Non-Motor Symptoms In Parkinson Disaese

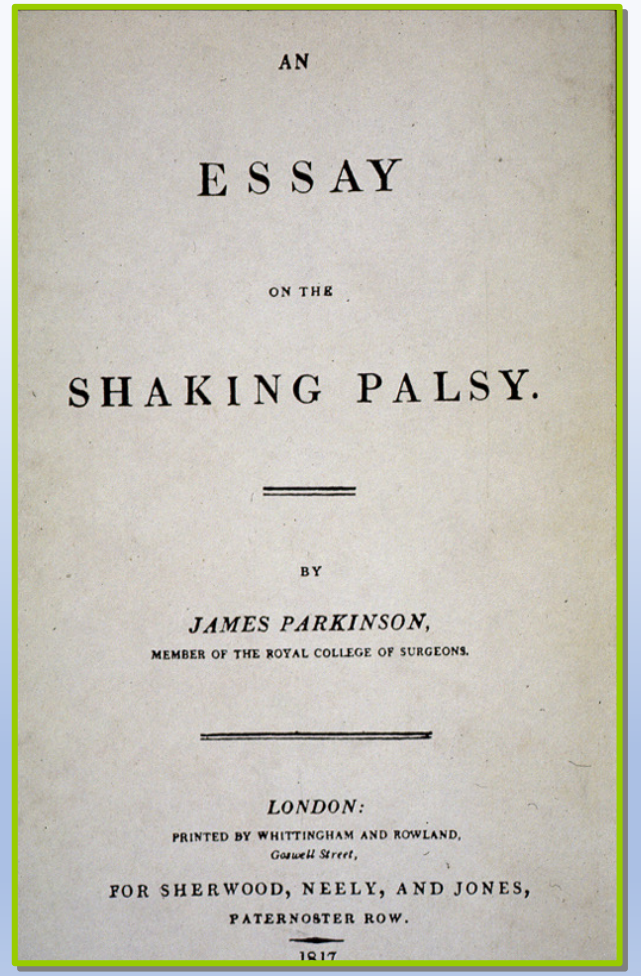
Fernando L. Pagán, M.D.
Vice Chair and Professor of Neurology
Director of Movement Disorders Program
Medical Director of Parkinson's Foundation
Center of Excellence at Georgetown University Hospital
Lewy Body Disease Research Center of Excellence
Translational Neurotherapeutics Branch

Objectives

- Understand the pathophysiology of PD
- Motor and non-motor symptoms in PD
- Understand the Treatment in nonmotor symptoms of PD
- Barriers identifying nOH in PD

What is Parkinson's Disease?

- 1817: James Parkinson
  - "An Essay on the Shaking Palsy"
- Diagnosis requires 2 of 3:
  - Bradykinesia; rigidity; tremor (rest)
- Other signs: Masked facies; hypohonia; micrographia; flexed posture; swallowing difficilties; shuffling gait; hesitancy and freezing gait.
- Onset: Insidious, unilateral progressing to bilateral.
- PD most likely multiple disorders


AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:

PRINTED BY WHITTINGHAM AND ROWLAND,

Goswell Street,

FOR SHERWOOD, NEELY, AND JONES,

PATERNOSTER ROW.

1817.

