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Treatment of autonomic dysfunction in Parkinson disease and other synucleinopathies

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Abstract

Dysfunction of the autonomic nervous system afflicts most patients with Parkinson disease and other synucleinopathies such as dementia with Lewy bodies, multiple system atrophy and pure autonomic failure, reducing quality of life and increasing mortality. For example, gastrointestinal dysfunction can lead to impaired drug pharmacodynamics causing a worsening in motor symptoms, and neurogenic orthostatic hypotension can cause syncope, falls, and fractures. When recognized, autonomic problems can be treated, sometimes successfully. Discontinuation of potentially causative/aggravating drugs, patient education, and non-pharmacological approaches are useful and should be tried first. Pathophysiology-based pharmacological treatments that have shown efficacy in controlled trials of patients with synucleinopathies have been approved in many countries and are key to an effective management. Here we review the treatment of autonomic dysfunction in patients with Parkinson disease and other synucleinopathies, summarize the non-pharmacological and current pharmacological therapeutic strategies including recently approved drugs, and provide practical advice and management algorithms for clinicians, with focus on neurogenic orthostatic hypotension, supine hypertension, dysphagia, sialorrhea, gastroparesis, constipation, neurogenic overactive bladder, underactive bladder, and sexual dysfunction.

Keywords

Parkinson disease; multiple system atrophy; non-motor symptoms; dysautonomia; autonomic failure; treatment

Introduction

Dysfunction of the autonomic nervous system is a characteristic feature of patients with synucleinopathies, a group of neurodegenerative diseases caused by the abnormal accumulation of misfolded phosphorylated α -synuclein (α Syn) in neurons, glia or both. Converging evidence indicates that abnormal α Syn spreads from cell to cell in a prion-like

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fashion¹⁻³ and that different types of α Syn assemblies with different structural characteristics called strains^{4, 5} may account for the different clinical phenotypes as they determine the nerve cell type and the regions of the nervous system that are affected.⁴

In patients with Parkinson disease (PD), dementia with Lewy bodies (DLB) and pure autonomic failure (PAF) aggregates of misfolded α Syn accumulate in the neuronal soma and throughout axons, called Lewy bodies (LB) and Lewy neurites, and peripheral autonomic neurons are always affected. In these patients, neurodegeneration usually progresses slowly with only a minor impact on survival.⁶ In patients with multiple system atrophy (MSA), a rare and devastating disease, α Syn accumulates primarily in oligodendroglia although neurons are also affected.^{7, 8} Autonomic dysfunction is very severe but, in contrast to PD, DLB and PAF (known as LB disorders), peripheral autonomic neurons are typically spared in MSA. The disease progresses much more rapidly than PD, with an average survival of ~9 years from symptom onset.^{9, 10} Autonomic dysfunction in synucleinopathies occurs at all stages of the disease and occasionally is its only manifestation.¹¹

Symptoms of autonomic dysfunction are among the most debilitating, and reduce quality of life in affected patients. When recognized, autonomic problems can be treated, sometimes successfully. Discontinuation of potentially causative/aggravating drugs, patient education, non-pharmacological approaches, and pathophysiology-based drug therapy are key to an effective management. Here we review the treatment of autonomic dysfunction in patients with PD and other synucleinopathies, summarize the non-pharmacological and pharmacological therapeutic strategies and provide practical advice and management algorithms.

Challenges in Clinical Trials of Autonomic Dysfunction in PD

Clinical trials for the treatment of symptoms of autonomic dysfunction are challenging. Despite the high prevalence of autonomic dysfunction in patients with PD only a few therapeutic options are backed by large, randomized, placebo-controlled trials.¹² In spite of its high prevalence, autonomic dysfunction is frequently under-diagnosed in patients with PD and other synucleinopathies. The natural history of autonomic dysfunction in PD and related disorders is still poorly understood [e.g., do orthostatic hypotension (OH) or constipation worsen, or remain stable over time?]. The lack of precise data on the occurrence and variability of autonomic abnormalities in these patients hampers the ability to detect clinically meaningful outcomes and contribute to difficulties when powering a clinical trial.

For instance, in the case of clinical trials of midodrine and droxidopa for neurogenic OH (nOH), assembling a large cohort of patients required the involvement of multiple recruiting sites.¹³⁻¹⁵ To enhance recruitment, the trial population was heterogeneous, including not only patients with PD but also DLB, MSA, PAF and, occasionally, other rare disorders causing nOH such as dopamine-beta hydroxylase deficiency. Although all these patients had nOH, the pathophysiology differs among them.¹⁶ An additional difficulty is the “background noise” caused by day-to-day fluctuations in symptom severity and blood pressure (BP) readings in patients with autonomic failure. This could be at least partially overcome with the use of ambulatory 24-hour blood pressure monitoring.^{17, 18} Clinical trials for nOH were

designed for relatively short period of times (typically < 4 weeks), and, therefore, significant clinical milestones, such as hospital admissions or mortality, were not used as endpoints. Patient-reported outcomes have limitations in subjects with nOH; reliance on symptoms alone may not always be an accurate indicator as symptoms of nOH can be non-specific, including fatigue and difficulty concentrating, and may occasionally mimic the levodopa “off” state in PD patients. Also, patients with PD can have difficulty distinguishing nOH-related lightheadedness from other causes of lightheadedness.¹⁹ Furthermore, the severity of nOH in PD and other synucleinopathies can be associated with disease progression; failure to demonstrate long-term improvement could conceivably be due to worsening of neurodegeneration rather than failure of the active agent.

Despite these challenges, there have been several accomplishments in the last years, including the initiation and completion of large clinical trials, and the approval of new medications.

Cardiovascular Autonomic Dysfunction

Cardiovascular autonomic dysfunction occurs in virtually all patients with synucleinopathies but only a minority of them is symptomatic.^{20, 21} Symptoms of cardiovascular autonomic dysfunction are due to tissue hypoperfusion as a result of OH, defined as a sustained fall in BP of 20 mmHg systolic or 10 mmHg diastolic when moving from supine to standing. OH is a clinical sign, and it can be symptomatic or asymptomatic. Lightheadedness, blurry vision, and feeling faint are easily recognized as caused by OH; other less specific symptoms include tiredness, cognitive impairment, dyspnea, neck and shoulder discomfort (“coat hanger pain”), or angina. Together with neurogenic OH (nOH), many patients with synucleinopathies have neurogenic hypertension in the supine position (nSH). nOH results in acute morbidity like syncope and falls whereas nSH causes end-target organ damage over time. Management of symptomatic nOH and nSH can be challenging as treating one usually aggravates the other.

Pathophysiology

Normally, unloading of the baroreceptors by standing up triggers norepinephrine release from sympathetic post-ganglionic nerves causing vasoconstriction, which maintains BP in the standing position. This compensatory vasoconstriction is absent or attenuated in patients with synucleinopathies resulting in nOH. The site of the “autonomic lesion” in the baroreflex pathways responsible for cardiovascular autonomic dysfunction is different in patients with LB disorders versus patients with MSA. In patients with LB disorders, cardiovascular dysautonomia is predominantly due to degeneration of post-ganglionic sympathetic neurons. There is robust imaging and neuropathological data showing that post-ganglionic peripheral sympathetic neurons innervating the myocardium are functionally affected due to α Syn deposits and fiber loss.^{20, 21} Sympathetic fibers innervating blood vessels are also affected. This results in impaired norepinephrine release and defective vasoconstriction upon standing causing the BP to fall (i.e., nOH).^{16, 20} Plasma norepinephrine, a marker of sympathetic neuronal integrity, is lower in patients with PD and nOH than in those without nOH.²²

In patients with MSA, cardiovascular autonomic dysfunction is caused by degeneration of CNS neurons involved in baroreflex control, while only a minority (< 30%) of patients has degeneration of post-ganglionic sympathetic nerves.²³⁻²⁷ Norepinephrine release from peripheral sympathetic terminals is also blunted but the nerves themselves are mostly spared.²¹ Plasma norepinephrine levels are mostly normal in patients with MSA²⁸ reflecting intact sympathetic neurons. These differences between LB disorders and MSA are relevant to determine the response to pharmacological treatment.

