REVIEW

Treatment of Autonomic Dysfunction in Parkinson Disease and Other Synucleinopathies

Jose-Alberto Palma, MD, PhD* and Horacio Kaufmann, MD*

Department of Neurology, Dysautonomia Center, New York University School of Medicine, New York, New York, USA

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 nonpharmacological 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 nonpharmacological 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. © 2018 International Parkinson and Movement Disorder Society

Key Words: Parkinson's disease; multiple system atrophy; nonmotor symptoms; dysautonomia; autonomic failure; treatment

*__Correspondence to__: Dr. Jose-Alberto Palma, Department of Neurology, New York University Langone Medical Center, 530 First Avenue, Suite 9Q, New York, NY 10016, USA; E-mail: JoseAlberto.PalmaCarazo@nyumc.org; and Dr. Horacio Kaufmann, Department of Neurology, New York University Langone Medical Center, 530 First Avenue, Suite 9Q, New York, NY 10016, USA; E-mail: Horacio.Kaufmann@nyumc.org

Funding agencies: National Institutes of Health (U54-NS065736-01) and Dysautonomia Foundation, Inc.

Relevant conflicts of interest/financial disclosures: Dr. Palma receives research support from The Dysautonomia Foundation, Inc.; the MSA Coalition; the National Institutes of Health (U54-NS065736-01); the Michael J. Fox Foundation, the Food and Drug Administration, and has received compensation as a consultant/advisory board member for Lundbeck. Dr. Palma serves as Managing Editor of *Clinical Autonomic Research*. Dr. Kaufmann receives research support from the National Institutes of Health (U54NS065736 [PI]) 1U01NS078025-01, the Food and Drug Administration (FD-R-3731-01 [PI]), the Michael J. Fox Foundation, and the Dysautonomia Foundation, Inc.; has received compensation as a consultant/advisory board member for Lundbeck, Eli Lilly, Pfizer, and Astra Zeneca. Dr. Kaufmann serves as Editor-in-Chief of *Clinical Autonomic Research*.

Full financial disclosures and author roles may be found in the online version of this article.

Received: 6 November 2017; **Revised:** 11 January 2018; **Accepted:** 24 January 2018

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.27344

Dysfunction of the autonomic nervous system (ANS) is a characteristic feature of patients with synucleinopathies, a group of neurodegenerative diseases caused by the abnormal accumulation of misfolded phosphorylated α-synuclein (αSyn) in neurons, glia, or both. Converging evidence indicates that abnormal αSyn spreads from cell to cell in a prion-like fashion,[1-3] and that different types of αSyn assemblies with different structural characteristics called strains[4,5] may account for the different clinical phenotypes given that they determine the nerve cell type and the regions of the nervous system that are affected.[4]

In patients with Parkinson's disease (PD), dementia with Lewy bodies (DLB) and pure autonomic failure (PAF) aggregates of misfolded αSyn 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, αSyn 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, nonpharmacological 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 nonpharmacological 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 underdiagnosed 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 BP monitoring.[17,18] Clinical trials for nOH were designed for relatively short periods of time (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 given that symptoms of nOH can be nonspecific, including fatigue and difficultly concentrating, and may occasionally mimic the levodopa *off* state in PD patients. Also, patients with PD can have difficultly distinguishing nOH-related lightheadedness from other causes of lightheadedness.[19] Furthermore, severity of nOH in PD and other synucleinopathies can be associated with disease progression; failure to demonstrate long-term improvement could conceivably be attributed to worsening of neurodegeneration rather than failure of the active agent.

Despite these challenges, there have been several accomplishments in the last years, including 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 are symptomatic.[20,21] Symptoms of cardiovascular autonomic dysfunction are attributed to tissue hypoperfusion as a result of OH, defined as a sustained fall in BP of ≥20 mm Hg systolic or 10 mm Hg 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 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 postganglionic 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 attributed to degeneration of postganglionic sympathetic neurons. There is robust imaging and neuropathological data showing that postganglionic peripheral sympathetic neurons innervating the myocardium are functionally affected because of αSyn 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, whereas only a minority (< 30%) of patients has degeneration of postganglionic 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 MSA,[28] 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% and 50% of patients with PD have OH, but less than one third of those patients are symptomatic, that is, only 16% of patients with PD have symptomatic OH.[16,29-31] Prevalence of OH in PD increases with age and disease duration.[29] In DLB, prevalence of OH is higher (50%–60%).[31,32] In patients with MSA, the diagnostic criteria for nOH are a fall of 30 mm Hg in systolic or 15 mm Hg in diastolic BP.[33] Even according to these more stringent criteria, 70% to 80% of patients with MSA have nOH.[9,34]

Treatment of 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: (1) correcting aggravating factors; (2) implementing nonpharmacological measures; and (3) drug therapies. When OH is asymptomatic, treatment may not be required or may be limited to nonpharmacological 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 (Fig. 1).

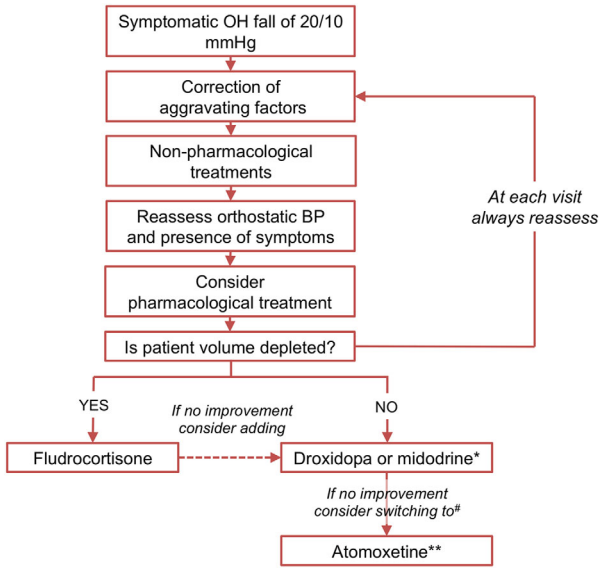

FIG. 1. Algorithm for the management of nOH in patients with synucleinopathies. A step-wise management of nOH includes: (1) correcting aggravating factors; (2) implementing nonpharmacological measures; and (3) drug therapies. When nOH is asymptomatic, treatment may not be required or may be limited to nonpharmacological measures. When nOH is symptomatic (i.e., causing symptoms of organ hypoperfusion such as dizziness, lightheadedness, and 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 LB 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 (NE) transporter (NET) inhibitors (e.g., atomoxetine), because this combination has not been systematically studied and there is a possibility of increasing the risk of arrhythmias and other adverse events. Ach, acetylcholine; AChoE, acetylcholine esterase. [Color figure can be viewed at wileyonlinelibrary.com]

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, and tricyclic antidepressants) worsen nOH and symptoms. L-dopa 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 U/kg, subcutaneous, 3 times a week) in conjunction with iron supplements may be beneficial in patients with nOH and anemia.[43]

Nonpharmacological 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) because of the hypotensive effects of high-glycemic index carbohydrates.[44] Fluid intake should be 2.0 to 2.5 L/day. Patients should be encouraged to increase salt intake by adding 1 to 2 teaspoon of

TABLE 1. Pharmacological treatments for nOH

Treatment	Recommended Dosing Regimen	Mechanism of Action	Adverse Events
Specifically approved for symptomatic nOH			
Midodrine	2.5 to 15 mg 2 or 3 times/day (dosed morning, midday, and 3-4 hours before 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 to 600 mg 3 times/day (dosed morning, midday, and 3-4 hours before 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
Not specifically approved for nOH			
Atomoxetine	10 to 18 mg twice-daily	NET blocker	Supine hypertension, insomnia, irritability, decreased appetite
Fludrocortisone	0.05 to 0.20 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 to 60 mg 2 or 3 times/day	Acetyl-cholinesterase inhibitor; Marginal efficacy in nOH	Abdominal cramps, diarrhea, sialorrhea, excessive sweating, urinary incontinence

salt to a healthy diet. Other patients prefer using 0.5- to 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 given that the pressor effect is quick (peaks in around 30 minutes), 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 because 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 hours 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, before 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 to 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 nonpharmacological 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 used in the treatment of nOH. Two complementary strategies are commonly used: (1) expanding intravascular volume with fludrocortisone and (2) increasing peripheral vascular resistance with midodrine, droxidopa, or norepinephrine transporter (NET) inhibitors. Selection of one or the others or both depends on the specific

