



Parkinson's Foundation

Non-motor Symptoms: What's New?

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OHSU Parkinson Center

Parkinson's Foundation Center of Excellence

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Better Lives. Together.

Journal Editing

- Elsevier – Parkinsonism & Related Disorders

Book Editing

- Taylor & Francis (CRC Press) – Parkinson's Disease
- Springer (Humana Press) – Parkinson's Disease and Nonmotor Dysfunction

Lecture Honoraria

- University of California-Irvine
- Mid-South Parkinson's Disease Support Group
- Vanderbilt University

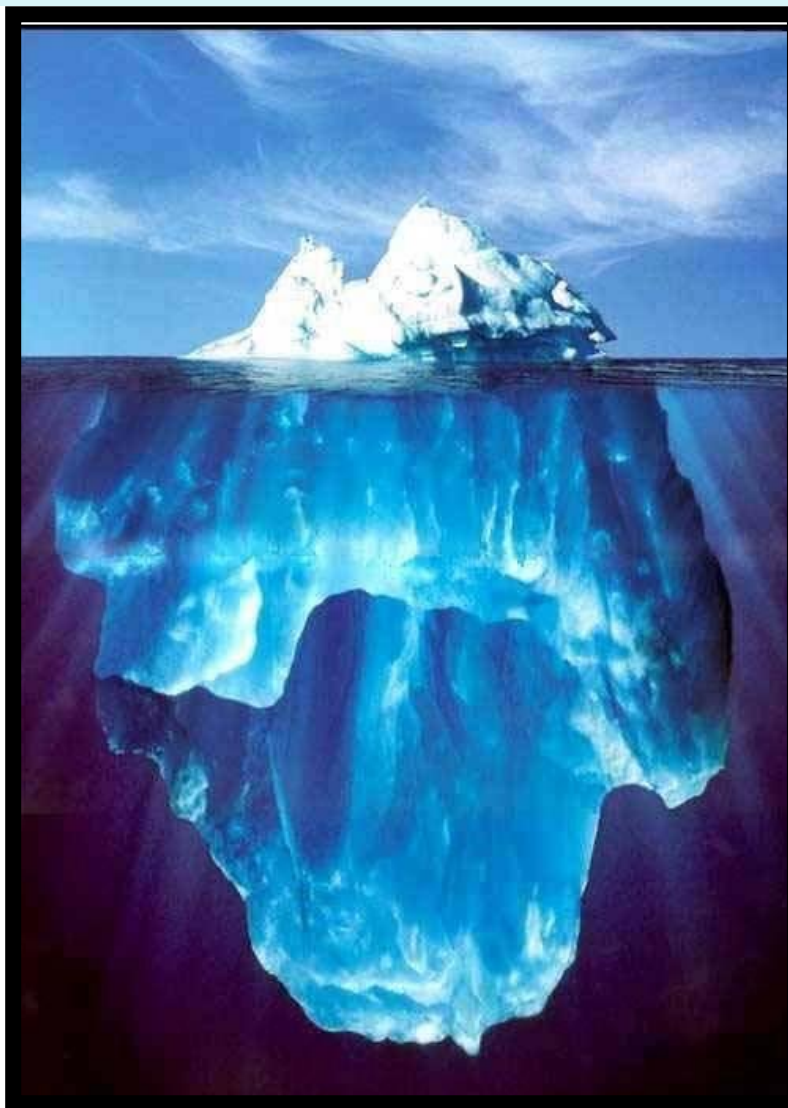
Medical Consulting

- Acadia
- Adamas



Tremor
Rigidity
Bradykinesia

NONMOTOR



MOTOR

Abnormalities of sensation
