonomic disturbances such as orthostatic hypotension, sialorrhea, sexual dysfunction, urinary dysfunction or gastrointestinal motility disorders are frequent in Parkinson's disease (PD) [1,2]. They can impair patient's quality of life, worsen the burden of their caregivers, cause hospitalization and institutionalization, and increase the cost of care of patients with PD by four times [1]. Their management and treatment have been recognized by the UK National Institute for Clinical Excellence as unmet needs in PD [3]. In this section we will review prevalence and clinical characteristics of autonomic disorders in PD. Their physiopathology and prognosis will be discussed in other sections of this review article.

Orthostatic hypotension affects 20–65% of patients with PD [4,5] and can be defined as a sustained reduction of systolic blood pressure of at least 20 mm Hg or diastolic blood pressure of 10 mm Hg within 3 min of standing or head-up tilt to at least 60° on a tilt table [6]. Symptoms include generalized weakness, lightheadedness, dizziness or syncope in the worst cases [7].

Sialorrhea affects approximately 70-75% of patients [8,9]. In severe cases where drooling is evident, patients are forced to constantly use a handkerchief and clothes or shoes may be wet or stained. In less evident cases, only mouth corners may be wet or stained. Disturbed eating or speaking may also be observed in connection with sialorrhea.

Impaired sexual function in PD occurs in both men and women [2]. Erectile dysfunction (ED) and sexual dissatisfaction affects more than 60% of men [10]. Several studies have demonstrated that erectile problems are nearly twice as frequent in men with PD than in controls [11]. ED greatly affects PD patients' quality of life and can take a serious psychological toll [12].

Several urinary dysfunctions are commonly observed in PD [1] and may affect up to 40% of patients [2]. The most common urinary problem in PD, involving 45–100% of individuals with urinary symptoms, is overactive bladder contraction, which produces urinary frequency, urgency, nocturia, and incontinence.

Reduced gastrointestinal motility resulting in constipation is also a very common symptom of PD, affecting up to 80% of patients [2]. Constipation frequently precedes the diagnosis of PD.

- **Medical Need**

Levodopa non-responsive non-motor symptoms, including autonomic dysfunction, are frequently the most disabling feature of PD, as shown in prospective studies. For example, a survey of 163 consecutive symptomatic patients showed that difficulties with balance, sleep disturbance, memory failure or confusional episodes, and dribbling of saliva were rated as the most disabling symptoms [1]. A recent study in 462 PD patients showed that depression, anxiety and non-motor symptoms were independent factors influencing quality of life in PD [13]. Comorbidities can also be found in connection with non-motor symptoms. For example, OH does not only cause significant morbidity and mortality, mainly from the sequelae of falls, but is also an independent risk factor for morbidity and mortality from heart disease, stroke and cardiovascular and all-cause mortality [14]. Sialorrhea may give rise to embarrassment, isolation and worsening of depressive symptoms [15]. Saliva that remains pooled in the mouth may become an aspiration source, and result in choking and pneumonia [16].

Urinary incontinence may also cause increased morbidity in PD. Moisture lesions or incontinence-associated dermatitis are painful and distressing consequences of prolonged exposure to urine [17]. They may adversely affect patients' physical and psychological wellbeing, so minimizing damage is of vital importance.

Gastro-intestinal hypomobility may reduce the absorption of levodopa. Indeed, the rate and extent of levodopa absorption of standard levodopa tables is affected by food and other gastric factors that modulate gastric emptying including gastric pH, intestinal transit time and digestive enzymes [18]. Anecdotic evidence suggests that in extreme cases, constipation might trigger worsening of PD symptoms or motor fluctuations and occurrence of the malignant syndrome was observed after fecal impactation in a subject previously affected by severe constipation [19].

- **Existing treatments**

Non-motor symptoms are frequently overlooked by neurologists [1]. Even though interest in such symptoms have greatly increased in the last years, treatments are still scarce for the majority of the conditions, as concluded by both the American Academy of Neurology [20] and the Movement Disorders Society [21] in their evidence-based medicine reviews. In this section we will review drugs with documented efficacy the treatment of autonomic dysfunction in PD and in other population of patients. Data is summarized in Table 1.

- *Orthostatic hypotension*

Identification of the mechanism of orthostatic hypotension (disease, drug or other causes) is the first step in the treatment, followed by non-pharmacological measures. In a recent cross-sectional study it has been shown that exposure to diuretics, amantadine and polypharmacy (i.e. intake of more than 5 drugs) was more frequent in PD patients with orthostatic hypotension [22]. Exposure to levodopa, dopamine agonists, alpha-adrenergic blockers used for prostatic hyperplasia, clonidine antihypertensives or many antidepressants can also produce or aggravate orthostatic hypotension [23,24]. Therefore the first therapeutic maneuver is to re-consider treatment with agents known to induce or aggravate hypotension [24]. Patients should also be advised to avoid precipitating factors such as sudden postural change, large meals, hot baths, alcohol and vasodilating medications [25]. Other non-pharmacological methods for treating OH include liberal addition of salt to the diet, exercise, compression stockings or physical maneuvers that help to raise blood pressure by increasing venous return and increasing peripheral resistance. A recent systematic review demonstrated that several common treatments for orthostatic hypotension have been examined only in low-quality randomized, placebo-controlled trials [26]. This includes non-pharmacological measures as well as drugs such like midodrine or fludrocortisone, which are the first line drugs [24]. Similarly, the Movement Disorders Society Evidence-based medicine (MDS-EBM) review did not identify any drug meeting its definition for being “clinically useful” [21].

- *Sialorrhea*

Treatment should begin by withdrawal of sialorrhea-inducing drug agents, such as cholinesterase inhibitors, clozapine or quetiapine [15]. The MDS-EBM review identified Botulinum toxin-A or -B (BTX-A or B respectively), an acetylcholine release inhibitor, as “clinically useful” and glycopirrolate, a peripheral-acting muscarinic receptor antagonist as “possibly useful” for sialorrhea in PD [21]. We will review evidence about efficacy and safety of these drugs.

- *Botulinum toxin*

Lagalla and colleagues conducted a double-blind, randomized, placebo-controlled trial on BTX-A [27]. Subjects received 50 Units of BTX-A or matching-placebo in each parotid gland. Sixteen patients were randomly assigned to each treatment arm. Patients under BTX-A showed a 40% reduction of VAS scores and a 50% reduction of buccal saliva contents, which were not observed in the placebo group (BTX-placebo difference p<0.001). One patient complained about transient swallowing difficulties. No other adverse events were reported.

