My Auto-Pilot Has Been Compromised:
Tips and Tricks for Dealing with Dysautonomia

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Epidemiology: Who is affected?

Dysautonomia is a frequent, underrecognized and disabling complication of Parkinson's disease (PD).

80% with Parkinson's disease have autonomic dysfunction

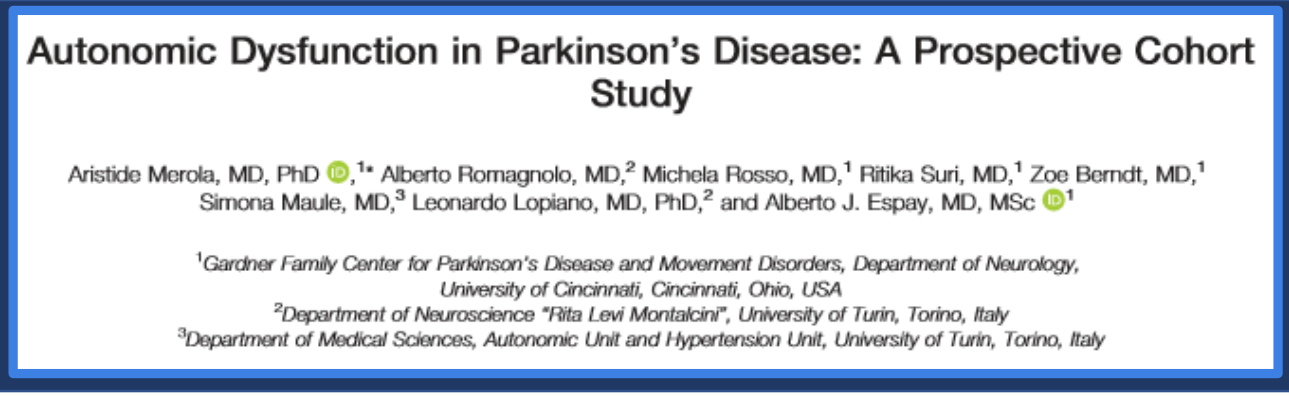
Most Common Symptoms of Dysautonomia:

1. Constipation: Reported by up to 90% of patients with PD
2. Orthostatic Hypotension (OH)
   - Definition: a fall of 20 mm Hg systolic and 10 mm Hg diastolic within 3 min of standing
   - 30-50% in PD
     - < 1/3 are Symptomatic (i.e. 16%)
     - Prevalence increases with age and disease duration

3. Merola A, Romagnolo A, Rosso M, Suri R, Berndt Z, Maule S, Lopiano L, Espay AJ. Autonomic dysfunction in Parkinson's disease: A prospective cohort study. Mov Disord. 2018 Mar;33(3):391-397. doi: 10.1002/mds.27268. Epub 2017 Dec 26. PubMed PMID: 29278286.

11. Romagnolo A, Zibetti M, Merola A, Canova D, Sarchioto M, Montanaro E, Artusi CA, Vallelonga F, Maule S, Lopiano L. Cardiovascular autonomic neuropathy and falls in Parkinson disease: a prospective cohort study. J Neurol. 2019 Jan;266(1):85-91. doi: 10.1007/s00415-018-9104-4. Epub 2018 Oct 31. PubMed PMID: 30382389.

12. Martínez-Fernández R, Schmitt E, Martinez-Martin P, Krack P. The hidden sister of motor fluctuations in Parkinson's disease: A review on nonmotor fluctuations. Mov Disord. 2016 Aug;31(8):1080-94. doi: 10.1002/mds.26731. Epub 2016 Jul 19. Review. PubMed PMID: 27431515.



Autonomic Dysfunction in Parkinson's Disease: A Prospective Cohort Study

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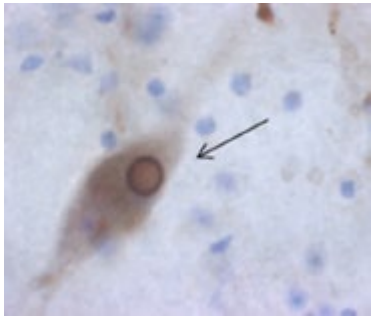
In a Prospective Cohort Study:

- 20-40% had cardiovascular features including: orthostatic hypotension (OH) and supine hypertension (SH)
- 20-60% of PD patient report urinary or sexual dysfunction
- 10-15% thermoregulatory dysregulation
- 10-20% pupillomotor disorders (impaired pupillary function and visual focus)

3. Merola A, Romagnolo A, Rosso M, Suri R, Berndt Z, Maule S, Lopiano L, Espay AJ. Autonomic dysfunction in Parkinson's disease: A prospective cohort study. Mov Disord. 2018 Mar;33(3):391-397. doi: 10.1002/mds.27268. Epub 2017 Dec 26. PubMed PMID: 29278286.

What is dysautonomia?

- Definition: dysfunction of the autonomic nervous system.
- The autonomic nervous system is responsible for control of the bodily functions not consciously directed:
  - blood pressure, heartbeat, temperature regulation and digestive processes.
- Autonomic dysfunction is a characteristic feature of synucleinopathies like Parkinson's disease (PD), Dementia with Lewy Bodies (DLB), and Pure Autonomic Failure (PAF)
- Autonomic dysfunction occurs in all disease stages



2. Leclair-Visonneau L, Magy L, Volteau C, Clairembault T, Le Dily S, Préterre C, Peyre A, Damier P, Neunlist M, Péréon Y, Derkinderen P. Heterogeneous pattern of autonomic dysfunction in Parkinson's disease. J Neurol. 2018 Apr;265(4):933-941. doi: 10.1007/s00415-018-8789-8. Epub 2018 Feb 20. PubMed PMID: 29464374.

4. Palma JA, Kaufmann H. Treatment of autonomic dysfunction in Parkinson disease and other synucleinopathies. Mov Disord. 2018 Mar;33(3):372-390. doi: 10.1002/mds.27344. Review. PubMed PMID: 29508455; PubMed Central PMCID: PMC5844369.

Common Dysautonomia Symptoms

- Autonomic dysfunction underlies some of the most frequent and debilitating non-motor symptoms in Parkinson's disease:
  - Constipation
  - Orthostatic lightheadedness
  - Urinary problems
  - Heat or cold intolerance
  - Sweating problems
  - Drooling
  - Swallowing problems

What is the Impact?

- Dysautonomia may occur early in PD, at 3x the rate of healthy age matched controls→ 8 fold increase in progression of cognitive deficits
- 20% difference in 10 year survival rate in PD with and without OH (74% vs. 93%)
- Prevalence of under-recognized dysautonomia in PD remains close to 50%

3. Merola A, Romagnolo A, Rosso M, Suri R, Berndt Z, Maule S, Lopiano L, Espay AJ. Autonomic dysfunction in Parkinson's disease: A prospective cohort study. Mov Disord. 2018 Mar;33(3):391-397. doi: 10.1002/mds.27268. Epub 2017 Dec 26. PubMed PMID: 29278286.

Autonomic Nervous System

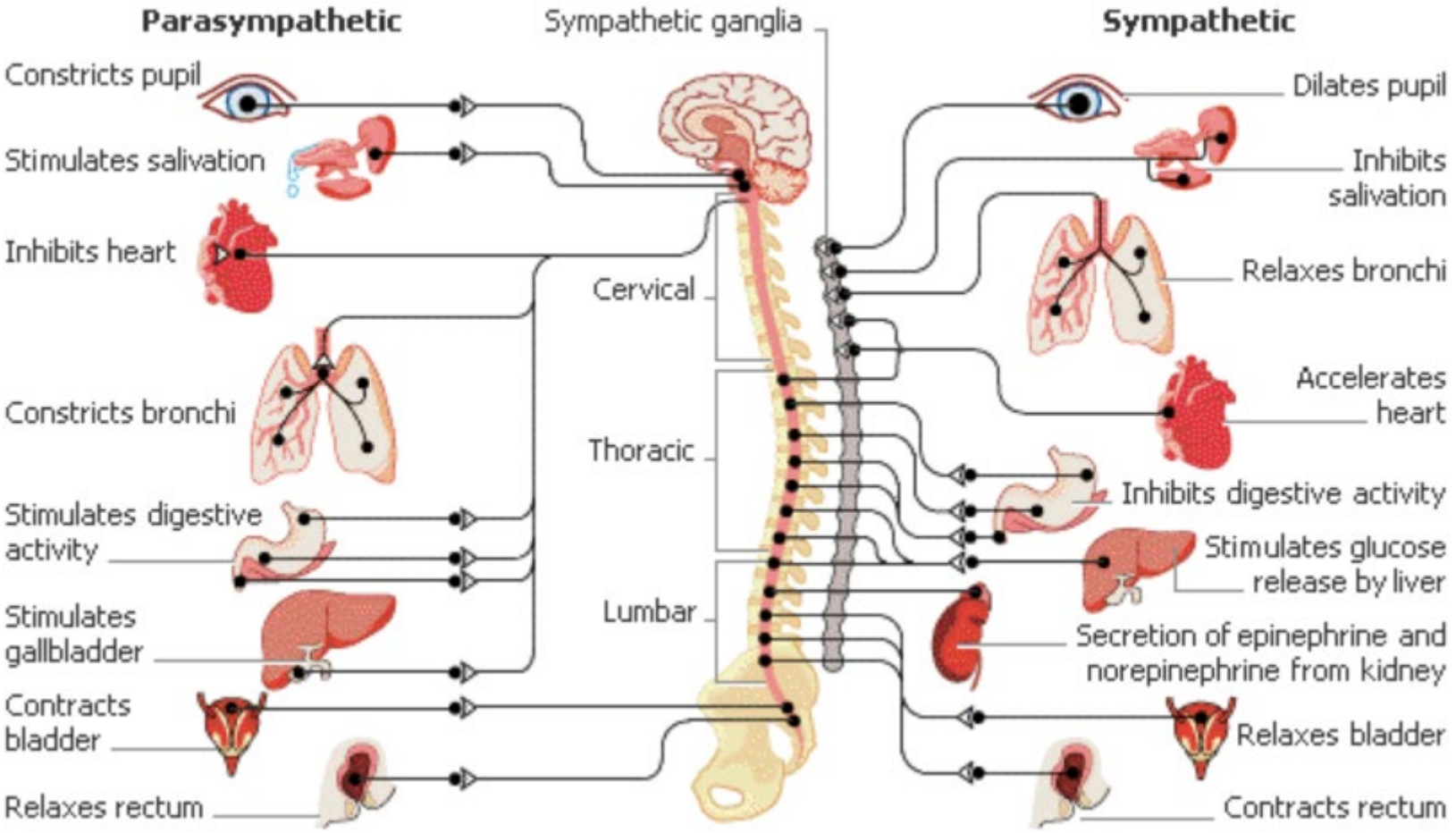


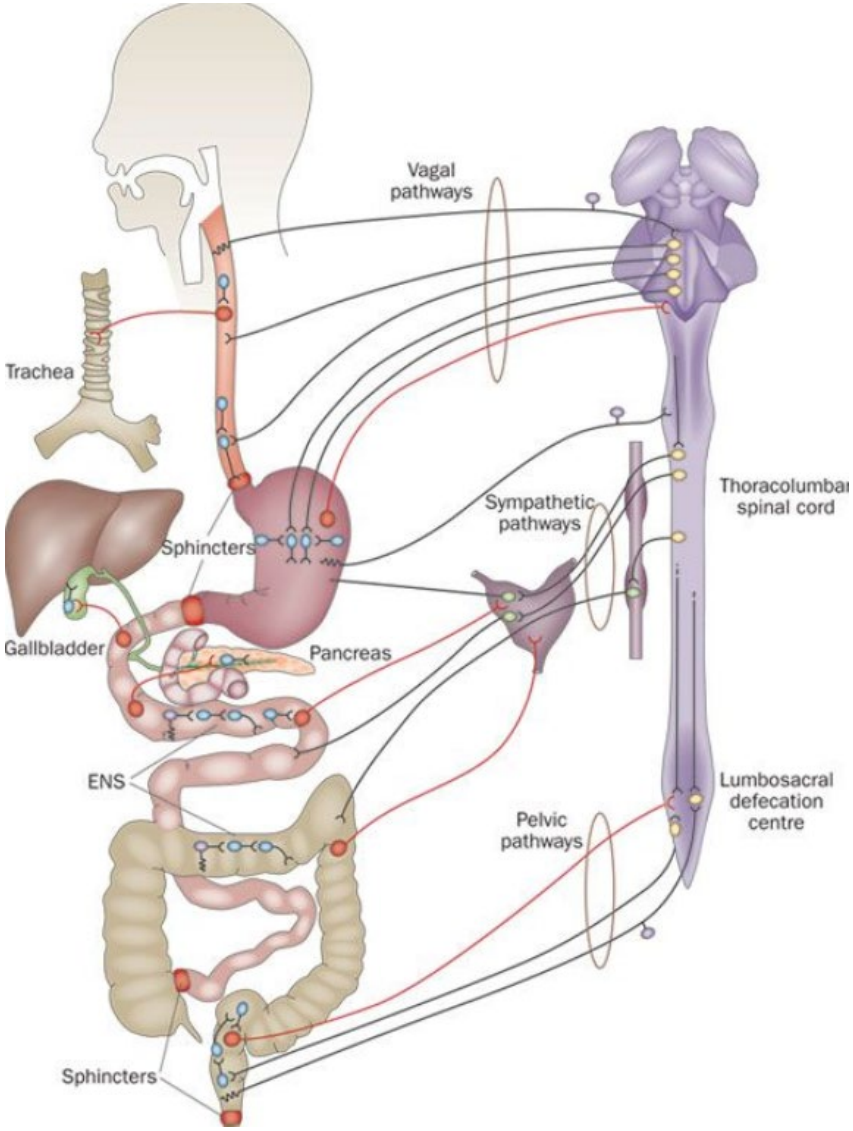
Image: http://lorigodin.com/para-and-sympathetic-system-2/

Symptoms of Autonomic Dysfunction

- Sympathetic nervous system dysfunction →
  - Orthostatic hypotension
  - Dyshidrosis (Sweating dysfunction)
  - Thermal intolerance
  - Altered pupillary dilation
  - Fecal incontinence
  - Urinary urgency
  - Unexplained Pain?

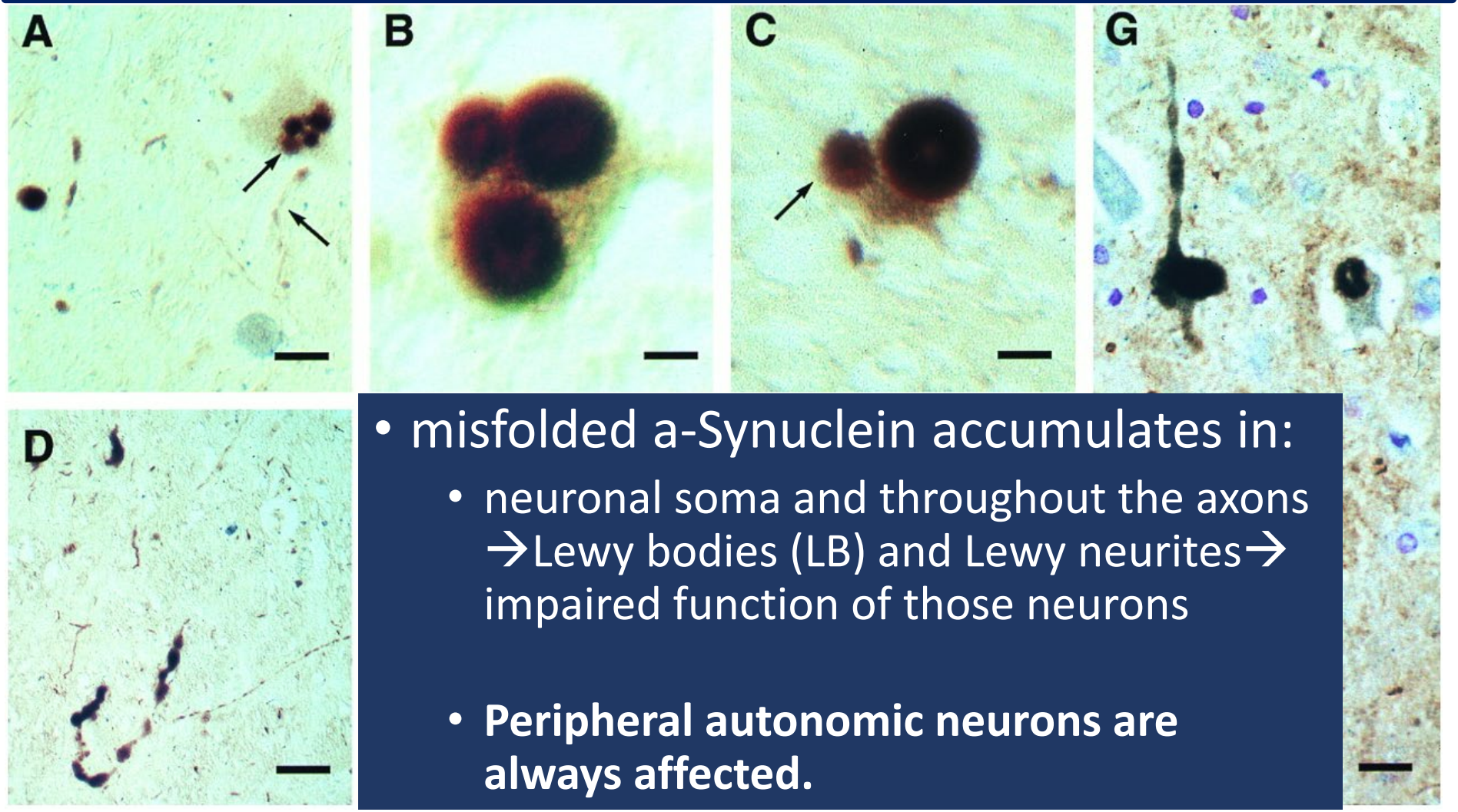
- Parasympathetic nervous system dysfunction →
  - Constipation
  - Dry mouth
  - Dry eyes
  - Invariable pulse rate
  - Swallowing problems (dysphagia)
  - Gastroparesis (delayed gastric emptying)
  - Urinary retention
  - Erectile dysfunction

- Enteric nervous system (ENS) dysfunction →
  - Delayed gastric emptying (early satiety, nausea)
  - Constipation



2. Leclair-Visonneau L, Magy L, Volteau C, Clairembault T, Le Dily S, Préterre C, Peyre A, Damier P, Neunlist M, Péréon Y, Derkinderen P. Heterogeneous pattern of autonomic dysfunction in Parkinson's disease. J Neurol. 2018 Apr;265(4):933-941. doi: 10.1007/s00415-018-8789-8. Epub 2018 Feb 20. PubMed PMID: 29464374.
Image: https://doi.org/10.1038/nrgastro.2012.3210.1038/nrgastro.2012.32

Why Does Dysautonomia Occur in Parkinson's Disease?