Sleep disorders

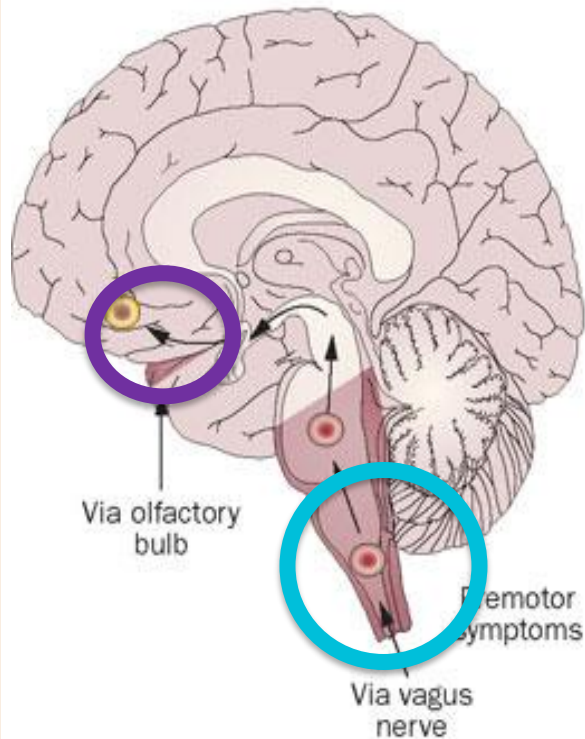
Autonomic dysfunction
Fatigue

Behavioral Changes

Braak Staging of PD

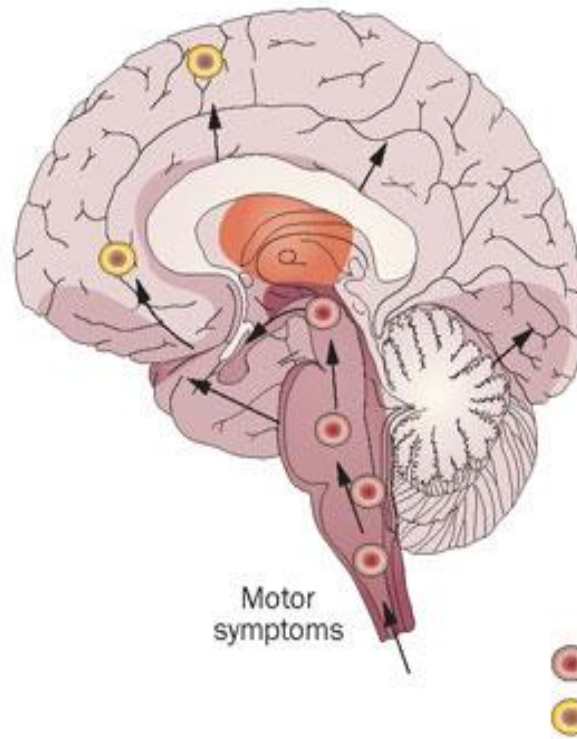
Braak stages 1 and 2

Autonomic and olfactory disturbances



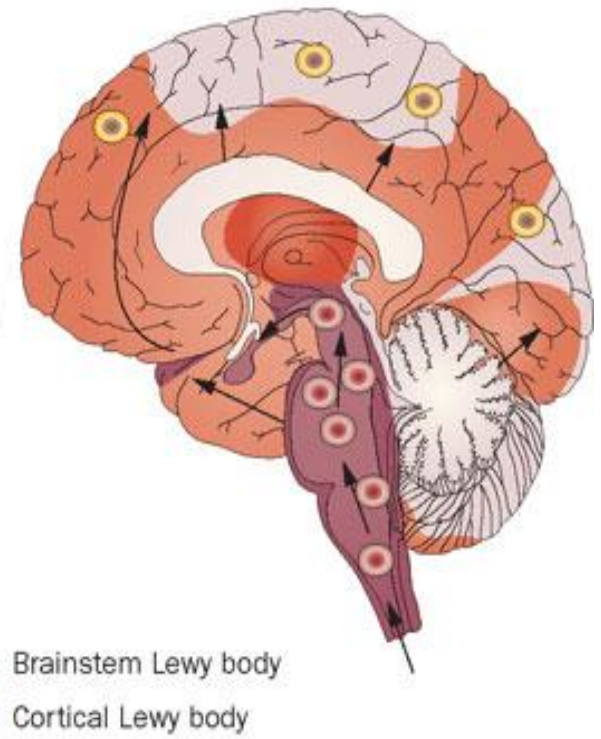
Braak stages 3 and 4

Sleep and motor disturbances



Braak stages 5 and 6

Emotional and cognitive disturbances

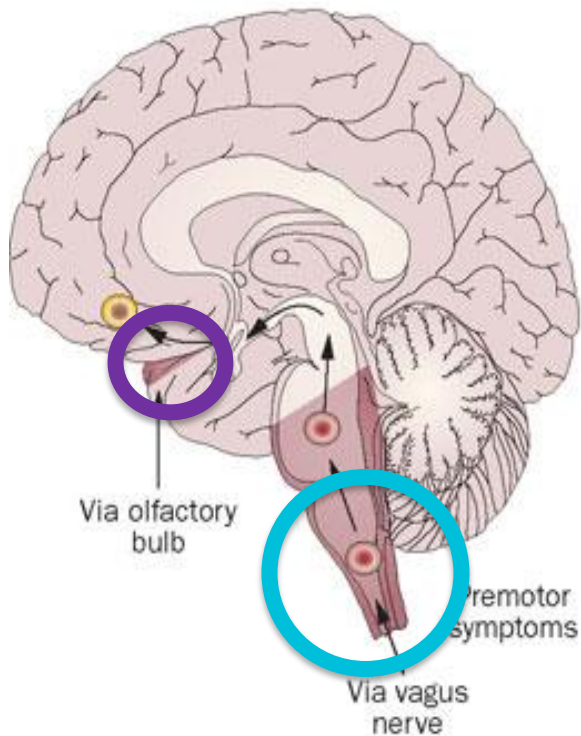


Doty RL. Nature Reviews Neurology 2012;8:329-339

Braak Staging of PD

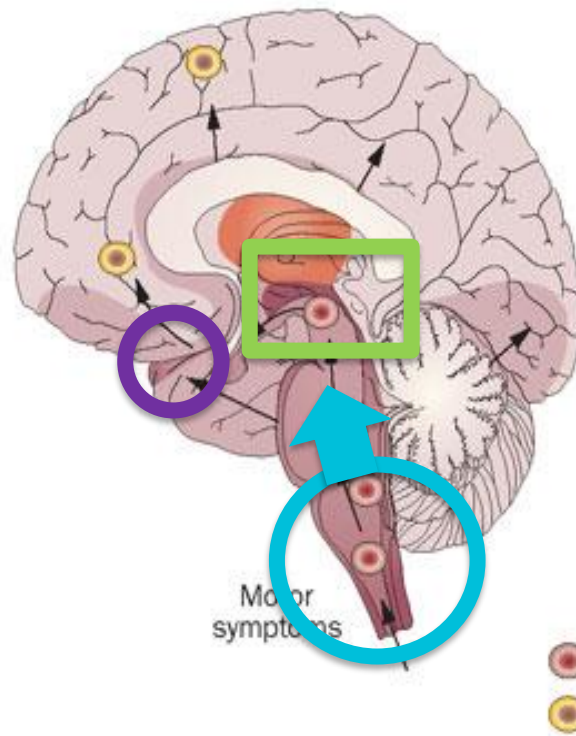
Braak stages 1 and 2

Autonomic and olfactory disturbances



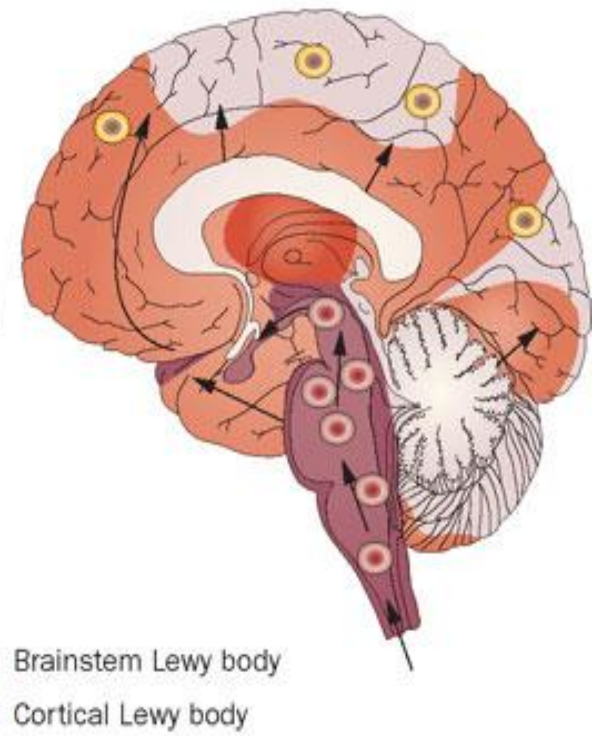
Braak stages 3 and 4

Sleep and motor disturbances



Braak stages 5 and 6

Emotional and cognitive disturbances



Doty RL. Nature Reviews Neurology 2012;8:329-339

Early Nonmotor Features

Impaired olfaction

Constipation

Erectile dysfunction

REM sleep behavior disorder

Depression

Anxiety

Onset of Constipation in Relation to Motor Symptoms

Onset of Constipation	Total # (%)	Men # (%)	Women # (%)
Before PD	49 (50.5)	23 (43.4)	26 (59.1)
After PD	14 (14.4)	11 (20.8)	3 (6.8)
Unknown	34 (35.1)	19 (35.8)	15 (34.1)
Total	97 (100.0)	53 (100.0)	44 (100.0)

In patients who had onset of constipation before onset of PD the mean age at which constipation began was 39.9 years

In these individuals constipation began a mean of 18.7 years before the appearance of motor symptoms

Ueki A, Otsuka M. J Neurol 2004;251(Suppl 7):VII/18-VII/23.