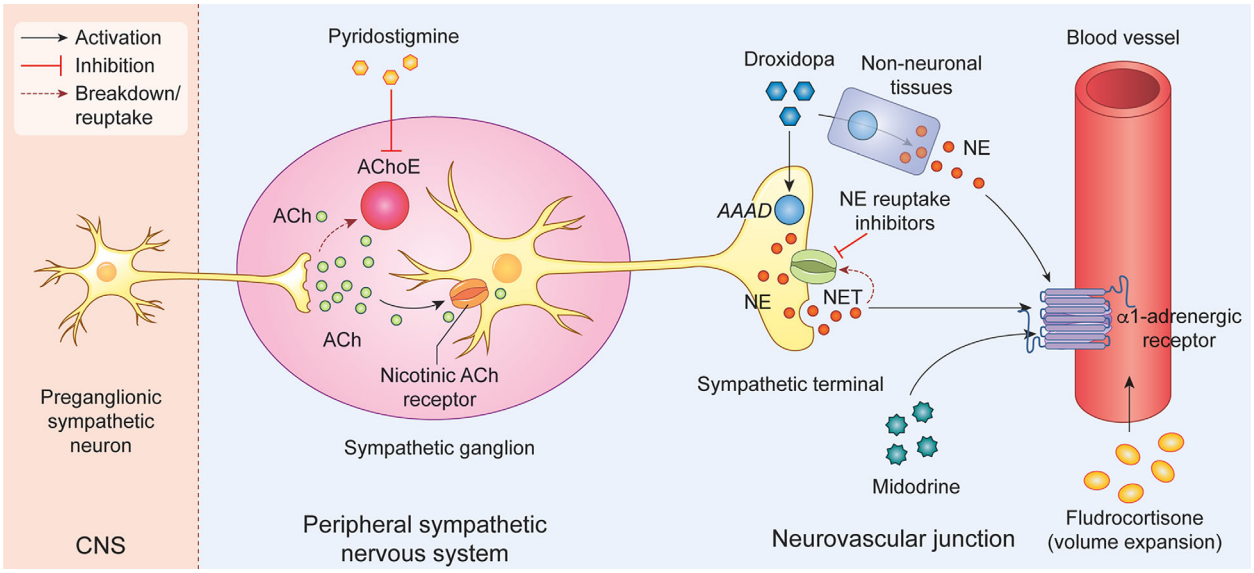

FIG. 2. Sites of action and mechanism of therapeutic agents used for the treatment of nOH. Pyridostigmine inhibits acetylcholine esterase (AChoE) in the sympathetic ganglion, thereby increasing the levels of acetylcholine (ACh) and enhancing sympathetic neurotransmission. Droxidopa is converted to norepinephrine (NE) through the action of the enzyme, AAAD, both in neuronal and extraneuronal 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.

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 central nervous system (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 (Fig. 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 are available on the combined use of any of these agents and its use may result in severe hypertension and cardiac arrhythmias.

Fludrocortisone. Fludrocortisone (9α-fluorocortisol) is a synthetic mineralocorticoid that increases BP by at least two mechanisms: It increases renal sodium and water reabsorption, thus expanding intravascular volume, and also enhances 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 countries.

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 United States, Europe, and Asia. Midodrine raises BP in the standing, sitting, and supine positions and its pressor effect is noticeable ~30 to 45 minutes after consumption, reaching a maximum after ~1 hour, and persists for a total of 2 to 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 to 4 hours before bedtime. Other adverse events owing to activation of α1-adrenergic receptors are piloerection ("goosebumps"), itching of the scalp, and urinary retention. Midodrine has no effect on heart rate because 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) 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 United States, the U.S. Food and Drug Administration (FDA) approved droxidopa in 2014 for 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 hours after oral administration. The dosage used in clinical trials was 100 to 600 mg 3 times/day, although clinical experience indicates that the dosage should be tailored to each patient's needs considering the periods of time when he or 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 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 minutes 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 nonmotor 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 NET. Atomoxetine (Strattera) is currently approved in the United States, Europe, and Asia for the treatment of attention deficit and hyperactivity disorder 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 mm Hg in standing systolic BP.[93] The combination of 5 mg of midodrine with 60 mg of 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-minute standing[29] because 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 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 or

TABLE 2. Pharmacological treatments for supine hypertension associated with nOH

Treatment[a]	Recommended Dosing Regimen
Captopril	25 mg at bedtime
Nebivolol[228]	5 mg at bedtime
Clonidine[b]	0.05 to 0.10 mg with dinner
Hydralazine	10 to 25 mg at bedtime
Losartan	50 mg at bedtime
Nitroglycerine patch	0.1 mg/hour patch at bedtime (remove patch in the morning)

[a]*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 2 or 3 times/day as recommended dosing, and patients may inadvertently start taking these medications during daytime hours and worsen symptoms of neurogenic orthostatic hypotension.
[b]Clonidine carries a risk of a severe morning hypotension as well as rebound hypertension.

her head and torso above his or 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 overnight volume depletion, and improving OH in the morning. Use of midodrine, droxidopa, or other pressor agents should be avoided before bedtime. Other nonpharmacological 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 BP is being currently studied in a clinical trial (NCT02417415).

Antihypertensive drugs may be necessary in patients with severe nocturnal nSH that persists after nonpharmacological 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 (attributed 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 through trigeminal, glossopharyngeal, and vagal afferents. The swallowing interneurons include neurons in the nucleus tractus solitarii (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 ambiguous, 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 the rest of the gastrointestinal tract, up to the splenic flexure of the colon and abdominal organs. Vagal efferents connect with neurons of the enteric nervous system (ENS).

In patients with synucleinopathies, involvement of medullary neurons (NTS, mesolimbic cholinergic, and pre-Bötzinger complex) results in oropharyngeal, vocal cord, and esophageal abnormalities.[107,111,112] In patients with PD, αSyn 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] 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 because of abnormal intrinsic (ENS) and extrinsic (vagal) innervation. Preliminary evidence also shows early enteric sympathetic denervation.[116] Autopsy findings in patients with PD and DLB show αSyn 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; αSyn accumulation spares the autonomic nerves in the abdominopelvic organs and the ENS.[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 result in excessive saliva (sialorrhea or drooling) in 50% to 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 premotor 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-to-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 and video-assisted swallowing therapy 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 DBS 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 drops[147] or ipratropium spray[148]) could be considered as alternative with no systemic adverse events, although the evidence is insufficient.[12] Botulinum toxin injections into the salivary glands are efficacious to reduce sialorrhea in patients with PD,[12] although repeat injections are typically required every 3 to 6 months.[149] Behavioral modification (e.g., instructing patients to carefully swallow their saliva at specific times)[150] and radiotherapy[151] were effective for patients with PD and MSA in small studies.

Treatment of Gastroparesis

The goals of gastroparesis treatment are 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, serotoninergic, and motilin receptors (Fig. 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

D_2 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 United States). 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 risk of arrhythmias. Domperidone, a dopamine blocker that does not cross the CNS, is not approved in the United States because of its potential to increase the QT interval. It is available in Europe and Canada. The International Parkinson and Movement Disorder Society (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 L-dopa and dopaminergic agonists.[156]

Motilin Receptor Agonists

Motilin, a hormone secreted by gastric M cells, stimulates gastric motility through motilin receptors in the smooth muscle. Erythromycin, a widely available antibiotic, is a potent prokinetic that stimulates

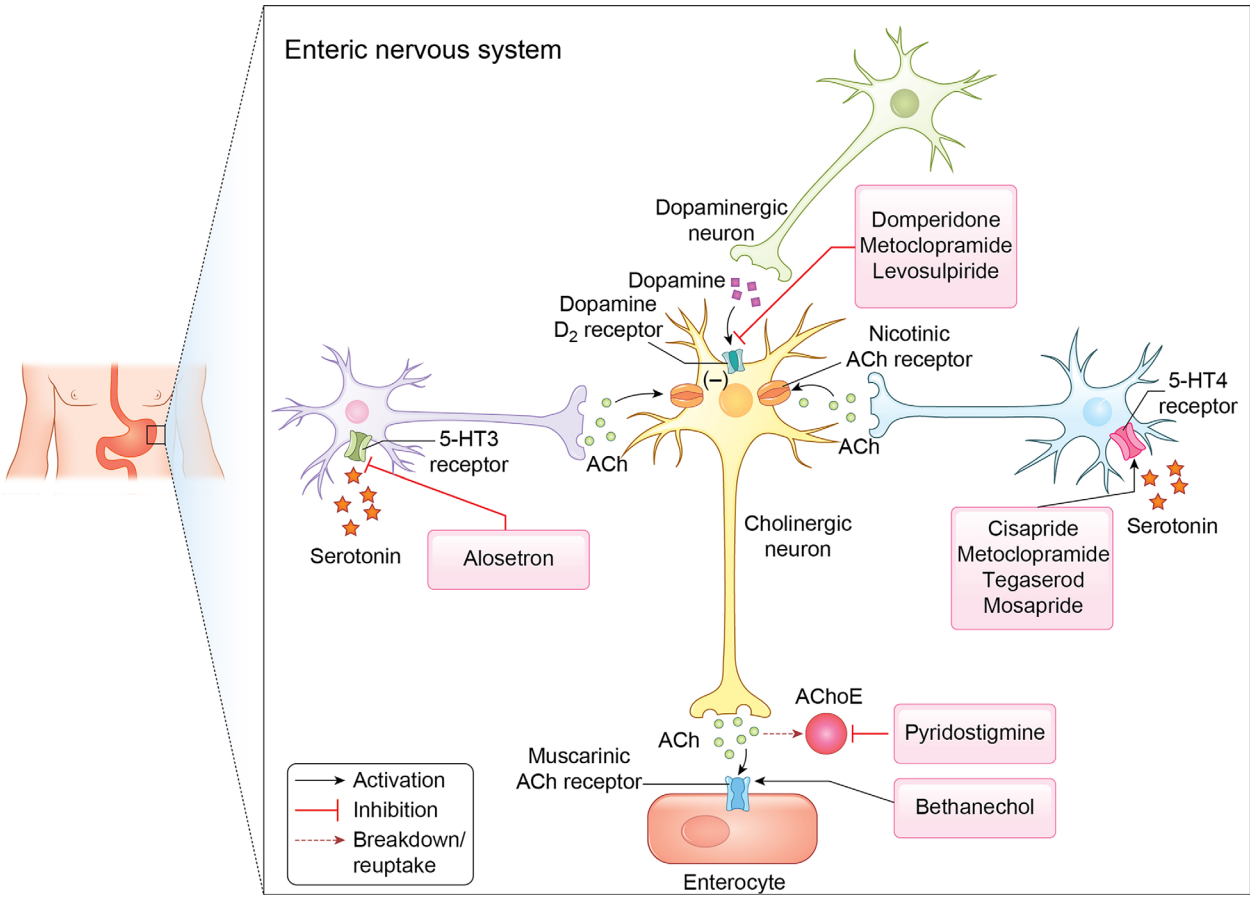

FIG. 3. Sites of action and mechanisms of therapeutic agents used for the treatment of gastroparesis. Several receptors (dopaminergic, cholinergic muscarinic, cholinergic nicotinic, and serotoninergic, among others) are involved in the regulation of gastric motility. Eventually, all modulate acetylcholine release in the enterocyte, which induces gastric motility. Agents used to increase motility include dopamine D_2 receptor blockers (e.g., domperidone and others), serotonin 5-HT_4 receptor agonists (e.g., cisapride and others), acetylcholinesterase inhibitors (e.g., pyridostigmine), and muscarinic agonists (e.g., betanechol). Conversely, 5-HT_3 antagonists (e.g., alosetron, ondansetron) reduce gastric motility and are used for diarrhea or vomiting.