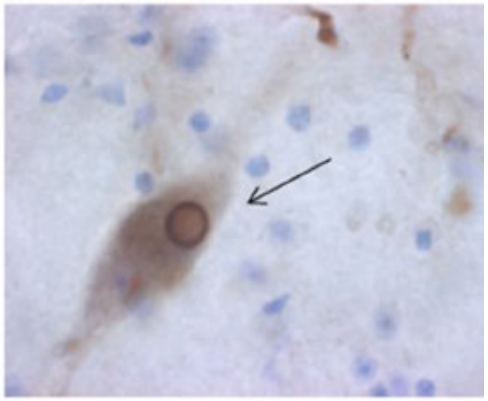


- misfolded a-Synuclein accumulates in:
  - neuronal soma and throughout the axons →Lewy bodies (LB) and Lewy neurites→ impaired function of those neurons
  - **Peripheral autonomic neurons are always affected.**

4. Palma JA, Kaufmann H. Treatment of autonomic dysfunction in Parkinson disease and other synucleinopathies. Mov Disord. 2018 Mar;33(3):372-390. doi: 10.1002/mds.27344. Review. PubMed PMID: 29508455; PubMed Central PMCID: PMC5844369.

17. Image: Parkinson's disease and dementia with lewy bodies. Proc Natl Acad Sci U S A. 1998 May 26;95(11):6469-73. PubMed PMID: 9600990; PubMed Central PMCID: PMC27806.

Lewy Body Disease



Impact of Dysautonomia

- Dysautonomia is a key driver of health-related quality of life (HRQoL), mobility and cognition in Parkinson's disease (PD).
- Cardiovascular Autonomic Neuropathy (cAN (including Orthostatic hypotension) can directly (chronic hypoperfusion) or indirectly (falls, fractures, and other secondary damages) contribute to disability and mortality in PD.
- cAN is associated with 15-fold increase in falls (even after adjusting for disease duration, axial symptom severity, cognitive impairment, and dopaminergic treatment).

3. Merola A, Romagnolo A, Rosso M, Suri R, Berndt Z, Maule S, Lopiano L, Espay AJ. Autonomic dysfunction in Parkinson's disease: A prospective cohort study. Mov Disord. 2018 Mar;33(3):391-397. doi: 10.1002/mds.27268. Epub 2017 Dec 26. PubMed PMID: 29278286.

11. Romagnolo A, Zibetti M, Merola A, Canova D, Sarchioto M, Montanaro E, Artusi CA, Vallelonga F, Maule S, Lopiano L. Cardiovascular autonomic neuropathy and falls in Parkinson disease: a prospective cohort study. J Neurol. 2019 Jan;266(1):85-91. doi: 10.1007/s00415-018-9104-4. Epub 2018 Oct 31. PubMed PMID: 30382389.

Impact on ADLs & HRQoL

ADL =Activities of Daily Living (any daily activity we perform for self-care such as feeding ourselves, bathing, dressing, grooming, work, homemaking, and leisure).

HRQoL: includes domains related to physical, mental, emotional, and social functioning. This focuses on the impact health status has on **quality of life**.

Worsening of autonomic symptoms is associated with deterioration in Activities of daily living (P= 0.021) and Health Related Quality of Life (P= 0.025)

TABLE 2. Autonomic symptoms, ADL, and HRQoL

Autonomic Symptoms Worsening	ADL Deterioration OR (95% CI)	*P* Value	HRQoL Deterioration OR (95% CI)	*P* Value
SCOPA-AUT total score	2.097 (1.171-5.084)	**0.021**	2.998 (1.143-8.445)	**0.025**
Gastrointestinal domain	2.235 (1.081-5.144)	**0.034**	2.909 (1.164-7.269)	**0.022**
Urinary-sexual domain	1.828 (0.795-4.202)	0.155	2.542 (1.005-6.435)	**0.049**
Cardiovascular domain	2.340 (1.021-6.067)	**0.041**	3.516 (1.342-9.215)	**0.011**
Thermoregulatory domain	2.151 (0.926-4.998)	0.075	3.487 (1.546-8.777)	**0.005**
Pupillomotor domain	2.201 (0.496-8.760)	0.299	2.098 (0.943-3.201)	0.147

Data adjusted for disease duration, Montreal Cognitive Assessment (MoCA) and Movement Disorders Society Unified Parkinson's disease Rating Scale (MDS-UPDRS) section-III scores modification during follow-up.
CI, confidence interval; ADL, activities of daily living and HRQoL for health related quality of life.

3. Merola A, Romagnolo A, Rosso M, Suri R, Berndt Z, Maule S, Lopiano L, Espay AJ. Autonomic dysfunction in Parkinson's disease: A prospective cohort study. Mov Disord. 2018 Mar;33(3):391-397. doi: 10.1002/mds.27268. Epub 2017 Dec 26. PubMed PMID: 29278286.

Dysautonomia Scales

- SCOPA-Aut (Scales for Outcomes in PD-Autonomic symptoms)
- NMS-Quest (Non-motor symptoms questionnaire)
- Rome III constipation criteria
- Orthostatic Hypotension Questionnaire (OHQ)

2. Leclair-Visonneau L, Magy L, Volteau C, Clairembault T, Le Dily S, Préterre C, Peyre A, Damier P, Neunlist M, Péréon Y, Derkinderen P. Heterogeneous pattern of autonomic dysfunction in Parkinson's disease. J Neurol. 2018 Apr;265(4):933-941. doi: 10.1007/s00415-018-8789-8. Epub 2018 Feb 20. PubMed PMID: 29464374.

7. Fanciulli A, Goebel G, Metzler B, Sprenger F, Poewe W, Wenning GK, Seppi K. Elastic Abdominal Binders Attenuate Orthostatic Hypotension in Parkinson's Disease. Mov Disord Clin Pract. 2015 Nov 27;3(2):156-160. doi: 10.1002/mdc3.12270. eCollection 2016 Mar-Apr. PubMed PMID: 30363559; PubMed Central PMCID: PMC6178725.

How to Recognize and Manage Dysautonomia in Parkinson's disease

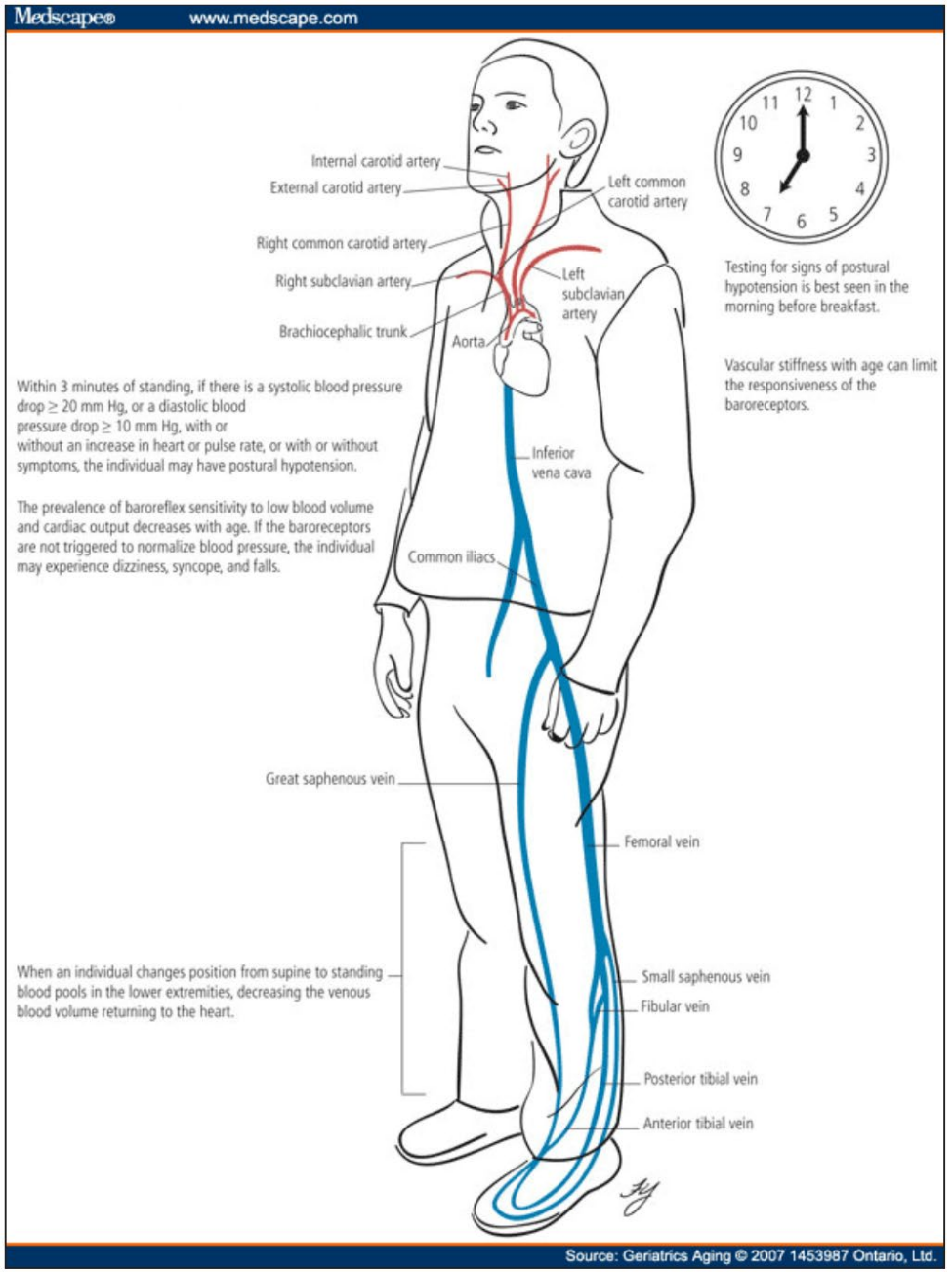
First Recognize: If the Autonomic Symptom is due to Non-Motor Fluctuation

Autonomic	Light-headedness	OFF > ON[a]
	Limb edema	OFF > ON
	Abdominal pain	OFF
	Abdominal bloating	OFF > ON
	Constipation	OFF > ON
	Nausea	OFF > ON
	Pyrosis	OFF > ON
	Hunger	OFF
	Sexual disorders	OFF > ON[a]
	Drenching sweats	OFF > ON[a]
	Facial flushing	OFF > ON
	Bladder dysfunction	OFF > ON[a]
	Belching	OFF > ON
	Drooling	OFF > ON
	Swallowing trouble	OFF > ON
	Chilling	OFF > ON
	Cough	OFF > ON
	Stridor	OFF
	Visual disorder	OFF > ON

12. Martínez-Fernández R, Schmitt E, Martinez-Martin P, Krack P. The hidden sister of motor fluctuations in Parkinson's disease: A review on nonmotor fluctuations. Mov Disord. 2016 Aug;31(8):1080-94. doi: 10.1002/mds.26731. Epub 2016 Jul 19. Review. PubMed PMID: 27431515.

Orthostatic Hypotension (OH)

- Prevalence:
- 30-50% in PD
  - < 1/3 are symptomatic (i.e. 16%)
  - Prevalence increases with age and disease duration
- 50-60% in Dementia with Lewy Bodies (DLB)
- 70-80% in MSA
  - using more stringent diagnostic criteria fall of 30 mm Hg systolic and 15 mm Hg diastolic
- Frequency:
  - Parkinson's disease (PD) range from 14% in early stages to 52% in more advanced or older patients



Clinical Signs of Postural Hypotension

3. Merola A, Romagnolo A, Rosso M, Suri R, Berndt Z, Maule S, Lopiano L, Espay AJ. Autonomic dysfunction in Parkinson's disease: A prospective cohort study. Mov Disord. 2018 Mar;33(3):391-397. doi: 10.1002/mds.27268. Epub 2017 Dec 26. PubMed PMID: 29278286.

Orthostatic Hypotension (OH)

Orthostatic Hypotension is a drop in blood pressure by ≥20 mm Hg systolic or ≥10 mm Hg diastolic within 3 minutes of standing

OH is a manifestation of cardiac autonomic neuropathy (cAN)

- Cardiac Autonomic Neuropathy is a complex neurologically mediated disorder not limited to OH, but including vasovagal syncope, situational syncope, carotid sinus syndrome, and postprandial hypotension (low blood pressure after meals)

Cardiac Autonomic Neuropathy and OH is a strong independent predictor of falls in PD

- Cardiovascular autonomic neuropathy (cAN) can be detected by Autonomic Testing.
- Autonomic Testing: heart rate variability (HRV) and blood pressure assessment during deep breathing, Valsalva maneuver, and laying to standing)

7. Fanciulli A, Goebel G, Metzler B, Sprenger F, Poewe W, Wenning GK, Seppi K. Elastic Abdominal Binders Attenuate Orthostatic Hypotension in Parkinson's Disease. Mov Disord Clin Pract. 2015 Nov 27;3(2):156-160. doi: 10.1002/mdc3.12270. eCollection 2016 Mar-Apr. PubMed PMID: 30363559; PubMed Central PMCID: PMC6178725.