Cardinal Features and Clinical Manifestations: Traditional Definition

Motor Signs

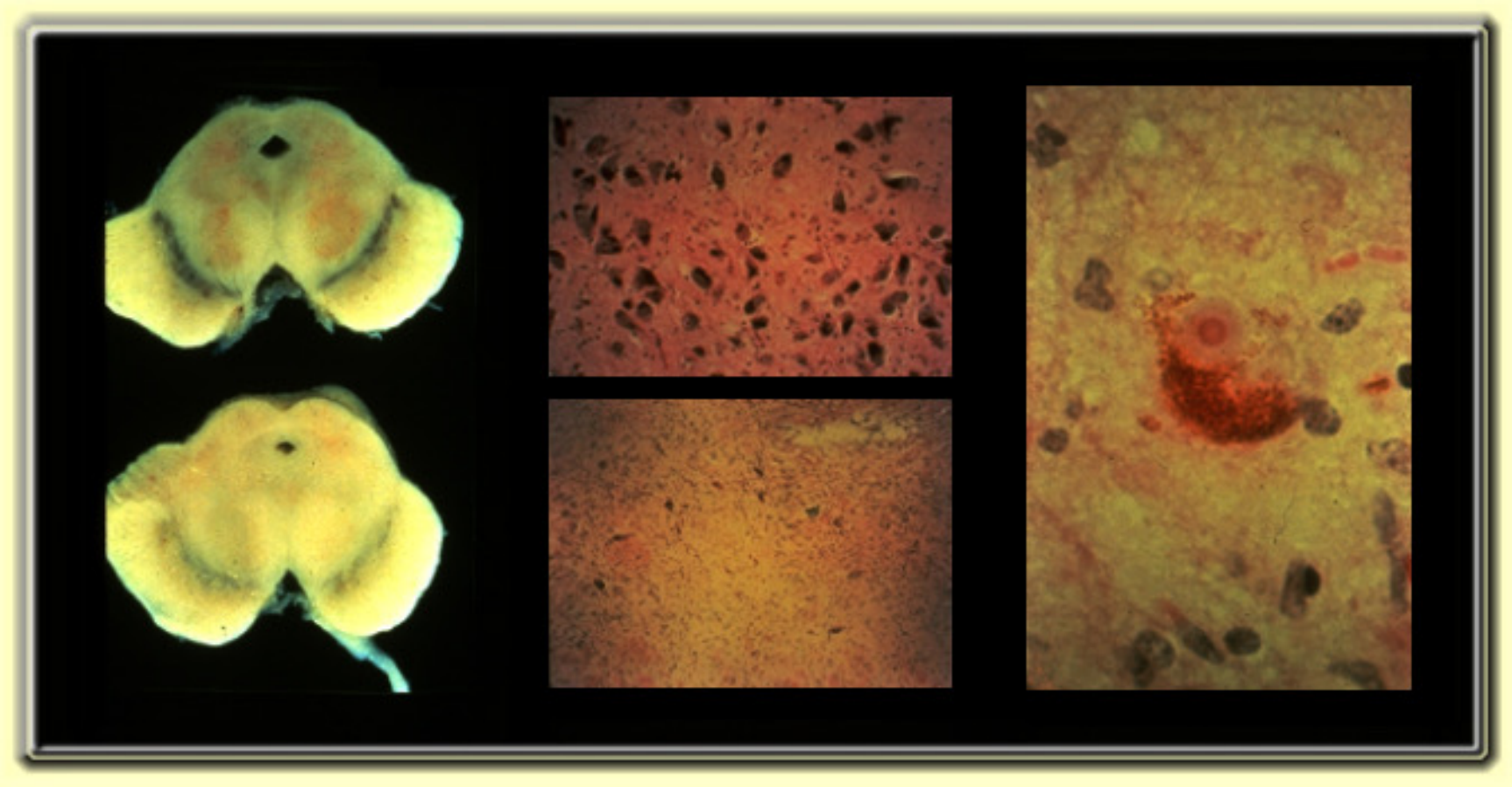
- Bradykinesia
- Tremor at rest
- Rigidity
- Postural instability