Epidemiology

In cross-sectional studies, between 30-50% of patients with PD have OH but less than a third of those patients are symptomatic, i.e., only 16% of patients with PD have symptomatic OH.^{16, 29-31} The prevalence of OH in PD increases with age and disease duration.²⁹ In DLB the prevalence of OH is higher, 50-60%.^{31, 32} In patients with MSA, the diagnostic criteria for nOH are a fall of 30 mmHg in systolic or 15 mmHg in diastolic BP.³³ Even according to these more stringent criteria, 70-80% of patients with MSA have nOH.^{9, 34}

Treatment of neurogenic orthostatic hypotension (nOH)

The goal of nOH treatment in patients with synucleinopathies is not to normalize standing BP, but to reduce symptom burden, improve quality of life, and reduce morbidity and mortality associated with nOH.³⁵ Consensus guidelines for the treatment of nOH are available.^{36, 37} The steps of nOH management include: a) correcting aggravating factors, b) implementing non-pharmacological measures and c) drug therapies. When OH is asymptomatic, treatment may not be required or may be limited to non-pharmacological measures. When nOH is symptomatic (i.e., causing symptoms of organ hypoperfusion such as dizziness, lightheadedness, blurry vision or feeling about to faint) pharmacological treatment is usually required (Figure 1).

Correction of aggravating factors—Drugs that reduce intravascular volume (diuretics), induce vasodilatation (sildenafil, nitrates), or block norepinephrine release/activity at the neurovascular junction (α -blockers, centrally acting α_2 -agonists, tricyclic antidepressants) worsen nOH and symptoms. Levodopa and dopamine agonists may also lower BP and a dose adjustment may be considered based on an individual risk-benefit assessment.³⁸⁻⁴¹ Anemia should be investigated and treated.⁴² Erythropoietin (25-50 units/kg, subcutaneous, 3 times a week) in conjunction with iron supplements may be beneficial in patients with nOH and anemia.⁴³

Non-pharmacological treatment and patient education—Patients should be aware of the diuretic effects of caffeine and alcohol and avoid sugary beverages (e.g., bottled juices, sodas) due to the hypotensive effects of high-glycemic index carbohydrates.⁴⁴ Fluid intake should be 2-2.5 L per day. Patients should be encouraged to increase salt intake by adding 1-2 teaspoon of salt to a healthy diet. Other patients prefer using 0.5-1.0 g salt tablets although they can cause abdominal discomfort. In patients with nOH, drinking 0.5 L of water produces a marked increase in BP.⁴⁵ This can be used as a rescue measure since the pressor effect is quick (peaks in around 30-min) although short-lived.

Symptomatic nOH can quickly lead to a reluctance to stand up and avoidance of physical activity. In turn, physical immobility worsens OH, leading to a “vicious cycle” of deconditioning.⁴⁶ Physical exercise is therefore a key component of the therapeutic regimen but because physical activity in the standing position can worsen hypotension in patients with autonomic failure,⁴⁷⁻⁵⁰ exercise should be performed in the recumbent or sitting position using a recumbent stationary bicycle or rowing machine. The exception is exercise in a pool as the hydrostatic pressure of water allows upright exercise without hypotension.⁵¹ Patients should be taught specific physical countermaneuvers.⁵² Eating results in blood pooling within the splanchnic circulation and patients can become severely hypotensive within 2-h of eating (i.e., postprandial hypotension), particularly after carbohydrate-rich meals.⁵³⁻⁵⁶ Eating smaller, more frequent meals, and reducing carbohydrates can improve postprandial hypotension. Alcohol is also a vasodilator and should be reserved for the evening, prior to going to bed.

Patients should be instructed to change positions gradually, and briefly sit before standing. Straining and Valsalva-like maneuvers during bowel movements are a common cause of syncope.⁵⁷ If this is the case, constipation must be treated aggressively.⁵⁸ High-waist compression stockings producing at least 15-20 mmHg of pressure can increase BP by augmenting venous return.⁵⁹ Patients with movement disorders struggle to put the stockings on, which limits their usefulness in everyday life. Elastic abdominal binders are a good alternative.^{60, 61} A recently developed abdominal binder that inflates automatically only on standing had promising results in patients with nOH.⁶²

Pharmacological management—Even when non-pharmacological methods are performed properly, many patients still require pharmacological treatment to improve symptomatic nOH (Table 1). Figure 2 shows the sites of action and mechanism of therapeutic agents currently employed in the treatment of nOH. Two complementary strategies are commonly used: a) Expanding intravascular volume with fludrocortisone, and b) Increasing peripheral vascular resistance with midodrine, droxidopa or norepinephrine transporter (NET) inhibitors. Selection of one or the others or both depends on the specific features and needs of each patient as well as the degree of peripheral sympathetic denervation.

That peripheral sympathetic neurons are affected in LB disorders but spared in MSA is an important difference when planning therapeutic strategies for nOH. In healthy subjects, NET inhibitors have little effect on BP. This is because the peripheral effects of NET inhibitors on the sympathetic neurovascular junction enhancing noradrenergic vasoconstriction are counteracted by the increase in CNS norepinephrine stimulating central α_2 -receptors thus reducing central sympathetic outflow. In patients with MSA, however, only the peripheral vasoconstriction is apparent. Preliminary studies show that atomoxetine, a short acting NET inhibitor, increases BP in patients with nOH according to their supine plasma norepinephrine levels. The higher the norepinephrine levels the greater the pressor effect and symptomatic improvement after atomoxetine.⁶³ Conversely, lower supine plasma norepinephrine levels appear to predict a greater symptomatic and pressor response to droxidopa, an oral norepinephrine synthetic precursor.⁶⁴ These responses can be explained by denervation supersensitivity of adrenergic receptors.⁶⁵ Thus, patients with low plasma

norepinephrine levels (usually LB disorders) may benefit more from droxidopa and midodrine, whereas patients with normal or high plasma norepinephrine levels (usually MSA) may potentially benefit more from NET inhibitors (Figure 1). In patients with refractory nOH, NET inhibition could be theoretically combined with droxidopa or midodrine, with or without fludrocortisone or pyridostigmine. However, no safety data is available on the combined use of any of these agents and its use may result in severe hypertension and cardiac arrhythmias.