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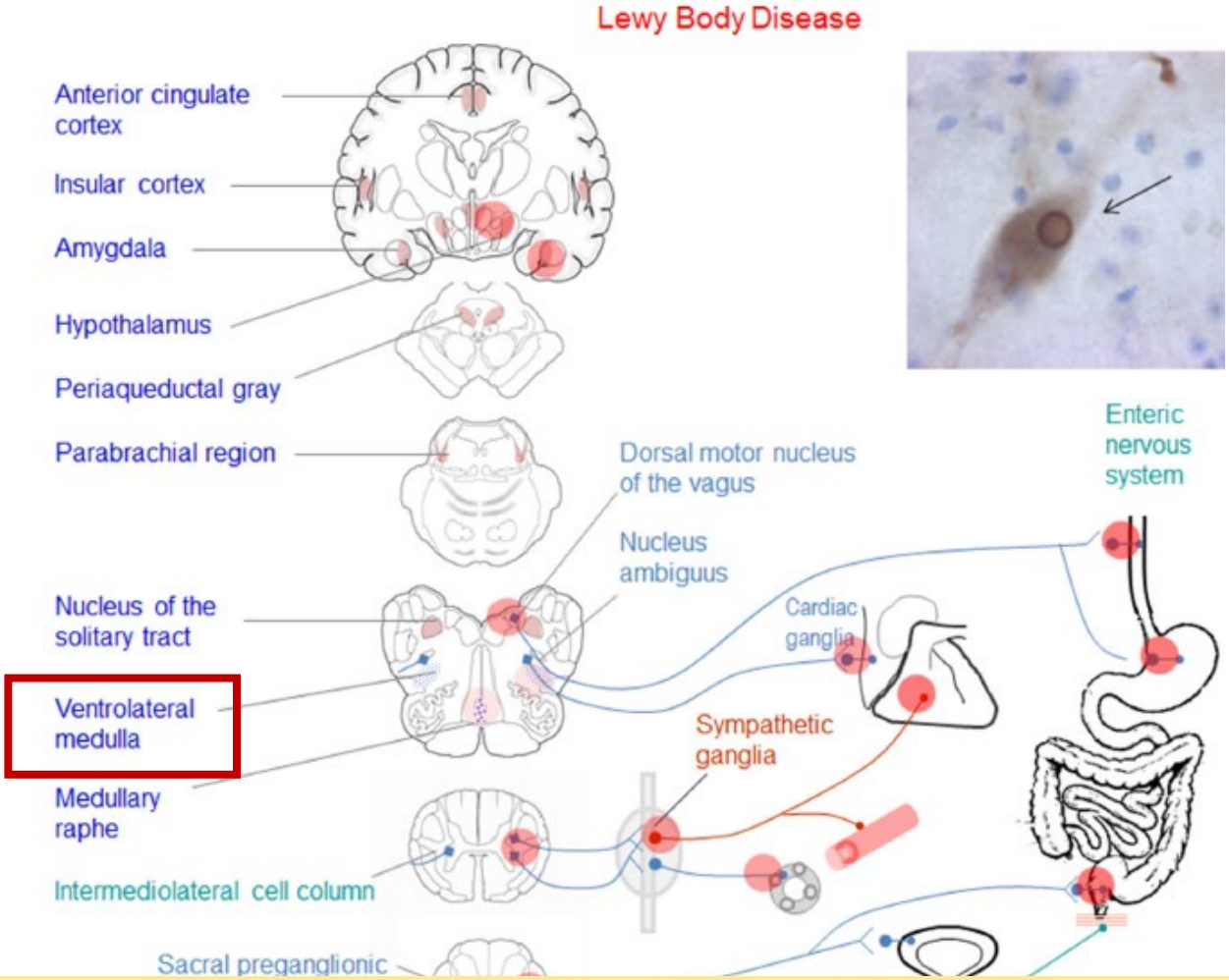
Rostral ventrolateral medulla (rVLM): critical for the tonic maintenance of sympathetic vasomotor tone, centrally generated sympathoexcitatory responses, and reflex control of blood pressure (baroreflex). Uses L-glutamate > epinephrine (C1 group only)



rVLM →projects to intermediolateral cell column →tonic excitation of sympathetic preganglionic neurons → control of cardiac output and total peripheral resistance

1. Coon EA, Cutsforth-Gregory JK, Benarroch EE. Neuropathology of autonomic dysfunction in synucleinopathies. Mov Disord. 2018 Mar;33(3):349-358. doi: 10.1002/mds.27186. Epub 2018 Jan 3. Review. PubMed PMID: 29297596.

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Orthostatic Hypotension Survey

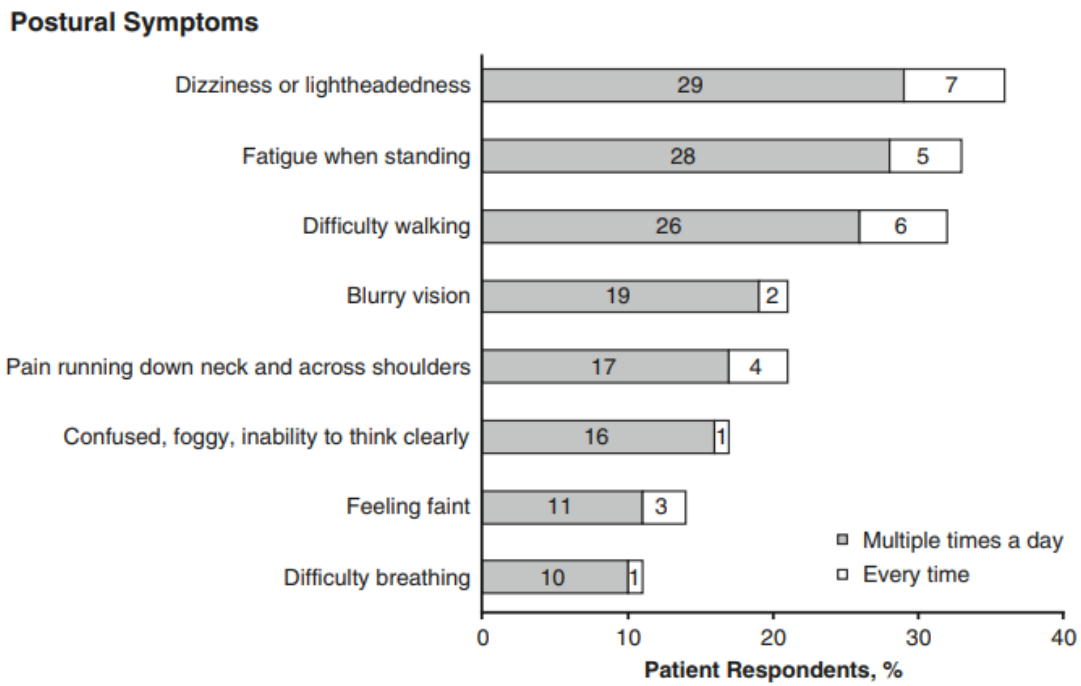

Fig. 1 Proportion of patient respondents reporting postural nOH symptoms.* nOH=neurogenic orthostatic hypotension. *Reported symptoms could be experienced upon sitting or standing up, when standing for long periods of time, or during a change in position

10. Claassen DO, Adler CH, Hewitt LA, Gibbons C. Characterization of the symptoms of neurogenic orthostatic hypotension and their impact from a survey of patients and caregivers. BMC Neurol. 2018 Aug 25;18(1):125. doi: 10.1186/s12883-018-1129-x. PubMed PMID: 30144800; PubMed Central PMCID: PMC6109309.

Orthostatic Hypotension

- Impact: increased risk of falls, reduced quality of life for patients and caregivers

- Symptoms:
  - Postural lightheadedness or dizziness, presyncope, falls and syncope
  - Additional symptoms:
    - Visual disturbances
    - Fatigue
    - Generalized weakness
    - Cognitive dysfunction
    - Neck pain or discomfort (i.e., coat hanger pattern)
    - Orthostatic shortness of breath

10. Claassen DO, Adler CH, Hewitt LA, Gibbons C. Characterization of the symptoms of neurogenic orthostatic hypotension and their impact from a survey of patients and caregivers. BMC Neurol. 2018 Aug 25;18(1):125. doi: 10.1186/s12883-018-1129-x. PubMed PMID: 30144800; PubMed Central PMCID: PMC6109309.

Orthostatic Hypotension: OH

- Orthostatic hypotension and constipation are more likely to occur in PD patients with cognitive alteration
- Cardiovascular dysfunction in PD related to parasympathetic (heart-rate variability) or sympathetic (orthostatic hypotension) dysfunction is associated with disease severity.
- Patients with orthostatic hypotension (OH) are at higher risk of developing dementia
- Association between OH and falls due to transient cerebral hypoperfusion due blood pooling in the lower limbs.

2. Leclair-Visonneau L, Magy L, Volteau C, Clairembault T, Le Dily S, Préterre C, Peyre A, Damier P, Neunlist M, Péréon Y, Derkinderen P. Heterogeneous pattern of autonomic dysfunction in Parkinson's disease. J Neurol. 2018 Apr;265(4):933-941. doi: 10.1007/s00415-018-8789-8. Epub 2018 Feb 20. PubMed PMID: 29464374.
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Prevalence of Falls and Health Care Utilization in Orthostatic Hypotension

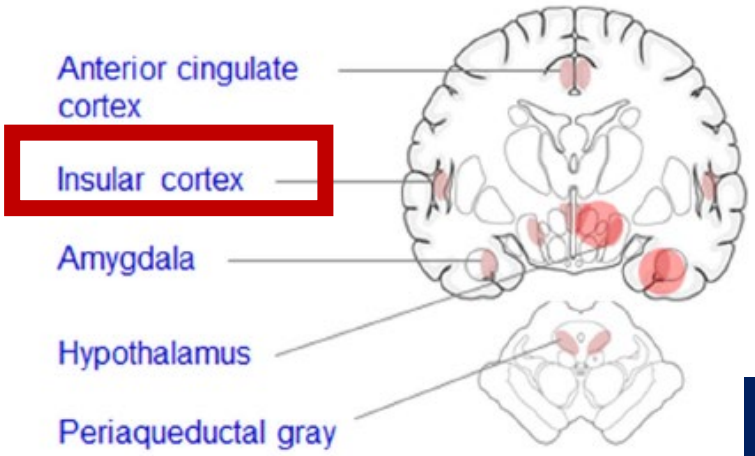
- 50% of PD patients with OH may not report orthostatic symptoms but “asymptomatic” OH is not benign.
- Higher prevalence of falls in patient with orthostatic hypotension (OR, 7.044; P<0.001)
  - Regardless of whether Symptomatic or Asymptomatic

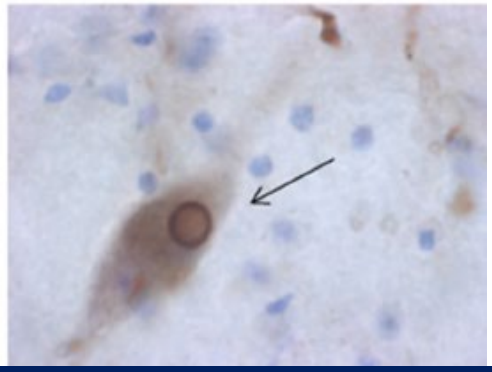
- Both symptomatic and asymptomatic OH →higher utilization of health care
  - Symptomatic and Asymptomatic OH in PD→ similar impairments in gait, balance and ADLs

  - Screening for OH even in absence of reported postural lightheadedness is encouraged.

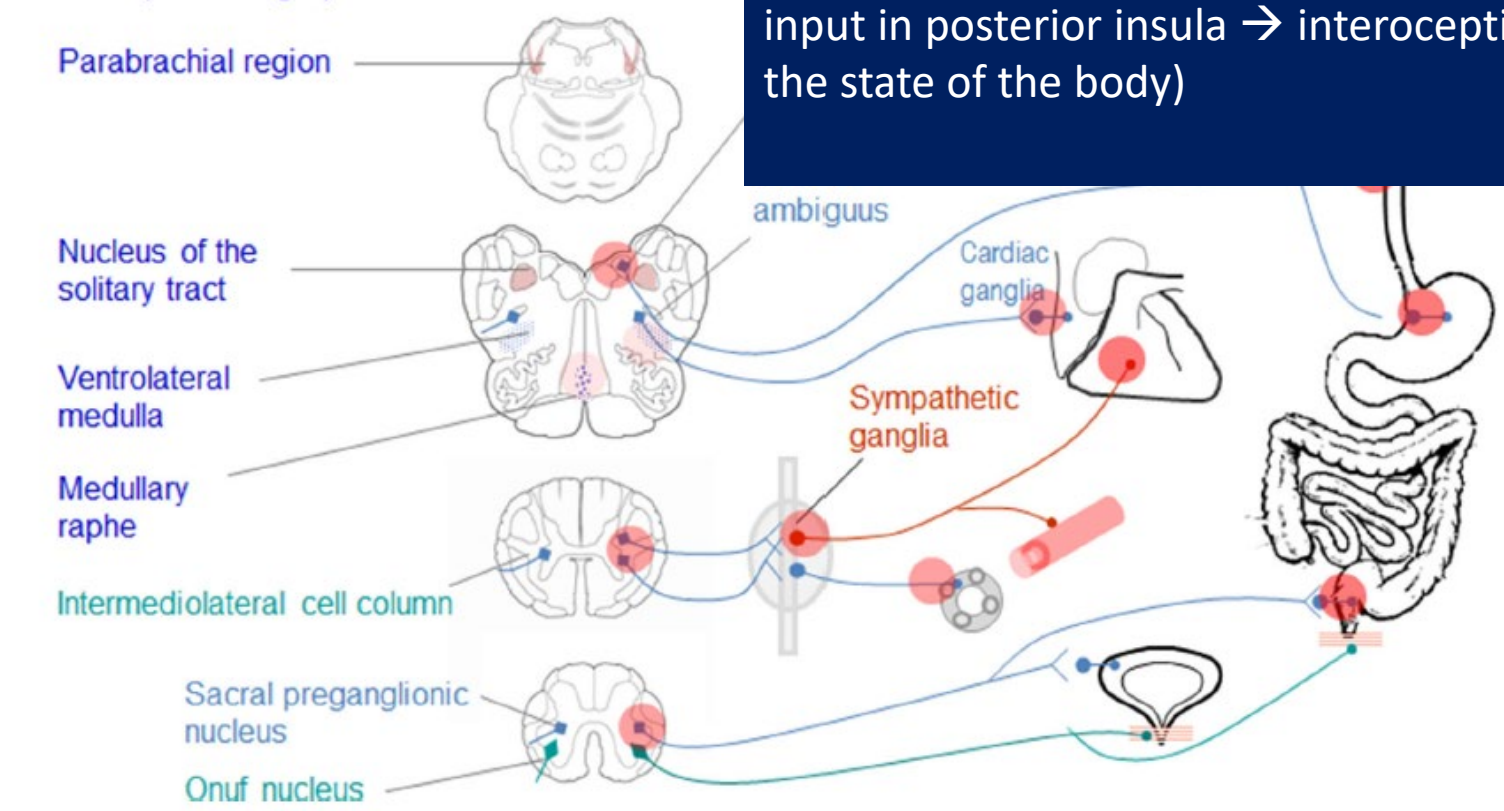
3. Merola A, Romagnolo A, Rosso M, Suri R, Berndt Z, Maule S, Lopiano L, Espay AJ. Autonomic dysfunction in Parkinson's disease: A prospective cohort study. Mov Disord. 2018 Mar;33(3):391-397. doi: 10.1002/mds.27268. Epub 2017 Dec 26. PubMed PMID: 29278286.

Lewy Body Disease





Viscerosensory cortex info integrated w/ anterior insula input in posterior insula → interoception (awareness of the state of the body)



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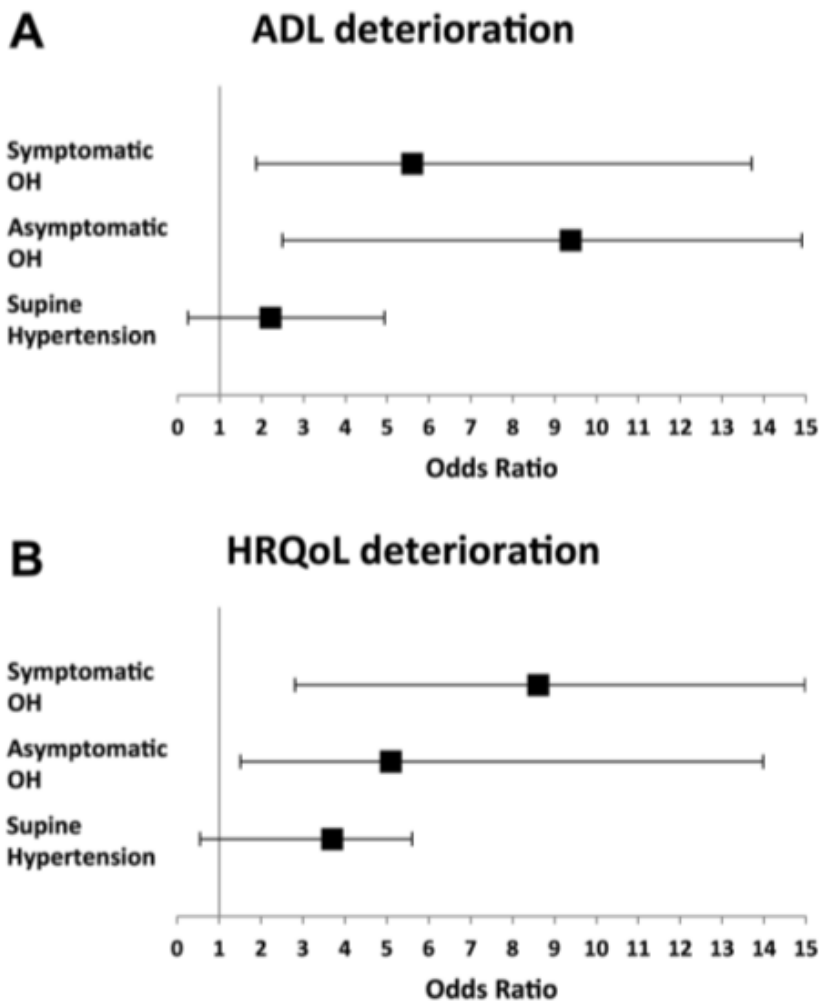


FIG. 2. Symptomatic/asymptomatic OH and SH: association with ADL and HRQoL. Both symptomatic and asymptomatic OH were associated with deterioration in ADL (A) and HRQoL (B). Data adjusted for changes in the MoCA and MDS-UPDRS-III score during follow-up and for disease duration.