Clinical Manifestations

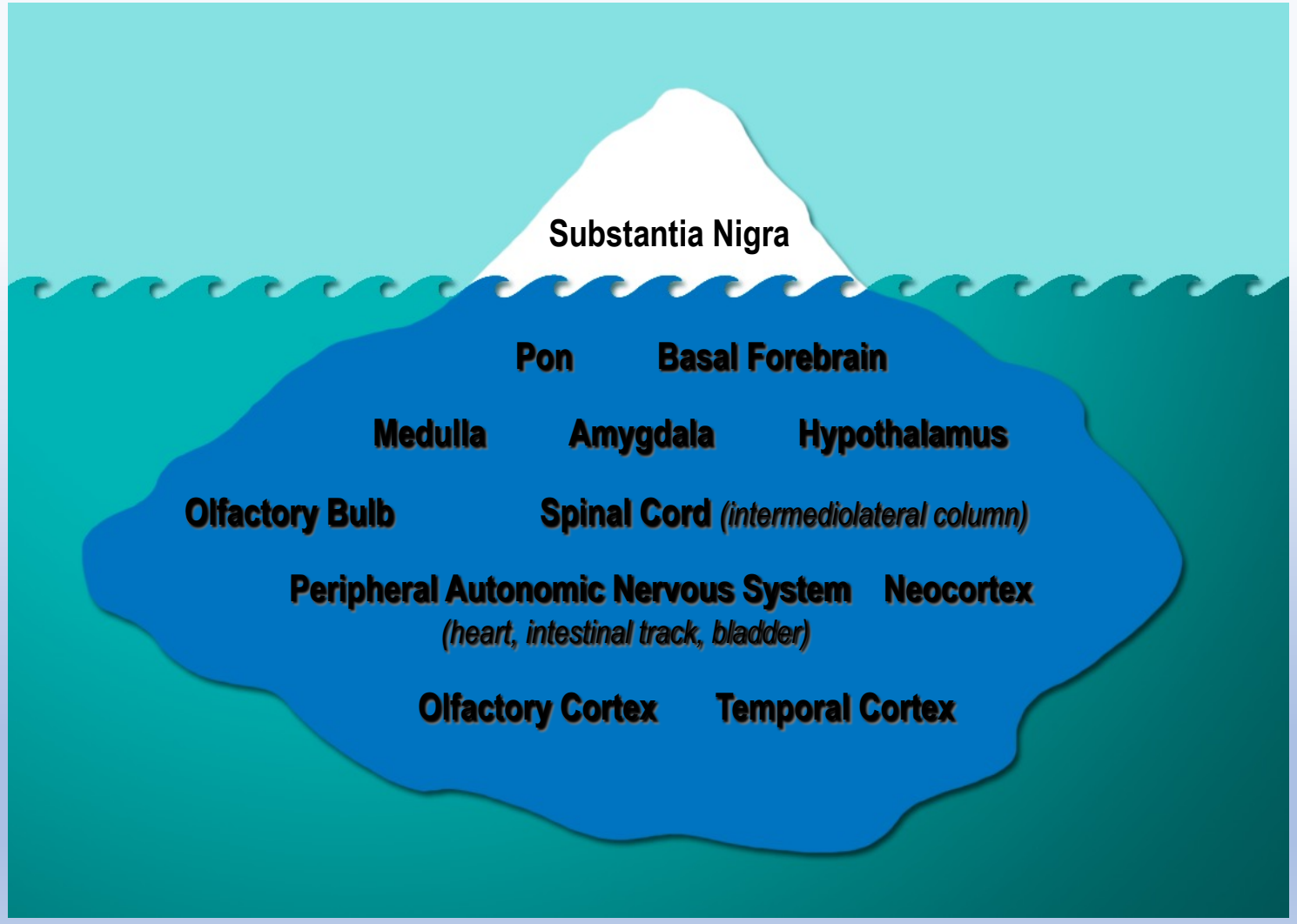
- Decreased arm swing
- Hypomimia
- Hypophonia
- Micrographia

Hughes AJ et al. *J Neurol Neurosurg Psychiatry*. 1992;55:181-184.
Jankovic J. *Handbook of Parkinson's Disease, 4th ed*. 2007:49-76.
Jankovic J. *J Neurol Neurosurg Psychiatry*. 2008;79:368-376.
Morgan J et al. *Handbook of Parkinson's Disease 4th ed*, 2007:29-47.