Ondo et al conducted a double-blind, randomized, placebo controlled study aiming to assess the efficacy and safety of intraglandular BTX-B injections [28]. Eight patients were randomly assigned to each treatment arm. Significant reductions in the Drooling Rating Scale (40%, p<0.05), DSFS (31%, p<0.01) and in the VAS assessment of drooling-induced disability were noted in the BTX-B group but not in the placebo group. Swallowing was not compromised.

Similar results were observed in a double-blind, randomized, placebo-controlled study conducted by Lagalla and coll [29]. In this study, 18 patients were assigned to each treatment arm. While a significant reduction in the sialorrhea rating scales (DSFS dropped from 77 to 40 points) and in the objective measurements (from 2.1 g to 1.4) were observed in the BTX-B treated group, no difference was found in the placebo group (for both p<0.01). Three patients on BTX-B complained about swallowing difficulties that resolved within 2-weeks of treatment. No other adverse events were observed.

- *Glycopirrolate*

Glycopyrrolate 1 mg 3 times per day were compared to placebo in 23 patients with PD [30]. Nine patients (39.1%) with glycopyrrolate had a clinically relevant improvement of at least 30% vs. 1 patient (4.3%) with placebo ($p<0.021$). There were no significant differences in adverse events between glycopyrrolate and placebo treatment.

- *Sexual dysfunction*

Patient counseling [31] and reevaluation of drug treatments potentially causing sexual dysfunction are the first step towards successful treatment [7]. Rigidity and bradykinesia contribute to general deterioration in sexual functioning [31]. Ageing, depression, fatigue, sleep disorders, reduced testosterone secretion can also be important contributing factors [32]. Some drugs, such as antihypertensives or antidepressants can also cause or aggravate erectile dysfunction [33], and thus patients' pharmacotherapy should be re-evaluated. Nonetheless, drug treatment often becomes necessary, based essentially on phosphodiesterase type 5 inhibitors, including sildenafil, tadalafil, and vardenafil [34]. Treatment options for patients who do not respond to these drugs or for whom they are contraindicated include intracavernous injections, intraurethral alprostadil, vacuum constriction devices, or implantation of a penile prosthesis.

Nevertheless, this is based on empirical approach, and the MDS-EBM review concluded that there were no drugs with documented efficacy for treatment of erectile dysfunction in PD [21].

- *Urinary dysfunction*

Its treatment should begin by considering external causes such as prostate hypertrophy or cancer. Drug treatment may be considered afterwards. A recent meta-analysis compared the efficacy of muscarinic receptor antagonists for the treatment of urgency urinary incontinence associated with bladder overactivity in women [35]. Continence was restored in 130 per 1000 women treated with fesoterodine (CI, 58 to 202), 85 with tolterodine (CI, 40 to 129), 114 with oxybutynin (CI, 64 to 163), 107 with solifenacin (CI, 58 to 156), and 114 with trospium. Rates of discontinuation were higher with oxybutynin as compared to other drugs. Many papers have reported on the clinical success of BTX-A as a method of management of various bladder dysfunctions [36]. Injection of botulinum toxin A appears to have a positive therapeutic effect in multiple urological conditions inducing urinary incontinence, such as refractory idiopathic detrusor overactivity, neurogenic detrusor overactivity, interstitial cystitis/painful bladder syndrome and benign prostatic hyperplasia. Nowadays, BTX-A has been approved by the Food and Drug Administration for the treatment of urinary incontinence as a result of neurogenic detrusor overactivity in adults who have an inadequate response to or are intolerant to anticholinergics. Non-pharmacological measures such as tibial nerve stimulation may also be considered in these cases [37].

The MDS-EBM review found no drug with documented efficacy for treatment of urinary dysfunction in PD [21].

- *Constipation*

Changes in the diet and physical activity are the first treatment measures to be taken. Increased fluid and fiber intake should be encouraged, adding fiber supplements and stool softeners if necessary. Tricyclic antidepressants, loperamide, codeine phosphate, opioids, antimuscarinics and some antiparkinsonian drugs are frequent causes for severe constipation [38], thus warranting evaluation of patients drug treatment before taking further measures. Then, osmotic laxatives may be employed as a second option. Drug treatments should be reserved as the last option.

A recent meta-analysis pooled data from placebo-controlled trials of laxatives or pharmacological therapies in adult patients with chronic idiopathic constipation [39]. Laxatives (RR=0.52; 95% CI 0.46 to 0.60), prucalopride (RR=0.82; 95% CI 0.76 to 0.88), lubiprostone (RR=0.67; 95% CI 0.56 to 0.80), and linaclotide (RR=0.84; 95% CI 0.80 to 0.87) were all superior to placebo in terms of a reduction in risk of failure with therapy. Laxatives included osmotic agents such as lactulose or polyethylene glycol (i.e. macrogol) and stimulant ones such as bisacodyl or sodium picosulfate, with similar results.

Mean number of stools per week was significantly higher with laxatives compared with placebo (weighted mean difference in number of stools per week=2.55; 95% CI 1.53 to 3.57). Diarrhea was more frequently with all assessed drugs.

Probiotics have been suggested to have favorable effects on gastrointestinal function including suppressing growth of pathogenic bacteria, blocking epithelial attachment by pathogens, enhancing mucosal function, and modulating host immune response [40]. In a randomized, placebo-controlled study, a yogurt containing a mixture of Bifidobacterium animalis and prebiotic fructoligosaccharide administered twice a day for 2 weeks produced a 22% increase in the number of bowel movements per week and a slight increase in stool quality as assessed by the Bristol Stool Questionnaire when compared to placebo [40]. There is insufficient evidence to propose the utilization of other agents such as trimebutin, erythromicyn or domperidone [41]. Tegaserod has been found to be effective, but due to safety issues it was withdrawn from the market [41].

- *Macrogol*

The MDS-EBM taskforce considered macrogol, an osmotic agent, as a “possibly useful” treatment for constipation in PD [21]. Zangaglia and colleagues studied the efficacy of an isosmotic 7.3 g macrogol electrolyte solution for the treatment of constipation in PD in a double-blind, randomized, placebo-controlled trial [42]. Fifty-seven patients were included in this study. Responders rate were higher in the macrogol group as compared with the placebo (80% vs. 30%, $p<0.001$). A higher rate of withdrawals was seen in the macrogol group compared to placebo.