Impact of Nonmotor Features of PD

May develop early in the course of PD

- May precede the development of motor features

May become dominant features in advanced PD

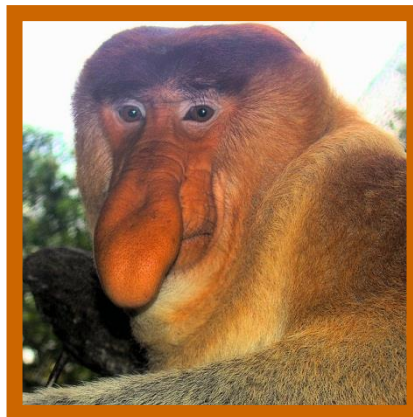
- May impair quality of life more than motor features

Major cause of hospitalization in PD

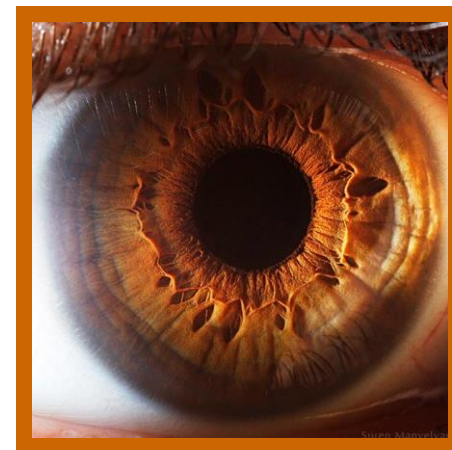
Major cause of institutionalization in PD

Abnormalities of Sensation

Olfactory Impairment



Pain



Visual Dysfunction

Olfactory Dysfunction

Impaired sense of smell

- Elevated threshold
- Impaired odor identification

Some impairment in 70-90%

Impairment is selective

- Licorice, coconut and banana especially impaired
- Chocolate, strawberry, onion, and others not affected

May develop very early

- May precede other features



Visual Dysfunction

Symptoms may include:

- “Tired eyes”
- Blurred vision
- Intermittent double vision
 - » Reported in 14% of PD patients
- Difficulty reading
- Difficulty seeing in dim lighting

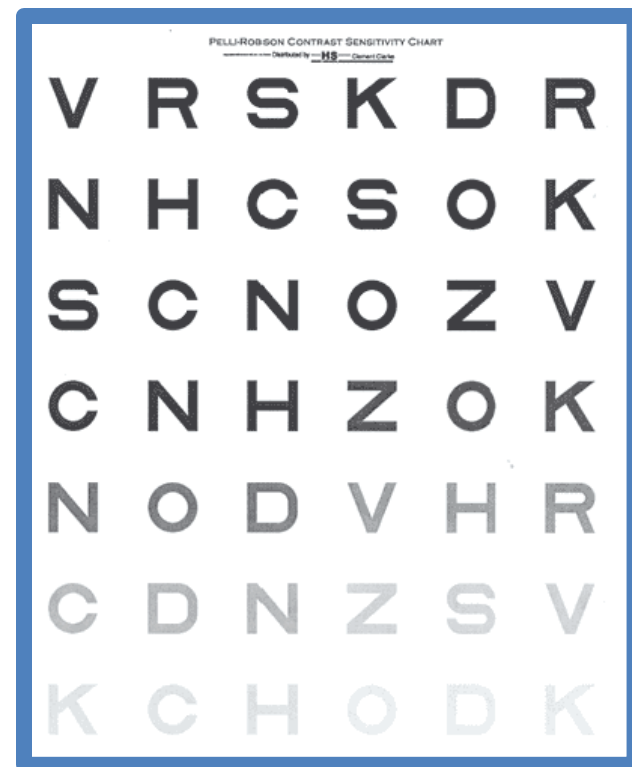


Visual Dysfunction

Routine eye exam often normal

Findings may include:

- Convergence insufficiency
- Impaired color perception
- Abnormalities of blinking
- Reduced contrast sensitivity