Pathology of Parkinson's Disease



The Parkinson's Complex

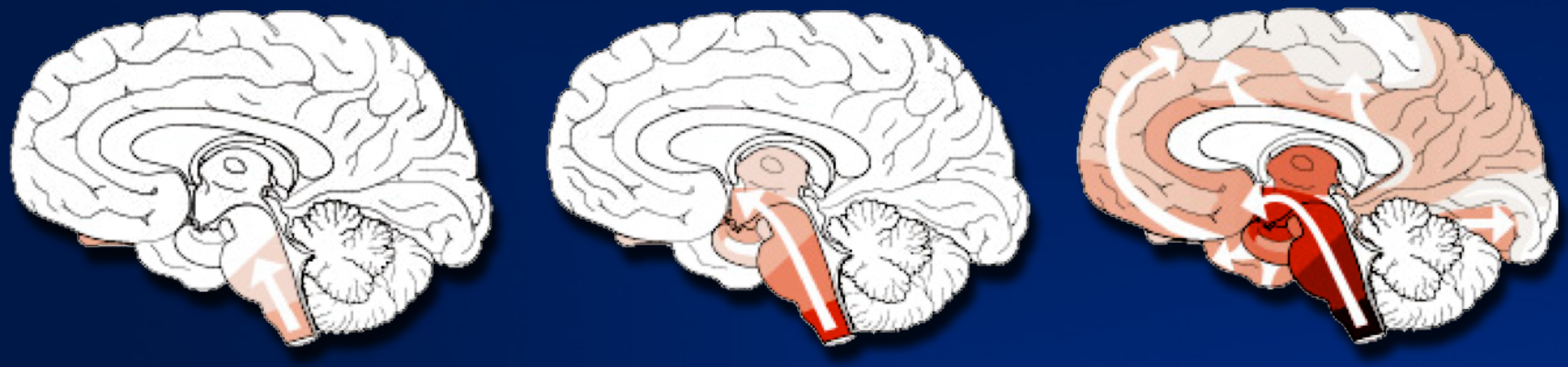


Reproduced from Langston JW. *Ann Neurol*. 2006;59:591-596.

Evolution of Lewy Body Pathology

Pre-clinical PD

Clinical PD



Stage 1/2

Stage 3/4

Stage 5/6

PD-related Lewy body pathology evolves in predictable stages. According to the staging system of Braak, Lewy bodies (LB) first form within in the olfactory bulb and dorsal motor nucleus of the vagal nerve (Stage 1). In Stages 2 and 3, LB pathology expands from these induction sites into additional brain stem nuclei (e.g. locus coeruleus and substantia nigra) and then into the amygdala. In Stages 5 to 6, the pathology extends into the cerebral cortex. Clinical symptoms arise during Stages 4 to 6, when the pathology involves significant regions of the substantia nigra and related brain areas.

Braak H et al. *Neurobiol Aging*. 2003; 24:197-211.

Non-motor Features of PD

- **Neuro-psychiatric and cognitive:**
  - Depression
  - Anxiety
  - Psychosis
  - Dementia
  - Apathy
  - Fatigue
  - Sleep disturbance
- **Autonomic:**
  - Constipation
  - Hyperhidrosis
  - Urinary dysfunction
    Sexual dysfunction
  - Sialorrhea
  - nOH
- **Sensory**
  - Pain
  - Smell loss

Common Problems in PD

- Depression
- Cognitive Dysfunction/Dementia
- Drooling
- Sleep Disorders
- Falls/ Balance Problems
- Motor Fluctuations
- Constipation
- Pain
- Orthostatic Hypotension
- Hypophonia

Treatment of Nonmotor PD Symptoms: Recommendations From the AAN QSS

Parameter	*Recommendation*	*Evidence Level**
Orthostatic Hypotension*	Insufficient evidence to support or refute treatment in PD	U
Urinary Incontinence	Insufficient evidence to support or refute treatment in PD	U
Constipation	Isosmotic macrogol (polyethylene glycol) may be considered	C
	Insufficient evidence to support or refute the use of botulinum toxin	U
Excessive Daytime Somnolence (EDS)	Modafinil† should be considered for patients to improve their subjective perception of EDS	A
Insomnia	Insufficient evidence to support or refute the benefit of LD/carbidopa on objective sleep parameters that are not affected by motor status	U
	Insufficient evidence to support or refute the benefit of LD on the treatment of poor sleep quality with melatonin	U

*Evidence level was based on the AAN's classification scheme

†:Off-label use

Zesiewicz TA, et al. *Neurology*. 2010;74:924-931.

Treatment of Nonmotor PD Symptoms: Recommendations From the AAN QSS

Parameter	*Recommendation*	*Evidence Level**
Periodic Limb Movements of Sleep	LD/carbidopa should be considered	B
	Insufficient evidence to support or refute treatment with nonergot dopamine agonists	U
RBD	Insufficient evidence to support or refute the treatment of RBD	U
	Clonazepam† and melatonin are often used in the general population	
Fatigue	Methylphenidate† may be considered	C
Sialorrhea	Botulinum toxins† should be considered (Myobloc and Xeomin FDA Approved)	A
Erectile Dysfunction	Sildenafil citrate (50 mg) may be efficacious	C
Anxiety	Insufficient evidence to support or refute the treatment of anxiety with LD	U

*Evidence level was based on the AAN's classification scheme

†:Off-label use

Zesiewicz TA, et al. *Neurology*. 2010;74:924-931.