- **Market review**

General population estimates of incidence for PD range from 1.5 to 2.6 per 100000 person-years [43,44]. Worldwide estimates of PD are projected to increase to 8.67 million by 2030 [45]. Prevalence of orthostatic hypotension, sialorrhea, sexual dysfunction, urinary dysfunction or constipation, ranges from 20-65%, 70-75%, 60%, 40% or up to 80% respectively [2,4,5,8-10]. As commented earlier, there are in general few studies about the efficacy of treatments for these conditions. This means that about 1.73 to 5.20 million PD patients may suffer from any kind of autonomic dysfunction and may not be treated. It is therefore of maximal important to develop and test treatments for autonomic disorders in PD.

- **Current research goals**

As commented earlier there are no approved treatments for autonomic dysfunction features in PD, except may be for the use of Botulinum Toxin in sialorrhea or macrogol in constipation. Therefore, the first research goal is to evaluate drugs showing efficacy for the same indication in other patients groups. Many of them will be reviewed in the “Competitive environment” section. Clinical trials should be designed with the highest quality standards, which in general has not been the case up to now. Recommendations for the conduction of such clinical trials will be given in the “Potential Development issues” section of this review. Trials for non-pharmacological measures are also needed. As commented earlier they represent early treatment measures, but their efficacy has been seldom studied.

Another important research goal is to find new targets and therapeutical agents to be tested. Such targets will be reviewed in the next section.

- **Scientific rationale**

In this section we will review the physiopathology of autonomic disorders in PD and will try to identify potential targets for future treatments.

- *Orthostatic hypotension*

Sympathetic dysfunction is a hallmark of orthostatic hypotension in PD. For example, compared with age-matched controls, patients with PD have low baroreflex-cardiovagal gain [46]. Reduced gain is even greater in PD with orthostatic hypotension. Therefore, orthostatic increments in norepinephrine release in blood vessels sympathetic terminals are reduced and total circulating norepinephrine levels are also reduced. Deposition of Lewy bodies in Locus Coeruleus and loss of sympathetic post-ganglionic cells have been implicated. But it has been suggested that reduced baroreflex gain is not the only factor related to orthostatic hypotension in PD. Indeed, sympathetic denervation of the heart appears to be also an important factor [46].

It can thus be hypothesized that restoring baroreflex gain may be an effective treatment for orthostatic hypotension in PD. Manipulating breathing patterns or frequency may increase baroreflex sensitivity at least in healthy or hypertensive individuals [47-49]. But, in the presence of organic lesions of the sympathetic nervous systems, such as those observed in PD, there effects might be less important than expected. In rats, orexin A injections into the medulla can also increase baroreflex sensitivity [50]. Ghrelin, a neuropeptide originally known for its growth hormone-releasing and orexigenic properties and which exerts important pleiotropic effects on the cardiovascular system, has also been shown to increase baroreflex gain in healthy individuals [51]. Particular combination of known antihypertensives can also sensitize baroreflex, probably following blood pressure reductions [52].

Reduced circulating norepinephrine levels in PD patients with orthostatic hypotension reveal decreased production and liberation. Therefore, administration of drugs with adrenergic properties such as alpha1-adrenergic agonists or alpha2-adrenergic auto receptors antagonists may also be effective for hypotension treatment. Midodrine, which is considered as the first line agent against orthostatic hypotension [24], acts by stimulating alpha1-adrenergic receptors. There is no study addressing the efficacy and safety of this drug in PD. Norepinephrine precursors, such as droxidopa, can be also administered.

- *Sialorrhea*

In adults, about 1.5 l of saliva are secreted daily by three pairs of major salivary glands [53]. The submandibular glands, the parotid glands, and the sublingual glands account for about 95% of the total secretion and the remaining 5% is produced by the minor salivary glands.

Salivary glands are controlled by the autonomic nervous system, and are primarily under parasympathetic cholinergic control [53]. It is generally agreed that an increase in the flow of saliva in response to muscarinic agonists is attributable to activation of muscarinic M1, M3 and M5 receptor subtypes [54]. Glands also receive a variable innervation from sympathetic nerves which released norepinephrine from which tends to evoke greater release of stored proteins, mostly from acinar cells but also ductal cells [55]. There is some ‘cross-talk’ between the calcium and cyclic AMP intracellular pathways coupling autonomic stimulation to secretion and salivary protein secretion is augmented during combined stimulation. Sympathetic stimulation on cells receiving parasympathetic impulses modulates the composition of saliva by increasing exocytosis from salivary cells, induces contraction of myoepithelial cells and regulates glandular blood flow.

Therefore, reducing parasympathetic or sympathetic stimulation will lead to reduced saliva outflow. Similarly, sympathetic norepinephrine inhibition may contribute to such reduction. Nonetheless, these interventions can be regarded as palliatives, as the physiopathology of sialorrhea in PD is related to reduced clearance due to impaired swallowing, and not to increased production [15]. It may seem thus more logical to try to find to ways to increase swallowing frequency. Lee Silverman Voice Treatment, which can improve dysarthria and dysphagia [56] may be a good candidate but its efficacy has not been explored in PD.

- *Sexual dysfunction*

Sexual dysfunction is mainly related to vascular autonomic malfunction [57], thus representing the primary target. Neurophysiologic and pharmacological research has elucidated that dopamine and serotonin have central roles in modulating erection and ejaculation [58]. Therefore, dopaminergic degeneration in PD can contribute to altered sexual behavior. Therefore, drugs enhancing penis vasodilation and/or increasing central dopaminergic tone might be good candidates for the treatment of erectile dysfunction in PD. Among such agents, apomorphine may offer special interest, as it has shown some efficacy for treatment of erectile dysfunction [59]. Action mechanism may be both vasodilation and enhancement of central dopaminergic tone. Regrettably its efficacy in PD has never been explored.

- *Urinary dysfunction*

The lower urinary tract consists of two major components, the bladder and urethra [60]. The bladder is mainly innervated by parasympathetic pelvic nerve. The urethra is innervated by sympathetic and somatic nerves.

Urinary storage is dependent on the reflex arc of the sacral spinal cord. The storage reflex is thought to be tonically facilitated by the brain, particularly the pontine storage center. The storage function is thought to be further facilitated by the hypothalamus, cerebellum, basal ganglia (particularly through the direct pathway), frontal cortex and by central cholinergic fibers from Meynert nucleus [60].

Reduced bladder capacity together with detrusor overactivity as well as uninhibited external sphincter relaxation are the hallmarks of urinary incontinence in PD [60]. Therefore, inhibition of detrusor activity may be an effective of treating incontinence in PD.