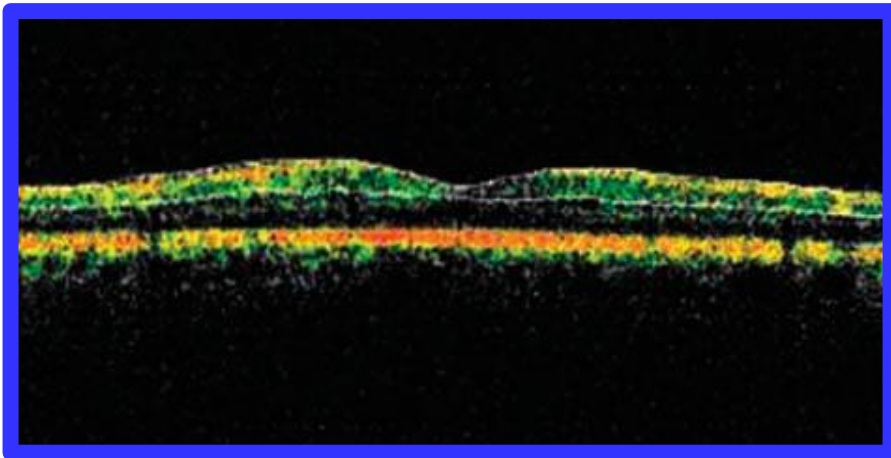
Inner Retinal Layer Thinning

Possible mechanisms:

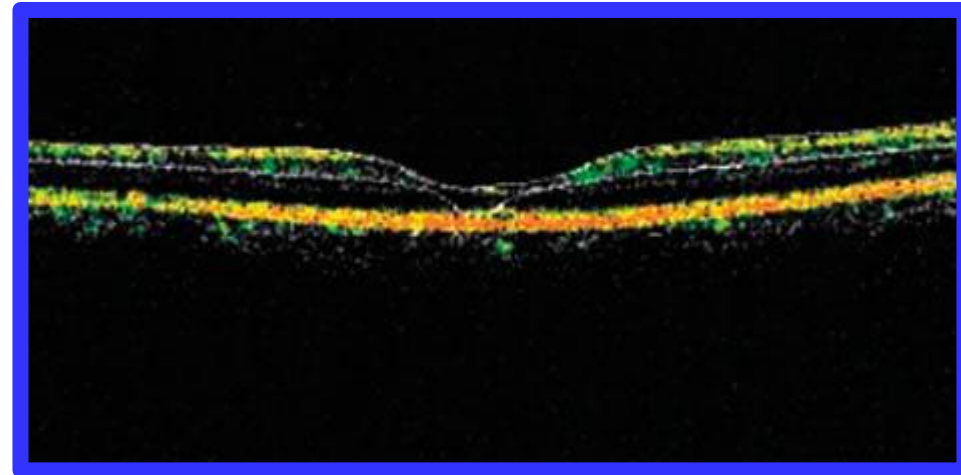
Retinal dopamine neuron loss

Dysfunction in other parts of the “visual brain”

Normal



Parkinson's Disease



Hajee ME, et al. Arch Ophthalmol 2009;127:737-741

Treatment of Visual Dysfunction

Impaired contrast sensitivity

video game playing???

Intermittent diplopia

prisms

Convergence insufficiency

eye-focusing exercises

- “pencil push-ups” and others

Blepharospasm or apraxia of eyelid opening

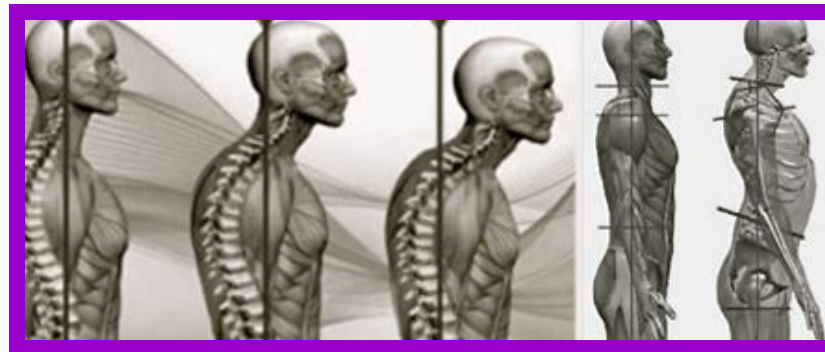
botulinum toxin injections

- An often neglected component of PD
- Exact prevalence is unclear
- Occurs in a variety of forms
- Has been divided into 5 types