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 intravenous erythromycin is 3 mg/kg every 8 hours. Oral erythromycin can be given 10 mg 3 times/day. Potential adverse events include abdominal pain and antibiotic resistance. Adverse events of erythromycin include gastrointestinal toxicity, ototoxicity, antibiotic resistance, and QT prolongation. Erythromycin is a strong cytochrome P450 inhibitor, which should be taken into consideration to avoid pharmacological interactions. Azithromycin has a longer half-life, fewer gastrointestinal adverse effects, and 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 nonselective serotonin 5-HT_4 agonists (cisapride and tegaserod) were developed to increase gastric motility, but were withdrawn in the United States and Asia and were severely restricted in Europe because of QT interval prolongation and heart ischemia. Highly selective serotonin agonists (mosapride or prucalopride) for the treatment of constipation, although not approved in the United States, 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 H_2-receptor antagonist with anticholinesterase activity, stimulates gastric emptying.[161] The benefit of endoscopic pyloric botulinum toxin injections has been documented in small

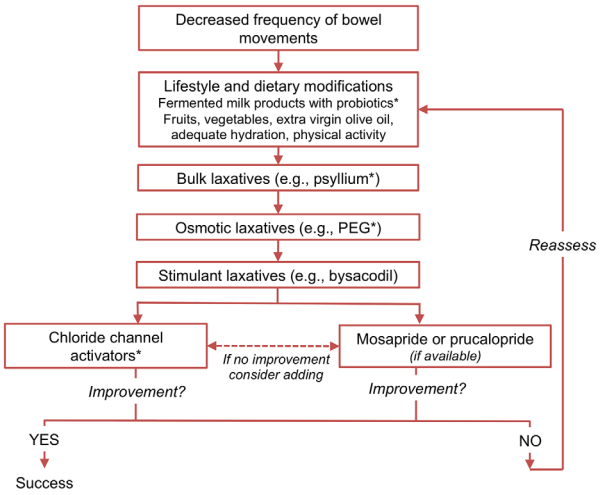

FIG. 4. Algorithm for the management of constipation in patients with synucleinopathies. Management includes nonpharmacological approaches, removal of aggravating factors (e.g., opioids), fiber supplements, stool softeners, and pharmacotherapy with laxatives. The asterisk (*) denotes nonpharmacological and pharmacological agents tested in clinical trials of patients with PD. Enemas and manual disimpactions may be required in severely affected patients (not shown in algorithm). [Color figure can be viewed at wileyonlinelibrary.com]

case series of PD patients.[162,163] STN-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] Constipation management includes nonpharmacological approaches, removal of aggravating factors (e.g., opioids), fiber supplements, stool softeners, and pharmacotherapy (Fig. 4). Enemas and manual disimpactions may be required in severely affected patients.

Nonpharmacological 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 (2.0-2.5 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 nonpharmacological 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, and lactulose) act by osmotically drawing water into the gastrointestinal lumen and softening the fecal mass. Some of them also have rectal administration. Polyethylene glycol (macroglol) 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, and senna) activate the gastrointestinal 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 ENS 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 United

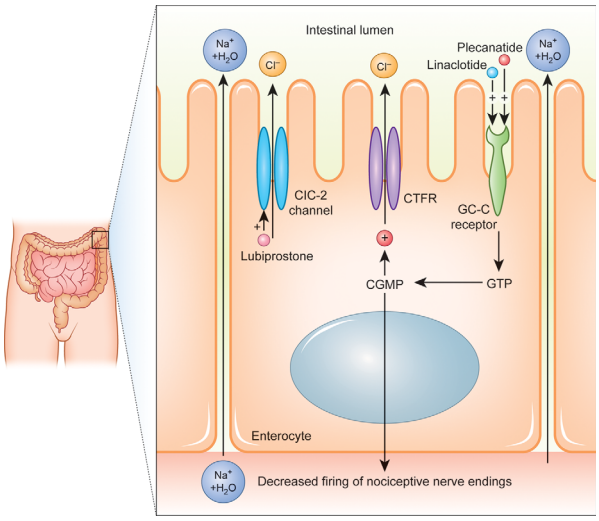

FIG. 5. Luminal chloride channel activators for the treatment of chronic constipation in patients with synucleinopathies. Lubiprostone is a locally acting chloride type 2 channel activator. Linaclotide is an agonist of the guanylate cyclase 2C receptor. Activation of guanylate receptors leads to a metabolic cascade that increases the secretion of chloride and HCO_3 through the CFTR receptor. Linaclotide 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.

States, 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 μg twice-daily 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 HCO_3 through 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 μg of linaclotide once-daily 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-HT_4 receptor agonists, were effective to improve constipation in patients with PD,[177-180] but were withdrawn in most countries because of severe adverse events. Prucalopride and mosapride are high-affinity 5-HT_4 receptor agonists with partial 4-HT_3-antagonist activity (available in several countries in Europe, Asia, and South America, but not in the United States). 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-daily, 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 premotor 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 αSyn-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]

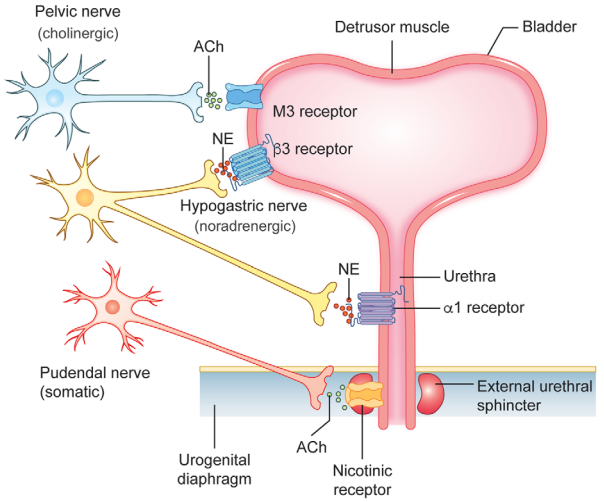

FIG. 6. Sites of action and mechanisms of therapeutic agents used for the treatment of neurogenic overactive bladder. Cholinergic pelvic nerves release acetylcholine (ACh), which, through activation of muscarinic M3 receptors, induce contraction of the detrusor muscle and emptying of the bladder. Antimuscarinic 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]

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

TABLE 3. Pharmacological treatments for neurogenic detrusor overactivity

Treatment	Recommended Dosing Regimen	Adverse Events	Receptor Selectivity	CNS Penetration
Antimuscarinic agents				
Darifenacin	7.5 or 15 mg/day	Constipation, dry mouth, urinary retention	M_3 selective	Low
Trospium	20 mg twice-daily 60 mg/day (extended release form)	Constipation, dry mouth, dry eyes, headache, urinary retention	Nonselective	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 to 30 mg/day (extended release form) 3 pumps once-daily (gel) 1 patch every 3 to 4 days (patch)	Constipation, dry mouth, blurred vision, nausea, dyspepsia, urinary retention	M_3 and M_1 selective	Moderate
Tolterodine	2 mg twice-daily 2 or 4 mg/day (long-acting form)	Constipation, dry mouth, dyspepsia, dizziness, blurry vision, urinary retention	Nonselective	Moderate
Fesoterodine	4 or 8 mg	Constipation, dry mouth, dyspepsia, dizziness, blurry vision, urinary retention	Nonselective	Moderate
β_3-adrenergic agonists				
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

(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 postvoid residual volume 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 a large amount of bladder postvoid 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 or 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 postvoid 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, darifernacine) 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 because they can aggravate

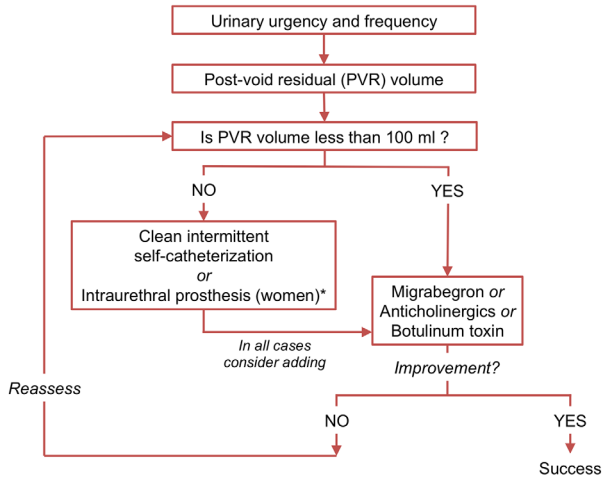

FIG. 7. Algorithm for the management of underactive bladder in patients with synucleinopathies. Incomplete bladder emptying as a consequence of detrusor underactivity is common in MSA, but seldom reported in patients with other synucleinopathies. Estimation of the PVR bladder volume is a simple and useful 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 intraurethral prosthesis for women with underactive bladder have been recently approved by the FDA. Our experience in women with MSA, although limited, is very positive. [Color figure can be viewed at wileyonlinelibrary.com]

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 PD,[201] but because of its high risk of adverse events (hyponatremia, cognitive impairment), it is not routinely recommended. STN-DBS appears to reduce urinary frequency and incontinence in patients with PD.[202] Globus pallidus DBS may yield similar results,[203] although controlled studies are warranted. Preliminary studies with implantable sacral nerve stimulation,[204,205] transcutaneous tibial nerve stimulation,[206,207] or transcranial magnetic stimulation[208] 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 postvoid 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 intraurethral prosthesis for women with underactive bladder have been recently approved by the 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 (Fig. 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 LB 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 biomakers 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, and 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 and 5α-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 an adverse event.