- *Constipation*

The pathophysiological basis for gastrointestinal dysfunction in PD may involve both peripheral and central mechanisms [2]. Damage of the dorsal motor nucleus of the vagus may be the hallmark of constipation in PD and may precede motor symptoms onset. Nonetheless, alpha synuclein deposition has also been demonstrated in the enteric nervous system, where loss of dopaminergic neurons has also been shown. Reduced dopaminergic tone may lead to altered peristaltic reflex [61], thus causing delayed colonic transit and anorectal dysfunction [62]. Therefore, therapies accelerating colonic transit may be effective for constipation treatment in PD.

In some patients pelvic floor dyssynergia may contribute to constipation [62]. Such cases can be regarded as episodes dystonia, and thus should be treated accordingly.

- **Competitive environment**

In this section we will review drugs potentially useful for the treatment of autonomic dysfunction in PD. Full searches were conducted in Pubmed, Clinicaltrials.gov and Movement Disorders Society International congress from 2002 up to 2012. We focused on drugs with insufficiently documented efficacy or for which there are clinical trials either planned or ongoing. Inefficacious or unsafe drugs will be briefly mentioned.

Results are summarized in Table 2.

- *Drugs for the treatment of orthostatic hypotension*
- *Fludrocortisone and Domperidone*

Schoeffer et al conducted a randomized double-blind cross-over trial to assess the efficacy and safety of domperidone or fludrocortisone [63]. Thirteen PD patients with symptomatic orthostatism were randomly assigned to one of two possible treatment sequences (fludrocortisone-domperidone or vice versa) allowing a 1-week wash-out period in between. Composite Autonomic Symptom Scale scores were 9±3 at baseline, 6±3 on fludrocortisone ($p<0.04$), and 7±2 on domperidone ($p<0.02$). Three patients had to be withdrawn during the first week of treatment (2 on domperidone and 1 on fludrocortisone). Five patients reported adverse events during domperidone treatment (nausea -2 cases-, chest pain, abdominal pain, palpitations and headache) and 6 during fludrocortisone (nausea -2 cases-, chest discomfort, morning headache, lightheadedness, and dizziness).

- *L-dihydroxyphenylserine (droxidopa)*

Droxidopa is an oral pro-drug that is converted to norepinephrine via decarboxylation which efficacy and safety has been explored in orthostatic hypotension related to a number of neurological conditions [64]. Droxidopa could exert its pressor effect by being converted to epinephrine and activating the sympathetic preganglionic neurons in the spinal cord; by converting to norepinephrine in post ganglionic sympathetic neurons and released when sympathetic neurons are activated; or Droxidopa could be converted to norepinephrine outside neurons (in the stomach, kidney and liver), and released into the blood stream as a circulating hormone [64]. Its efficacy and safety was explored 121 patients with either MSA or PD were randomized and received doses of 100, 200, 300 mg of Droxidopa or matching placebo. Droxidopa treatment resulted in a reduction in the orthostatic fall in blood pressure [65], with an overall trend towards improvement in symptoms that did not reach statistical significance. A preliminary analysis of efficacy data from 51 PD patients with orthostatic enrolled in a longer-term (8-10 week) double-blind, placebo-controlled study showed that there was there was no statistically significant difference at the end of the study in terms of orthostatic hypotension signs and symptoms [52,66]. A post-hoc analysis of data coming from clinical trials in PD evaluated the clinical efficacy and safety of droxidopa in repeat fallers with orthostatic hypotension [67]. Patients treated with droxidopa (n=24) experienced fewer falls compared to placebo (n=27): 79 vs. 197. The repeat fallers group (n=22) showed greater benefit from droxidopa therapy vs. the non-repeat fallers group (n=29) as measured by dizziness, HY, and MDS-UPDRS scores.

- *Fipamezole*

Fipamezole is an alpha 2-adrenergic receptor antagonist with a moderate affinity for histamine H1 and H3 receptors and the serotonin transporter and low affinity for the norepinephrine and dopamine transporters, the alpha-adrenergic 1A and 1B receptors and the 5-HT1A and 5-HT7 receptors [68,69]. Fipamezole (JP-1730) is a potent alpha2-adrenergic receptor antagonist that reduces levodopa-induced dyskinesia in the MPTP-lesioned primate model of Parkinson's disease. [68]. The acute hemodynamic effects of fipamezole were evaluated in a double blind placebo controlled study in 21 PD patients [70]. Blood pressure was evaluated during an acute intravenous levodopa challenge. Continuous levodopa treatment significantly decreased mean blood pressure ($P<0.01$). Compared to placebo, fipamezole returned blood pressure to preinfusion values in a dose-dependent fashion ($p<0.01$). A clinical trial is underway to confirm these results (NCT00758849).

- *Partial weight supported treadmill gait training*

Partial weight supported treadmill gait training is sometimes used in rehabilitation in PD. Its cardiovascular effects have been recently evaluated in a controlled open-label study [71]. Sixty PD patients were randomly assigned to undergo conventional gait training or treadmill gait training or no specific intervention.

Results showed that while blood pressure did not varied in any group, baroreflex sensitivity improved 80.4% following treadmill gait and by less than 10% in the other groups.

- *Entacapone*

Circumstantial evidence suggesting that entacapone might be effective for treating orthostatic hypotension was found in a cross-sectional study conducted by our group to evaluate factors related to orthostatic hypotension in PD [22]. In that study, 20% of patients on entacapone reported hypotension, compared to 45% and 32% of patients on levodopa or on other antiparkinsonian drugs ($p<0.01$). We hypothesized that this effect might be achieved by the blockage of norepinephrine degradation by the COMT enzyme.

- *Drugs for the treatment of sialorrhea*
- *Tropicamide*

Tropicamide is a rapid-onset, short-acting muscarinic receptor antagonist. The efficacy of a slowly-dissolving, mucoadhesive intra-oral thin film containing tropicamide (NH004) has been explored in a proof-of-concept randomized, double-blind, placebo-controlled, crossover trial [72]. Nineteen PD patients who complained of sialorrhea received 3 doses (0.3, 1, 3 mg) of tropicamide and placebo in random order, separated by 7 days. For the last 7 patients, saliva volume was measured at baseline and 75 min after treatment. The mean decrease in VAS score from baseline to120 min were −0.55±0.54, −1.08±0.54, -1.53±0.52

and −0.81±0.51 for placebo and 0.3, 1 and 3 mg tropicamide, respectively ($F=0.6$ $p=0.6$, ANOVA). Tropicamide 1 mg resulted in a significant VAS score decrease (95%CI: −2.57 to −0.48). Saliva volume was reduced by 27%, 33% or 20% after tropicamide 0.3, 1 or 3 mg vs. 5% with placebo. No adverse events were detected in any of the treatment sequences.