Pain

Musculoskeletal
Neuropathic/Radicular
Dystonic
Central
Akathisia

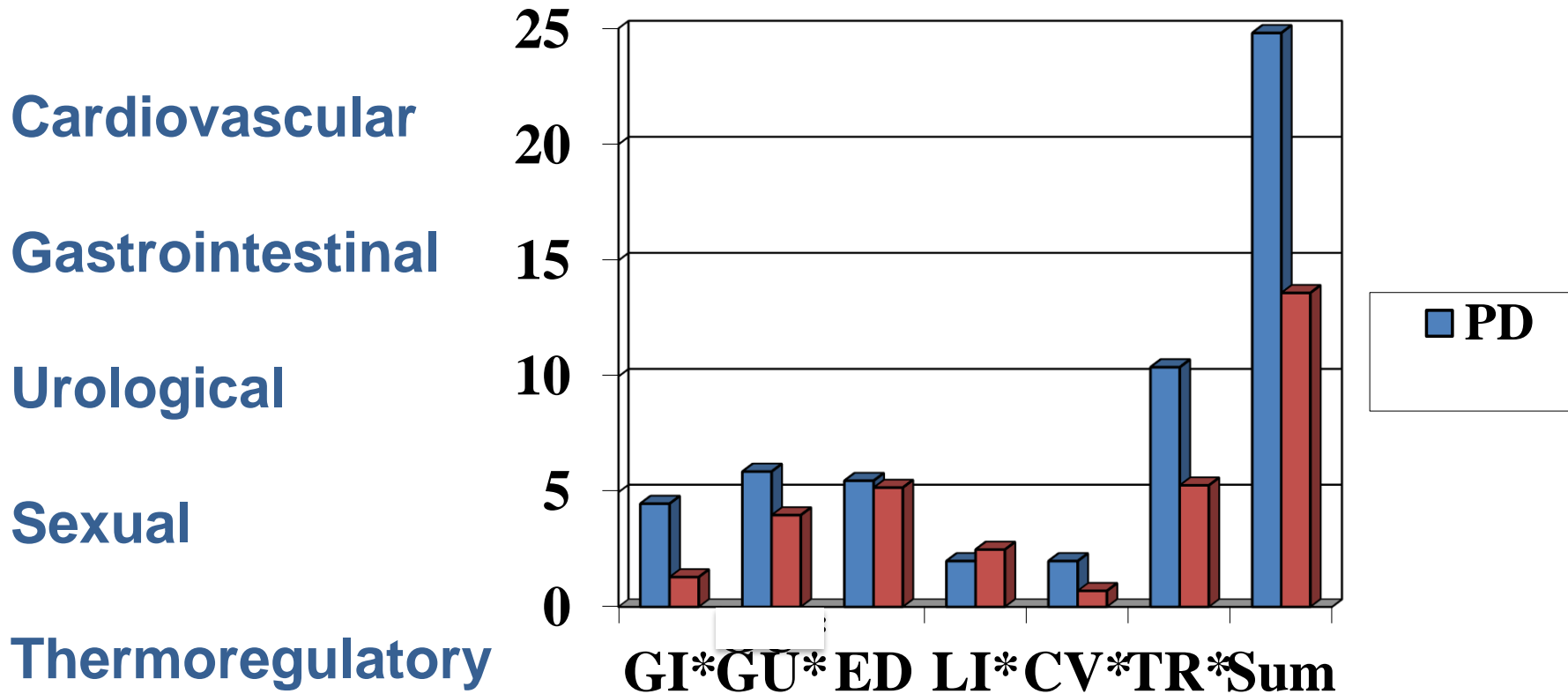


Treatment of Pain in PD

- Adjust PD meds if pain occurs as an “off” phenomenon
- Muscle relaxant medications are not usually effective
- PT or surgery if the pain is due to a pinched nerve
- Botulinum toxin injections if the pain is due to dystonia
- Central pain is resistant to treatment

Autonomic Dysfunction

Autonomic Symptom Survey



Siddiqui MF, Rast S, Lynn MJ, Auchus AP, Pfeiffer RF. Parkinsonism Relat Disord 2002;8:277-284.