Treatment of Nonmotor PD Symptoms: Recommendations From the AAN QSS

Parameter	*Recommendation*	*Evidence Level**
Depression	Amitriptyline may be considered	C
	Insufficient evidence for other treatments	U
Psychosis	Clozapine should be considered, monitor neutrophil count	B
	[Pimavanserin is FDA Approved]	A
	Quetiapine may be considered	C
	Olanzepine should not be considered	B
Dementia	Donepezil† should be considered	B
	Rivastigmine should be considered	B
	Insufficient evidence to support or refute the treatment of dementia with piracetam#	U

*Evidence level was based on the AAN's classification scheme †:Off-label use
#:Investigational product

Miyasaki JM, et al. *Neurology*. 2006;66:996-1002.

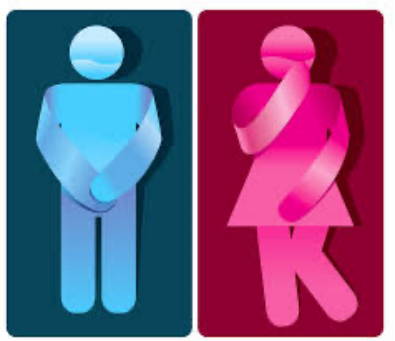
CONSTIPATION

- PD may begin in the gut
- DA and 5HT neurons in the gut accumulate misfolded alpha-synuclein
- Water, Fiber and OTC drugs used for constipation
- Prune Juice Cocktail (Prune Juice, Applesauce and Bran Fiber cereal)
- No one drug FDA approved yet in Constipation with PD
- Constipation can predate PD motor symptoms by 4-20 years
- Bloating, increase gas production, decrease appetite, medication ineffectiveness can be signs of constipation/gastroparesis
- MiraLAX, Milk of Magnesia, Colace, Pericolace, Fleet enema's etc
- **Enterin** (Bile salt of dogfish shark) in clinical trials now: KARMET STUDY

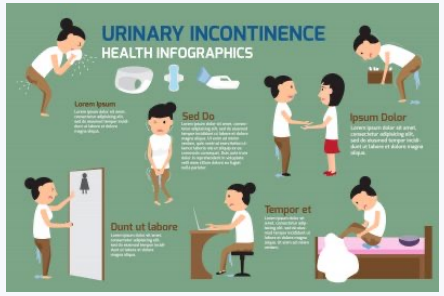
Excessive Sweating (Hyperhidrosis)

- Patients with PD can experience heat and cold intolerances
- When L-dopa wears off Excessive sweating can often be seen
- “Night sweats” in PD patients can often be seen
- This is variable from patient to patient
- This is also a sign of ANS dysfunction and may or may not respond to the routine PD medications

Urinary Dysfunction



- Voiding difficulties in up to 70% of patients
- Common symptoms:
  - Increased frequency of urination
  - Nocturia (frequent urination at night)
  - Urgency
  - Urge incontinence
- Bladder symptoms correlate with Dopamine Deficiency
- Detrusor muscle overactivity in PD can sometimes be treated with moderate L-dopa
- Worsening frequency can be a sign of wearing off



Urinary Dysfunction Treatments

- Referral to Urologist or PT
- Neurogenic Bladder treatments
- Caution with Anti-cholinergics
  - Can cause confusion
  - Delirium
  - Hallucinations
- BTX
- Stimulators now FDA cleared for Neurogenic Bladders

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

Neurogenic Orthostatic Hypotension

- The peripheral nervous system can also be affected in PD, more common in LBD and MSA
- Up to 30% in PD
- Symptoms Include:
  - Light-headness, fatigue, low energy, need to sit down
  - “Coat Hanger” pain, Headache
  - Fainting (Syncope)
  - Can be mistaken for “Wearing Off”

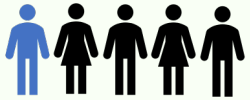
nOH is a Type of Orthostatic Hypotension (OH) Caused By Sympathetic Nervous System Dysfunction

OH

- Defined as a sustained drop in systolic blood pressure (BP) of ≥20 mmHg or in diastolic BP of ≥10 mmHg within 3 minutes of standing[1]