Therapeutic options for erectile dysfunction include phosphodiesterase type 5 (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 to 60 minutes before 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: (1) they do not result in an immediate erection; (2) they do not cause an erection without sexual stimulation; and (3) 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 minutes with this method is not recommended. These devices can result as 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 to 15 minutes 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 2 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 ANS dysfunction 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 ANS 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. OH 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. Nonpharmacological 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.

REFERENCES

1. Woerman AL, Stohr J, Aoyagi A, et al. Propagation of prions causing synucleinopathies in cultured cells. Proc Natl Acad Sci U S A 2015;112:E4949-E4958.
2. Masuda-Suzukake M, Nonaka T, Hosokawa M, et al. Prion-like spreading of pathological alpha-synuclein in brain. Brain 2013;136(Pt 4):1128-1138.
3. Prusiner SB, Woerman AL, Mordes DA, et al. Evidence for alpha-synuclein prions causing multiple system atrophy in humans with parkinsonism. Proc Natl Acad Sci U S A 2015;112:E5308-E5317.
4. Peelaerts W, Bousset L, Van der Perren A, et al. α-Synuclein strains cause distinct synucleinopathies after local and systemic administration. Nature 2015;522:340-344.
5. Peelaerts W, Baekelandt V. α-Synuclein strains and the variable pathologies of synucleinopathies. J Neurochem 2016;139(Suppl 1):256-274.
6. Marras C, McDermott MP, Rochon PA, et al. Survival in Parkinson disease: thirteen-year follow-up of the DATATOP cohort. Neurology 2005;64:87-93.

7. Halliday GM. Re-evaluating the glio-centric view of multiple system atrophy by highlighting the neuronal involvement. Brain 2015;138(Pt 8):2116-2119.
8. Cykowski MD, Coon EA, Powell SZ, et al. Expanding the spectrum of neuronal pathology in multiple system atrophy. Brain 2015;138(Pt 8):2293-2309.
9. Roncevic D, Palma JA, Martinez J, Goulding N, Norcliffe-Kaufmann L, Kaufmann H. Cerebellar and parkinsonian phenotypes in multiple system atrophy: similarities, differences and survival. J Neural Transm (Vienna) 2014;121:507-512.
10. Wenning GK, Geser F, Krismer F, et al. The natural history of multiple system atrophy: a prospective European cohort study. Lancet Neurol 2013;12:264-274.
11. Kaufmann H, Norcliffe-Kaufmann L, Palma JA, et al. Natural history of pure autonomic failure: a United States prospective cohort. Ann Neurol 2017;81:287-297.
12. Seppi K, Weintraub D, Coelho M, et al. The Movement Disorder Society Evidence-Based Medicine Review Update: Treatments for the non-motor symptoms of Parkinson's disease. Mov Disord 2011;26(Suppl 3):S42-S80.
13. Kaufmann H, Norcliffe-Kaufmann L, Palma JA. Droxidopa in neurogenic orthostatic hypotension. Exp Rev Cardiovasc Ther 2015;13:875-891.
14. Kaufmann H, Freeman R, Biaggioni I, et al. Droxidopa for neurogenic orthostatic hypotension: a randomized, placebo-controlled, phase 3 trial. Neurology 2014;83:328-335.
15. Jankovic J, Gilden JL, Hiner BC, et al. Neurogenic orthostatic hypotension: a double-blind, placebo-controlled study with midodrine. Am J Med 1993;95:38-48.
16. Palma JA, Kaufmann H. Epidemiology, Diagnosis, and Management of Neurogenic Orthostatic Hypotension. Mov Disord Clin Pract 2017;4:298-308.
17. Kaufmann H, Norcliffe-Kaufmann L, Hewitt LA, Rowse GJ, White WB. Effects of the novel norepinephrine prodrug, droxidopa, on ambulatory blood pressure in patients with neurogenic orthostatic hypotension. J Am Soc Hypertens 2016;10:819-826.
18. Norcliffe-Kaufmann L, Kaufmann H. Is ambulatory blood pressure monitoring useful in patients with chronic autonomic failure? Clin Auton Res 2014;24:189-192.
19. Palma JA, Gomez-Esteban JC, Norcliffe-Kaufmann L, et al. Orthostatic hypotension in Parkinson disease: how much you fall or how low you go? Mov Disord 2015 Apr 15;30(5):639-645. doi: 10.1002/mds.26079. Epub 2015 Feb 12.
20. Jain S, Goldstein DS. Cardiovascular dysautonomia in Parkinson disease: from pathophysiology to pathogenesis. Neurobiol Dis 2012;46:572-580.
21. Kaufmann H, Goldstein DS. Autonomic dysfunction in Parkinson disease. Handb Clin Neurol 2013;117:259-278.
22. Goldstein DS, Holmes CS, Dendi R, Bruce SR, Li ST. Orthostatic hypotension from sympathetic denervation in Parkinson's disease. Neurology 2002;58:1247-1255.
23. Nagayama H, Yamazaki M, Ueda M, et al. Low myocardial MIBG uptake in multiple system atrophy with incidental Lewy body pathology: an autopsy case report. Mov Disord 2008;23:1055-1057.
24. Nagayama H, Ueda M, Yamazaki M, Nishiyama Y, Hamamoto M, Katayama Y. Abnormal cardiac [(123)I]-meta-iodobenzylguanidine uptake in multiple system atrophy. Mov Disord 2010;25:1744-1747.
25. Goldstein DS. Dysautonomia in Parkinson disease. Compr Physiol 2014;4:805-826.
26. Orimo S, Oka T, Miura H, et al. Sympathetic cardiac denervation in Parkinson's disease and pure autonomic failure but not in multiple system atrophy. J Neurol Neurosurg Psychiatry 2002;73:776-777.
27. Braune S. The role of cardiac metaiodobenzylguanidine uptake in the differential diagnosis of parkinsonian syndromes. Clin Auton Res 2001;11:351-355.
28. Kaufmann H, Oribe E, Miller M, Knott P, Wiltshire-Clement M, Yahr MD. Hypotension-induced vasopressin release distinguishes between pure autonomic failure and multiple system atrophy with autonomic failure. Neurology 1992;42(3 Pt 1):590-593.
29. Palma JA, Gomez-Esteban JC, Norcliffe-Kaufmann L, et al. Orthostatic hypotension in Parkinson disease: how much you fall or how low you go? Mov Disord 2015;30:639-645.
30. Velseboer DC, de Haan RJ, Wieling W, Goldstein DS, de Bie RM. Prevalence of orthostatic hypotension in Parkinson's disease: a systematic review and meta-analysis. Parkinsonism Relat Disord 2011;17:724-729.
31. Thaisetthawatkul P, Boeve BF, Benarroch EE, et al. Autonomic dysfunction in dementia with Lewy bodies. Neurology 2004;62:1804-1809.
32. Horimoto Y, Matsumoto M, Akatsu H, et al. Autonomic dysfunctions in dementia with Lewy bodies. J Neurol 2003;250:530-533.
33. Gilman S, Low P, Quinn N, et al. Consensus statement on the diagnosis of multiple system atrophy. American Autonomic Society and American Academy of Neurology. Clin Auton Res 1998;8:359-362.
34. Low PA, Reich SG, Jankovic J, et al. Natural history of multiple system atrophy in the USA: a prospective cohort study. Lancet Neurol 2015;14:710-719.
35. Kaufmann H, Palma JA. Neurogenic orthostatic hypotension: the very basics. Clin Auton Res 2017;27(Suppl 1):39-43.
36. Gibbons CH, Schmidt P, Biaggioni I, et al. The recommendations of a consensus panel for the screening, diagnosis, and treatment of neurogenic orthostatic hypotension and associated supine hypertension. J Neurol 2017;264:1567-1582.
37. Lahrmann H, Cortelli P, Hilz M, Mathias CJ, Struhal W, Tassinari M. EFNS guidelines on the diagnosis and management of orthostatic hypotension. Eur J Neurol 2006;13:930-936.
38. Rose KM, Eigenbrodt ML, Biga RL, et al. Orthostatic hypotension predicts mortality in middle-aged adults: the Atherosclerosis Risk In Communities (ARIC) Study. Circulation 2006;114:630-636.
39. Rose KM, Tyroler HA, Nardo CJ, et al. Orthostatic hypotension and the incidence of coronary heart disease: the Atherosclerosis Risk in Communities study. Am J Hypertens 2000;13(6 Pt 1):571-578.
40. Kamaruzzaman S, Watt H, Carson C, Ebrahim S. The association between orthostatic hypotension and medication use in the British Women's Heart and Health Study. Age Ageing 2010;39:51-56.
41. Fotherby MD, Potter JF. Orthostatic hypotension and antihypertensive therapy in the elderly. Postgrad Med J 1994;70:878-881.
42. Biaggioni I, Robertson D, Krantz S, Jones M, Haile V. The anemia of primary autonomic failure and its reversal with recombinant erythropoietin. Ann Intern Med 1994;121:181-186.
43. Perera R, Isola L, Kaufmann H. Effect of recombinant erythropoietin on anemia and orthostatic hypotension in primary autonomic failure. Clin Auton Res 1995;5:211-213.
44. Shibao C, Gamboa A, Diedrich A, et al. Acarbose, an alpha-glucosidase inhibitor, attenuates postprandial hypotension in autonomic failure. Hypertension 2007;50:54-61.
45. May M, Jordan J. The osmopressor response to water drinking. Am J Physiol Regul Integr Comp Physiol 2011;300:R40-R46.
46. Freeman R. Clinical practice. Neurogenic orthostatic hypotension. N Engl J Med 2008;358:615-624.
47. Low DA, Vichayanrat E, Iodice V, Mathias CJ. Exercise hemodynamics in Parkinson's disease and autonomic dysfunction. Parkinsonism Relat Disord 2014;20:549-553.
48. Puvi-Rajasingham S, Smith GD, Akinola A, Mathias CJ. Abnormal regional blood flow responses during and after exercise in human sympathetic denervation. J Physiol 1997;505(Pt 3):841-849.
49. Smith GD, Mathias CJ. Postural hypotension enhanced by exercise in patients with chronic autonomic failure. QJM 1995;88:251-256.
50. Smith GD, Watson LP, Mathias CJ. Neurohumoral, peptidergic and biochemical responses to supine exercise in two groups with primary autonomic failure: Shy-Drager syndrome/multiple system atrophy and pure autonomic failure. Clin Auton Res 1996;6:255-262.
51. Rowell LB. Human Circulation: Regulation During Physical Stress. New York, NY: Oxford University Press; 1986.
52. Wieling W, van Lieshout JJ, van Leeuwen AM. Physical manoeuvres that reduce postural hypotension in autonomic failure. Clin Auton Res 1993;3:57-65.
53. Kooner JS, Raimbach S, Watson L, Bannister R, Peart S, Mathias CJ. Relationship between splanchnic vasodilation and