Fludrocortisone: Fludrocortisone (9 α -fluorocortisol) is a synthetic mineralocorticoid that increases BP by at least two mechanisms: It increases renal sodium and water re-absorption, thus expanding intravascular volume, and also enhances the pressor responsiveness to endogenous catecholamine and pressor drugs.⁶⁶ Fludrocortisone exacerbates SH and end organ target damage (left ventricular hypertrophy and renal failure) and may increase the risk of all-cause hospitalization.⁶⁷ Additional, frequent adverse events include hypokalemia and ankle edema.^{66, 68} To reduce the risk of hypokalemia, patients taking fludrocortisone should be instructed to eat potassium-rich foods or potassium chloride supplements 10-20 mEq/day. Fludrocortisone dosage should not exceed 0.2 mg/day. Higher dosages are rarely more effective but intensify adverse events. Appreciable clinical improvements usually require ~7 days of treatment. Fludrocortisone is available in most countries, although it is not specifically approved for the treatment of nOH in any.

Pressor agents

Midodrine: Midodrine is an oral α_1 -adrenoceptor agonist that induces vasoconstriction and increases BP.^{15, 69-71} Midodrine is approved for the treatment of symptomatic OH in the U.S., Europe and Asia. Midodrine raises BP in the standing, sitting, and supine positions and its pressor effect is noticeable ~30-45 minutes after consumption, reaching a maximum after ~1 hour, and persists for a total of 2-3 hours. Treatment should begin with a 2.5 or 5 mg dose, which can then be increased up to 10 mg to be taken up to 3 times a day. nSH is common, hence patients should not take midodrine less than 3-4 hours before bedtime. Other adverse events owing to activation of α_1 -adrenergic receptors are piloerection ("goosebumps"), itching of the scalp, and urinary retention. Midodrine has no effect on heart rate as it does not activate β -adrenoreceptors and, given its poor diffusion across the blood-brain barrier, has no CNS adverse effects.⁷²

Droxidopa: Droxidopa (L-threo-3,4-dihydroxyphenyl-serine, L-DOPS) is an oral synthetic amino acid that is converted to norepinephrine in the body.¹³ Droxidopa is decarboxylated to norepinephrine by the enzyme aromatic amino-acid decarboxylase (AAAD) the same enzyme the converts L-dopa to dopamine. Droxidopa was approved in Japan in 1989 for the treatment of nOH in PD, MSA, and familial amyloid polyneuropathy. In the U.S., the Food and Drug Administration (FDA) approved droxidopa in 2014 for the treatment of symptomatic nOH associated with PAF, PD, and MSA.^{14, 73-76} Droxidopa is not approved in Europe. Extensive clinical experience shows that droxidopa is safe and well tolerated.⁷⁷⁻⁸⁵ Peak plasma concentrations of droxidopa are reached ~3-h after oral administration. The dosage used in clinical trials was 100-600 mg three times/day although clinical experience indicates that the dosage should be tailored to each patient's needs considering the periods of

time when he/she is going to be active or inactive.^{13, 78, 83} Because the pressor effect of droxidopa varies among patients, a titration procedure supervised by a clinician is highly recommended.¹⁶ Ambulatory 24-hour BP monitoring (ABPM) is useful to evaluate the BP profile before and after initiating treatment with droxidopa.¹⁷

Inhibition of the AAAD with high doses of carbidopa can abolish the pressor effect of droxidopa by preventing its peripheral conversion to norepinephrine. This was shown in studies using a single 200 mg dose of carbidopa administered 30-min before droxidopa.⁸⁶ In clinical practice the dose of carbidopa in patients treated with L-dopa is lower than 200 mg, thus carbidopa appears not to block the pressor effect of droxidopa significantly.⁷⁷ Further studies are warranted to determine whether droxidopa has beneficial effects on other motor and non-motor symptoms that result from norepinephrine deficiency in patients with PD.⁸⁷

Norepinephrine transporter blockers: Atomoxetine and similar medications increase norepinephrine concentration in the sympathetic neurovascular junction by selectively blocking the norepinephrine transporter (NET). Atomoxetine (Strattera®) is currently approved in the U.S., Europe and Asia for the treatment of attention deficit and hyperactivity disorder (ADHD) in children, adolescents and adults. The rationale for using atomoxetine as an off-label medication for symptomatic nOH originates from three randomized, placebo-controlled short-term trials,⁸⁸⁻⁹⁰ all of which showed that atomoxetine significantly increased standing BP and reduced the burden of symptoms compared to placebo. Atomoxetine is a very safe medication; the most common adverse events are decreased appetite, dry mouth, insomnia and nausea.⁹¹ Severe hepatitis has been anecdotally reported.⁹² An oligo-center double blind placebo-controlled crossover clinical trial to confirm the efficacy of atomoxetine for nOH is currently underway (NCT02796209). Because atomoxetine has a relatively short biological effect (~4-5 hours), longer active NET blockers may be required. In this regard, an investigational long-acting NET blocker and serotonin reuptake inhibitor (TD-9855), previously studied in patients with fibromyalgia, is being currently assessed in a phase 2, multicenter single blind placebo-controlled trial with an open label extension phase (NCT02705755).

Pyridostigmine: Pyridostigmine, a cholinesterase inhibitor, potentiates cholinergic neurotransmission in sympathetic and parasympathetic autonomic ganglia. Pyridostigmine is widely available in most countries. A double-blind study showed that pyridostigmine increases, on average, 4 mmHg in standing systolic BP.⁹³ The combination of 5 mg midodrine with 60 mg pyridostigmine was more effective than pyridostigmine alone. Pyridostigmine appears to be less effective than midodrine to improve nOH-related symptoms.⁹⁴

Neurogenic supine hypertension

nSH occurs in up to 50% of patients with PD and with MSA.^{29, 95-97} In patients with MSA, residual sympathetic neurovascular tone may contribute to SH. In contrast, SH in patients with LB disorders has a mechanism other than increased sympathetic outflows, yet to be fully identified.^{98, 99} Patients with nOH who also have nSH are less likely to develop symptomatic nOH after 3-min standing²⁹ as their BP in the standing position is above the

lower level of cerebral autoregulatory capacity. Cerebral vasomotor reactivity is preserved in patients with PD, which may contribute to lack of symptoms of cerebral hypoperfusion during hypotension.^{100, 101}

The goal of treatment of nSH in patients with synucleinopathies is to minimize the risk of end-target organ damage without worsening hypotension, thus reducing morbidity and mortality. Achieving this goal is challenging. During daytime, avoiding the supine position is the best treatment. If needing to rest, patients should sit in a reclining chair with the feet on the floor. At night, tilting the bed to achieve a 30- or a 45-degree angle (so that the patient sleeps with his/her head and torso above his/her legs) lowers BP.¹⁰² This is best accomplished with an electric bed or mattress, rather than just using extra pillows or a wedge. In addition, lowering BP during the night reduces the exaggerated nocturia and natriuresis of these patients, therefore reducing the overnight volume depletion, and improving OH in the morning. The use of midodrine, droxidopa or other pressor agents should be avoided before bedtime. Other non-pharmacological measures such as eating carbohydrates snacks or have an alcoholic drink before bedtime also contribute to decrease nocturnal nSH. The application of local abdominal heat to reduce supine blood pressure is being currently studied in a clinical trial (NCT02417415).

Antihypertensive drugs may be necessary in patients with severe nocturnal nSH that persists after non-pharmacological measures, particularly if they already have end-organ target damage (Table 2).^{35, 103, 104} When antihypertensive drugs are prescribed, patients should be warned about the increased risk of hypotension and falls when they get up at night to urinate. To avoid this, the use of a urinal or bedside commode should be encouraged.