Symptomatic and asymptomatic OH were both associated with significant impairments in ADL and HRQoL.

Odds of deterioration in **symptomatic** OH were 5-fold higher for ADL (P=0.002) and 8-fold higher for HRQoL (P=0.001);

Odds of deterioration in **asymptomatic** OH was 9-fold higher for ADL (P=0.001) and 5-fold higher for HRQoL (P=0.009)

Concurrent Supine hypertension (SH) was not associated with changes in ADL or HRQoL.

3. Merola A, Romagnolo A, Rosso M, Suri R, Berndt Z, Maule S, Lopiano L, Espay AJ. Autonomic dysfunction in Parkinson's disease: A prospective cohort study. Mov Disord. 2018 Mar;33(3):391-397. doi: 10.1002/mds.27268. Epub 2017 Dec 26. PubMed PMID: 29278286.

Claassen et al. Orthostatic Hypotension Survey

Important point:
There was often a lack of distinct daily pattern for frequency and severity of nOH symptoms

OH symptoms do NOT always occur at a specific time or event (e.g., morning or after a meal)

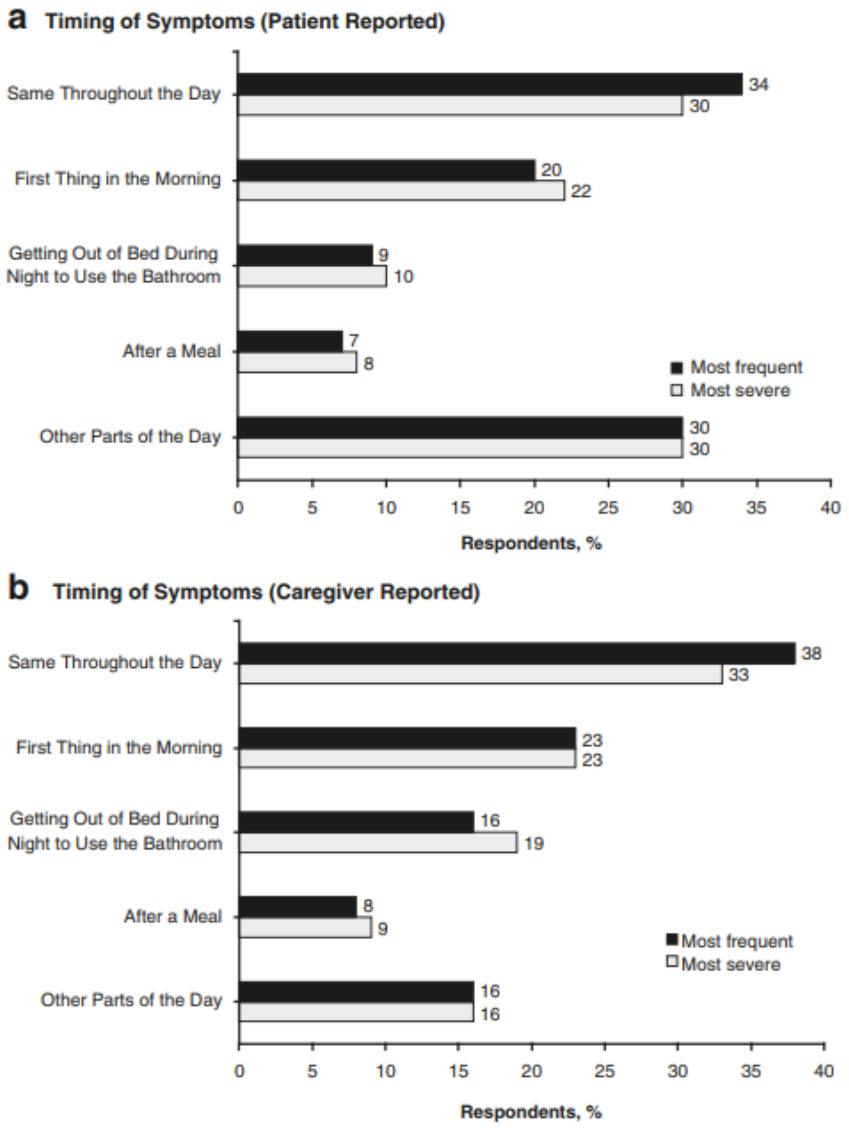


Fig. 2 Daily pattern of most frequent/severe nOH symptoms as reported by **a** patients and **b** caregivers.* nOH = neurogenic orthostatic hypotension. *Respondents in the patient and caregiver cohorts were not paired

10. Claassen DO, Adler CH, Hewitt LA, Gibbons C. Characterization of the symptoms of neurogenic orthostatic hypotension and their impact from a survey of patients and caregivers. BMC Neurol. 2018 Aug 25;18(1):125. doi: 10.1186/s12883-018-1129-x. PubMed PMID: 30144800; PubMed Central PMCID: PMC6109309.

Claassen et al. Orthostatic Hypotension Survey

¼ of patients (26% of patients and 33% of caregivers) somewhat or strongly agreed patients had to mention their nOH to their healthcare provider to draw attention to it.

43% reported seeing more than 3 providers before being diagnosed with OH or nOH

50% of patients formally diagnosed agreed path to diagnosis was very frustrating.

70% patients formally diagnosed strongly agreed symptoms improved after diagnosis.

There is often a delay of 6 months or more between symptom onset to discussion.

Majority of patients reported minimizing or hiding their OH symptoms

Stratification based on duration of symptoms (< 10 years or >10 years) did NOT increase likelihood of formal diagnosis of OH or nOH.

10. Claassen DO, Adler CH, Hewitt LA, Gibbons C. Characterization of the symptoms of neurogenic orthostatic hypotension and their impact from a survey of patients and caregivers. BMC Neurol. 2018 Aug 25;18(1):125. doi: 10.1186/s12883-018-1129-x. PubMed PMID: 30144800; PubMed Central PMCID: PMC6109309.

Claassen et al.
Orthostatic Hypotension Survey

Survey by Claassen et al. reveals many patients have a delay or lack of diagnosis of nOH →diagnostic uncertainty slows symptom management.

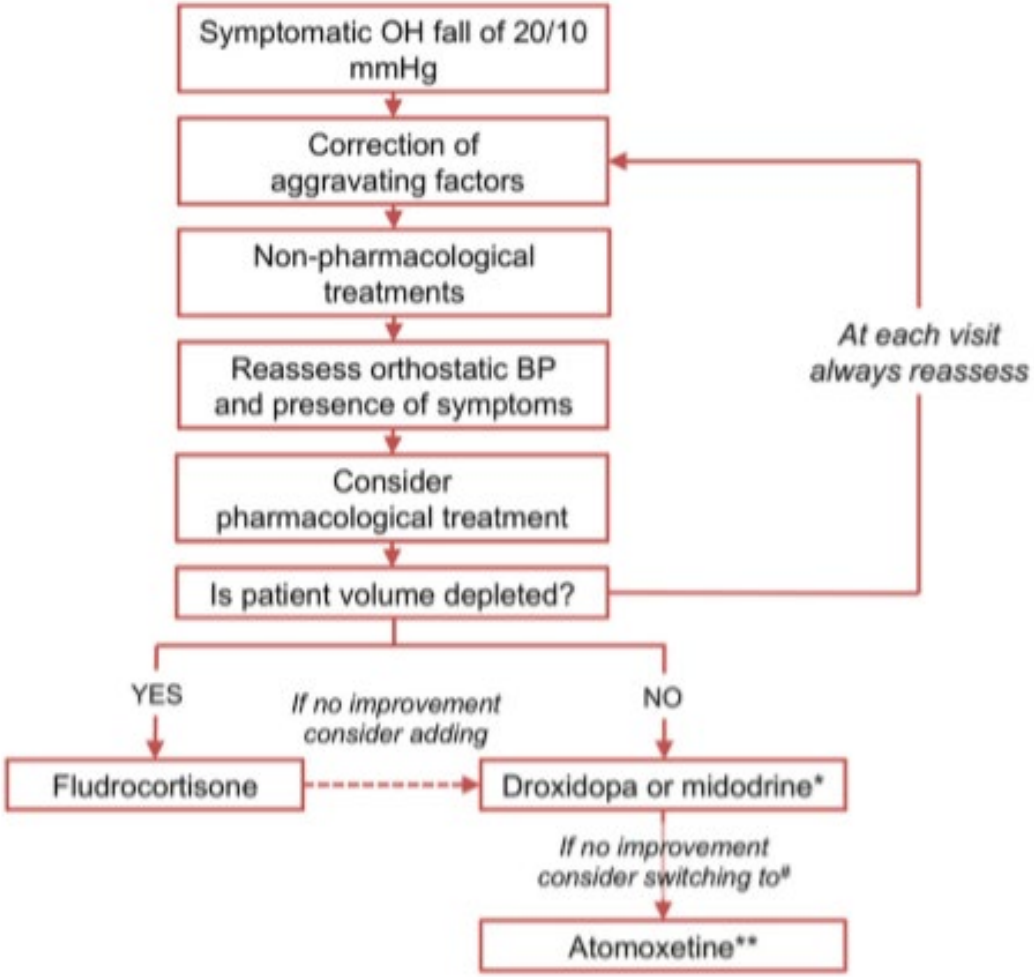
- Under-recognition of nOH→ increased risk of falls and associated morbidity

- Heightened awareness regarding nOH and its symptom burden should be an educational priority for patients, as well as for their caregivers and for health care providers.

10. Claassen DO, Adler CH, Hewitt LA, Gibbons C. Characterization of the symptoms of neurogenic orthostatic hypotension and their impact from a survey of patients and caregivers. BMC Neurol. 2018 Aug 25;18(1):125. doi: 10.1186/s12883-018-1129-x. PubMed PMID: 30144800; PubMed Central PMCID: PMC6109309.

Approach to OH Treatment

- Goal: reduce symptom burden, improve quality of life, and reduce morbidity and mortality



4. Palma JA, Kaufmann H. Treatment of autonomic dysfunction in Parkinson disease and other synucleinopathies. Mov Disord. 2018 Mar;33(3):372-390. doi: 10.1002/mds.27344. Review. PubMed PMID: 29508455; PubMed Central PMCID: PMC5844369.

OH: Correct Aggravating Factors

Table 2

Some drugs that may decrease blood pressure or exacerbate orthostatic hypotension

CLASS	EXAMPLES
Narcotics	Morphine
Tricyclic antidepressants	Imipramine (Tofranil)
Nontricyclic antidepressants	Trazodone (Desyrel), paroxetine (Paxil), venlafaxine (Effexor)
Monoamine oxidase inhibitors	Phenelzine (Nardil)
Neuroleptics	Chlorpromazine (Thorazine), quetiapine (Seroquel)
Antihypertensive agents	Clonidine (Catapres), labetalol (Normodyne, Trandate), verapamil (Calan, Isoptin, Verelan), captopril (Capoten), hydralazine (Apresoline)
Nitrates	
Diuretics	Furosemide (Lasix)
Antiparkinsonian agents	Levodopa (Sinemet), bromocriptine (Parlodel), ropinirole (Requip), pramipexole (Mirapex)
Drugs for prostatism	Prazosin (Minipress), terazosin (Hytrin)
Drugs for erectile dysfunction	Sildenafil (Viagra)
Drugs that induce autonomicneuropathy	Amiodarone (Cordarone, Pacerone), vincristine (Oncovin, Vincasar), cisplatin (Platinol)
Insulin (in diabetic patients with autonomic failure)	

6. Figueroa JJ, Basford JR, Low PA. Preventing and treating orthostatic hypotension: As easy as A, B, C. Cleve Clin J Med. 2010 May;77(5):298-306. doi: 10.3949/ccjm.77a.09118. Review. PubMed PMID: 20439562; PubMed Central PMCID: PMC2888469.

OH: Correct Aggravating Factors

- Discontinue medications that exacerbate OH:
  - i.e. medications that:
    - reduce intravascular volume (diuretics)
    - induce vasodilation (sildenafil, nitrates)
    - block norepinephrine release/activity at the neurovascular junction (alpha blockers, centrally acting a2-agonists, and tricyclic antidepressants).
  - Adjust levodopa and dopamine agonists (if needed)

- Evaluate and treat anemia
  - Erythropoietin (20-50 U/kg, subcutaneous, 3x per week) w/ iron supplements improve nOH in setting of anemia

4. Palma JA, Kaufmann H. Treatment of autonomic dysfunction in Parkinson disease and other synucleinopathies. Mov Disord. 2018 Mar;33(3):372-390. doi: 10.1002/mds.27344. Review. PubMed PMID: 29508455; PubMed Central PMCID: PMC5844369.

OH: Correct Aggravating Factors

Conditions that can decrease blood pressure or exacerbate orthostatic hypotension

- Dehydration
- Time of day (early morning after nocturnal diuresis)
- Rising quickly after prolonged sitting or recumbency
- Prolonged motionless standing
- Physical exertion, especially vigorous or isometric exercise
- Alcohol ingestion
- Carbohydrate-heavy meals
- Heat exposure or fever
- Straining during micturition or defecation

6. Figueroa JJ, Basford JR, Low PA. Preventing and treating orthostatic hypotension: As easy as A, B, C. Cleve Clin J Med. 2010 May;77(5):298-306. doi: 10.3949/ccjm.77a.09118. Review. PubMed PMID: 20439562; PubMed Central PMCID: PMC2888469.

OH: Nonpharmacologic Treatments

- Dietary Adjustments:
  - Avoid sugary beverages (hypotensive effect of high glycemic index carbohydrates) AND alcohol and caffeine (diuretic effects)
    - If alcohol intake desired, reserve for nighttime
  - Increase water intake to 2 - 2.5 L/day
    - Drinking 0.5 L water at once → marked increase in BP (peaks in 30 min) = Short lived rescue measure
  - Increase salt intake by adding 1-2 tsp salt (or 0.5 to 1 g salt tablet daily)
  - Eat smaller, more frequent meals, reduce carbohydrates.

4. Palma JA, Kaufmann H. Treatment of autonomic dysfunction in Parkinson disease and other synucleinopathies. Mov Disord. 2018 Mar;33(3):372-390. doi: 10.1002/mds.27344. Review. PubMed PMID: 29508455; PubMed Central PMCID: PMC5844369.

OH: Nonpharmacologic Strategies

1) Expand blood volume: take in extra fluid and salt

2) Decrease nocturia (nighttime urination): raise the head of the bed

3) Decrease venous pooling: wear an abdominal binder (20-40 mmHg), perform counter maneuvers, engage in physical activity

4) Induce a pressor response: drink a bolus of cold water (0.5 L) prior to standing –effect peaks @ 30 min.

6. Figueroa JJ, Basford JR, Low PA. Preventing and treating orthostatic hypotension: As easy as A, B, C. Cleve Clin J Med. 2010 May;77(5):298-306. doi: 10.3949/ccjm.77a.09118. Review. PubMed PMID: 20439562; PubMed Central PMCID: PMC2888469.

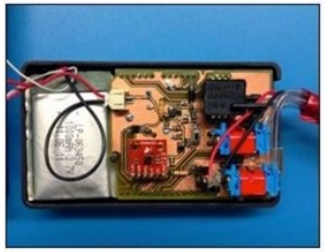
OH: Nonpharmacologic Treatments

- Maintain/improve physical fitness:
  - Why: Natural Patient Response to orthostatic lightheadedness→ avoid exercise →vicious cycle of deconditioning and worsening lightheadedness
- Best Exercise Options:
  - Choose Recumbent bike or rowing machine (avoid upright posture)
  - or pool exercises (hydrostatic pressure allows upright exercise)

4. Palma JA, Kaufmann H. Treatment of autonomic dysfunction in Parkinson disease and other synucleinopathies. Mov Disord. 2018 Mar;33(3):372-390. doi: 10.1002/mds.27344. Review. PubMed PMID: 29508455; PubMed Central PMCID: PMC5844369.