postprandial hypotension in patients with primary autonomic failure. J Hypertens Suppl 1989;7:S40-S41.

54. Freeman R, Wieling W, Axelrod FB, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clin Auton Res 2011;21:69-72.
55. Jansen RW, Lipsitz LA. Postprandial hypotension: epidemiology, pathophysiology, and clinical management. Ann Intern Med 1995;122:286-295.
56. Pavelic A, Krbot Skoric M, Crnosija L, Habek M. Postprandial hypotension in neurological disorders: systematic review and meta-analysis. Clin Auton Res 2017;27:263-271.
57. Goldstein DS, Cheshire WP, Jr. Beat-to-beat blood pressure and heart rate responses to the Valsalva maneuver. Clin Auton Res 2017;27:361-367.
58. Krediet CT, van Lieshout JJ, Bogert LW, Immink RV, Kim YS, Wieling W. Leg crossing improves orthostatic tolerance in healthy subjects: a placebo-controlled crossover study. Am J Physiol Heart Circ Physiol 2006;291:H1768-H1772.
59. Diedrich A, Biaggioni I. Segmental orthostatic fluid shifts. Clin Auton Res 2004;14:146-147.
60. Smit AA, Wieling W, Fujimura J, et al. Use of lower abdominal compression to combat orthostatic hypotension in patients with autonomic dysfunction. Clin Auton Res 2004;14:167-175.
61. Fanciulli A, Goebel G, Metzler B, et al. Elastic Abdominal Binders Attenuate Orthostatic Hypotension in Parkinson's Disease. Mov Disord Clin Pract 2016;3:156-160.
62. Okamoto LE, Diedrich A, Baudenbacher FJ, et al. Efficacy of Servo-Controlled Splanchnic Venous Compression in the Treatment of Orthostatic Hypotension: A Randomized Comparison With Midodrine. Hypertension 2016;68:418-426.
63. Shibao C, Martinez J, Palma J-A, Kaufmann H, Biaggioni I. Norepinephrine levels predicts the improvement in orthostatic symptoms after atomoxetine in patients with neurogenic orthostatic hypotension (P5.320). Neurology 2017;88(16 Suppl):P5.320.
64. Palma J-A, Martinez J, Perez M, Kaufmann H. Predictors of response to droxidopa in patients with neurogenic orthostatic hypotension (P5.318). Neurology 2017;88(16 Suppl):P5.318.
65. Jordan J, Shibao C, Biaggioni I. Multiple system atrophy: using clinical pharmacology to reveal pathophysiology. Clin Auton Res 2015;25:53-59.
66. Chobanian AV, Volicer L, Tifft CP, Gavras H, Liang CS, Faxon D. Mineralocorticoid-induced hypertension in patients with orthostatic hypotension. N Engl J Med 1979;301:68-73.
67. Grijalva CG, Biaggioni I, Griffin MR, Shibao CA. Fludrocortisone Is Associated With a Higher Risk of All-Cause Hospitalizations Compared With Midodrine in Patients With Orthostatic Hypotension. J Am Heart Assoc 2017;6. pii: e006848. doi: 10.1161/JAHA.117.006848.
68. Norcliffe-Kaufmann L, Axelrod FB, Kaufmann H. Developmental abnormalities, blood pressure variability and renal disease in Riley Day syndrome. J Hum Hypertens 2013;27:51-55.
69. Low PA, Gilden JL, Freeman R, Sheng KN, McElligott MA. Efficacy of midodrine vs placebo in neurogenic orthostatic hypotension. A randomized, double-blind multicenter study. Midodrine Study Group. JAMA 1997;277:1046-1051.
70. Wright RA, Kaufmann HC, Perera R, et al. A double-blind, dose-response study of midodrine in neurogenic orthostatic hypotension. Neurology 1998;51:120-124.
71. Smith W, Wan H, Much D, Robinson AG, Martin P. Clinical benefit of midodrine hydrochloride in symptomatic orthostatic hypotension: a phase 4, double-blind, placebo-controlled, randomized, tilt-table study. Clin Auton Res 2016;26(4):269-277.
72. McTavish D, Goa KL. Midodrine. A review of its pharmacological properties and therapeutic use in orthostatic hypotension and secondary hypotensive disorders. Drugs 1989;38:757-777.
73. Kaufmann H, Biaggioni I. Autonomic failure in neurodegenerative disorders. Semin Neurol 2003;23:351-363.
74. Kaufmann H, Malamut R, Norcliffe-Kaufmann L, Rosa K, Freeman R. The Orthostatic Hypotension Questionnaire (OHQ): validation of a novel symptom assessment scale. Clin Auton Res 2012;22:79-90.
75. Hauser RA, Isaacson S, Lisk JP, Hewitt LA, Rowse G. Droxidopa for the short-term treatment of symptomatic neurogenic orthostatic hypotension in Parkinson's disease (nOH306B). Mov Disord 2015;30:646-654.
76. Elgebaly A, Abdelazeim B, Mattar O, Gadelkarim M, Salah R, Negida A. Meta-analysis of the safety and efficacy of droxidopa for neurogenic orthostatic hypotension. Clin Auton Res 2016;26:171-180.
77. Kaufmann H. Droxidopa for symptomatic neurogenic orthostatic hypotension: what can we learn? Clin Auton Res 2017;27(Suppl 1):1-3.
78. Gupta F, Karabin B, Mehdirad A. Titrating droxidopa to maximize symptomatic benefit in a patient with Parkinson disease and neurogenic orthostatic hypotension. Clin Auton Res 2017;27(Suppl 1):15–16.
79. Vernino S, Claassen D. Polypharmacy: droxidopa to treat neurogenic orthostatic hypotension in a patient with Parkinson disease and type 2 diabetes mellitus. Clin Auton Res 2017;27(Suppl 1):33-34.
80. Kremens D, Lew M, Claassen D, Goodman BP. Adding droxidopa to fludrocortisone or midodrine in a patient with neurogenic orthostatic hypotension and Parkinson disease. Clin Auton Res 2017;27(Suppl 1):29-31.
81. Mehdirad A, Karabin B, Gupta F. Managing neurogenic orthostatic hypotension with droxidopa in a patient with Parkinson disease, atrial fibrillation, and hypertension. Clin Auton Res 2017;27(Suppl 1):25-27.
82. Claassen D, Lew M. Initiating droxidopa for neurogenic orthostatic hypotension in a patient with Parkinson disease. Clin Auton Res 2017;27(Suppl 1):13-14.
83. Goodman BP, Claassen D, Mehdirad A. Adjusting droxidopa for neurogenic orthostatic hypotension in a patient with Parkinson disease. Clin Auton Res 2017;27(Suppl 1):17-19.
84. Goodman BP, Gupta F. Defining successful treatment of neurogenic orthostatic hypotension with droxidopa in a patient with multiple system atrophy. Clin Auton Res 2017;27(Suppl 1):21-23.
85. Gupta F, Kremens D, Vernino S, Karabin B. Managing neurogenic orthostatic hypotension in a patient presenting with pure autonomic failure who later developed Parkinson disease. Clin Auton Res 2017;27(Suppl 1):9-11.
86. Kaufmann H, Saadia D, Voustianiouk A, et al. Norepinephrine precursor therapy in neurogenic orthostatic hypotension. Circulation 2003;108:724-728.
87. Espay AJ, LeWitt PA, Kaufmann H. Norepinephrine deficiency in Parkinson's disease: the case for noradrenergic enhancement. Mov Disord 2014;29:1710-1719.
88. Okamoto LE, Shibao C, Gamboa A, et al. Synergistic effect of norepinephrine transporter blockade and alpha-2 antagonism on blood pressure in autonomic failure. Hypertension 2012;59:650-656.
89. Shibao C, Raj SR, Gamboa A, et al. Norepinephrine transporter blockade with atomoxetine induces hypertension in patients with impaired autonomic function. Hypertension 2007;50:47-53.
90. Ramirez CE, Okamoto LE, Arnold AC, et al. Efficacy of atomoxetine versus midodrine for the treatment of orthostatic hypotension in autonomic failure. Hypertension 2014;64:1235-1240.
91. Camporeale A, Porsdal V, De Bruyckere K, et al. Safety and tolerability of atomoxetine in treatment of attention deficit hyperactivity disorder in adult patients: an integrated analysis of 15 clinical trials. J Psychopharmacol 2015;29:3-14.
92. Bangs ME, Jin L, Zhang S, et al. Hepatic events associated with atomoxetine treatment for attention-deficit hyperactivity disorder. Drug Saf 2008;31:345-354.
93. Singer W, Sandroni P, Opfer-Gehrking TL, et al. Pyridostigmine treatment trial in neurogenic orthostatic hypotension. Arch Neurol 2006;63:513-518.
94. Byun JI, Moon J, Kim DY, et al. Efficacy of single or combined midodrine and pyridostigmine in orthostatic hypotension. Neurology 2017;89:1078-1086.
95. Fanciulli A, Gobel G, Ndayisaba JP, et al. Supine hypertension in Parkinson's disease and multiple system atrophy. Clin Auton Res 2016;26:97-105.
96. Berganzo K, Diez-Arrola B, Tijero B, et al. Nocturnal hypertension and dysautonomia in patients with Parkinson's disease: are they related? J Neurol 2013;260:1752-1756.