Swallowing and Gastrointestinal Dysfunction

In patients with synucleinopathies gastrointestinal function is affected at all levels, from chewing to defecation.^{105, 106} Dysphagia in patients with PD and DLB is usually mild and occurs late in the disease course, whereas in patients with MSA it can be early and severe.¹⁰⁷ Aspiration pneumonia, the most feared complication of dysphagia, is a common cause of death in patients with synucleinopathies.¹⁰⁸ Upper gastrointestinal symptoms (due to esophageal dysmotility and gastroparesis), and lower gastrointestinal symptoms, such as constipation, are virtually universal in patients with PD, DLB and MSA and contribute to decreased quality of life.¹⁰⁹

Pathophysiology

Swallowing is a complex stereotyped motor activity. Like gait, swallowing is controlled by a central pattern generator in the medulla, which receives cortical and subcortical projections and is modulated by the pedunculopontine tegmental nuclei.¹¹⁰ Sensory input from the oropharynx initiates and controls swallowing via trigeminal, glossopharyngeal and vagal afferents. The swallowing interneurons include neurons in the nucleus tractus solitarius (NTS) that receive sensory afferents from oropharynx, and other neurons of the reticular formation. Effector neurons are in the hypoglossal (XII) nuclei in the medulla, which innervates extrinsic and intrinsic muscles of the tongue, the nucleus ambiguus, which innervates all striated muscles of the pharynx and larynx through vagal fibers, and the dorsal nucleus of

the vagus, which provides efferent parasympathetic preganglionic fibers to the esophagus and rest of the gastro-intestinal tract, up to the splenic flexure of the colon and abdominal organs. Vagal efferents connect with neurons of the enteric nervous system.

In patients with synucleinopathies, involvement of medullary neurons (NTS, mesolimbic cholinergic, pre-Bötzinger complex) results in oropharyngeal, vocal cord, and esophageal abnormalities.^{107, 111, 112} In patients with PD, α Syn aggregates in the glossopharyngeal nerve, the pharyngeal sensory branch of the vagus nerve, and the internal superior laryngeal, a sensory branch of the vagus nerve innervating the laryngopharynx correlate with the severity of dysphagia.¹¹³ The involvement of pharyngeal sensory nerves causes decreased pharyngeal sensation, contributing to dysphagia and aspiration.

Esophageal abnormalities in patients with PD include incomplete relaxation of the upper and lower esophageal sphincters, diffuse esophageal spasms, and reduced esophageal peristalsis.^{114, 115}

Stool transit time is prolonged in patients with LB disorders because colonic motility is reduced due to abnormal intrinsic (enteric nervous system) and extrinsic (vagal) innervation. Preliminary evidence also shows early enteric sympathetic denervation.¹¹⁶ Autopsy findings in patients with PD and DLB show α Syn pathology in enteric neurons along the entire gastrointestinal tract, from the esophagus to the colon, particularly in neurons of Auerbach plexus in the lower esophagus.^{117, 118} Some symptoms, such as delayed gastric emptying, can be aggravated by the effect of L-dopa on dopaminergic enteric receptors that slow motility.¹¹⁹ In patients with MSA, neurodegeneration of brainstem nuclei (including the dorsal motor nucleus of the vagus), the intermediolateral cell column in the thoracic and lumbar spinal cord account for the gastrointestinal symptoms; α Syn accumulation spares the autonomic nerves in the abdominopelvic organs and the enteric nervous system.^{8, 120}

Epidemiology

Dysphagia in patients with LB disorders is related to the severity of the disease. It is a complaint of at least 35% of patients with PD and 73% of patients with MSA.¹²¹⁻¹²³ Videofluoroscopy reveals abnormal swallowing in the majority of patients with PD and MSA. Reduced efficiency and frequency of swallowing results in excessive saliva (sialorrhea or drooling) in 50-60% patients with PD and MSA, particularly in advanced stages.^{106, 124} Virtually all patients with LB disorders and MSA have gastroparesis (i.e., delayed gastric emptying) causing them to suffer nausea, early satiety, gastric retention, and abdominal distension.¹²⁵⁻¹²⁸ Constipation is the single most common autonomic and gastrointestinal symptom, reported by up to 90% of patients with PD and 80% of patients with MSA.^{109, 129-132} Constipation is now recognized as a reliable autonomic disturbance in the premotor phase of PD and DLB, and can also occur in the pre-motor stages of MSA.^{11, 133-135} Disorders associated with constipation in PD and MSA include colonic volvulus, intestinal pseudo-obstruction, megacolon, fecal impaction, or overflow diarrhea.^{136, 137}

Treatment of dysphagia and drooling

Patients with mild-moderate dysphagia may benefit from postural changes, behavioral changes (e.g., reduced meal volumes and eating slowing), and modified meal consistencies (e.g., liquid thickeners).¹⁰⁷ Expiratory muscle strength training (EMST) and video-assisted swallowing therapy (VAST) may be effective treatments for dysphagia in patients with PD and may also be helpful in patients with MSA.¹³⁸ Botulinum toxin injections in the distal esophagus have shown some promise to improve esophageal dysphagia in patients with PD.¹³⁹ Neuromuscular electrical stimulation of the suprahyoid muscles in patients with PD showed no benefits compared to behavioral/postural modifications.¹⁴⁰ The role of dopaminergic drugs and deep-brain stimulation surgery is controversial.¹⁴¹⁻¹⁴³ Some patients with MSA underwent tracheostomy and laryngeal closure surgery for the treatment of dysphagia with conflicting outcomes.^{144, 145} If dysphagia is severe, avoidance of the oral route with a gastrostomy tube placement to ensure adequate nutrition/hydration and reduce the risk of aspiration should be discussed with the patient.

Patients with sialorrhea may benefit from several treatment approaches. Oral glycopyrrolate (1 mg twice daily) is efficacious for the very short-term treatment of sialorrhea in PD.^{12, 146} Side effects include dry mouth, urinary retention, constipation and blurry vision. Local administration of anticholinergics (e.g., sublingual atropine drops¹⁴⁷ or ipratropium spray¹⁴⁸) could be considered as alternative with no systemic adverse events, although the evidence is insufficient¹². Botulinum toxin injections into the salivary glands are efficacious to reduce sialorrhea in patients with PD¹², although repeat injections are typically required every 3-6 months.¹⁴⁹ Behavioral modification (e.g., instructing patients to carefully swallow their saliva at specific times)¹⁵⁰ and radiotherapy¹⁵¹ were effective for patients with PD and MSA in small studies.

Treatment of gastroparesis

The goals of gastroparesis treatment are the alleviation of symptom burden, correction of malnutrition, and resumption of oral intake, when possible.¹⁵² Dietary modifications, including a low-fat diet with small frequent meals and liquid nutrients, can help with gastroparesis. The modulation of gastric motility is complex and involves cholinergic, dopaminergic, serotonergic, and motilin receptors (Figure 3). Available pharmacotherapy for gastroparesis includes dopamine blockers, cholinergic enhancers, serotonin agonists, and motilin receptor agonists, although none of these have been tested in controlled clinical trials in PD.