- *Clonidine*

Clonidine is an imidazolic, selective alpha2-adrenergic receptors agonist. Serrano-Dueñas conducted a double-blind, randomized, placebo-controlled trial to assess the efficacy and safety of clonidine 0.15 mg/day during 3 months in 32 PD patients [73]. On average, patient had to dry their mouths 9 times per 5-min at baseline without between-groups differences. After 3-month of clonidine treatment, patients had to dry their mouths on average 1.47 times, while patients on placebo showed no difference ($p<0.0001$). Adverse events were only observed in the clonidine group: diurnal somnolence (2), dizziness (1) and dry mouth (1).

The efficacy and safety of a combination of clonidine and oxybutinin is being explored in a double-blind, randomized, placebo-controlled 4-way crossover study [74]. Preliminary result of the data from the first 5 completed patients showed a trend in saliva secretion rate inhibition.

Clonidine may cause or aggravate orthostatic hypotension, suggesting that this side-effect should be specifically evaluated in clinical trials with the drug.

- *Radiotherapy*

The long-term efficacy and safety of radiotherapy to the major salivary glands was explored retrospectively [75]. Twenty-eight patients (78% PD, 11% multiple system atrophy, 11% other parkinsonism) received a bilateral dose of 12 Gy to the parotid and part of the submandibular glands. Sialorrhea improved significantly at 1 month post radiotherapy and this effect was maintained for at least 1 year. Most frequent adverse events were loss of taste and a dry mouth, 75% of which were transient.

- *Other drugs*

Efficacy and safety of some muscarinic receptor antagonists have been tested in the past. Ipratropium was found to be ineffective in a double-blind, randomized, cross-over trial [76]. Conversely, atropine showed a potent antisialorrheic effect, but was associated with delirium and hallucinations in 3 out of 7 studied patients [77].

- *Sexual dysfunction*
- *Sildenafil*

Hussain et al conducted a randomized, double blind, cross-over trial to assess the efficacy and safety of Sildenafil in 10 PD patients [78]. Subjects were treated during 10-week with flexible doses of sildenafil from 25 mg to 100 mg on an “as needed” basis 1 h before initiation the sexual intercourse or with placebo. Significant improvements in the ability to achieve and maintain an erection were found after sildenafil but not after placebo. One patient reported headache and a flushing after sildenafil.

In a larger double blind, placebo-controlled study PD patients randomized to receive 100mg sildenafil on demand 1 h before sexual activity (n=118), or similar regimen of placebo (n=118) [79]. At the end of the trial, differences between sildenafil and placebo groups were significant for the international index of erectile function score (22.6±4.6 vs. 14.8±4.2, p<0.01). Sildenafil was generally well tolerated.

- *Other drugs*

Significant improvements in international index of erectile function have been observed with pergolide [80], but the drug is considered nowadays a second line antiparkinsonian therapy as it can induce cardiac valvulopathy.

- *Urinary dysfunction*
- *Botulinum Toxin A*

The efficacy of intravesical Botulinum toxin injection for overactive bladder symptoms was explored in an open-label uncontrolled study in 16 PD patients [81]. Patients were injected with 500 i.u. of botulinum toxin-A into the detrusor. Initial mean functional bladder capacity for the group was 198.6±33.7 mL, which increased to 319±41.1 mL three months after treatment. The initial mean SEAPI (stress, emptying, anatomy, protection, inhibition) Incontinence Quality of Life Assessment questionnaire score was 32±3 and 26±6 at 12 months ($p < 0.05$). No neurological deterioration, confusion or disorientation was noted. None of the evaluated patients needed intermittent or indwelling catheterization after the procedure.

- *Behavioral therapy*

The intervention consisted in training patients to control their pelvic muscles [82]. Computer-assisted anorectal (or vaginal) dual-channel EMG biofeedback was used to help participants identify pelvic floor muscles and teach them to contract and relax these muscles in isolation while keeping rectus abdominis muscles relaxed. Participants were given guidance regarding fluid management (decrease caffeine, drink 6 to 8 8-ounce glasses of fluid daily) and education regarding constipation as indicated (increase physical activity, fiber, and fluid; over-the-counter agent use if needed).

The feasibility and efficacy of this intervention was tested in an uncontrolled, open-label study in 17 PD patients. The median (interquartile range) weekly frequency of baseline UI episodes was 9 (4–11) and following intervention was 1 (0–3), representing an 83.3% reduction (45.5–100.0, $p<0.0001$). Quality of life scores as measured by the International Consultation on Incontinence Questionnaire for overactive bladder instrument improved from 71.1±23.9 to 54.7±15.4 ($p<0.002$).

A randomized, blinded study including 60 patients is underway to further test the efficacy and safety of the intervention (NCT01520948).

- *Solifenacin succinate*

Solifenacin is a M3 muscarinic receptor antagonist which has shown efficacy for the treatment of overactive bladder in the general population [83]. A randomized, double-blind, placebo-controlled clinical trial in a reduced number of PD patients testing the efficacy and safety of solifenacin succinate up to 10 mg/day is underway (NCT01018264).

- *Other drugs*

Efficacy and safety of intranasal desmopressin was assessed in 5 PD patients [84]. Three patients dropped out from the study, one due to hyponatremic confusion and two due to lack of efficacy.

- *Constipation*
- *Mosapride*

Liu et al conducted an open-label study to assess the efficacy of mosapride 15 mg/day for the treatment of constipation in PD and MSA [85]. Mosapride is a 5-HT4 Agonist and Partial 5-HT3 antagonist. Six out of the 7 included patients completed the study. Colonic transit time was increased by 30%. One patient manifested epigastric discomfort and thus was removed from the study. No worsening of parkinsonism was observed.

- *Neurotrophin 3*

Recently, neurotrophin 3 has been studied for the treatment of gastrointestinal motility problems in PD. Neurotrophin 3 has been shown to produce diarrhea in healthy subjects [86] and was effective in functional constipation [87], the action mechanism remaining unknown. Pfeiffer et al conducted a randomized, controlled clinical trial in 6 PD patients [88]. Increments in stool frequency, reductions in the amount of days without bowel movements and reduced colonic transit time were noticed in the Neurotrophin 3 group as compared to placebo, although they were not statistically significant. Neurotrophin 3 was generally well tolerated, but 3 patients did reduce dosage due to abdominal cramps or diarrhea.