97. Umehara T, Matsuno H, Toyoda C, Oka H. Clinical characteristics of supine hypertension in de novo Parkinson disease. Clin Auton Res 2016;26:15-21.

98. Shannon JR, Jordan J, Diedrich A, et al. Sympathetically mediated hypertension in autonomic failure. Circulation 2000;101: 2710-2715.

99. Goldstein DS, Pechnik S, Holmes C, Eldadah B, Sharabi Y. Association between supine hypertension and orthostatic hypotension in autonomic failure. Hypertension 2003;42:136-142.

100. Hanby MF, Panerai RB, Robinson TG, Haunton VJ. Is cerebral vasomotor reactivity impaired in Parkinson disease? Clin Auton Res 2017;27(2):107-111.

101. Norcliffe-Kaufmann L, Galindo-Mendez B, Garcia-Guarniz AL, Villarreal-Vitorica E, Novak V. Transcranial Doppler in autonomic testing: standards and clinical applications. Clin Auton Res. 2017 Aug 18. doi: 10.1007/s10286-017-0454-2. [Epub ahead of print]

102. MacLean AR, Allen EV. Orthostatic hypotension and orthostatic tachycardia—treatment with the "head-up" bed. JAMA 1940; 115:2162-2167.

103. Arnold AC, Biaggioni I. Management approaches to hypertension in autonomic failure. Curr Opin Nephrol Hypertens 2012;21: 481-485.

104. Di Stefano C, Maule S. Treatment of supine hypertension in autonomic failure: a case series. Clin Auton Res. 2017 Oct 28. doi: 10.1007/s10286-017-0479-6. [Epub ahead of print]

105. Fasano A, Visanji NP, Liu LW, Lang AE, Pfeiffer RF. Gastrointestinal dysfunction in Parkinson's disease. Lancet Neurol 2015; 14:625-639.

106. Pfeiffer RF. Gastrointestinal dysfunction in Parkinson's disease. Parkinsonism Relat Disord 2011;17:10-15.

107. Suttrup I, Warnecke T. Dysphagia in Parkinson's Disease. Dysphagia 2016;31:24-32.

108. Iwasaki S, Narabayashi Y, Hamaguchi K, Iwasaki A, Takakusagi M. Cause of death among patients with Parkinson's disease: a rare mortality due to cerebral haemorrhage. J Neurol 1990;237: 77-79.

109. Park H, Lee JY, Shin CM, Kim JM, Kim TJ, Kim JW. Characterization of gastrointestinal disorders in patients with parkinsonian syndromes. Parkinsonism Relat Disord 2015;21:455-460.

110. Jean A. Brain stem control of swallowing: neuronal network and cellular mechanisms. Physiol Rev 2001;81:929-969.

111. Schmeichel AM, Buchhalter LC, Low PA, et al. Mesopontine cholinergic neuron involvement in Lewy body dementia and multiple system atrophy. Neurology 2008;70:368-373.

112. Schwarzacher SW, Rub U, Deller T. Neuroanatomical characteristics of the human pre-Botzinger complex and its involvement in neurodegenerative brainstem diseases. Brain 2011;134(Pt 1):24-35.

113. Mu L, Sobotka S, Chen J, et al. Parkinson disease affects peripheral sensory nerves in the pharynx. J Neuropathol Exp Neurol 2013;72:614-623.

114. Suttrup I, Suttrup J, Suntrup-Krueger S, et al. Esophageal dysfunction in different stages of Parkinson's disease. Neurogastroenterol Motil 2017;29. doi: 10.1111/nmo.12915. Epub 2016 Jul 31.

115. Su A, Gandhy R, Barlow C, Triadafilopoulos G. Clinical and manometric characteristics of patients with Parkinson's disease and esophageal symptoms. Dis Esophagus 2017;30:1-6.

116. Arnhold M, Dening Y, Chopin M, et al. Changes in the sympathetic innervation of the gut in rotenone treated mice as possible early biomarker for Parkinson's disease. Clin Auton Res 2016;26: 211-222.

117. Derkinderen P, Rouaud T, Lebouvier T, Bruley des Varannes S, Neunlist M, De Giorgio R. Parkinson disease: The enteric nervous system spills its guts. Neurology 2011;77:1761-1767.

118. Gelpi E, Navarro-Otano J, Tolosa E, et al. Multiple organ involvement by alpha-synuclein pathology in Lewy body disorders. Mov Disord 2014;29:1010-1018.

119. Bestetti A, Capozza A, Lacerenza M, Manfredi L, Mancini F. Delayed Gastric Emptying in Advanced Parkinson Disease: Correlation With Therapeutic Doses. Clin Nucl Med 2017;42:83-87.

120. Yoshida M. Multiple system atrophy: alpha-synuclein and neuronal degeneration. Neuropathology 2007;27:484-493.

121. Kalf JG, de Swart BJ, Bloem BR, Munneke M. Prevalence of oropharyngeal dysphagia in Parkinson's disease: a meta-analysis. Parkinsonism Relat Disord 2012;18:311-315.

122. O'Sullivan SS, Massey LA, Williams DR, et al. Clinical outcomes of progressive supranuclear palsy and multiple system atrophy. Brain 2008;131(Pt 5):1362-1372.

123. Muller J, Wenning GK, Verny M, et al. Progression of dysarthria and dysphagia in postmortem-confirmed parkinsonian disorders. Arch Neurol 2001;58:259-264.

124. Kalf JG, de Swart BJ, Borm GF, Bloem BR, Munneke M. Prevalence and definition of drooling in Parkinson's disease: a systematic review. J Neurol 2009;256:1391-1396.

125. Mathias CJ. Gastrointestinal dysfunction in multiple system atrophy. Semin Neurol 1996;16:251-258.

126. Thomaides T, Karapanayiotides T, Zoukos Y, et al. Gastric emptying after semi-solid food in multiple system atrophy and Parkinson disease. J Neurol 2005;252:1055-1059.

127. Suzuki A, Asahina M, Ishikawa C, et al. Impaired circadian rhythm of gastric myoelectrical activity in patients with multiple system atrophy. Clin Auton Res 2005;15:368-372.

128. Tanaka Y, Kato T, Nishida H, et al. Is there delayed gastric emptying in patients with multiple system atrophy? An analysis using the (13)C-acetate breath test. J Neurol 2012;259:1448-1452.

129. Verbaan D, Marinus J, Visser M, van Rooden SM, Stiggelbout AM, van Hilten JJ. Patient-reported autonomic symptoms in Parkinson disease. Neurology 2007;69:333-341.

130. Knudsen K, Krogh K, Ostergaard K, Borghammer P. Constipation in parkinson's disease: Subjective symptoms, objective markers, and new perspectives. Mov Disord 2017;32:94-105.

131. Schmidt C, Herting B, Prieur S, et al. Autonomic dysfunction in different subtypes of multiple system atrophy. Mov Disord 2008; 23:1766-1772.

132. Sakakibara R, Odaka T, Uchiyama T, et al. Colonic transit time, sphincter EMG, and rectoanal videomanometry in multiple system atrophy. Mov Disord 2004;19:924-929.

133. Gao X, Chen H, Schwarzschild MA, Ascherio A. A prospective study of bowel movement frequency and risk of Parkinson's disease. Am J Epidemiol 2011;174:546-551.

134. Palma JA, Kaufmann H. Autonomic disorders predicting Parkinson's disease. Parkinsonism Relat Disord 2014;20(Suppl 1):S94-S98.

135. Stokholm MG, Danielsen EH, Hamilton-Dutoit SJ, Borghammer P. Pathological alpha-synuclein in gastrointestinal tissues from prodromal Parkinson disease patients. Ann Neurol 2016;79:940-949.