OH: Nonpharmacologic Treatments Compression Devices

- Compression stockings (15-20 mmHg) – help if good compliance –but hard to apply in PD
- Elastic abdominal binders typically produce better results
- Abdominal binder (20-40 mmHg)
  - Static compression –apply when supine in a.m. wear all day, remove at bedtime
- Vanderbilt Study:
  - Automated inflatable abdominal binder that provides sustained servo-controlled venous compression (40 mmHg) activated only on standing is as effective as midodrine. Patent/availability pending.



Intellectual Property Status
• A Patent Application has been filed: US20150313608

5. Okamoto LE, Diedrich A, Baudenbacher FJ, Harder R, Whitfield JS, Iqbal F, Gamboa A, Shibao CA, Black BK, Raj SR, Robertson D, Biaggioni I. Efficacy of Servo-Controlled Splanchnic Venous Compression in the Treatment of Orthostatic Hypotension: A Randomized Comparison With Midodrine. Hypertension. 2016 Aug;68(2):418-26. doi: 10.1161/HYPERTENSIONAHA.116.07199. Epub 2016 Jun 6. PubMed PMID: 27271310; PubMed Central PMCID: PMC4945429.

OH: Pharmacologic Management

- Two complimentary strategies:
  - 1) expand intravascular volume with fludrocortisone
  - 2) increase peripheral vascular resistance with midodrine, droxidopa, or norepinephrine transporter (NET) inhibitors.

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

4. Palma JA, Kaufmann H. Treatment of autonomic dysfunction in Parkinson disease and other synucleinopathies. Mov Disord. 2018 Mar;33(3):372-390. doi: 10.1002/mds.27344. Review. PubMed PMID: 29508455; PubMed Central PMCID: PMC5844369.

OH Treatment: Sites of Action

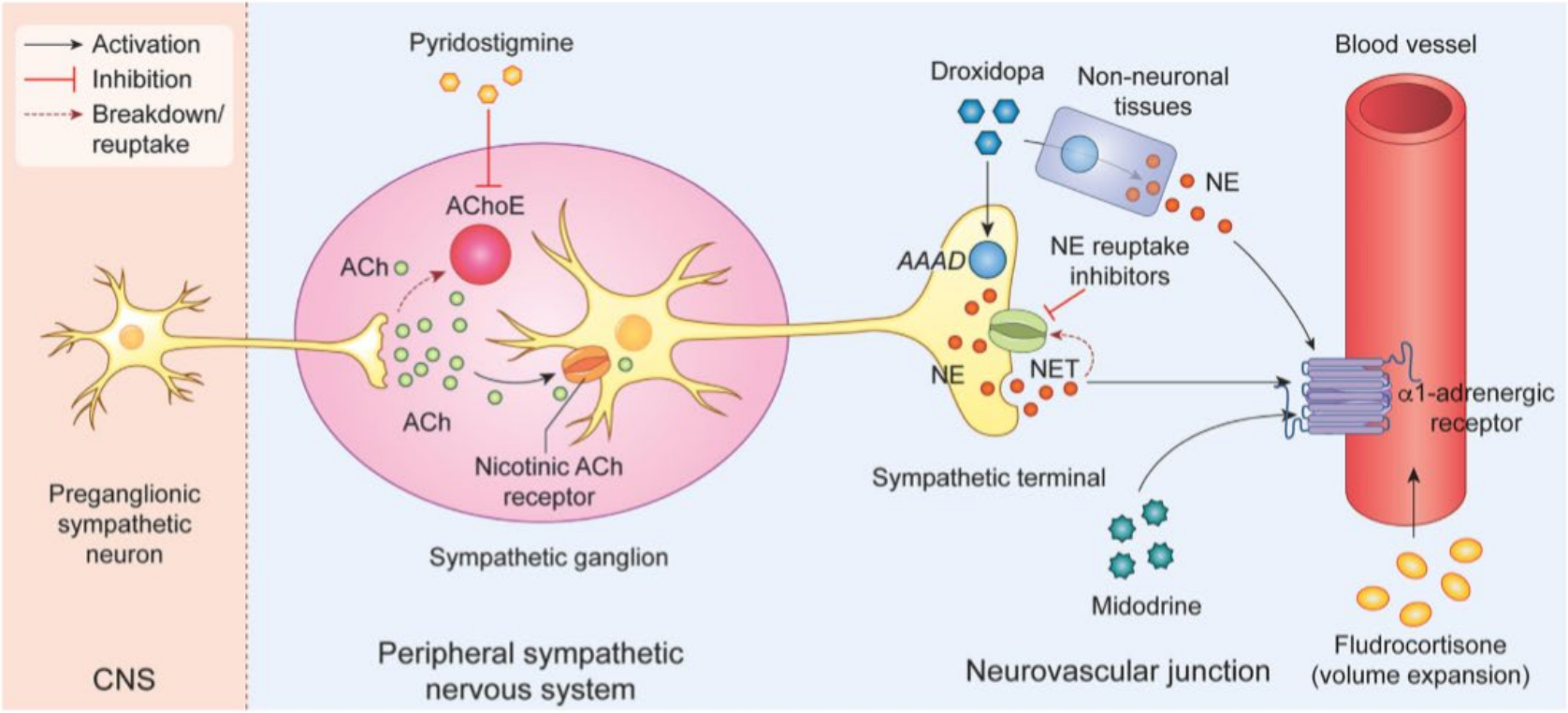


FIG. 2. Sites of action and mechanism of therapeutic agents used for the treatment of nOH. Pyridostigmine inhibits acetylcholine esterase (AChoE) in the sympathetic ganglion, thereby increasing the levels of acetylcholine (ACh) and enhancing sympathetic neurotransmission. Droxidopa is converted to norepinephrine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

4. Palma JA, Kaufmann H. Treatment of autonomic dysfunction in Parkinson disease and other synucleinopathies. Mov Disord. 2018 Mar;33(3):372-390. doi: 10.1002/mds.27344. Review. PubMed PMID: 29508455; PubMed Central PMCID: PMC5844369.

Treatment of OH: Special circumstances

Nocturnal supine hypertension

Instruct patients to:

- Not take pressor medications after 6 PM
- Elevate the head of the bed to lower intracranial blood pressure
- Try a bedtime snack with a glass of warm fluid (to induce nighttime postprandial hypotension)
- Try a glass of wine at bedtime (for vasodilator effects)
- Remove abdominal binder before bedtime.

Anemia in orthostatic hypotension
(can exacerbate symptoms)

Mild to moderate normocytic normochronic anemia is not uncommon.

Consider erythropoietin (Epogen, Procrit) 50 units/kg subcutaneously three times a week (monitor reticulocytes and hematocrit).

6. Figueroa JJ, Basford JR, Low PA. Preventing and treating orthostatic hypotension: As easy as A, B, C. Cleve Clin J Med. 2010 May;77(5):298-306. doi: 10.3949/ccjm.77a.09118. Review. PubMed PMID: 20439562; PubMed Central PMCID: PMC2888469.

Treatment of OH: special circumstances

Orthostatic decompensation
(more severe or less responsive to pressor agents)

Consider aggravating conditions such as anemia, hypovolemia, heart failure, deconditioning.

Salty soups and about five 8-ounce servings of fluid over half a day, if acute, or:

Salt tablets 2 g three times a day with a minimum of eight 8-ounce servings of fluid over 1 day.

Fludrocortisone (Florinef) 0.2 mg three times a day for 1 week.

During this time, an abdominal binder can be useful.

If severe, provide acute hospital management with intravenous fluid expansion.

Early morning orthostatic hypotension

Instruct patients to:

- Be careful on awakening
- Elevate the head of the bed (reducing nocturia)
- Drink two cups of cold water 30 minutes before arising
- Shift from supine to an erect position in gradual stages.

Postprandial orthostatic hypotension
(common in patients with diabetic neuropathy)

Tell patients to take frequent, small meals and reduce alcohol intake.

Hot drinks, hot foods, and meals rich in carbohydrates may be troublesome.

6. Figueroa JJ, Basford JR, Low PA. Preventing and treating orthostatic hypotension: As easy as A, B, C. Cleve Clin J Med. 2010 May;77(5):298-306. doi: 10.3949/ccjm.77a.09118. Review. PubMed PMID: 20439562; PubMed Central PMCID: PMC2888469.

Summary Recommendations for Orthostatic Hypotension: From A to F

Your physician has determined that you have orthostatic hypotension. This means that your blood pressure drops when you stand up, making you feel dizzy or perhaps even pass out. The following may help.

A: Abdominal compression

Wear an abdominal binder when out of bed.

B: Bolus of water

On bad days, drink two 8-ounce glasses of cold water prior to prolonged standing.

B (continued): Bed up

Sleep with the head of the bed elevated 4 inches.

C: Countermaneuvers

Contract the muscles below your waist for about half a minute at a time to raise your blood pressure during prolonged standing or when you become symptomatic.

D: Drugs

Drugs such as midodrine (ProAmatine), pyridostigmine (Mestinon), and fludrocortisone & droxidopa (Northera) can help raise blood pressure

Recognize that some drugs you take can lower blood pressure.

E: Education

Recognize symptoms that indicate your standing blood pressure is falling.

Recognize the conditions that lower blood pressure, such as a heavy meal, positional changes, heat, exercise, or a hot bath.

Learn the things you can do to raise your blood pressure.

E (continued): Exercise

Avoid inactivity and consider a gentle exercise program.

F: Fluids and salt

You need plenty of salt and fluids.

6. Figueroa JJ, Basford JR, Low PA. Preventing and treating orthostatic hypotension: As easy as A, B, C. Cleve Clin J Med. 2010 May;77(5):298-306. doi: 10.3949/ccjm.77a.09118. Review. PubMed PMID: 20439562; PubMed Central PMCID: PMC2888469.

Orthostatic Hypotension Summary

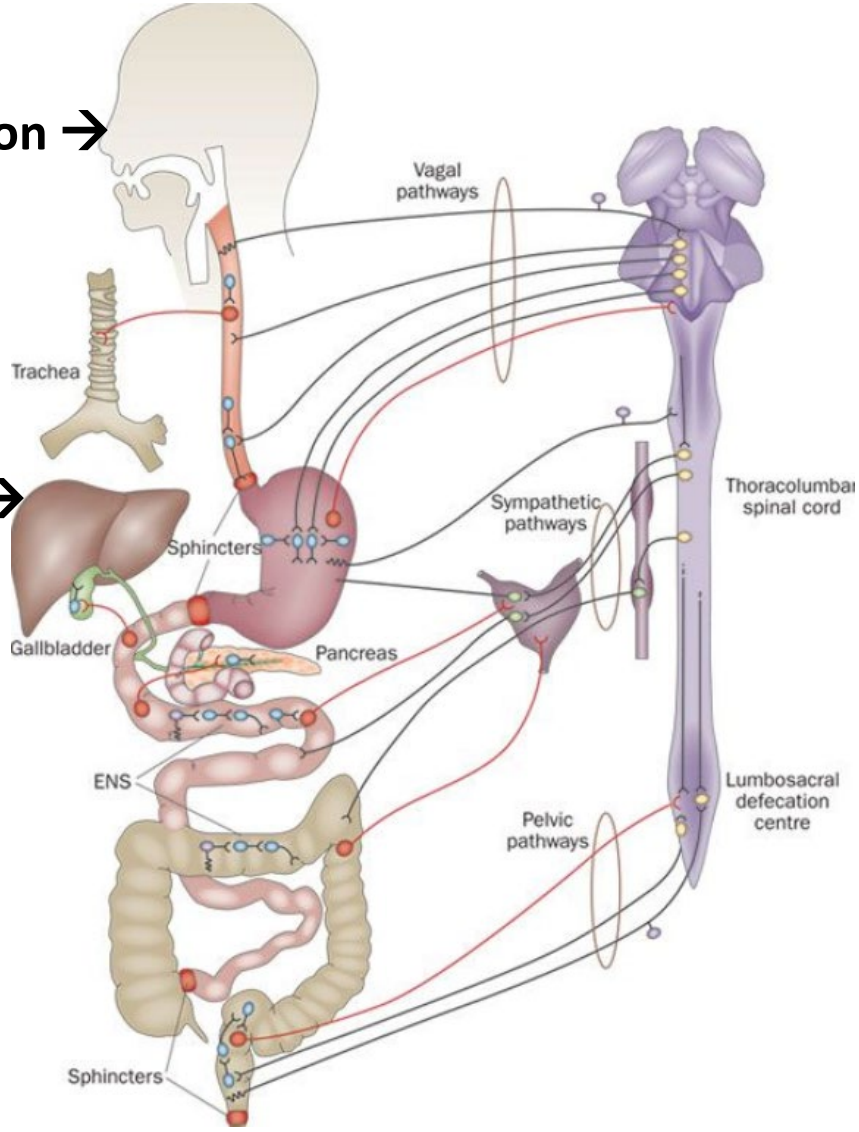
- Clinicians identify symptoms by history, exam and adjunct testing.
  - Doctors and Nurse Practitioners may not ask you about OH symptoms
  - Be your own advocate:
    - Communicate your symptoms to you physician even if you are not asked, as quality of life improves with treatment of OH.
- Keys to effective management:
  - Discontinuation of potentially causative scenarios and aggravating drugs
  - patient education
  - nonpharmacological approaches
  - pathophysiology based drug therapy

4. Palma JA, Kaufmann H. Treatment of autonomic dysfunction in Parkinson disease and other synucleinopathies. Mov Disord. 2018 Mar;33(3):372-390. doi: 10.1002/mds.27344. Review. PubMed PMID: 29508455; PubMed Central PMCID: PMC5844369.

Swallowing & Gut Motility

- **Parasympathetic nervous system dysfunction →**
  - Swallowing problems (dysphagia)
  - Gastroparesis (delayed gastric emptying)
  - Constipation

- **Enteric nervous system (ENS) dysfunction →**
  - Delayed gastric emptying (early satiety, nausea)
  - Constipation

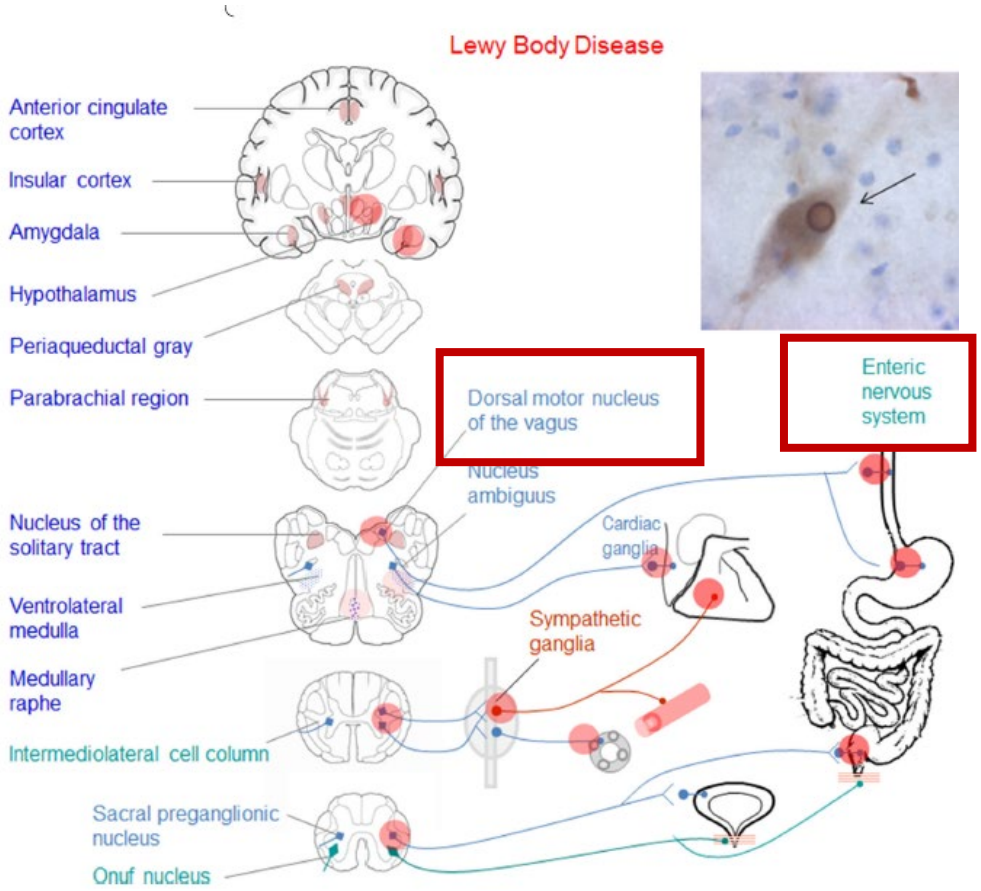


2. Leclair-Visonneau L, Magy L, Volteau C, Clairembault T, Le Dily S, Préterre C, Peyre A, Damier P, Neunlist M, Péréon Y, Derkinderen P. Heterogeneous pattern of autonomic dysfunction in Parkinson's disease. J Neurol. 2018 Apr;265(4):933-941. doi: 10.1007/s00415-018-8789-8. Epub 2018 Feb 20. PubMed PMID: 29464374.
Image: https://doi.org/10.1038/nrgastro.2012.3210.1038/nrgastro.2012.32