- *Lubiprostone*

Ondo and coll evaluated the efficacy and safety of lubiprostone, a chloride channel activator, in a double-blind, randomized, placebo-controlled study in PD [89]. Lubiprostone was titrated up to 48 mcg/day. Results showed a marked or very marked clinical global improvement was reported by 16 of 25 (64.0%) subjects receiving drug vs. 5 of 27 (18.5%) subjects receiving placebo ($p<0.001$). Number of bowel movements per day increased after drug treatment ($p<0.001$). Adverse events with drug were mild, most commonly intermittent loose stools, with 12 cases in the lubiprostone group vs. 1 in the placebo group.

- *Probiotics*

The effects of milk fermented with the probiotic strain Lactobacillus casei Shirota on constipation in PD was explored in an uncontrolled open-label study in 40 PD patients [90]. After probiotic intake a statistically significant increase in the number of days per week in which stools were of normal consistency ($P<0.01$) were observed. The number of days per week in which patients felt bloated ($P<0.01$), experienced abdominal pain ($P<0.01$) and had sensation of incomplete emptying ($P<0.01$) were also reduced.

- *Biofeedback therapy*

This intervention involves retraining of muscles involved in defecation and is especially useful in functional constipation with dyssynergic defecation or rectal hyposensitivity. The clinical effects of this intervention are being explored in an uncontrolled, open-label study in a reduced number of PD patients (NCT00869830).

- *Other drugs*

Efficacy and safety of tegaserod, a 5-HT4 agonist, was studied in a randomized, double-blind, placebo-controlled trial in 15 patients [91]. Overall, there was a non-significant trend for decreased constipation in the group that took tegaserod compared to the group that took placebo. No side effects were reported. Tegaserod has been withdrawn from the market because of cardiovascular safety issues.

- **Potential development issues**

There is a paucity of methodologically sound clinical trials for non-motor symptoms in PD [20,21]. Randomized, controlled clinical trials, using validated outcome measures on appropriate populations are the gold standard for demonstrating drugs safety and efficacy [92]. Phase III studies duration should be at least 3 months, considering that dysautonomia represents a chronic condition. Conversely, proof-of-concept Phase II studies can be of shorter duration. As commented earlier, dysautonomic symptoms can be related to PD or to other factors, frequently including drug treatments. It is essential that such drugs treatments are controlled during the trial to avoid confounding effects.

In this section we will give some recommendations about study population, outcome measures, study duration and safety assessment when conducting clinical trials for autonomic dysfunction in PD. A summary can be found in Table 3.

- *Orthostatic hypotension*

There are many unresolved issues regarding the clinical evaluation of orthostatic hypotension. In first place, the extent of the blood pressure fall after orthostatism does not always correlate with the presence of symptoms of orthostatism such as lightheadedness or dizziness [22,93]. Moreover it is not clear whether blood pressure fall should be evaluated by tilt test or standing test and how long should it last after position change [6,93]. The Malmo Preventive Project, which showed that orthostatic hypotension is an independent and significant risk factor for all-cause mortality, was based on the classical definition of orthostatic definition and not on the presence of orthostatism symptoms. It may be thus considered that drugs with the ability to reduce the orthostatic blood pressure drop after orthostatism may reduce mortality, irrespective of their effect on symptoms. Therefore, some experts may favor using orthostatic blood pressure fall extent as a primary outcome and presence orthostatism symptoms, standing time patient’s ability in orthostatic activities of daily living [94] as a secondary variable in PD clinical trials. SCOPA-AUT or COMPASS scales have been recommended for the evaluation of orthostatic symptoms in PD [95]. Patients are usually selected on the basis of the results of standing test. This test, which consists in the evaluation of blood pressure in the supine position and during 3 minutes after orthostatism, is easy to administer in routine practice [6]. However, it is a problem to consider treating patients simply on the basis of a fall in blood pressure, and to expose them to potentially troublesome adverse drug reactions if they do not complain of clinical symptoms. Therefore, proof-of-concept trials may use changes in blood pressure as a primary endpoint, and effects on symptoms as a secondary. On the opposite, in phase III trials, the effects on clinical symptoms might be preferred as a primary outcome, while the changes in blood pressure might be used a secondary explicative outcomes. Patients should also be required to be either untreated or to remain on stable co-treatments with any drugs that could influence blood pressure values. Patients with other forms of neurogenic hypotension, such as multiple system atrophy or pure autonomic failure, should be excluded as the mechanisms of orthostatic hypotension may differ (for example, orthosympathetic dysfunction in MSA is believed to be rather central and pre-ganglionic, while it is supposed to be mainly peripheral and post-ganglionic in PD patients).

One common side effect of drugs for orthostatic hypotension being supine hypertension [96,97], safety assessment should include careful regular assessment of this condition.

- *Sialorrhea*

Sialorrhea can be measured either by quantification of buccal saliva levels or clinical scales. Among the clinical scales, the Drooling Severity and Frequency Scale (DSFS), the Drooling Rating Scale or the Sialorrhea Clinical Scale for PD have been suggested for sialorrhea assessment in PD [98,99]. The modified

Teacher's Drooling Scale (mTDS) has also been used for sialorrhea evaluation in PD [30]. DSFS can be used for the retrospective evaluation of sialorrhea, while mTDS can provide on-the-fly evaluations. For inclusion in clinical trials, patients may be selected on the basis of the sialorrhea item in the UPDRS. Patients with xerostomic drugs such as clozapine or other neuroleptics or with significant oral pathology should be excluded or at least studied separately. Xerostomia can be observed as a side-effect of drugs for sialorrhea and represents a risk factor for swallowing dysfunction [100]. Dysphagia is frequent in PD and frequently accompanies sialorrhea [101]. Therefore, drug-induced xerostomia can potentially aggravate dysphagia and should thus be always explored in sialorrhea trials in PD. Additionally, if anticholinergics are explored, then cognitive function should be monitored [102].

- *Sexual dysfunction*

Studies on sexual dysfunction should include sexually active males or females and should have at least one sexual encounter per week [79]. Patients with other sexual disorders, such as premature ejaculation or suffering from vasculogenic, psychogenic or endocrinological causes of sexual dysfunction should be excluded. Outcomes may be evaluated by the International Index of Erectile Function [103] or by the Sexual Health Inventory Scale-M version [104], but it should be mentioned that no consensus has been reached on the subject.