136. Tezuka T, Ozawa T, Takado Y, Sato Y, Oyake M, Nishizawa M. Megacolon in multiple system atrophy: safety concerns related to PEG. Mov Disord 2009;24:1096-1097.

137. Su A, Gandhy R, Barlow C, Triadafilopoulos G. A practical review of gastrointestinal manifestations in Parkinson's disease. Parkinsonism Relat Disord 2017;39:17-26.

138. van Hooren MR, Baijens LW, Voskuilen S, Oosterloo M, Kremer B. Treatment effects for dysphagia in Parkinson's disease: a systematic review. Parkinsonism Relat Disord 2014;20:800-807.

139. Triadafilopoulos G, Gandhy R, Barlow C. Pilot cohort study of endoscopic botulinum neurotoxin injection in Parkinson's disease. Parkinsonism Relat Disord 2017;44:33-37.

140. Heijnen BJ, Speyer R, Baijens LW, Bogaardt HC. Neuromuscular electrical stimulation versus traditional therapy in patients with Parkinson's disease and oropharyngeal dysphagia: effects on quality of life. Dysphagia 2012;27:336-345.

141. Menezes C, Melo A. Does levodopa improve swallowing dysfunction in Parkinson's disease patients? J Clin Pharm Ther 2009;34: 673-676.

142. Sutton JP. Dysphagia in Parkinson's disease is responsive to levodopa. Parkinsonism Relat Disord 2013;19:282-284.

143. Troche MS, Brandimore AE, Foote KD, Okun MS. Swallowing and deep brain stimulation in Parkinson's disease: a systematic review. Parkinsonism Relat Disord 2013;19:783-788.

144. Ueha R, Nito T, Sakamoto T, Yamauchi A, Tsunoda K, Yamasoba T. Post-operative swallowing in multiple system atrophy. Eur J Neurol 2016;23:393-400.

145. Higo R, Tayama N, Watanabe T, Nitou T, Takeuchi S. Vocal fold motion impairment in patients with multiple system atrophy: evaluation of its relationship with swallowing function. J Neurol Neurosurg Psychiatry 2003;74:982-984.

146. Arbouw ME, Movig KL, Koopmann M, et al. Glycopyrrolate for sialorrhea in Parkinson disease: a randomized, double-blind, crossover trial. Neurology 2010;74:1203-1207.

147. Hyson HC, Johnson AM, Jog MS. Sublingual atropine for sialorrhea secondary to parkinsonism: a pilot study. Mov Disord 2002; 17:1318-1320.

148. Thomsen TR, Galpern WR, Asante A, Arenovich T, Fox SH. Ipratropium bromide spray as treatment for sialorrhea in Parkinson's disease. Mov Disord 2007;22:2268-2273.

149. Srivanitchapoom P, Pandey S, Hallett M. Drooling in Parkinson's disease: a review. Parkinsonism Relat Disord 2014;20:1109-1118.

150. Marks L, Turner K, O'Sullivan J, Deighton B, Lees A. Drooling in Parkinson's disease: a novel speech and language therapy intervention. Int J Lang Commun Disord 2001;36(Suppl):282-287.

151. Postma AG, Heesters M, van Laar T. Radiotherapy to the salivary glands as treatment of sialorrhea in patients with parkinsonism. Mov Disord 2007;22:2430-2435.

152. Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L; American College of Gastroenterology. Clinical guideline: management of gastroparesis. Am J Gastroenterol 2013;108:18-37; quiz, 38.

153. Magnifico F, Pierangeli G, Barletta G, et al. The cardiovascular effects of metoclopramide in multiple system atrophy and pure autonomic failure. Clin Auton Res 2001;11:163-168.

154. Shin HW, Kim MJ, Kim JS, Lee MC, Chung SJ. Levosulpiride-induced movement disorders. Mov Disord 2009;24:2249-2253.

155. Soykan I, Sarosiek I, Shifflett J, Wooten GF, McCallum RW. Effect of chronic oral domperidone therapy on gastrointestinal symptoms and gastric emptying in patients with Parkinson's disease. Mov Disord 1997;12:952-957.

156. Sigurdardottir GR, Nilsson C, Odin P, Grabowski M. Cardiovascular effects of domperidone in patients with Parkinson's disease treated with apomorphine. Acta Neurol Scand 2001;104:92-96.

157. Janssens J, Peeters TL, Vantrappen G, et al. Improvement of gastric emptying in diabetic gastroparesis by erythromycin. Preliminary studies. N Engl J Med 1990;322:1028-1031.

158. Larson JM, Tavakkoli A, Drane WE, Toskes PP, Moshiree B. Advantages of azithromycin over erythromycin in improving the gastric emptying half-time in adult patients with gastroparesis. J Neurogastroenterol Motil 2010;16:407-413.

159. Sanger GJ, Furness JB. Ghrelin and motilin receptors as drug targets for gastrointestinal disorders. Nat Rev Gastroenterol Hepatol 2016;13:38-48.

160. Malagelada JR, Rees WD, Mazzotta LJ, Go VL. Gastric motor abnormalities in diabetic and postvagotomy gastroparesis: effect of metoclopramide and bethanechol. Gastroenterology 1980;78: 286-293.

161. Futagami S, Shimpuku M, Song JM, et al. Nizatidine improves clinical symptoms and gastric emptying in patients with functional dyspepsia accompanied by impaired gastric emptying. Digestion 2012;86:114-121.

162. Gil RA, Hwynn N, Fabian T, Joseph S, Fernandez HH. Botulinum toxin type A for the treatment of gastroparesis in Parkinson's disease patients. Parkinsonism Relat Disord 2011;17:285-287.

163. Bai Y, Xu MJ, Yang X, et al. A systematic review on intrapyloric botulinum toxin injection for gastroparesis. Digestion 2010;81: 27-34.

164. Arai E, Arai M, Uchiyama T, et al. Subthalamic deep brain stimulation can improve gastric emptying in Parkinson's disease. Brain 2012;135(Pt 5):1478-1485.

165. Heckert J, Sankineni A, Hughes WB, Harbison S, Parkman H. Gastric Electric Stimulation for Refractory Gastroparesis: A Prospective Analysis of 151 Patients at a Single Center. Dig Dis Sci 2016;61:168-175.

166. Stern T, Davis AM. Evaluation and Treatment of Patients With Constipation. JAMA 2016;315:192-193.

167. Coggrave M, Norton C, Cody JD. Management of faecal incontinence and constipation in adults with central neurological diseases. Cochrane Database Syst Rev 2014;(1):CD002115.

168. Barichella M, Pacchetti C, Bolliri C, et al. Probiotics and prebiotic fiber for constipation associated with Parkinson disease: An RCT. Neurology 2016;87:1274-1280.

169. Pare P, Fedorak RN. Systematic review of stimulant and nonstimulant laxatives for the treatment of functional constipation. Can J Gastroenterol Hepatol 2014;28:549-557.

170. Ashraf W, Pfeiffer RF, Park F, Lof J, Quigley EM. Constipation in Parkinson's disease: objective assessment and response to psyllium. Mov Disord 1997;12:946-951.

171. Zangaglia R, Martignoni E, Glorioso M, et al. Macrogol for the treatment of constipation in Parkinson's disease. A randomized placebo-controlled study. Mov Disord 2007;22:1239-1244.

172. Siegel JD, Di Palma JA. Medical treatment of constipation. Clin Colon Rectal Surg 2005;18:76-80.

173. Ondo WG, Kenney C, Sullivan K, et al. Placebo-controlled trial of lubiprostone for constipation associated with Parkinson disease. Neurology 2012;78:1650-1654.

174. Lembo AJ, Schneier HA, Shiff SJ, et al. Two randomized trials of linaclotide for chronic constipation. N Engl J Med 2011;365:527-536.

175. Miner PB, Jr., Koltun WD, Wiener GJ, et al. A Randomized Phase III Clinical Trial of Plecanatide, a Uroguanylin Analog, in Patients With Chronic Idiopathic Constipation. Am J Gastroenterol 2017;112:613-621.

176. Al-Salama ZT, Syed YY. Plecanatide: First Global Approval. Drugs 2017;77:593-598.

177. Jost WH, Schimrigk K. Long-term results with cisapride in Parkinson's disease. Mov Disord 1997;12:423-425.

178. Jost WH, Schimrigk K. Cisapride treatment of constipation in Parkinson's disease. Mov Disord 1993;8:339-343.

179. Morgan JC, Sethi KD. Tegaserod in constipation associated with Parkinson disease. Clin Neuropharmacol 2007;30:52-54.

180. Sullivan KL, Staffetti JF, Hauser RA, Dunne PB, Zesiewicz TA. Tegaserod (Zelnorm) for the treatment of constipation in Parkinson's disease. Mov Disord 2006;21:115-116.

181. Liu Z, Sakakibara R, Odaka T, et al. Mosapride citrate, a novel 5-HT4 agonist and partial 5-HT3 antagonist, ameliorates constipation in parkinsonian patients. Mov Disord 2005;20:680-686.

182. Chey WD, Camilleri M, Chang L, Rikner L, Graffner H. A randomized placebo-controlled phase IIb trial of a3309, a bile acid transporter inhibitor, for chronic idiopathic constipation. Am J Gastroenterol 2011;106:1803-1812.

183. Corsetti M, Tack J. New pharmacological treatment options for chronic constipation. Expert Opin Pharmacother 2014;15:927-941.

184. Camilleri M, Acosta A. Emerging treatments in Neurogastroenterology: relamorelin: a novel gastrocolokinetic synthetic ghrelin agonist. Neurogastroenterol Motil 2015;27:324-332.