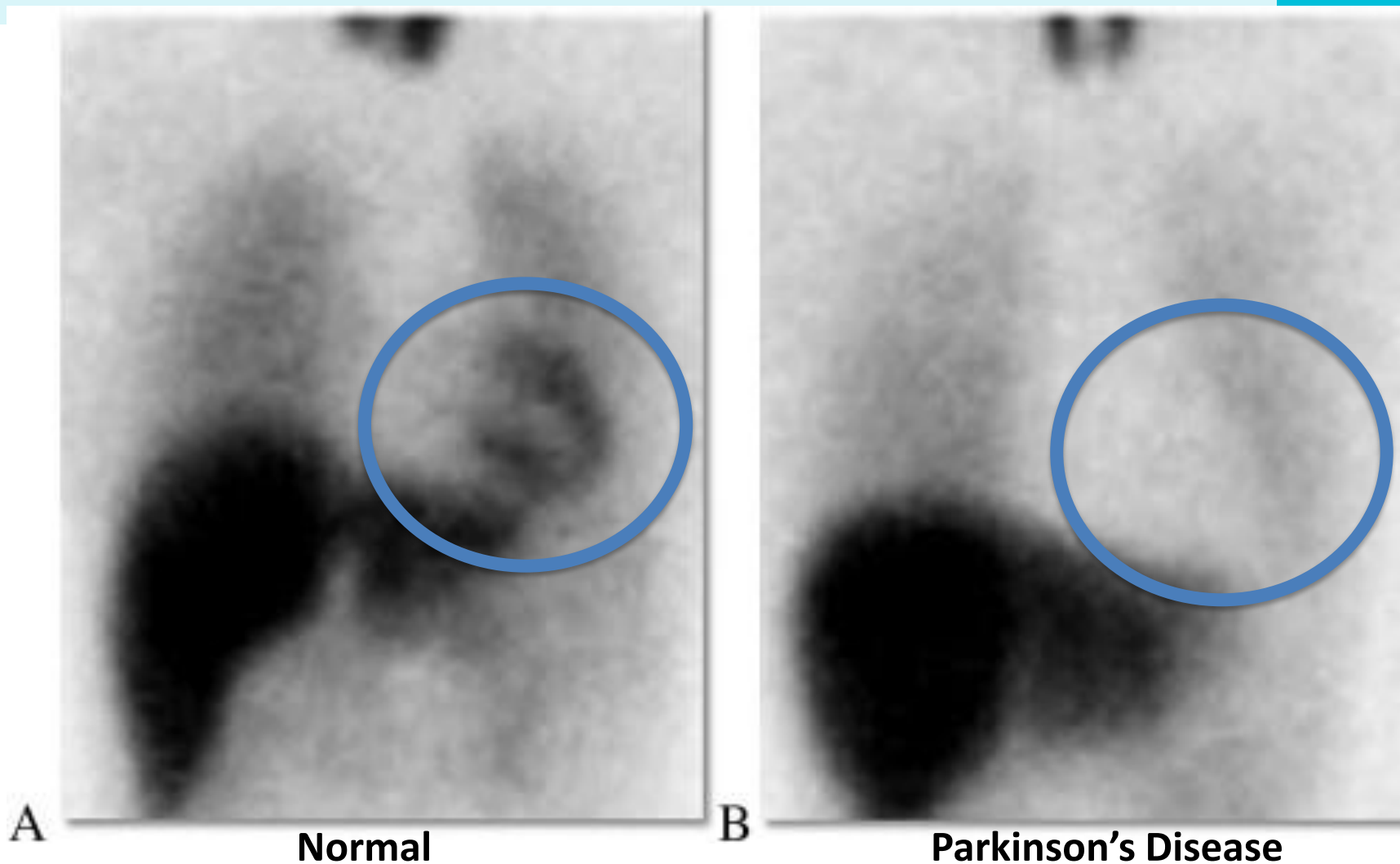
Cardiovascular Dysfunction

Cardiovascular Dysfunction

- Cardiac sympathetic denervation
- Orthostatic hypotension
- Postprandial hypotension



^{123}I -MIBG Myocardial Scintigraphy



Sakakibara R, et al. Parkinsonism Relat Disord 2014;20:267-273.