Enteric Nervous System

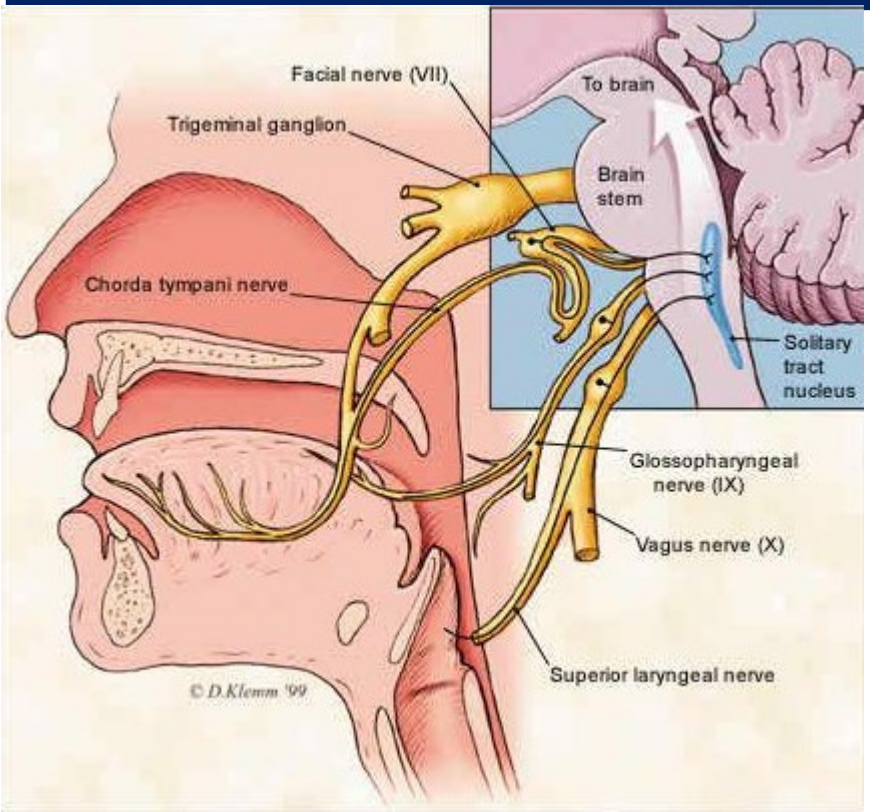
Early a-synuclein involvement of enteric nervous system (ENS) is hallmark of autonomic pathology in PD →constipation which precedes motor symptoms by years

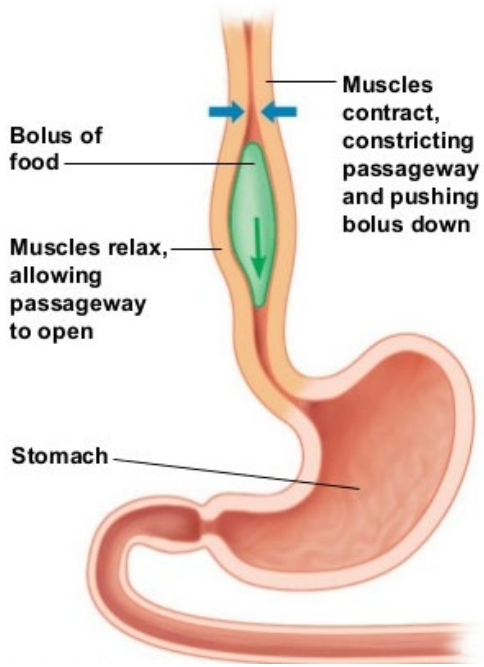
ENS and Dorsal motor nucleus of the Vagus nerve →upper GI symptoms of bloating, nausea and early satiety

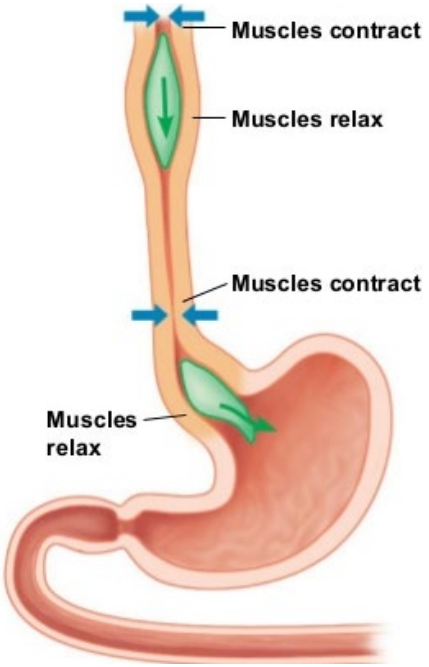


1. Coon EA, Cutsforth-Gregory JK, Benarroch EE. Neuropathology of autonomic dysfunction in synucleinopathies. Mov Disord. 2018 Mar;33(3):349-358. doi: 10.1002/mds.27186. Epub 2018 Jan 3. Review. PubMed PMID: 29297596.

Dysphagia, Peristalsis and Constipation







a-Syn aggregates in nerves involved in swallowing correlate with severity of dysphagia.

Esophageal abnormalities occur in PD → incomplete relaxation of the upper and lower esophageal sphincters, diffuse esophageal spasms, and reduced esophageal peristalsis

abnormal intrinsic (ENS) and extrinsic (vagal) innervation→ reduced gut motility and longer stool transit times.

4. Palma JA, Kaufmann H. Treatment of autonomic dysfunction in Parkinson disease and other synucleinopathies. Mov Disord. 2018 Mar;33(3):372-390. doi: 10.1002/mds.27344. Review. PubMed PMID: 29508455; PubMed Central PMCID: PMC5844369.
18. Innervation of swallow image https://www.researchgate.net/figure/Cranial-nerves-related-to-swallowing_fig2_301764706

Constipation

- 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.

- 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.

4. Palma JA, Kaufmann H. Treatment of autonomic dysfunction in Parkinson disease and other synucleinopathies. Mov Disord. 2018 Mar;33(3):372-390. doi: 10.1002/mds.27344. Review. PubMed PMID: 29508455; PubMed Central PMCID: PMC5844369.

Constipation

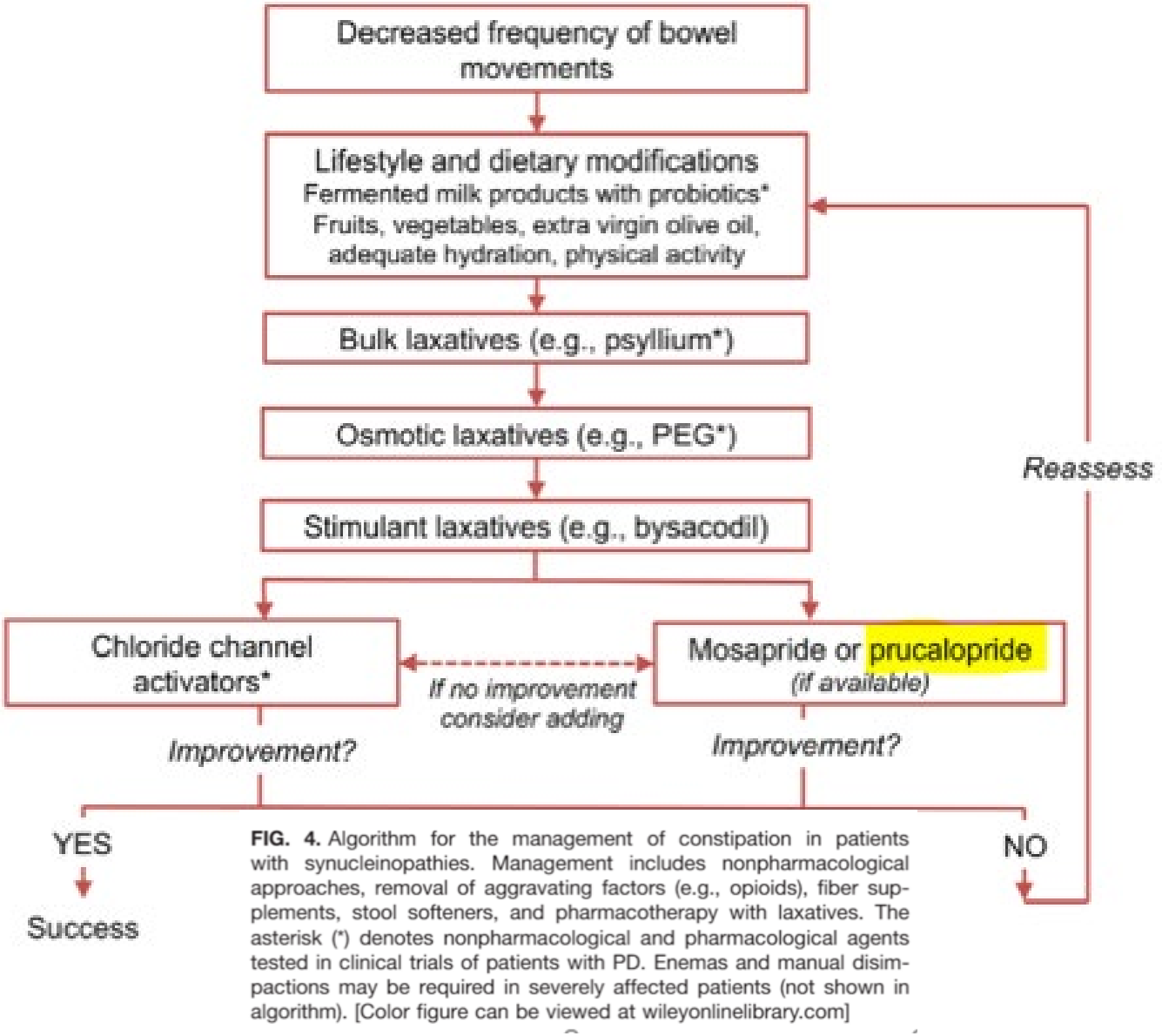


FIG. 4. Algorithm for the management of constipation in patients with synucleinopathies. Management includes nonpharmacological approaches, removal of aggravating factors (e.g., opioids), fiber supplements, stool softeners, and pharmacotherapy with laxatives. The asterisk (*) denotes nonpharmacological 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]

4. Palma JA, Kaufmann H. Treatment of autonomic dysfunction in Parkinson disease and other synucleinopathies. Mov Disord. 2018 Mar;33(3):372-390. doi: 10.1002/mds.27344. Review. PubMed PMID: 29508455; PubMed Central PMCID: PMC5844369.

Constipation: Lifestyle modifications

Water and Fiber:
Drink 8, 8 oz glasses of water/day

Diet: Add probiotics, extra virgin olive oil, fish oil

Increase foods rich in fiber include:
bran fiber
whole wheat products
lentils and beans
prunes or prune juice
dried apricots
chia Seeds

Rancho Recipe:
Recipe: Mix together one cup each of bran, applesauce, and prune juice
Instructions: take 2 tablespoons every morning; the mixture can be refrigerated for one week then discarded.

Remove Aggravating Factors: opioids, etc

Exercise: Do moderate exercise most days of the week

Set a Routine: schedule a time to sit on the toilet every day for a bowel movement. Even if one does not occur, the routine improves regularity.

Gain mechanical advantage: Elevate your legs using a stool when you sit on the toilet (squatty potty)

4. Palma JA, Kaufmann H. Treatment of autonomic dysfunction in Parkinson disease and other synucleinopathies. Mov Disord. 2018 Mar;33(3):372-390. doi: 10.1002/mds.27344. Review. PubMed PMID: 29508455; PubMed Central PMCID: PMC5844369.

Constipation Medications

Continue lifestyle measures and ADD medications in following order:

Try each step for 2-4 weeks

Step 2: Add daily Bulk laxative (fiber supplements: Fibercon, psyllium, Benefiber) *(needs H2O to work best)*

Step 3: Add daily Emollient (lubricating laxative, like docusate)

Step 4: Add daily Osmotic laxative (polyethylene glycol/MiraLAX)- *needs H2O to work*

Step 5: Add stimulant laxative as needed (bisacodyl (Dulcolax), milk of magnesia or Senna

Note: Stimulant laxatives are rescue medications if no bowel movement after 3-4 days (do NOT use regularly, will lose efficacy over time)

Appendix A: List of Oral Laxatives

This list is incomplete, but will help to familiarize you with some products on the market. The list is given in alphabetical order with no preference given to one brand over the other.

Brand Name	Category	Non-Stimulation	Stimulating
A-3 Revised	Combination	X	
Alocass	Stimulant		X
Bisacodyl (Dulcolax®)	Stimulant		X
Castor Oil	Stimulant		X
Cellulose (Unifiber®)	Bulk	X	
Dehydrocholic Acid (Cholan-HMB®)	Stimulant		X
Docusate Sodium (Colace®)	Emollient	X	
Docusate and Senna (Doc-Q-Lax®)	Stimulant		X
Docusate (Docucal®)	Emollient	X	
Docusate (Surfak®)	Emollient	X	
Fleet® Mineral Oil	Lubricant	X	
Guar Gum (Benefiber®)	Bulk	X	
Lactulose (Kristalose®)	Osmotic	X	
Magnesium Citrate (Citrate Of Magnesia)	Saline		X
Magnesium Hydroxide (Phillips® Milk of Magnesia)	Saline		X
Magnesium Supplement (Mag-Gel 600®)	Stimulant		X
Methylcellulose (Citrucel®)	Bulk	X	
Phospho-Soda (Fleet® Phospho-Soda)	Saline		X
Polyethylene Glycol (GaviLAX®)	Osmotic	X	
Polyethylene Glycol (GaviLyte-N® with Flavor Pack)	Osmotic	X	
Polyethylene Glycol (GlycoLax®)	Osmotic	X	
Polycarbophil (Fibercon®)	Bulk	X	
Polyethylene Glycol (NuLYTELY®)	Combination		X
Psyllium (Metamucil®)	Bulk	X	
Rite Aid® Senna	Stimulant		X
Senna (Black-Draught®)	Stimulant		X
Senna and Docusate (Senna-S)	Stimulant		X
Senna and Docusate (Senokot®)	Stimulant		X

Adapted from: Mayo Clinic Website, accessed April 26, 2016, www.mayoclinic.com/health/drug-information/DR602359

Constipation Management: Prescription Medications

Chloride channel activators*

If no improvement consider adding

~~Mosapride~~ or prucalopride *(if available)*

Lubiprostone (Amitiza)-locally acting type 2 channel activator.

*Linactolide (Linzess)-guanylate cyclase 2C receptor agonist.