- *Urinary dysfunction*

Subjective patient-centered outcomes should be employed in Phase III type clinical trials for urinary dysfunction [105]. Simple Likert scales exploring patients' feelings or treatment benefices can be used. Diaries exploring the frequency of incontinence episodes during a week may result in more significant data. Other symptoms may also be evaluated by standard questionnaires such as the International Prostate Symptom Score or the Danish Prostate Symptom Score [106,107]. Objective tests may also be used, as primary outcomes of early development phase or explanatory secondary outcomes of Phase III trials. The pad weighing test consists in weighting protective pads before and after treatment. Less frequent leakage will result in dry pads, weighing less. Study duration should be at least 12 weeks, as a "learning" effect has been found for week diaries, producing pronounced placebo effects.

Drugs intended for use in urinary incontinence may affect bladder emptying. It is therefore important to monitor patients for increases in residual urine or urinary tract infections.

- *Constipation*

There are no validated scales for constipation in PD [98]. A patient-reported outcome assessment is recommended [108]. The use of "adequate relief of abdominal pain and discomfort" as an endpoint does not seem adequate in PD as it is not the main symptom. On the other hand, mean number of stools per week, which is also frequently used a primary endpoint in clinical trials, may be used in PD (Ford/Suares2010). To be included patients should comply with the ROME III criteria for functional constipation [108]. Patients with irritable bowel disorders should be excluded, but this diagnosis may be problematic in PD. The trials must be long enough to determine if any response will be sustained and to determine the effects of withdrawal of treatment, probably 12 weeks or more. Loose stools or diarrhea are common adverse events of drugs for constipation and should thus be evaluated in all clinical trials.

- **Conclusion**

Autonomic dysfunction is a frequent feature of PD for which there are not many available treatments at the moment. Botulinum Toxin or glycopirrolate might be used for sialorrhea whereas macrogol could be useful in constipation. On the other hand, there are many drugs under study for these indications. There is preliminary evidence suggesting that fludrocortisone, domperidone, droxidopa or fipamezole may be effective for the treatment of orthostatic hypotension. Tropicamide, clonidine or radiotherapy are under development for sialorrhea. Sildenafil may be effective for the treatment of erectile dysfunction; Botulinum toxin or behavioral therapy for urinary incontinence and lubiprostone or probiotics for constipation. Autonomic dysfunctions are frequent adverse drug reactions. Therefore, before any treatment is administered, patients' pharmacological treatment should be revisited. In many cases, non-pharmacological measures are available and should be administered in first place. When pharmacological treatments are administered, safety becomes an important concern, and physicians needs to bear in mind that many drugs for dysautonomic troubles may treat one symptom while worsening other at the same time (for ex. Muscarinic receptor antagonists may cause or aggravate constipation). Clinical trials employing valid outcome measures, targeting specific populations and of appropriate duration are needed to further evaluate efficacy and safety of drugs for autonomic dysfunction. Moreover, animal models are needed to boost our understanding on the physiopathology of these troubles and to test new drugs.

- **Expert opinion**

Although treatment of non-motor symptoms has been recognized as an unmet need [3], there is a paucity of clinical trials for drugs aiming to treat them. Apart from botulinum toxin and glycopirrolate for sialorrhea and macrogol for constipation, there are no recommended treatments based on good evidence for other autonomic disorders. Most of our practice is then manly based on empirical extrapolations from clinical use in other disorders than PD, with consequent uncertainty regarding safety and efficacy. Notwithstanding, there are many potential targets that could be translated into efficacious molecules for these disorders. Increasing sympathetic tone, vascular norepinephrine bioavailability or baroreflex sensitivity might all be effective for the treatment of orthostatic hypotension, including using drugs like Fipamezole or Droxidopa. Therapies for sialorrhea have been based in reducing saliva production by inhibition of acetylcholine secretion using muscarinic blockade. Muscarinic blockers should not cross the blood-brain barrier in order to avoid memory loss and hallucinations, which precludes the use of atropine. It remains to be assessed if selective targeting at different muscarinic receptor subtypes might reduce the risk of other parasympatholytic adverse effects. On the other hand, therapies aimed at increasing swallowing frequency are pathophysiological sounder and probably more effective.

Treatment of erectile dysfunction with sildenafil seems attractive in the light of available evidence in other groups of patients. Nonetheless, mood disorders cannot be neglected in PD and their treatment may contribute to ameliorating sexual function. Female sexual dysfunction has been less studied in PD, and thus, its evaluation may be taken as the next immediate step. Non ergot dopamine agonists may be also effective for this indication.

Detrusor overactivity appears to be a hallmark of incontinence in PD, as it is in other group of patients. Thus, efficacy of anticholinergic drugs can be anticipated. Indeed, botulinum toxin has shown some efficacy. Nonetheless, muscarinic antagonists, such as solifenacin, should be used with caution as PD patients are at high risk of experiencing limiting side effects of these drugs, including memory loss and hallucinations.

As delayed colonic transit is a common feature in PD, therapies aiming at accelerating it may be effective. Indeed, macrogol, an osmotic laxative and lubiprostone, an activator of chloride channels, have shown some efficacy. Other prokinetics, such as mosapride, should probably be used with caution, in the light of its potential cardiovascular safety problems, which led to tegaserod withdrawal from the market.

We would like to finish this review article by firmly encouraging the conduction of sound clinical trials for autonomic dysfunction in PD. Even if research may begin by less stringent proof-of-concept studies, high quality clinical trials are needed in order to allow firm evidence-based recommendations for practicing physicians.

- **Conflict of interests**

MVR and AP have no conflicts to declare. SPLL has consulted for UCB Pharma and Neurohealing Pharmaceuticals Inc. OR has act as an advisor for most drug companies developing antiparkinsonian medications.

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Table 1. Efficacy and safety in PD of drugs used for the treatment of autonomic dysfunction in other population of patients.

