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EDITORIAL

# Investigational drugs for autonomic dysfunction in Parkinson's disease



## 1. Drugs for autonomic dysfunction in Parkinson's disease

Autonomic disturbances are common symptoms of Parkinson's disease (PD),[1,2] with orthostatic hypotension affecting 20%–65% of patients,[3,4] sialorrhea about 75%,[5,6] sexual dysfunction 60% of men, urinary dysfunction up to 40%, and gastrointestinal motility disorders causing constipation up to 80%.[2] These symptoms can impair patients' 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]

There are multiple factors contributing to autonomic dysfunction in PD. Deposition of Lewy bodies in the locus coeruleus, neuronal loss at the intermediolateral nucleus of the spinal cord, the ventrolateral medulla, and at the sympathetic ganglia have been implicated in the genesis of orthostatic hypotension.[7–9] Furthermore, exposure to dopamine agonists, alpha-adrenergic blockers used for prostatic hyperplasia, antihypertensives, and some antidepressants can also produce or aggravate orthostatic hypotension.[10] Reduced saliva deglutition appears to be main cause of sialorrhea.[6] Reduced bladder capacity, detrusor overactivity, and uninhibited external sphincter relaxation resulting from parasympathetic dysfunction are the hallmarks of urinary incontinence in PD.[11] Sexual dysfunction is mainly related to vascular autonomic malfunction, but some antidepressants may worsen it.[12] Finally, constipation might be related to the degeneration of autonomic innervation coming either from central autonomic nuclei or from the enteric nervous system within the colon itself.[13,14] Other secondary factors associated with constipation in PD might be poor bowel habits, reduced water intake, immobility, and drugs like antacids with aluminum, opioids, calcium channel blockers, anticholinergics, tricyclic antidepressants, antipsychotics, or amantadine.[15]

Management and treatment of autonomic dysfunction is a major unmet need in PD,[16] with poorly documented efficacy and safety for the majority of drugs currently used for this indication (Table 1).[17] A number of studies of variable quality have explored the efficacy and safety of experimental interventions for autonomic dysfunction in PD,[17–19] as summarized in Table 2. Brief discussions for the most important studies will be provided in the next paragraphs.

Droxidopa showed positive results in two recent double-blind, randomized, placebo-controlled trials including patients with neurogenic orthostatic hypotension due to PD, multiple system atrophy, pure autonomic failure, or nondiabetic autonomic neuropathy.[19] In another double-blind, randomized, placebo-controlled trial involving 171 PD patients, droxidopa significantly improved dizziness (item no. 1 of the Orthostatic Hypotension Questionnaire) and significantly increased the pressor response to orthostatism, at day 7.[20] The FDA recently granted Northera® (droxidopa capsules) marketing authorization based on these short-term efficacy results, but additional long-term efficacy studies were requested.

A double-blind, randomized, controlled trial with midodrine for orthostatic hypotension is going on (NCT02365012), but follow-up will probably be insufficient to allow firm conclusions on the long-term efficacy of the drug. Fludrocortisone, fipamezole and yohimbine showed significant results in low-quality studies. There appears to be no further studies on their way for these drugs. Partial weight–supported treadmill gait training increased baroreflex sensitivity in an open-label, controlled trial, but it is uncertain if this may translate into reductions in blood pressure fall after orthostatism. A cross-sectional study found that orthostatism was less frequent with entacapone, but randomized clinical trials are needed to confirm these findings. A small double-blind randomized trial with pyridostigmine is also under way (NCT01993680).

Reductions in buccal saliva levels were observed with tropicamide and clonidine in small and/or low-quality studies. A double-blind, crossover trial with tropicamide is under way and results are expected soon (NCT01844648). Improvements in sialorrhea were also seen with radiotherapy in an uncontrolled study, but results have not been replicated and the risk/benefit ratio of this irreversible intervention is not clear.