Dopamine receptor blockers—D₂ receptor blockers can have both central and peripheral activity. Central and peripheral dopamine blockers include metoclopramide, itopride and levosulpiride (the latter two not available in the U.S.). Because of their CNS adverse events, including aggravation of parkinsonism and dyskinesias, and because they can worsen hypotension,¹⁵³ central dopamine receptor blockers are contraindicated in patients with parkinsonism or with autonomic failure.¹⁵⁴ Moreover, metoclopramide can prolong the QT interval and increase the risk of arrhythmias. Domperidone, a dopamine blocker that does not cross the CNS is not approved in the US because of its potential to increase the QT interval. It is available in Europe and Canada. The MDS Evidence-Based

Medicine Review on Non-Motor Treatments for PD considered domperidone as likely efficacious for the treatment of gastroparesis.^{146, 155} Interestingly, domperidone has been extensively used to blunt the potential hypotensive effects of levodopa and dopaminergic agonists.¹⁵⁶

Motilin receptor agonists—Motilin, a hormone secreted by gastric M cells, stimulates gastric motility via motilin receptors in the smooth muscle. Erythromycin, a widely available antibiotic, is a potent prokinetic that stimulates motilin receptors.¹⁵² Although gastric emptying is increased with oral erythromycin, this improvement appears to be smaller than with intravenous erythromycin.¹⁵⁷ The dosage of IV erythromycin is 3 mg/kg every 8 hours. Oral erythromycin can be given 10 mg three times/day. Potential adverse events include abdominal pain and antibiotic resistance. Adverse events of erythromycin include gastrointestinal toxicity, ototoxicity, antibiotic resistance, QT prolongation. Erythromycin is a strong CYP3A4 inhibitor, which should be taken into consideration to avoid pharmacological interactions. Azithromycin has a longer half-life, fewer gastrointestinal adverse effects, less drug interactions than, and similar efficacy to erythromycin, although it may also cause QT prolongation and arrhythmias.¹⁵⁸ Synthetic motilin receptor agonists without antibiotic properties, such as camicinal, are undergoing clinical trials.¹⁵⁹

Serotonin agonists—Two non-selective serotonin 5-HT₄ agonists (cisapride and tegaserod) were developed to increase gastric motility but were withdrawn in the U.S. and Asia, and were severely restricted in Europe due to QT interval prolongation and heart ischemia. Highly selective serotonin agonists (mosapride or prucalopride) for the treatment of constipation, although not approved in the U.S., are available in other world regions such as Europe, Asia and South America. Because they are highly selective and have little effect on cardiac potassium channels, no cardiovascular adverse events have been reported, although their usefulness for gastroparesis has not been systematically investigated.

Other treatments—Muscarinic agonists (e.g., bethanechol) and acetylcholinesterase inhibitors (e.g., pyridostigmine) can increase lower esophageal sphincter pressure and trigger fudoantral contractions, and may be used for gastroparesis.¹⁶⁰ Nizatidine, an H₂-receptor antagonist with anticholinesterase activity, stimulates gastric emptying.¹⁶¹ The benefit of endoscopic pyloric botulinum toxin injections has been documented in small case series of PD patients.^{162, 163} Subthalamic nucleus (STN) deep brain stimulation (DBS) can improve gastric emptying in PD.¹⁶⁴ Gastric electrical stimulation could potentially be considered for severe and refractory gastroparesis.¹⁶⁵ Ghrelin receptor agonists are being tested in clinical trials.¹⁵⁹

Treatment of constipation

Guidelines for the management of constipation in patients with synucleinopathies are lacking.^{166, 167} Management of constipation includes non-pharmacological approaches, removal of aggravating factors (e.g., opioids), fiber supplements, stool softeners, and pharmacotherapy (Figure 4). Enemas and manual disimpactions may be required in severely affected patients.

Non-pharmacological measures—A controlled clinical trial showed that fermented milk products with probiotics (e.g., kefir) improved constipation in patients with PD.¹⁶⁸ Additional dietary modifications usually recommended although not studied in clinical trials include eating at the same time of the day, increasing high-fiber fruits and vegetables, extra virgin olive oil, wholegrain breads and wholegrain cereals in daily meals, as well as hydration (2-2.5 L per day) and physical activity.

Bulk laxatives and osmotic laxatives—Oral bulking agents (fiber supplements such as psyllium or methylcellulose) can be added to the dietary and non-pharmacological modifications.¹⁶⁹ Of these, psyllium is the only one studied, showing efficacy to increase bowel movement frequency in a randomized trial of PD patients.¹⁷⁰ Adequate hydration is required with bulk formers; otherwise constipation may worsen. Osmotic laxatives (polyethylene glycol, magnesium, docusate sodium, lactulose) act by osmotically drawing water into the gastrointestinal lumen and softening the fecal mass. Some of them also have rectal administration. Polyethylene glycol (macrogol) showed efficacy to increase bowel movement frequency in a controlled trial of patients with PD and was considered likely efficacious in the *MDS* Evidence-Based Review on Non-Motor Treatments for PD.^{12, 171} Adverse events are usually limited to mild gas/bloating, mild nausea and, occasionally, diarrhea.

Stimulant laxatives—Stimulant laxatives (bisacodyl, sodium picosulfate, senna) activate the GI mucosa by chemical irritation inducing fluid and sodium chloride secretion and colonic motility. Adverse events include salt overload, hypokalemia, and protein-losing enteropathy. Although initial observations suggested that long-term use could induce enteric nervous system damage, biological evidence and guidelines indicate that stimulant laxatives are safe and effective for chronic constipation.^{169, 172}

Chloride channel activators—Luminal chloride channel activators are approved for the treatment of chronic constipation in the U.S., Europe, and Asia (Figure 5). Lubiprostone is a locally acting chloride type 2 channel activator. In a randomized placebo-controlled clinical trial of, lubiprostone in 52 patients with PD, lubiprostone 24 mcg twice a day significantly reduced the burden of constipation and increased the number of daily bowel movements compared to placebo.¹⁷³ Adverse events were mild, most commonly intermittent diarrhea. Other reported adverse events in controlled trials include nausea and headache. Linaclotide is an agonist of the guanylate cyclase 2C receptor. Activation of guanylate receptors leads to a metabolic cascade that increases the secretion of chloride and HCO₃ via the CFTR receptor (the one affected in cystic fibrosis). In addition, linaclotide also increases smooth muscle contraction, promoting bowel movements, and reduces activation of colonic afferent sensory neurons, theoretically reducing gastrointestinal pain. Although it has not been specifically studied in patients with synucleinopathies, randomized placebo-controlled trials performed in subjects with chronic constipation showed that 290 or 145 mcg of linaclotide once a day 30 minutes before breakfast significantly increased daily spontaneous bowel movements.¹⁷⁴ Potential adverse events include diarrhea, abdominal bloating and flatulence. Plecanatide, another oral guanylate cyclase-C receptor agonist, also showed efficacy in placebo-controlled randomized trials to increase spontaneous bowel movements.^{175, 176} It

was FDA-approved in 2017 for the treatment of chronic idiopathic constipation and may prove useful in patients with synucleinopathies.

Serotonin agonists and others—Cisapride and tegaserod, both 5-HT₄ receptor agonists, were effective to improve constipation in patients with PD,¹⁷⁷⁻¹⁸⁰ but were withdrawn in most countries due to severe adverse events. Prucalopride and mosapride are high-affinity 5-HT₄ receptor agonists with partial 4-HT₃-antagonist activity (available in several countries in Europe, Asia and South America but not in the U.S.). Mosapride specifically ameliorated constipation in an open label study including 14 patients with PD.¹⁸¹ New compounds such as elobixibat, an ileal bile acid transporter inhibitor,¹⁸² and relamorelin, a centrally-acting ghrelin receptor agonist, are being tested in clinical trials.^{159, 183} In a single-center randomized, double-blind placebo-controlled trial, relamorelin administered subcutaneously once or twice a day, relieved constipation and accelerated colonic transit compared to placebo during a 14-day treatment period.¹⁸⁴ Further clinical trials are underway.