Drug	Action mechanism	Proved efficacy in PD	Potential safety issues
Orthostatic hypotension			
Non-pharmacological measures	Increase venous blood flow	No	None
Midodrine	Alpha1-receptor agonist	No	Supine hypertension
Fludrocortisone	Increase blood volume	No	Supine hypertension
Sialorrhea			
Botulinum toxin A or B	Inhibition of acetylcholine release	Yes	Dysphagia
Atropine, scopolamine, glycopirrolate, tropicamide, etc	Muscarinic antagonists	Yes (Glycopirrolate)	Memory loss and hallucinations (atropine, scopolamine)
Sildenafil	Phosphodiesterase-5 inhibitor	No	None
Urinary dysfunction			
Fesoterodine, tolterodine, solifenacin	Muscarinic antagonists	No	Memory loss, hallucinations
Botulinum Toxin	Inhibition of acetylcholine release	No	Post-void residue
Lactulose, macrogol, bisacodyl, sodium	Osmotic or secretive laxatives	Yes (macrogol)	Diarrhea

picosulfate			
Mosapride, prucalopride	5HT-4 receptors agonist	No	Diarrhea, cardiac arrhythmias
Lubiprostone	Activator of intestinal chloride receptors	No	Diarrhea
Linaclotide	Guanilate ciclase 2C agonist	No	Diarrhea

Table 2. Experimental treatments for autonomic dysfunctions in PD.

Drug or intervention	Study type	Efficacy results	Safety results
Orthostatic hypotension			
Fludrocortisone and domperidone	DB CO RCT	Reduced orthostatism symptoms	No major issues
Droxidopa	DB PC RCT	No significant effect on signs and symptoms. Reduced fall rate	Supine hypertension
Fipamezole	DB PC RCT	Fipamezole counteracted levodopa-induced BP fall. A confirmatory RCT in underway	No major issues
Partial weight supported treadmill gait training	PC OL RCT	increased baroreflex sensitivity	No major issues
Entacapone	UC OL CS	Orthostatic hypotension was less frequent in patients exposed to entacapone	Not explored
Sialorrhea			
Tropicamide	DB PC RCT	Tropicamide 1 mg reduced buccal saliva levels. A confirmatory RCT in underway	No major issues
Clonidine	DB PC RCT	Patients on clonidine had to dry their mouth less frequently	Somnolence, dizziness
Radiotherapy	OL UC study	Sialorrhea improved after radiotherapy	Loss of taste, dry mouth
Sexual dysfunction			
Sildenafil	DB PC RCT	Improved erectile function	No major issues
Urinary dysfunction			
Botulinum toxin A	OL UC study	Increased bladder capacity and reduced incontinence episodes	Post-void residue
Behavioral therapy	OL UC study	reduced incontinence episodes	No major issues
Solifenacin succinate	DB PC RCT	Results are not available	Results are not available

Constipation			
Mosapride	OL UC study	Non-significant improvements in colonic transit	No major issues
Neurotrophin 3	DB RCT	Non-significant increments in stool frequency	Diarrhea, abdominal cramps
Lubiprostone	DB PC RCT	Increased number of bowel movements per day	Diarrhea
Probiotics	OL UC study	Less frequent bloating, abdominal pain, tenesmus	No major issues
Biofeedback therapy	OL UC study	Results are not available	Results are not available

DB=double blind, CO=crossover, PC=placebo-controlled, RCT= Randomized clinical trial, BP=Blood pressure, OL=open-label, CS=Cross sectional study; UC=uncontrolled

Drugs with documented lack of efficacy or with significant safety issues are not included in this table but reviewed in the text.

Table 3. Empirical recommendations for clinical trials in autonomic dysfunction in PD.

Indication	Study population	Primary outcome measures	Study duration	Safety assessments
Orthostatic hypotension (OH)	PD patients fulfilling international OH criteria	orthostatic blood pressure fall extent	≥ 12 weeks	Supine hypertension
Sialorrhea	PD patients with UPDRS item 6 ≥ 2 or 3	DSFS, mTDS.	≥ 12 weeks	Dry mouth, Dysphagia
Sexual dysfunction	Exclude non-PD erectile dysfunction and mood disorders	International Index of Erectile Function	≥ 12 weeks	No specific recommendation
Urinary dysfunction	Exclude non-PD causes of incontinence	Frequency of incontinence episodes	≥ 12 weeks	Post-void residue
Constipation	PD patients fulfilling ROME III criteria	Frequency of bowel movements	≥ 12 weeks	Diarrhea

DSFS: Drooling Severity and Frequency Scale, mTDS: modified Teacher's Drooling Scale

Responses to reviewers:

Referee 1.

1. Amantadine and postural hypotension: Perez-Loret and colleagues looked at amantadine with/without other drugs & postural hypotension retrospectively, but not amantadine alone. I think it is too early to say amantadine is a risk for postural hypotension.

We agree with the reviewer, the sentence was changed to: "In a recent cross-sectional study it has been shown that exposure to diuretics, amantadine and polypharmacy (i.e. intake of more than 5 drugs) was more frequent in PD patients with orthostatic hypotension [22]" (page 7 paragraph 1).

2. Mechanism of postural hypotension in PD: You mentioned that deposition of Lewy bodies in Locus Coeruleus and loss of sympathetic pre-ganglionic cells have been implicated. However, recently, low resting norepinephrine level and sympathetic nerve ending image by MIBG myocardial scintigraphy implicates sympathetic nerve ending to be a pathological substrate.

This is already discussed in the text: "Indeed, sympathetic denervation of the heart appears to be also an important factor [45]" (page 14 pagraph 1).

3. Mechanism of bladder dysfunction in PD: you should mention that basal ganglia circuit, particularly the D1 direct pathway, has inhibitory effect on the micturition reflex in experimental animals and possibly in human. Disruption of this circuit

seems to lead to detrusor overactivity.

We thank the reviewer for his/her suggestion. A sentence was added: "The storage function is thought to be further facilitated by the hypothalamus, cerebellum, basal ganglia (particularly through the direct pathway), frontal cortex and by central cholinergic fibers from Meynert nucleus [60]" (page 17 paragraph 1).

4. Mechanism of constipation in PD: The strength of cholinergic transmission in the enteric nervous system is thought to be regulated by opposing receptors; serotonin 5-HT4-mediating excitation and dopamine D2 /VIP-mediating inhibition; pathologically reduced dopamine /VIP neurons are only reported in PD. Constipation in PD consists of slow transit constipation and anorectal constipation; the former presumably peripheral, the latter both peripheral and central. See recent reviews (Sakakibara et al. Parkinson's Disease 2011, Article ID 924605, 21 pages, doi:10.4061/2011/924605).

We thank the reviewer for his/her observations. The text was updated accordingly: "Reduced dopaminergic tone may lead to altered peristaltic reflex [61], thus causing delayed colonic transit and anorectal dysfunction [62]" (Page 17 paragraph 3).