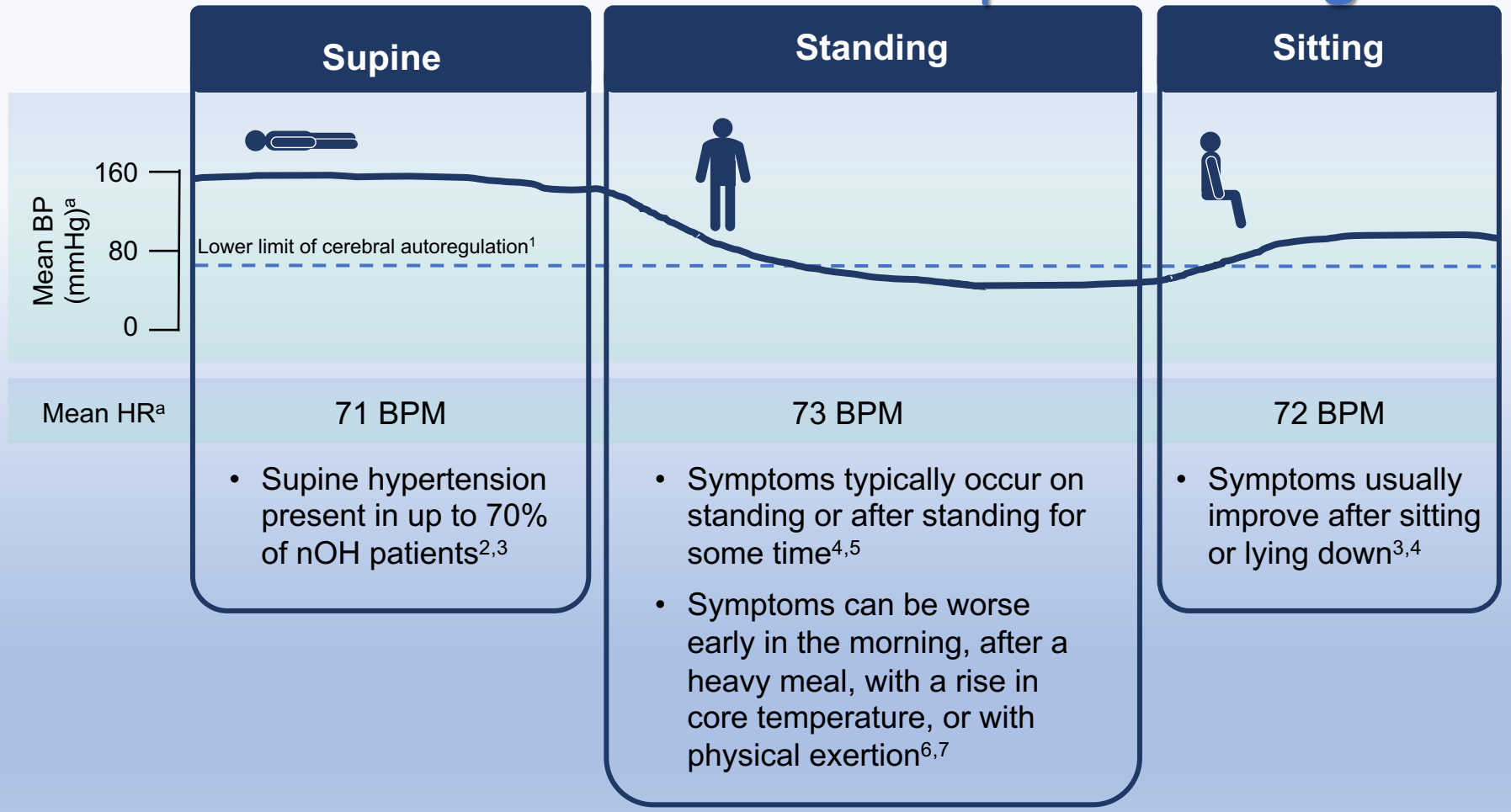
nOH

- **OH due to dysfunction of the sympathetic nervous system that impacts norepinephrine (NE) release upon standing[1,2]**
- Inadequate vasoconstriction and compensatory heart rate (HR) increase to maintain BP can result in symptoms[1-3]

Parkinson's Disease (PD)[4]	Multiple system atrophy (MSA)[4]	Pure autonomic failure (PAF)[5]
		
• About 1 in 5 people with PD have nOH with symptoms	• About 4 in every 5 people with MSA have nOH with symptoms	• 5 out of 5 people with PAF have nOH

1. Freeman R, et al. *Clin Auton Res*. 2011;21(2):69-72; 2. Isaacson SH, Skettini J. *Vasc Health Risk Manag*. 2014;10:169-176;
3. Kaufmann H, et al. *Expert Rev Cardiovasc Ther*. 2015;13:875-891; 4. Ha AD, et al. *Parkinsonism Relat Disord*. 2011;17:625-628;
5. Kaufmann H. *Clin Auton Res*. 1996;6:125-126.