Urinary Dysfunction

Urinary symptoms, related to neurogenic detrusor overactivity or underactivity, are very common in patients with synucleinopathies.¹⁸⁵ These include nocturia, frequency, urgency and, in some patients, urinary retention. In patients with LB disorders urinary dysfunction is mild or moderate and typically appears later whereas in patients with MSA, urinary dysfunction is universal, severe, and one of the earliest presenting features.^{11, 186} Indeed, male patients with pre-motor MSA frequently undergo surgery for suspected benign prostate hyperplasia without realizing that MSA is the actual cause of their urinary problems. In these cases, urological surgery outcomes are rarely favorable. Urinary dysfunction in LB disorders is probably a combination α Syn-mediated disruption of peripheral genitourinary autonomic pathways and basal ganglia dysfunction, whereas disruption of the Onuf nucleus is the main contributor to urinary dysfunction in patients with MSA.^{118, 187-189}

Epidemiology

Urinary symptoms affect up to 80% of patients with LB disorders, mostly related to neurogenic detrusor overactivity.¹⁸⁸⁻¹⁹⁰ Nocturia is the most commonly reported symptom (up to 80%) followed by frequency (up to 70%), urgency (up to 70%), and urge incontinence (up to 40%) both in women and men.¹⁹⁰ Hesitancy affects up to 40% of PD patients.¹⁸⁸

In patients with MSA voiding difficulty is the most frequently reported urinary symptom (80%) followed by nocturia (74%), urgency (63%), incontinence (63%), diurnal frequency (45%), nocturnal enuresis (19%), and urinary retention (8%).¹⁹¹ Around 40% of patients with MSA have neurogenic detrusor overactivity (i.e., overactive bladder) during the filling phase, and this may be accompanied by uninhibited external sphincter relaxation (i.e., detrusor-sphincter-dyssynergia), which worsens the severity of urge-incontinence.^{192, 193}

Detrusor underactivity resulting in increased post-void residual volume in is infrequent (10%) in LB disorders and urinary catheterization is seldom required.¹⁹⁰ In patients with MSA, however, detrusor underactivity occurs in approximately 70% resulting in large

amount of bladder post-void residual volume.¹⁹² Poor management of bladder dysfunction can increase the risk of urosepsis and death.¹⁹⁴

Treatment of neurogenic detrusor overactivity

Figure 6 summarizes the autonomic control of the bladder with its pharmacological targets. Management with mirabegron or antimuscarinic agents and behavioral treatment (e.g., prompted/timed bladder emptying) is the treatment of choice of neurogenic detrusor overactivity although only one controlled clinical trial (with solifenacin) has been performed in this population so far.¹⁹⁵ An uncontrolled study showed that exercise-based biofeedback-assisted behavioral training was effective to reduce the frequency of urination and improve quality of life in patients with PD with urinary incontinence.¹⁹⁶

β_3 -adrenergic agonists— β_3 -adrenergic receptors contribute to detrusor muscle relaxation. Mirabegron, a selective β_3 -adrenergic receptor, elicits relaxation of the detrusor muscle during the storage phase, thereby improving bladder capacity without impeding bladder voiding. Mirabegron is available in most countries. Oral mirabegron administered once daily (25-50 mg) is effective to improve urinary frequency, urgency, and incontinence in patients with overactive bladder. Mirabegron is devoid of anticholinergic adverse events but can cause urinary retention, pelvic/abdominal pain, and hypertension.¹⁹⁷

Antimuscarinic agents—Antimuscarinic drugs improve symptoms of detrusor overactivity by reducing cholinergic output to the bladder and, thus, relaxing the detrusor muscle and reducing the urge to urinate.

Antimuscarinic agents can worsen the post-void residual volume and cause urinary retention, dry mouth, dry eyes, gastroparesis and constipation. There are several antimuscarinic agents, the majority of which are available in most world regions: they share mechanism of action but differ in selectivity of M_3 receptors, and CNS permeability (Table 3). Centrally acting antimuscarinic (e.g., atropine or scopolamine) or predominantly peripheral with CNS penetrance (oxybutynin, fesoterodine) can cause/aggravate cognitive impairment and should be avoided. Peripherally acting antimuscarinics with low CNS penetrance (e.g., trospium, darifenacin) are preferable. Only solifenacin 5-10 mg daily has been specifically studied in a randomized placebo-controlled trial of patients with PD showing a significant reduction in urinary frequency compared to placebo.¹⁹⁵

Other treatments—Alpha-adrenergic blockers (tamsulosin, silodosin) should be used very cautiously, or not at all, in patients with autonomic dysfunction as they can aggravate OH and increase the risk of falls and syncope. Open label studies showed that intramural botulinum toxin injections in the bladder can improve refractory neurogenic detrusor overactivity in patients with PD and MSA; potential adverse events include urinary retention.¹⁹⁸⁻²⁰⁰ Nocturnal natriuresis in patients with supine hypertension and nOH should be distinguished from neurogenic detrusor overactivity. Treatment with intranasal desmopressin can reduce nocturia in PD²⁰¹, but because of its high risk of adverse events (hyponatremia, cognitive impairment) it is not routinely recommended. Subthalamic nucleus (STN) deep brain stimulation (DBS) appears to reduce urinary frequency and incontinence

in patients with PD.²⁰² Globus pallidus DBS may yield similar results²⁰³ although controlled studies are warranted. Preliminary studies with implantable sacral nerve stimulation,^{204, 205} transcutaneous tibial nerve stimulation,^{206, 207} or transcranial magnetic stimulation²⁰⁸ in PD or MSA showed promising results to ameliorate neurogenic overactive bladder, although controlled studies are required.

Treatment of detrusor underactivity

Incomplete bladder emptying as a consequence of detrusor underactivity is common in MSA and seldom reported in patients with PD, DLB or PAF. Estimation of the post-void residual (PVR) bladder volume is a simple and useful test in patients with MSA; even though their urinary complaints may be limited to urinary urgency or frequency, patients are usually unaware that their bladders do not empty completely. PVR can be measured by ultrasound echography or transurethral catheterization. If the patient has a PVR > 100 ml, clean intermittent self-catheterization must be recommended. Either the patient or the caregiver can usually perform this after education is provided. In patients with advanced disease and severe neurological disability, a permanent indwelling catheter, usually suprapubic, may be required. Antimuscarinic or β_3 -adrenergic treatment to reduce bladder overactivity should be added regardless of the PVR. The caveats are the same as with the treatment of overactive bladder. Replaceable remote-controlled intra-urethral prosthesis for women with underactive bladder have been recently approved by the U.S. FDA;²⁰⁹ these do not require surgery, increase quality of life, and reduce the risk of urinary complications, although the experience in patients with MSA is still limited (Figure 7).

Sexual Dysfunction

Sexual dysfunction, including erectile dysfunction, ejaculation problems, and difficulties achieving orgasm, is an extremely common problem in patients with synucleinopathies, typically appearing early in the course of the disease. Erectile dysfunction in Lewy bodies and MSA may reflect dopamine deficiency in addition to disruption of autonomic pathways.