Low-quality studies showed promising results for botulinum toxin A, behavioral therapy, and transcutaneous

**Table 1.** Drugs currently used for autonomic dysfunction in PD.

| Drug | Available evidence in PD | Practice implications[a] | Approved for the indication by any Regulatory Agency? |
|---|---|---|---|
| ***Orthostatic hypotension*** | | | |
| Midodrine | No | Investigational | Yes |
| Fludrocortisone | 1 low-quality RCT | Investigational | No |
| Droxidopa | 2 RCT | Not yet assessed | Yes |
| ***Sialorrhea*** | | | |
| Botulinum toxin A or B | 3 RCT | Clinically Useful | No |
| ***Urinary dysfunction*** | | | |
| Tolterodine, Oxybutinin | No | Investigational | Yes |
| ***Sexual dysfunction*** | | | |
| Sildenafil | 1 low-quality RCT | Investigational | Yes |
| ***Constipation*** | | | |
| Macrogol | 1 RCT | Possibly useful | Yes |
| Lubiprostone | 1 RCT | Investigational | Yes |

RCT: randomized controlled trial.
[a]According to the most recent Movement Disorders Society Evidence-Based Medicine Review [17] and its annual updates.

**Table 2.** Experimental treatments for autonomic dysfunction in PD.

| Drug or intervention | Mechanism of action | Quality of evidence | Efficacy results | Safety results |
|---|---|---|---|---|
| ***Orthostatic hypotension*** | | | | |
| Droxidopa | Norepinephrine prodrug | I | Reduced frequency of dizziness and improved pressor response to orthostatism (short term) | Headache, supine hypertension |
| Midodrine | Alpha1-adrenoreceptor agonist | II | Reduced orthostatic blood pressure drop | Hypertension |
| Fludrocortisone | Mineralocorticoid | II | Reduced orthostasis symptoms | No major issues |
| Pyridostigmine | Cholinesterase enzyme inhibitor | II | No results available | No results available |
| Fipamezole | Alpha2-adrenoreceptor antagonist | II | Reduced levodopa-induced BP fall | No major issues |
| Partial weight supported treadmill gait training | Physical therapy | II | Increased baroreflex sensitivity | No major issues |
| Entacapone | Inhibitor of the COMT enzyme | III | Orthostatic hypotension was less frequent in patients exposed to entacapone | Not explored |
| Yohimbine | Alpha2-adrenoreceptor antagonist | II | Improved standing diastolic blood pressure | No data available |
| ***Sialorrhea*** | | | | |
| Tropicamide | Muscarinic antagonist | II | Tropicamide 1 mg reduced buccal saliva levels. A confirmatory RCT in underway | No major issues |
| Clonidine | Alpha2-adrenoreceptor agonist | II | Patients on clonidine had to dry their mouth less frequently | Somnolence, dizziness |
| Radiotherapy | Salivary gland ablation | III | Sialorrhea improved after radiotherapy | Loss of taste, dry mouth |
| ***Urinary dysfunction*** | | | | |
| Botulinum toxin A | Cholinergic blocker | III | Increased bladder capacity and reduced incontinence episodes | Post-void residue |
| Behavioral therapy | Behavioral modification | III | Reduced incontinence episodes | No major issues |
| Solifenacin | Muscarinic antagonist | I | No significant reductions in micturition episodes per 24-hour period | No major issues |
| Fesoterodine | Muscarinic antagonist | I | No results available | No results available |
| Transcutaneous tibial nerve stimulation | Stimulation of the sacral nerve plexus | II | Significant reductions in the number of urgency and nocturia episodes | No major issues |
| ***Sexual dysfunction*** | | | | |
| Sildenafil | PDE-5 enzyme inhibitor | II | Improved erectile function | No major issues |
| ***Constipation*** | | | | |
| Mosapride | 5-HT4 agonist | III | Nonsignificant improvements in colonic transit | No major issues |
| Neurotrophin 3 | Neurotrophic factor | II | Nonsignificant increments in stool frequency | Diarrhea, abdominal cramps |
| Probiotics | Restoration of colonic flora | III | Less frequent bloating, abdominal pain, tenesmus | No major issues |
| Biofeedback therapy | Behavioral modification | III | No results available | No results available |
| Relamorelin | Ghrelin peptide agonist | I | No results available | No results available |

I = double blind, randomized, prospective, controlled studies with more than 20 patients and lasting for more than 12 weeks; II = nonrandomized and/or open-label, prospective, controlled studies or level I studies with insufficient sample size, mixed populations, or short follow-up; III = noncontrolled, retrospective, or cross-sectional studies.

tibial nerve stimulation in the treatment of urinary dysfunction, which have not been replicated. Behavioral therapy may be an interesting option since it is related to virtually no side effects. Results from a small randomized controlled study with solifenacin showed negative results. A randomized study with fesoterodine, which efficacy is

documented in the general population, is going on and results are awaited (NCT02385500).