185. Sakakibara R, Tateno F, Yamamoto T, Uchiyama T, Yamanishi T. Urological dysfunction in synucleinopathies: epidemiology, pathophysiology and management. Clin Auton Res 2018;28:83-101.

186. McKay JH, Cheshire WP. First symptoms in multiple system atrophy. Clin Auton Res 2018 Jan 8. doi: 10.1007/s10286-017-0500-0. [Epub ahead of print]

187. Beach TG, Adler CH, Sue LI, et al. Multi-organ distribution of phosphorylated alpha-synuclein histopathology in subjects with Lewy body disorders. Acta Neuropathol 2010;119:689-702.

188. McDonald C, Winge K, Burn DJ. Lower urinary tract symptoms in Parkinson's disease: Prevalence, aetiology and management. Parkinsonism Relat Disord 2017;35:8-16.

189. Sakakibara R, Ito T, Uchiyama T, et al. Lower urinary tract function in dementia of Lewy body type. J Neurol Neurosurg Psychiatry 2005;76:729-732.

190. Tateno F, Sakakibara R, Ogata T, et al. Lower urinary tract function in dementia with Lewy bodies (DLB). Mov Disord 2015;30: 411-415.

191. Ogawa T, Sakakibara R, Kuno S, Ishizuka O, Kitta T, Yoshimura N. Prevalence and treatment of LUTS in patients with Parkinson disease or multiple system atrophy. Nat Rev Urol 2017;14:79-89.

192. Sakakibara R, Hattori T, Uchiyama T, Yamanishi T. Videourodynamic and sphincter motor unit potential analyses in Parkinson's

disease and multiple system atrophy. J Neurol Neurosurg Psychiatry 2001;71:600-606.

193. Stocchi F, Carbone A, Inghilleri M, et al. Urodynamic and neurophysiological evaluation in Parkinson's disease and multiple system atrophy. J Neurol Neurosurg Psychiatry 1997;62:507-511.

194. Coon EA, Sletten DM, Suarez MD, et al. Clinical features and autonomic testing predict survival in multiple system atrophy. Brain 2015;138(Pt 12):3623-3631.

195. Zesiewicz TA, Evatt M, Vaughan CP, et al. Randomized, controlled pilot trial of solifenacin succinate for overactive bladder in Parkinson's disease. Parkinsonism Relat Disord 2015;21:514-520.

196. Vaughan CP, Juncos JL, Burgio KL, Goode PS, Wolf RA, Johnson TM II. Behavioral therapy to treat urinary incontinence in Parkinson disease. Neurology 2011;76:1631-1634.

197. Kuo HC, Lee KS, Na Y, et al. Results of a randomized, double-blind, parallel-group, placebo- and active-controlled, multicenter study of mirabegron, a beta3-adrenoceptor agonist, in patients with overactive bladder in Asia. Neurourol Urodyn 2015;34:685-692.

198. Giannantoni A, Conte A, Proietti S, et al. Botulinum toxin type A in patients with Parkinson's disease and refractory overactive bladder. J Urol 2011;186:960-964.

199. Kulaksizoglu H, Parman Y. Use of botulinim toxin-A for the treatment of overactive bladder symptoms in patients with Parkinsons's disease. Parkinsonism Relat Disord 2010;16:531-534.

200. Giannantoni A, Rossi A, Mearini E, Del Zingaro M, Porena M, Berardelli A. Botulinum toxin A for overactive bladder and detrusor muscle overactivity in patients with Parkinson's disease and multiple system atrophy. J Urol 2009;182:1453-1457.

201. Suchowersky O, Furtado S, Rohs G. Beneficial effect of intranasal desmopressin for nocturnal polyuria in Parkinson's disease. Mov Disord 1995;10:337-340.

202. Witte LP, Odekerken VJJ, Boel JA, et al. Does deep brain stimulation improve lower urinary tract symptoms in Parkinson's disease? Neurourol Urodyn. 2017 May 2. doi: 10.1002/nau.23301. [Epub ahead of print]

203. Mock S, Osborn DJ, Brown ET, et al. The Impact of Pallidal and Subthalamic Deep Brain Stimulation on Urologic Function in Parkinson's Disease. Neuromodulation 2016;19:717-723.

204. Possover M. The laparoscopic implantation of neuroprothesis to the sacral plexus for therapy of neurogenic bladder dysfunctions after failure of percutaneous sacral nerve stimulation. Neuromodulation 2010;13:141-144.

205. Wallace PA, Lane FL, Noblett KL. Sacral nerve neuromodulation in patients with underlying neurologic disease. Am J Obstet Gynecol 2007;197:96.e1-e5.

206. Kabay SC, Kabay S, Yucel M, Ozden H. Acute urodynamic effects of percutaneous posterior tibial nerve stimulation on neurogenic detrusor overactivity in patients with Parkinson's disease. Neurourol Urodyn 2009;28:62-67.

207. Ohannessian A, Kabore FA, Agostini A, et al. [Transcutaneous tibial nerve stimulation in the overactive bladder syndrome in patients with Parkinson's syndromes]. Prog Urol 2013;23:936-939.

208. Brusa L, Finazzi Agro E, Petta F, et al. Effects of inhibitory rTMS on bladder function in Parkinson's disease patients. Mov Disord 2009;24:445-448.

209. Chen TY, Ponsot Y, Carmel M, Bouffard N, Kennelly MJ, Tu LM. Multi-centre study of intraurethral valve-pump catheter in women with a hypocontractile or acontractile bladder. Eur Urol 2005;48:628-633.

210. Kirchhof K, Apostolidis AN, Mathias CJ, Fowler CJ. Erectile and urinary dysfunction may be the presenting features in patients with multiple system atrophy: a retrospective study. Int J Impot Res 2003;15:293-298.

211. Ozcan T, Benli E, Ozer F, Demir EY, Kaya Y, Ayyildiz A. The association between symptoms of sexual dysfunction and age at onset in Parkinson's disease. Clin Auton Res 2016;26:205-209.

212. Gao X, Chen H, Schwarzschild MA, et al. Erectile function and risk of Parkinson's disease. Am J Epidemiol 2007;166:1446-1450.

213. Mobley DF, Khera M, Baum N. Recent advances in the treatment of erectile dysfunction. Postgrad Med J 2017;93:679-685.

214. Wright PJ. Comparison of phosphodiesterase type 5 (PDE5) inhibitors. Int J Clin Pract 2006;60:967-975.

215. Zesiewicz TA, Helal M, Hauser RA. Sildenafil citrate (Viagra) for the treatment of erectile dysfunction in men with Parkinson's disease. Mov Disord 2000;15:305-308.

216. Raffaele R, Vecchio I, Giammusso B, Morgia G, Brunetto MB, Rampello L. Efficacy and safety of fixed-dose oral sildenafil in the treatment of sexual dysfunction in depressed patients with idiopathic Parkinson's disease. Eur Urol 2002;41:382-386.

217. Hussain IF, Brady CM, Swinn MJ, Mathias CJ, Fowler CJ. Treatment of erectile dysfunction with sildenafil citrate (Viagra) in parkinsonism due to Parkinson's disease or multiple system atrophy with observations on orthostatic hypotension. J Neurol Neurosurg Psychiatry 2001;71:371-374.

218. Rocinante M. Living with autonomic failure. Clin Auton Res 2008;18:48-51.

219. Costa P, Potempa AJ. Intraurethral alprostadil for erectile dysfunction: a review of the literature. Drugs 2012;72:2243-2254.

220. O'Sullivan JD, Hughes AJ. Apomorphine-induced penile erections in Parkinson's disease. Mov Disord 1998;13:536-539.

221. Dula E, Bukofzer S, Perdok R, George M, Apomorphine SLSG. Double-blind, crossover comparison of 3 mg apomorphine SL with placebo and with 4 mg apomorphine SL in male erectile dysfunction. Eur Urol 2001;39:558-553; discussion, 564.

222. Dula E, Keating W, Siami PF, Edmonds A, O'Neil J, Buttler S. Efficacy and safety of fixed-dose and dose-optimization regimens of sublingual apomorphine versus placebo in men with erectile dysfunction. The Apomorphine Study Group. Urology 2000;56:130-135.

223. Perimenis P, Markou S, Gyftopoulos K, et al. Efficacy of apomorphine and sildenafil in men with nonarteriogenic erectile dysfunction. A comparative crossover study. Andrologia 2004;36:106-110.

224. Allahdadi KJ, Tostes RC, Webb RC. Female sexual dysfunction: therapeutic options and experimental challenges. Cardiovasc Hematol Agents Med Chem 2009;7:260-269.

225. Holmqvist S, Chutna O, Bousset L, et al. Direct evidence of Parkinson pathology spread from the gastrointestinal tract to the brain in rats. Acta Neuropathol 2014;128:805-820.

226. Pan-Montojo F, Schwarz M, Winkler C, et al. Environmental toxins trigger PD-like progression via increased alpha-synuclein release from enteric neurons in mice. Sci Rep 2012;2:898.

227. Svensson E, Horvath-Puho E, Thomsen RW, et al. Vagotomy and subsequent risk of Parkinson's disease. Ann Neurol 2015;78:522-529.

228. Okamoto LE, Gamboa A, Shibao CA, et al. Nebivolol, but not metoprolol, lowers blood pressure in nitric oxide-sensitive human hypertension. Hypertension 2014;64:1241-1247.

229. Espinosa-Medina I, Saha O, Boismoreau F, Brunet JF. The "sacral parasympathetic": ontogeny and anatomy of a myth. Clin Auton Res 2018;28:13-21.