Epidemiology

Up to 79% of men with PD acknowledge erectile dysfunction, ejaculation problems, and difficulties achieving orgasm. This increases up to 100% in patients with MSA.²¹⁰ The severity of sexual problems increases with disease duration.²¹¹ Erectile dysfunction can appear years before the diagnosis of PD or MSA, adding sexual dysfunction to the constellation of premotor autonomic biomarkers of synucleinopathies.^{11, 212} Up to 75% of women with PD and MSA report sexual problems such as vaginal dryness, decreased libido, and difficulties reaching orgasm.

Treatment of erectile dysfunction

Psychogenic causes (anxiety, depression, stress), and excessive use of alcohol and tobacco can contribute to erectile dysfunction.²¹³ Several medications can induce erectile dysfunction and decreased libido. These include hydrochlorothiazide and β -blockers (which can also induce OH). Selective serotonin reuptake inhibitors (SSRI) and 5 α -reductase inhibitors (finasteride) can also contribute to erectile dysfunction. Prostate cancer treatments

(radical prostatectomy, radiotherapy, luteinizing hormone-releasing agonists and antagonist) frequently have erectile dysfunction as adverse event.

Therapeutic options for erectile dysfunction include PDE-5 inhibitors, intracavernosal injection therapy, vacuum pump devices, intraurethral prostaglandin suppositories, and surgical placement of penile prostheses.

PDE-5 inhibitors enhance blood flow in the corpora cavernosa promoting and maintaining the erection of the penis. PDE-5 inhibitors have been the mainstay of erectile dysfunction treatment since the release of sildenafil in 1998, with the subsequent development of other similar agents, which differ in half-life.²¹⁴ Sildenafil is the shorter acting (half-life of ~4 hours), and should be taken 30-60 minutes prior to intercourse. Sildenafil improved erectile dysfunction in small open label studies of patients with PD,^{215, 216} and in a small randomized placebo-controlled trial of patients with PD and MSA.²¹⁷ Although PDE-5 inhibitors are usually safe and effective in patients with synucleinopathies, their main limiting factor is that they induce systemic vasodilation that can cause dramatic reductions in BP, with symptomatic OH and syncope. Thus, it is important for clinicians recommending PDE-5 inhibitors to patients with autonomic synucleinopathies to always prescribe the shorter acting one (i.e., sildenafil) and to advise against being standing for several hours after taking a dose. In addition, clinicians should make the patient aware of the action of the drugs, with the following caveats: a) they do not result in an immediate erection; b) they do not cause an erection without sexual stimulation; c) they may not work every time.

Vacuum pump devices are clear plastic chambers placed over the penis, tightened against the lower abdomen with a mechanism to create a vacuum inside the chamber. This results in increased blood flow into the penis. If an adequate erection occurs inside the chamber, the patient slips a small constriction band off the end of the vacuum pump device and onto the base of the penis. An erection beyond 30-min with this method is not recommended. These devices can result a bit cumbersome, but are safe and tolerable, and patients with autonomic dysfunction can get used to them.²¹⁸ Implantable inflatable prostheses were introduced in 1973 and are still used today.²¹³

The use of direct injections of alprostadil, either intracavernosal or intraurethral is another option.²¹⁹ A small needle is used to inject the medication into the lateral aspect of the penis through a small-gauge needle. Response is dose related and usually occurs within 10–15 min, and does not require sexual stimulation. The intraurethral preparation (MUSE) consists of a small amount of drug inserted into the urethral meatus. Response is also dose related, and onset similar to the cavernosal preparations. Adverse events include painful erection, erection lasting > 6 hours, and testicular pain/swelling. Apomorphine, a dopaminergic agonist used in subcutaneous injections in patients with PD and severe motor fluctuations, induces penile erection.²²⁰ Sublingual apomorphine 2mg or 3 mg to treat erectile dysfunction had promising results in clinical trials, and is approved in some countries (e.g., France) for this indication; however nausea, dizziness and hypotension are relatively common adverse events.²²¹⁻²²³

Treatment of female sexual dysfunction

Therapeutic options for female sexual dysfunction are limited and include vaginal lubrication, hormonal therapy, and psychotherapy.²²⁴

Conclusions

The role of the autonomic nervous system in PD and other synucleinopathies has evolved from just an adverse event to playing a key role in the etiology, treatment, and biomarker of early diagnosis and disease progression.²²⁵⁻²²⁷ Dysfunction of the autonomic nervous system afflicts most patients with synucleinopathies affecting quality of life and mortality. Successful treatment of autonomic dysfunction is possible and symptomatic treatments are available. Gastrointestinal dysfunction can lead to impaired drug pharmacodynamics causing a worsening in motor function. Orthostatic hypotension can cause syncope, falls, and fractures. Urinary retention can cause sepsis and death. Thus, there should be a low threshold for ancillary testing to better detect and treat autonomic dysfunction in patients with synucleinopathies. Non-pharmacological treatments are useful and should be tried first. Pharmacological treatments that have shown efficacy in controlled trials of patients with synucleinopathies have been approved in many countries. Novel therapeutic approaches currently being tested in clinical trials will expand the therapeutic arsenal against autonomic dysfunction in forthcoming years.

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Figure 1. Algorithm for the management of neurogenic orthostatic hypotension in patients with synucleinopathies

A stepwise management of neurogenic orthostatic hypotension (nOH) includes: a) correcting aggravating factors, b) implementing non-pharmacological measures and c) drug therapies. When OH is asymptomatic, treatment may not be required or may be limited to non-pharmacological measures. When nOH is symptomatic (i.e., causing symptoms of organ hypoperfusion such as dizziness, lightheadedness, blurry vision or feeling about to faint) pharmacological treatment is usually required. *Droxidopa appears to be particularly effective in patients with low baseline plasma norepinephrine levels (usually patients with Lewy body disorders).⁶⁴ **Atomoxetine appears to be particularly effective in patients with high baseline plasma norepinephrine levels (usually patients with multiple system atrophy).⁶³ #Caution is advised when combining droxidopa, with norepinephrine transporter (NET) inhibitors (e.g., atomoxetine) as this combination has not been systematically studied and there is a possibility of increasing the risk of arrhythmias and other adverse events. BP: blood pressure. OH: orthostatic hypotension.

Figure 2. Sites of action and mechanism of therapeutic agents used for the treatment of neurogenic orthostatic hypotension

Pyridostigmine inhibits acetylcholine esterase (AChE) in the sympathetic ganglion thereby increasing the levels of acetylcholine (ACh) and enhancing sympathetic neurotransmission. Droxidopa is converted to norepinephrine (NE) through the action of the enzyme aromatic amino acid decarboxylase (AAAD) both in neuronal and extra-neuronal tissues. Atomoxetine and similar medications block the NE transporter (NET) thereby increasing NE levels in the sympathetic terminal. Midodrine is a direct alpha-adrenergic agonist that activates the same receptor as NE. Finally, fludrocortisone is a synthetic mineralocorticoid that increases intravascular volume.