Results of a low-quality study showed significant results with sildenafil for erectile dysfunction, but results have not been replicated. There are no other studies under way for this indication.

Mosapride and neurotrophin 3 induced nonsignificant improvements in constipation in low-quality pilot trials. Conversely, improvements with probiotics were significant, but the uncontrolled nature of the study precludes obtaining firm conclusions. A well-designed, randomized, controlled study with relamorelin is under way (NCT01955616).

## 2. Conclusion

There is a paucity of well-designed clinical trials assessing the efficacy and safety of treatments for autonomic dysfunction in PD. Furthermore, only few of the most recent trials provided high-quality evidence to support the use of new experimental therapies.

## 3. Expert opinion

Well-designed, double-blind, randomized, controlled studies are the hallmark of evidence-based medicine.[21] Without such trials, management decisions are based on personal experience, opinions from experts, or potentially biased studies, thus frequently resulting in suboptimal health care. It is therefore essential that high-quality evidence is produced to support the efficacy and safety of interventions for autonomic dysfunction in PD.

High-quality evidence about drug efficacy can only come from randomized, double-blind, controlled trials, [21] as it minimizes the risk of selection and observation bias.[22] Ideally, trials for autonomic dysfunction in PD should last for at least 12 weeks and include at least 20 subjects.[17] Primary outcomes should be measures of autonomic dysfunction specifically validated for use in PD. For example, studies about orthostatic hypotension might use the extent of orthostatic blood pressure fall or questionnaires assessing orthostatism symptoms, such as the SCOPA-AUT or COMPASS scales, as primary outcome measures.[18] The Drooling Severity and Frequency Scale, the Drooling Rating Scale, or the Sialorrhea Clinical Scale for PD have been suggested for sialorrhea evaluation in PD, but only the latter has been validated. Urinary dysfunction may be assessed by Likert scales exploring patients' feelings or treatment benefices, but there are no validation studies in PD. The International Index of Erectile Function or the Sexual Health Inventory Scale-M version can be used for the evaluation of sexual function. Constipation can be evaluated by patient-reported assessments of the frequency of bowel movements. It should be mentioned that outcomes measurement tools have not been validated for use in PD in urinary, sexual dysfunctions, or constipation.

Study populations should be appropriately defined. Studies on orthostatic hypotension should use the internationally validated diagnostic criteria (i.e. the 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). It has been suggested that patients with mean standing blood pressure < 75 mmHg may be the most beneficiated ones by pharmacological treatment for orthostatic hypotension,[23] and thus are probably very good candidates for clinical trials. Patients with sialorrhea can be identified by the Unified PD Rating Scale Part II (Activities of daily living). PD patients to be included in studies on sexual dysfunction should not be affected by mood disorders. Patients participating in constipation studies should fulfill ROME III criteria. In all cases, secondary causes of autonomic dysfunction, including drug treatments, should be ruled out before inclusion in trials.

Safety issues should also be assessed in clinical trials. Besides general assessments, some events need to be specifically monitored.[18] This is the case of supine hypertension with pressor drugs for orthostatic hypotension. Dry mouth and dysphagia are frequently observed with interventions for sialorrhea and thus also need special attention. Hypotension is a common adverse event of those drugs for erectile dysfunction acting on genital blood vessels and thus should be specifically monitored if the drug in study acts via a similar mechanism. Finally, post-void residue and diarrhea are common adverse reactions to drugs for urinary dysfunction and constipation, respectively.

In summary, management of autonomic dysfunction is a major unmet need in PD and there is a paucity of well-designed clinical trials to support the efficacy and safety of many of the most commonly used agents. Furthermore, only few of the most recent trials provided level I evidence to support the efficacy of experimental therapies. In this context, practitioners can seldom take evidence-based treatment decisions, frequently exposing patients to suboptimal care. Therefore, investments from the medical research community and the drug/device-selling companies are needed to overcome this gap in the evidence. The fact that high-quality clinical trials with some drugs are under way or have been recently finished is encouraging and will mark the path for future trials with other interventions. The importance of having high-quality evidence cannot be overemphasized and hopefully, in the near future, practitioners will be able to rely on solid

evidence coming from well-designed trials for managing autonomic dysfunction in PD patients.

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