Plecanatide (Trulance)-guanylate cyclase-C receptor agonist

MOTEGRITY™ (prucalopride) is a serotonin-4 (5-HT4) receptor agonist indicated for the treatment of chronic idiopathic constipation

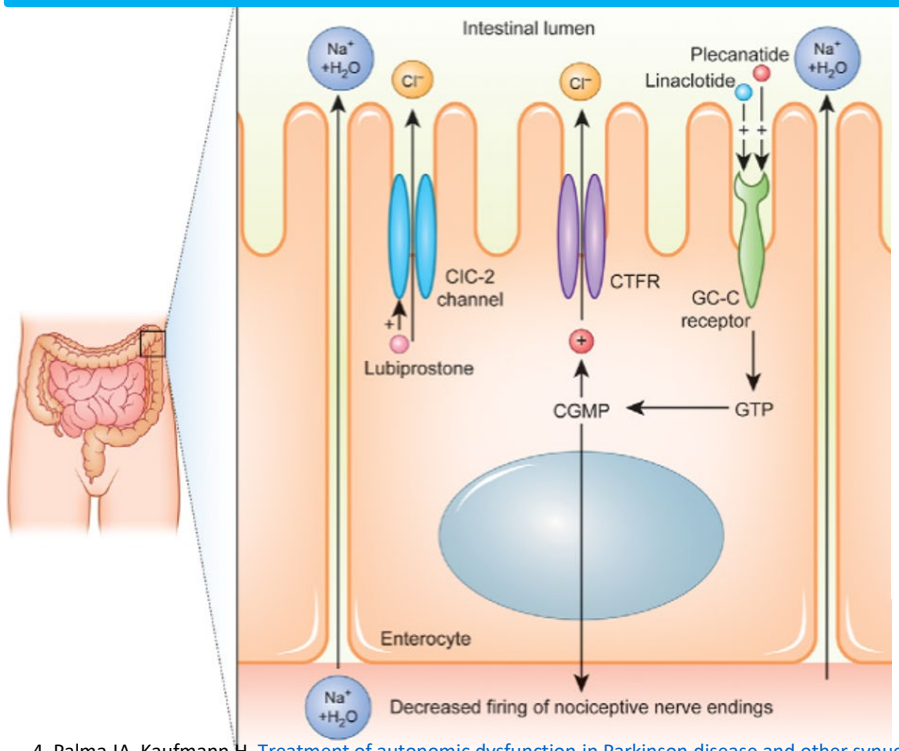


FIG. 5. Luminal chloride channel activators for the treatment of chronic constipation in patients with synucleinopathies. Lubiprostone is a locally acting chloride type 2 channel activator. Linaclotide is an agonist of the guanylate cyclase 2C receptor. Activation of guanylate receptors leads to a metabolic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

4. Palma JA, Kaufmann H. Treatment of autonomic dysfunction in Parkinson disease and other synucleinopathies. Mov Disord. 2018 Mar;33(3):372-390. doi: 10.1002/mds.27344. Review. PubMed PMID: 29508455; PubMed Central PMCID: PMC5844369.

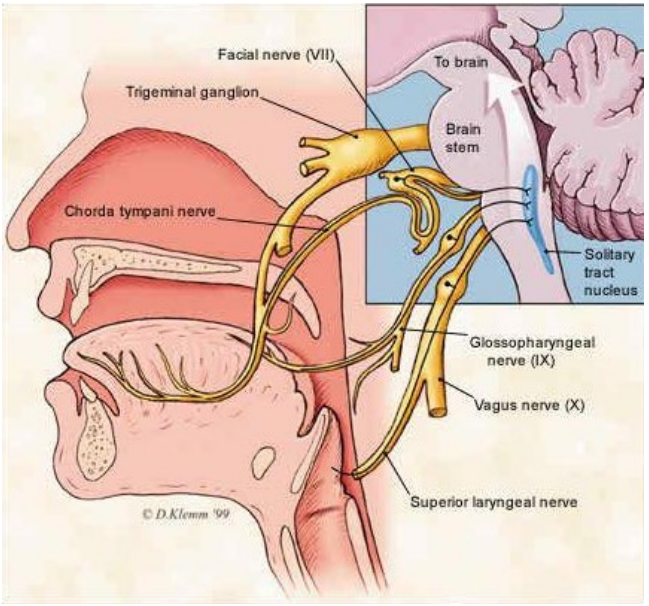
Dysphagia

- 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

4. Palma JA, Kaufmann H. Treatment of autonomic dysfunction in Parkinson disease and other synucleinopathies. Mov Disord. 2018 Mar;33(3):372-390. doi: 10.1002/mds.27344. Review. PubMed PMID: 29508455; PubMed Central PMCID: PMC5844369.

Dysphagia: 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
- Sensory input from the oropharynx initiates and controls swallowing through trigeminal, glossopharyngeal, and vagal afferents.



- Effector neurons are in:
  - Hypoglossal (XII) nuclei in the medulla, which innervates extrinsic and intrinsic muscles of the tongue
  - Nucleus ambiguous, which innervates all striated muscles of the pharynx and larynx through vagal fibers
  - 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)

4. Palma JA, Kaufmann H. Treatment of autonomic dysfunction in Parkinson disease and other synucleinopathies. Mov Disord. 2018 Mar;33(3):372-390. doi: 10.1002/mds.27344. Review. PubMed PMID: 29508455; PubMed Central PMCID: PMC5844369.

Dysphagia Evaluation / Treatment

- **Diagnosis:**
  - Refer to Speech Therapy for evaluation and treatment
  - Often barium swallow study or Fiberoptic endoscopic evaluation of **swallowing** (**FEES**) needed
- **Treatments:**
- **Exercise and Swallow Hard.**
  - Just as exercise can ease other PD-related movement difficulties, it can also help with swallowing.
  - The Lee Silverman Voice Technique® (LSVT®) helps a person exaggerate speaking and swallowing.
  - Working with an SLP on an individualized program helps the person to swallow hard and move food from the mouth down the throat.
- **Expiratory Muscle Strength Training.**
  - This therapy strengthens respiratory muscles, improves cough and swallowing and reduces aspiration.

https://parkinson.org/Understanding-Parkinsons/Symptoms/Non-Movement-Symptoms/Speech-and-Swallowing-Problems

Dysphagia Treatment

- Postural changes, behavioral changes (e.g., reduced meal volumes and eating slowing), and modified meal consistencies (e.g., liquid thickeners).

- Botulinum toxin injections in the distal esophagus have shown some promise to improve esophageal dysphagia in patients with PD.
  - Note: Neuromuscular electrical stimulation of the suprahyoid muscles in patients with PD showed NO benefits compared to behavioral/postural modifications.

- G-Tube: 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

4. Palma JA, Kaufmann H. Treatment of autonomic dysfunction in Parkinson disease and other synucleinopathies. Mov Disord. 2018 Mar;33(3):372-390. doi: 10.1002/mds.27344. Review. PubMed PMID: 29508455; PubMed Central PMCID: PMC5844369.

Gastroparesis

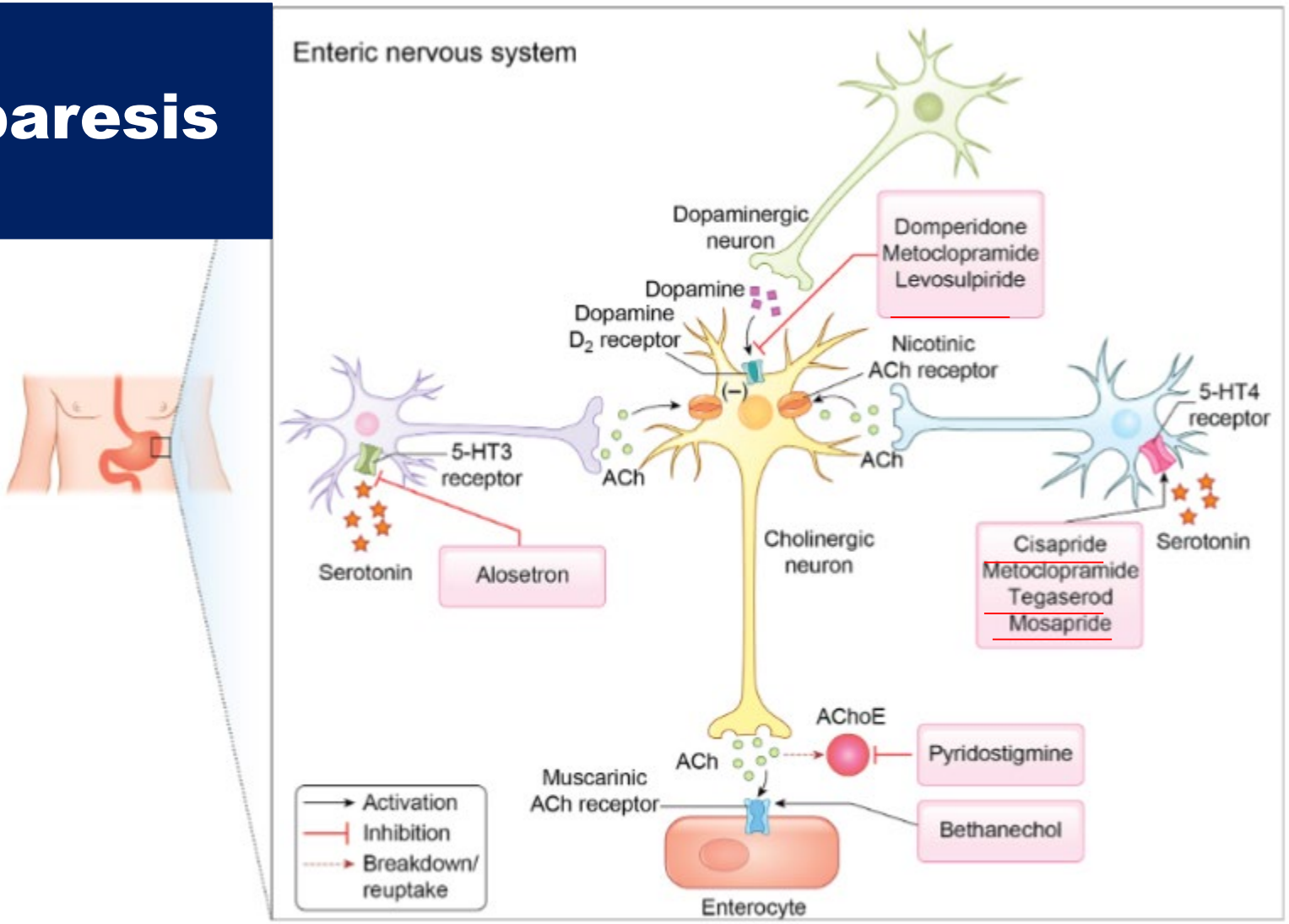


FIG. 3. Sites of action and mechanisms of therapeutic agents used for the treatment of gastroparesis. Several receptors (dopaminergic, cholinergic muscarinic, cholinergic nicotinic, and serotoninergic, among others) are involved in the regulation of gastric motility. Eventually, all modulate acetylcholine 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), acetcylcholinesterase 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.

4. Palma JA, Kaufmann H. Treatment of autonomic dysfunction in Parkinson disease and other synucleinopathies. Mov Disord. 2018 Mar;33(3):372-390. doi: 10.1002/mds.27344. Review. PubMed PMID: 29508455; PubMed Central PMCID: PMC5844369.

Dry Mouth

- Dry mouth was reported by 60.8% of PD patients and 27.9% of controls ($p < 0.0001$).
- Dry mouth and drooling coexisted in 30% of cases.
- Only 12% of patients had reported dry mouth to their physicians.

13. Cersosimo MG, Raina GB, Calandra CR, Pellene A, Gutiérrez C, Micheli FE, Benarroch EE. Dry mouth: an overlooked autonomic symptom of Parkinson's disease. J Parkinsons Dis. 2011;1(2):169-73. doi: 10.3233/JPD-2011-11021. PubMed PMID: 23939300.

Dry Mouth

- Cause may be multifactorial:
  - autonomic dysfunction +/- impact from medications (benztropine or trihexyphenidyl, etc.)

- Dry Mouth Treatments:
  - Nonpharmacologic strategies:
    - Sip water frequently
    - Let ice melt in your mouth
    - Restrict caffeine intake
    - Use a humidifier in sleeping area
  - Temporarily increase saliva flow by sucking on sugarless lemon drops or chewing sugarless gum (sorbitol-based is good)
  - Avoid: mouthwashes with alcohol which can be drying
  - Try OTC Biotene dry mouth lubricating products

  - Rx: Saliva substitutes Xero-lube, Salivart, MoiStir and Orex, or Sodium carboxymethyl cellulose 0.5% aqueous solution: oral rinse used several times per day

https://www.ohsu.edu/xd/health/services/brain/getting-treatment/diagnosis/parkinsons/education-resources/patient-education/upload/Dental-Care.pdf

Dry Lips

- Dry Lips Treatments:
  - Use: K-Y Jelly, Surgi-Lube or Hydrous lanolin (ask pharmacist).
  - Avoid: petroleum and Vaseline based products which make lips dryer by pulling water from tissues

Drooling

- 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.

- **Treatments:**
  - Oral glycopyrrolate (1 mg twice-daily): efficacious for short-term treatment of sialorrhea in PD
    - Side effects include dry mouth, urinary retention, constipation, and blurry vision.
  - Local administration of anticholinergics (e.g., sublingual atropine drops or ipratropium spray could be considered as alternative with no systemic adverse events, although the evidence is insufficient.
  - Botulinum toxin injections into the salivary glands are efficacious to reduce sialorrhea in patients with PD.
    - Repeat injections typically required every 3 to 6 months.
  - Behavioral modification (e.g., instruct patients to carefully swallow their saliva at specific times, chew sugarless gum or use sugarless lemon drops to stimulate swallowing of saliva)
  - Radiotherapy was effective in PD and MSA in small studies

4. Palma JA, Kaufmann H. Treatment of autonomic dysfunction in Parkinson disease and other synucleinopathies. Mov Disord. 2018 Mar;33(3):372-390. doi: 10.1002/mds.27344. Review. PubMed PMID: 29508455; PubMed Central PMCID: PMC5844369.

Urinary Dysfunction

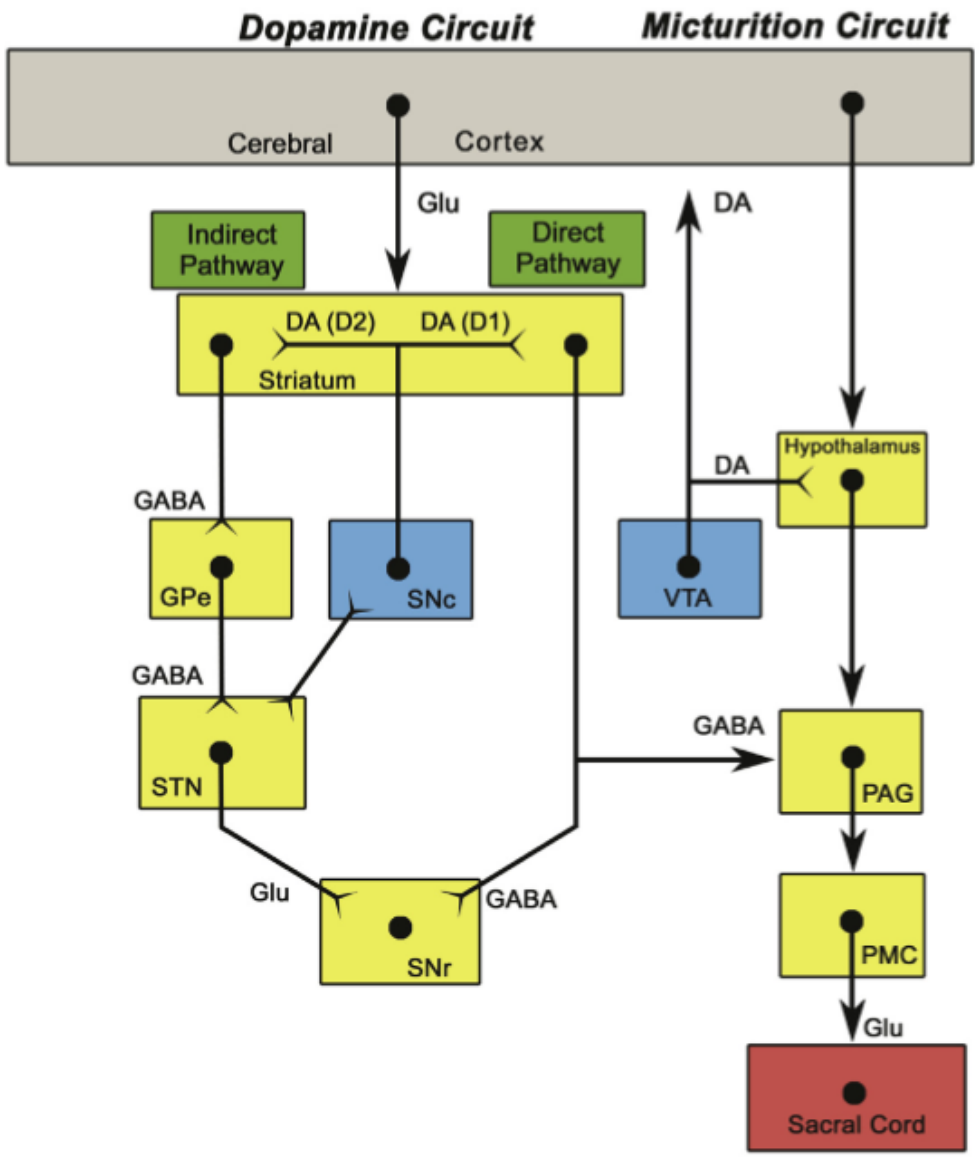


Fig. 1. Micturition and the brain–dopamine relationship. The micturition reflex (*right side pathway*) is under the influence of dopamine (DA; inhibitory D1 and facilitatory D2 receptors) and gamma-aminobutyric acid (GABA) (inhibitory). The substantia nigra pars compacta (SNc) dopaminergic neuronal firing activates the dopamine D1–GABAergic direct pathway, inhibits the basal ganglia output nuclei (eg, SNr), and also inhibit the micturition reflex through GABAergic collateral to the micturition circuit. High-frequency stimulation of the D2 receptor (indirect pathway) inhibits the subthalamic nuclei (STN) and also results in bladder inhibition. Glu, glutamate; GPe, globus pallidus externus; PAG, eriaqueductal gray matter; PMC, pontine micturition center; SNr, substantia nigra pars reticulate; VTA, ventral tegmental area. (*Adapted from* Sakakibara R, Tateno F, Kishi M, et al. Pathophysiology of bladder dysfunction in Parkinson's disease. Neurobiol Dis 2012;46:567; with permission.)