Symptoms of nOH Are Associated With a Drop in Blood Pressure That Can Occur Upon Standing

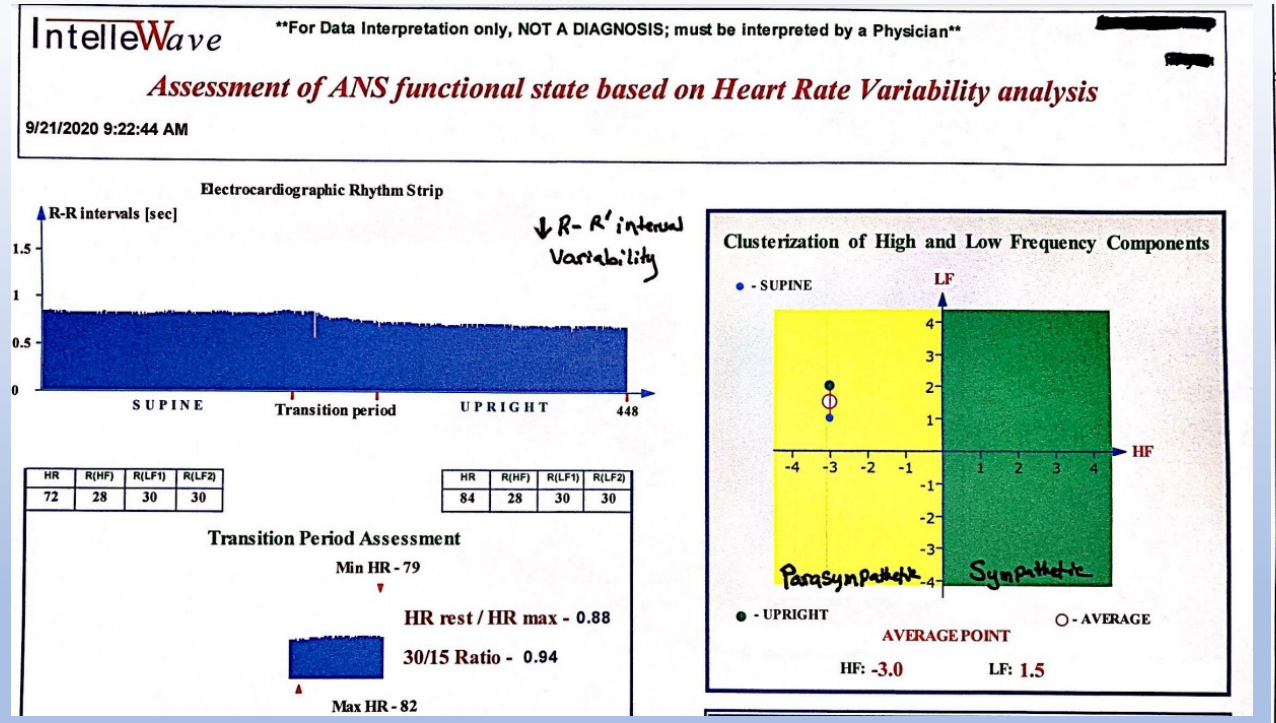


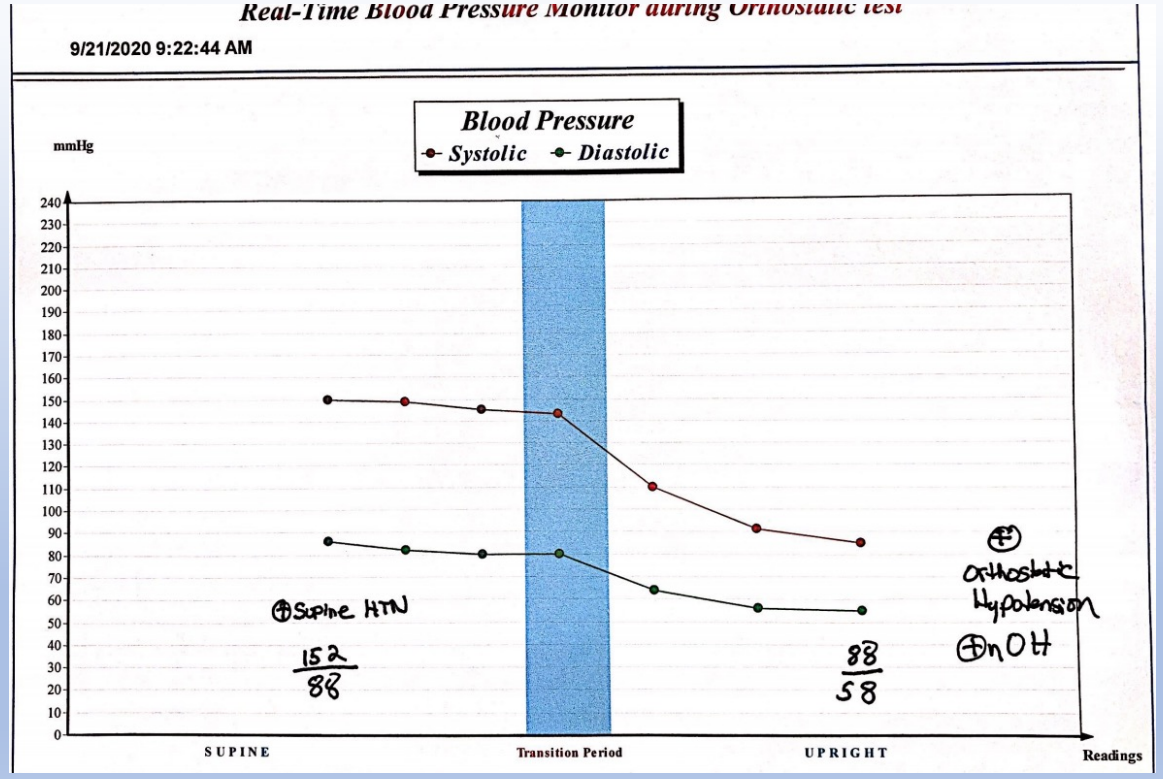
Graphic adapted from: Kaufmann H, Palma JA. *Clin Auton Res*. 2017;27:39-43.

[a] BP trace and HR are not from an actual patient and are for demonstrative purposes only.

1. Palma JA, et al. *Mov Disord*. 2015;30:639-645; 2. Berganzo K, et al. *J Neurol*. 2013;260:1752-1756;
3. Kaufmann H, et al. *Expert Rev Cardiovasc Ther*. 2015;13:875-891; 4. Kaufmann H, et al. *Clin Auton Res*. 2012;22:79-90;
5. Isaacson SH, Skettini J. *Vasc Health Risk Manag*. 2014;10:169-176; 6. Mathias CJ. *J Neurol Neurosurg Psychiatry*. 2003;74:iii31-iii41;
7. Freeman R, et al. *Clin Auton Res*. 2011;21(2):69-72.

Tilt Table Test





nOH Symptoms Can Result From Reduced Blood Perfusion Throughout the Body[1]

Cardinal Symptoms[1-3]:

- Lightheadedness
- Dizziness
- Presyncope
- Syncope

Additional Symptoms:

- Cognitive deficits[1,3,4]
- Visual blurring[1,3]
- Headache[1,3]
- Neck and shoulder pain[1,3]
- Orthostatic dyspnea[1,3]
- Chest pain[1,3]
- Falls and leg buckling[1,3,5]
- Generalized weakness[1,3]
- Fatigue[1,3]
- Nausea[1]

1. Freeman R. *N Engl J Med*. 2008;358(6):615-624; 2. Isaacson SH, Skettini J. *Vasc Health Risk Manag.* 2014;10:169-176;
3. Freeman R. *Clin Auton Res.* 2011;21:69-72; 4. Centi J, et al. *Neurology.* 2017;88:17-24;
5. Goldstein DS, Sharabi Y. *Circulation*. 2009;119:139-146.

Treatment of nOH

- Conservative Measures
  - Fluids- Hydration
  - Increase Salt
  - Compression stocking
  - Compression bands
  - Head of Bed elevation
  - Small meals
  - Avoid alcohol/diuretics
- Droxidopa (Northera)
- Midodrine
- Fludrocortisone?
- Pyridostigmine (Mestinon)

Speak with you Healthcare Provider

- ANS dysfunction can be treated
- Pay attention to affects of your medications
- PD medication can help or worsen ANS dysfunction
- Sometimes addition test may help solve the problem

THANK YOU!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