Figure 3. Sites of action and mechanisms of therapeutic agents used for the treatment of gastroparesis

Several receptors (dopaminergic, cholinergic muscarinic, cholinergic nicotinic, serotonergic) are involved in the regulation of gastric motility. Eventually, all modulate acetylcholine release in the enterocyte, which induces gastric motility. Agents used to increase motility include dopamine D₂ receptor blockers (e.g., domperidone and others), serotonin 5-HT₄ receptor agonists (e.g., cisapride and others), acetylcholinesterase inhibitors (e.g., pyridostigmine) and muscarinic agonists (e.g., bethanechol). Conversely, 5-HT₃ antagonists (e.g., alosetron, ondansetron) reduce gastric motility and are used for diarrhea or vomiting.

Figure 4. Algorithm for the management of constipation in patients with synucleinopathies
Management includes non-pharmacological approaches, removal of aggravating factors (e.g., opioids), fiber supplements, stool softeners, and pharmacotherapy with laxatives. The asterisk (*) denotes non-pharmacological and pharmacological agents tested in clinical trials of patients with Parkinson disease. Enemas and manual disimpactions may be required in severely affected patients (not shown in algorithm).

Figure 5. Luminal chloride channel activators for the treatment of chronic constipation in patients with synucleinopathies

Lubiprostone is a locally acting chloride type 2 channel activator. Linaclootide is an agonist of the guanylate cyclase 2C receptor. Activation of guanylate receptors leads to a metabolic cascade that increases the secretion of chloride and HCO₃ via the CFTR receptor.

Linaclootide also increases smooth muscle contraction, promoting bowel movements, and reduces activation of colonic afferent sensory neurons, theoretically reducing gastrointestinal pain. Plecanatide, another oral guanylate cyclase-C receptor agonist, also showed efficacy in placebo-controlled randomized trials to increase spontaneous bowel movements.

Figure 6. Sites of action and mechanisms of therapeutic agents used for the treatment of neurogenic overactive bladder

Cholinergic pelvic nerves release acetylcholine (ACh), which, via activation of muscarinic M3 receptors, induce contraction of the detrusor muscle and emptying of the bladder. Anti-muscarinic agents (e.g., solifenacin) block the muscarinic receptor and reduce detrusor muscle contractions. Hypogastric adrenergic nerves release norepinephrine (NE), which causes urinary retention by activating β_3 -adrenergic receptors in the detrusor muscle and alpha-adrenergic receptors in the internal sphincter of the urethra. Mirabegron, a β_3 -adrenergic receptor agonist, reduces bladder contractions in patients with neurogenic detrusor overactivity. Of note, the classical nomenclature of the sacral autonomic outflow has been recently challenged.²²⁹

Figure 7. Algorithm for the management of underactive bladder in patients with synucleinopathies

Incomplete bladder emptying as a consequence of detrusor underactivity is common in multiple system atrophy (MSA) but seldom reported in patients with other synucleinopathies. Estimation of the post-void residual (PVR) bladder volume is a simple and useful test in patients with MSA; even though their urinary complaints may be limited to urinary urgency or frequency, patients are usually unaware that their bladders do not empty completely. PVR can be measured by ultrasound echography or transurethral catheterization. If the patient has a PVR > 100 ml, clean intermittent self-catheterization must be recommended. Either the patient or the caregiver can usually perform this after education is provided. In patients with advanced disease and severe neurological disability, a permanent indwelling catheter, usually suprapubic, may be required. Antimuscarinic or β_3 -adrenergic treatment to reduce bladder overactivity should be added regardless of the PVR. (*) Replaceable remote-controlled intra-urethral prosthesis for women with underactive bladder have been recently approved by the Food and Drug Administration. Our experience in women with MSA, although limited, is very positive.

Table 1

Pharmacological treatments for neurogenic orthostatic hypotension.

Treatment	Recommended dosing regimen	Mechanism of action	Adverse events
<i>Specifically approved for symptomatic neurogenic OH</i>			
Midodrine	2.5–15 mg twice or three times/day (dosed morning, midday, and 3–4 hours prior to bedtime)	Direct α_1 -adrenergic receptor agonist	Supine hypertension, piloerection (“goose bumps”), scalp itching, and urinary retention; caution in congestive heart failure and chronic renal failure
Droxidopa	100–600 mg three times/day (dosed morning, midday, and 3–4 hours prior to bedtime) or tailored to the patients' needs	Synthetic norepinephrine precursor	Supine hypertension, headache, dizziness, nausea, and fatigue; caution in congestive heart failure and chronic renal failure
<i>Not specifically approved for neurogenic OH</i>			
Atomoxetine	10–18 mg twice a day	Norepinephrine transporter (NET) blocker	Supine hypertension, insomnia, irritability, decreased appetite
Fludrocortisone	0.05–0.2 mg/day; little benefit observed with dosages beyond 0.2 mg/day	Synthetic mineralocorticoid. Volume expander that increases sodium and water reabsorption	Supine hypertension, hypokalemia, renal failure, and edema; caution in congestive heart failure
Pyridostigmine	30–60 mg twice or three times/day	Acetyl-cholinesterase inhibitor. Marginal efficacy in neurogenic orthostatic hypotension.	Abdominal cramps, diarrhea, sialorrhea, excessive sweating, urinary incontinence.

Table 2

Pharmacological treatments for supine hypertension associated with neurogenic orthostatic hypotension.

Treatment [*]	Recommended dosing regimen
Captopril	25 mg at bedtime
Nebivolol ²²⁸	5 mg at bedtime
Clonidine [‡]	0.05-0.1 mg with dinner
Hydralazine	10–25 mg at bedtime
Losartan	50 mg at bedtime
Nitroglycerine patch	0.1 mg/hour patch at bedtime (remove patch in the morning)

^{*} No controlled trials have been performed for most of these interventions. The risk-benefit ratio should be individually assessed. Short-acting antihypertensives should be administered at bedtime only, not during daytime hours. Many medications have twice or three times/day as recommended dosing and patients may inadvertently start taking these medications during daytime hours and worsen symptoms of neurogenic orthostatic hypotension.

[‡] Clonidine carries a risk of a severe morning hypotension as well as rebound hypertension.

Table 3
Pharmacological treatments for neurogenic detrusor overactivity

Treatment	Recommended dosing regimen	Adverse events	Receptor selectivity	CNS penetration
<i>Anticholinergic agents</i>				
Darifenacin	7.5 or 15 mg/day	Constipation, dry mouth, urinary retention	M ₃ selective	Low
Trospium	20 mg twice a day 60 mg/day (extended release form)	Constipation, dry mouth, dry eyes, headache, urinary retention	Non-selective	Low
Solifenacin	5 or 10 mg/day	Constipation, dry mouth, blurred vision, nausea, dyspepsia, urinary retention	M ₃ and M ₁ selective	Moderate
Oxybutinin	5 mg up to 4 times/day 5-30 mg/day (extended release form) 3 pumps once a day (gel) 1 patch every 3-4 days (patch)	Constipation, dry mouth, blurred vision, nausea, dyspepsia, urinary retention	M ₃ and M ₁ selective	Moderate
Tolterodine	2 mg twice a day 2 or 4 mg/day (long acting form)	Constipation, dry mouth, dyspepsia, dizziness, blurry vision, urinary retention	Non-selective	Moderate
Fesoterodine	4 or 8 mg	Constipation, dry mouth, dyspepsia, dizziness, blurry vision, urinary retention	Non-selective	Moderate
<i>β₃-adrenergic agonists</i>				
Mirabegron	25 or 50 mg/day	Hypertension, irregular heart rate, abdominal or pelvic pain, worsening dyskinesias in PD (one case report)	β ₃ -selective	Low