Kalra S. Parkinson's Disease and Its Effect on the Lower Urinary Tract: Evaluation of Complications and Treatment Strategies. Urol Clin North Am. 2017 Aug;44(3):415-428. doi: 2017.04.008. Review. PubMed PMID: 28716322.

Urinary Dysfunction: Diagnosis/Monitoring

- Bladder diary (~3 days): fluid intake, voiding frequency, time of each void, severity of urge to void, voided volumes, urine leakage episodes, pad usage.
  - Helpful to document symptoms and monitor progress after behavioral changes / treatment

Urinary Dysfunction

- **<u>Conservative management:</u>**
  - behavioral modification (scheduled urination)
  - patient education
  - bladder training
  - fluid and diet management
  - pelvic floor education
  - biofeedback training
  - bedside commode or urinal for nighttime

Table 3
Detrusor overactivity treatment recommendations in Parkinson's disease

Therapy	Level of Evidence
Bladder training	1
Anticholinergics	2[25]
Botulinum toxin	2[26]
Surgical intervention	2[27]

Data from Sakakibara R, Panicker J, Finazzi-Agro E, et al. A guideline for the management of bladder dysfunction in Parkinson's disease and other gait disorders. Neurourol Urodyn 2016;35:551–63.

Urinary Dysfunction: Treatment

- Alpha blockers – Tamsulosin (Flomax), doxazosin (Cardura), terazosin (Hytrin), alfuzosin (Uroxatral).
  - Used to treat urge and overflow incontinence in men with enlarged prostates
  - Side effects include orthostatic hypotension and dizziness.
- Anticholinergic drugs – Oxybutynin (Ditropan), tolterodine (Detrol), darifenacin (Enablex), solifenacin (Vesicare), fesoterodine (Toviaz), and trospium (Sanctura).
  - Most common medications used to treat urge incontinence and overactive bladder (OAB) in both men and women.
  - Side effects include blurred vision, dry mouth, constipation, fast heart rate and confusion/hallucinations.
  - Shouldn't take if have narrow angle glaucoma, severe constipation or if on memory drugs such as Aricept.
- Mirabegron (Myrbetriq) (beta-3 adrenergic receptor agonist) is now being used in patients with urge incontinence (overactive bladder) who can't tolerate anticholinergic medicine.
  - Associated with less dry mouth and constipation.
  - Can cause high blood pressure.
  - May precipitate dyskinesias
- Selective serotonin reuptake inhibitors
  - 5-hydroxytyrptamine (serotonin) reuptake inhibitors facilitate urine storage.
  - Duloxetine and milnacipran can be used off label for OAB in PD.
- Botox injections – weaken the bladder muscle.
  - Helpful for urgency/urge incontinence which could be helpful in Parkinson's.
  - Caution against patients with atypical Parkinsonism such as MSA because the problem there is often bladder Underactivity and could result in not being able to empty the bladder.
- Deep brain stimulation – subthalamic nuclei (STN)
  - Patients with STN DBS had similar amount of lower urinary tract symptoms as those with conventional treatments or an apomorphine pump; however, they had less nocturia ($P = 0.007$)

Brucker BM, Kalra S. Parkinson's Disease and Its Effect on the Lower Urinary Tract: Evaluation of Complications and Treatment Strategies. Urol Clin North Am. 2017 Aug;44(3):415-428. doi: 10.1016/j.ucl.2017.04.008. Review. PubMed PMID: 28716322.

Neurogenic Overactive Bladder:

Medication Sites of Action

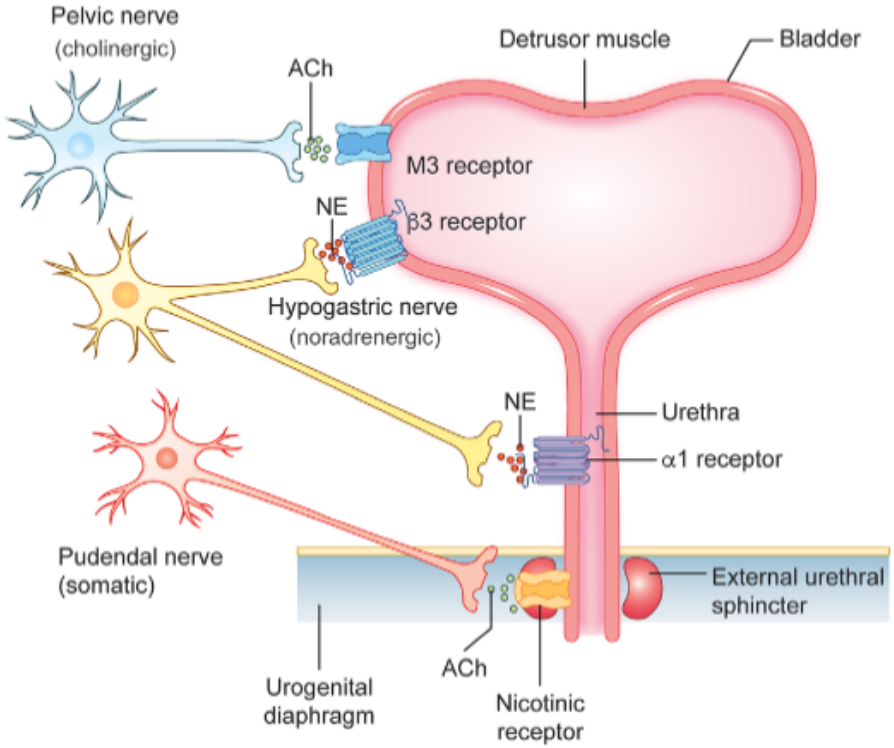
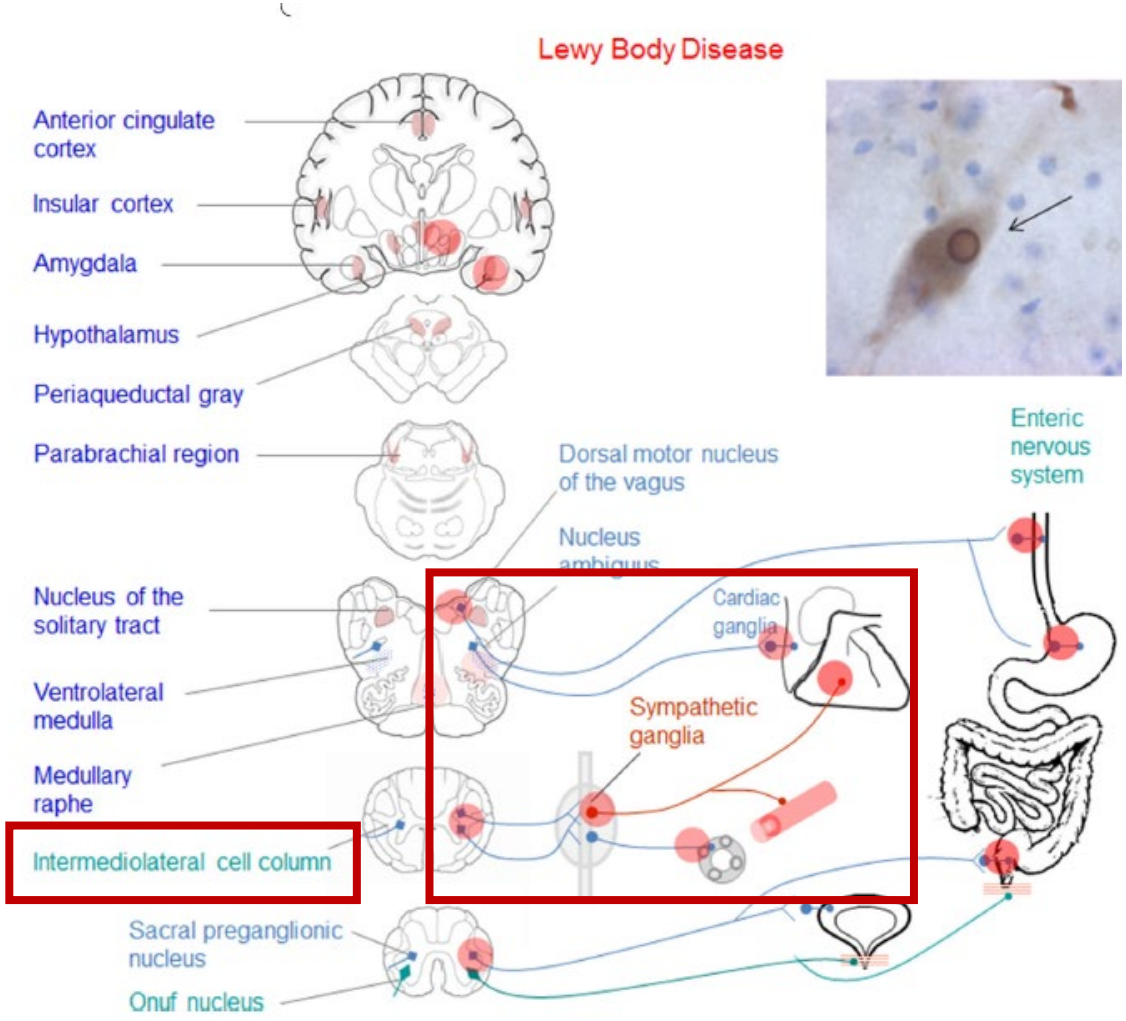


FIG. 6. Sites of action and mechanisms of therapeutic agents used for the treatment of neurogenic overactive bladder. Cholinergic pelvic nerves release acetylcholine (ACh), which, through activation of muscarinic M3 receptors, induce contraction of the detrusor muscle and emptying of the bladder. Antimuscarinic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

4. Palma JA, Kaufmann H. Treatment of autonomic dysfunction in Parkinson disease and other synucleinopathies. Mov Disord. 2018 Mar;33(3):372-390. doi: 10.1002/mds.27344. Review. PubMed PMID: 29508455; PubMed Central PMCID: PMC5844369.

Drenching Sweats:

Peripheral sympathetic pathways to the sweat glands impaired



Skin biopsies in PD show = Loss of sympathetic fibers to blood vessels, sweat glands, and erector pili muscles → thermoregulatory problems

1. Coon EA, Cutsforth-Gregory JK, Benarroch EE. Neuropathology of autonomic dysfunction in synucleinopathies. Mov Disord. 2018 Mar;33(3):349-358. doi: 10.1002/mds.27186. Epub 2018 Jan 3. Review. PubMed PMID: 29297596.

Sweating

- Sweating episodes in PD occurred predominantly during:
- *off* periods or
- *on* with dyskinesia
- A wide variety of body parts can be affected

Table 3. Pattern, anatomical, and temporal distribution of sweating in patients

Sweating and motor state	Patients (N = 49)
Off state	17 (35)
Dyskinesia	9 (18)
On without dyskinesia	4 (8)
No noticeable pattern	19 (39)
Sweating occurred predominantly at	
Day	21 (43)
Night	23 (47)
Both day and night	5 (10)
Pattern of hyperhidrosis	
Trunk and head	19 (39)
Trunk only	14 (29)
Head and neck	8 (16)
Whole body	7 (14)
Feet only	1 (2)

16. Swinn L, Schrag A, Viswanathan R, Bloem BR, Lees A, Quinn N. Sweating dysfunction in Parkinson's disease. Mov Disord. 2003 Dec;18(12):1459-63. PubMed PMID: 14673882.

Sweating Impact

Table 5. Impact of sweating on daily life of patients who reported problems

Problem reported	Patients (N = 49)	
	Frequent	Infrequent
Felt cold/uncomfortable	16 (33)	15 (31)
Day-time wash/change clothes	—	33 (67)
Disturbed sleep	14 (29)	16 (33)
Having to change nightwear	4 (8)	17 (35)
Having to disturb partner at night to change nightwear	3 (6)	9 (18)
Limiting social activities	2 (4)	14 (29)
Felt embarrassed	4 (8)	17 (35)
Felt down	10 (20)	18 (37)

16. Swinn L, Schrag A, Viswanathan R, Bloem BR, Lees A, Quinn N. Sweating dysfunction in Parkinson's disease. Mov Disord. 2003 Dec;18(12):1459-63. PubMed PMID: 14673882.

Patient Tips for Excessive Sweating (Hyperhidrosis:

Identify patterns (time of day, time after last dose of Parkinson's medication).

Write patterns down to review with your Parkinson's doctor.

If no clear relationship to OFF times or ON times with dyskinesias then your doctor may recommend lifestyle modifications or the following treatments to address sweating.

- Identify: food or drinks triggers (i.e. alcohol, caffeine or spicy foods).
- Use an antiperspirant frequently to reduce sweating (a deodorant will only reduce odor).
- Avoid tight-fitting or synthetic (e.g. nylon) clothes.
- Wear clothes that don't show sweat marks.
- Use armpit or sweat shields to absorb excess sweat and protect your clothes.
- Wear socks and clothes made of natural fibers, such as cotton, or fabrics designed to absorb moisture.
- Try to avoid situations that may trigger sweating, such as crowded rooms or situations you may find stressful.

https://www.mayoclinic.org/diseases-conditions/hyperhidrosis/diagnosis-treatment/drc-20367173

Sweating Treatments

Pharmacologic Treatments:

Prescription antiperspirant with aluminum chloride (Drysol, Xerac Ac).

Prescription creams. Containing glycopyrrolate may help sweating on face and head.

Antidepressants Some medications used for depression can also decrease sweating.

- TCAs or medications with anticholinergic properties help.
- SSRIs can increase sweating.

Botulinum toxin injections. Treatment with botulinum toxin (Botox, Myobloc, others) temporarily blocks the nerves that cause sweating.

Advanced Treatment of Non-motor Symptoms in PD

TABLE 3. Available evidence of the effect of advanced treatments on fluctuating NMS in PD

Fluctuating NMS	STN-DBS	GPi-DBS	Apomorphine Pump	L-dopa-Carbidopa Pump
Neuropsychiatric				
Depression	Improvement[200-205] Worsening[77,206,207]	Improvement[208]	Improvement[182]	Improvement[182,193,209]
Anxiety	Improvement[200,201,203,205] Worsening[a,207,210]	NA	NA	Improvement[193,194]
Fatigue	Improvement[205,211]	NA	Improvement[181,182]	Improvement[34,182,193,209]
Apathy	Improvement[197,212] Worsening[a,77,105,173,195,201,213,214]	NA	Improvement[182]	Improvement[182]
Attention/cognition	Improvement[212]	NA	Improvement[182]	Improvement[34,182]
ICD/hyperdopaminergic behaviors	Improvement[a,90,195,196,215-219] Worsening/onset[201,210,220-225]	NA	Improvement[182]	Improvement[182,193,226]
Hallucination	Improvement[a,227] Worsening[227]	NA	Improvement[182]	Improvement[182]
Autonomic				
Cardiovascular	Improvement[228]	NA	NA	Improvement[182] Worsening
Constipation	Improvement[211,229]	NA	Improvement[182] Worsening	Improvement[34,182,193,208] Worsening
Drenching sweats	Improvement[230]	NA	Improvement[181]	Improvement[193]
Bladder dysfunction	Improvement[231-235]	NA	Improvement[181,182]	Improvement[34,182,209]
Swallowing	Improvement[236,237] Worsening[238]	NA	NA	NA
Sexual disorders	Improvement[239]	NA	NA	Improvement[182]
Sensory/pain				
Pain	Improvement[211,240-242]	Improvement[243]	NA	Improvement[193,209]
Dysesthesia	NA	Improvement[243]	NA	NA
Restless legs	Improvement[244,245] Worsening[a,246]	NA	NA	NA

[a]Attributed to either stimulation itself or to reduction in dopaminergic drugs.
GPi-DBS, globus pallidus internus DBS; NA, not available; STN-DBS, subthalamic nucleus DBS.

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