Orthostatic Hypotension

Drop in blood pressure with standing
Occurs in 58% of persons with PD

- Produces symptoms in 20%
- Without symptoms in 38%

Medications may magnify



Orthostatic Hypotension

Lightheadedness is the typical sensation

- May progress to fainting

Other symptoms may also occur

- Disturbances of vision
- Impaired thinking
- Headache in a “coat hanger” distribution
- Lower back or buttock ache
- Lethargy or fatigue

Goals of Treatment

- Decrease symptom frequency & severity
- Restore function (standing and walking)
- Prevent fainting and falling
- Minimize BP increases when laying down

Treatment of Orthostatic Hypotension

Non-pharmacologic treatment

Immediate

- drinking 12-16 oz. of ice water
- physical maneuvers

Chronic

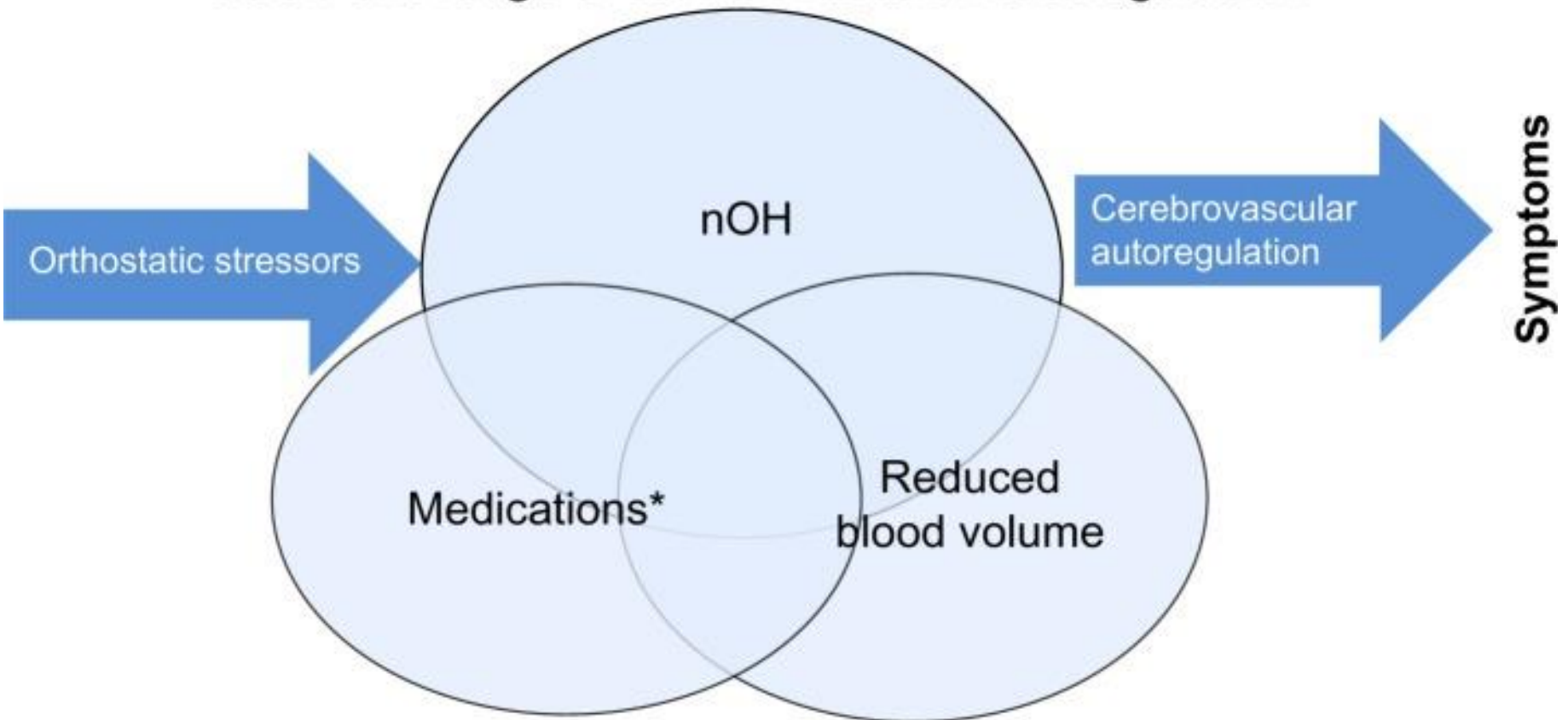
- increase fluid and
- increase salt consumption
- elevate head of bed
- abdominal binder
- pressure stockings

Pharmacologic treatment

- fludrocortisone
- midodrine
- pyridostigmine
- droxidopa
- Others (less supportive evidence)
 - Octreotide
 - Yohimbine
 - Desmopressin
 - Caffeine
 - Domperidone

Treatment of Orthostatic Hypotension

Symptomatic nOH occurs when s-SBP falls below the range of cerebrovascular autoregulation



Postprandial Hypotension

- Blood pressure drops after meals
- Sitting or standing may accentuate
- Carbohydrates are most likely to trigger
- May develop within 15 minutes of eating
- May persist up to 3 hours

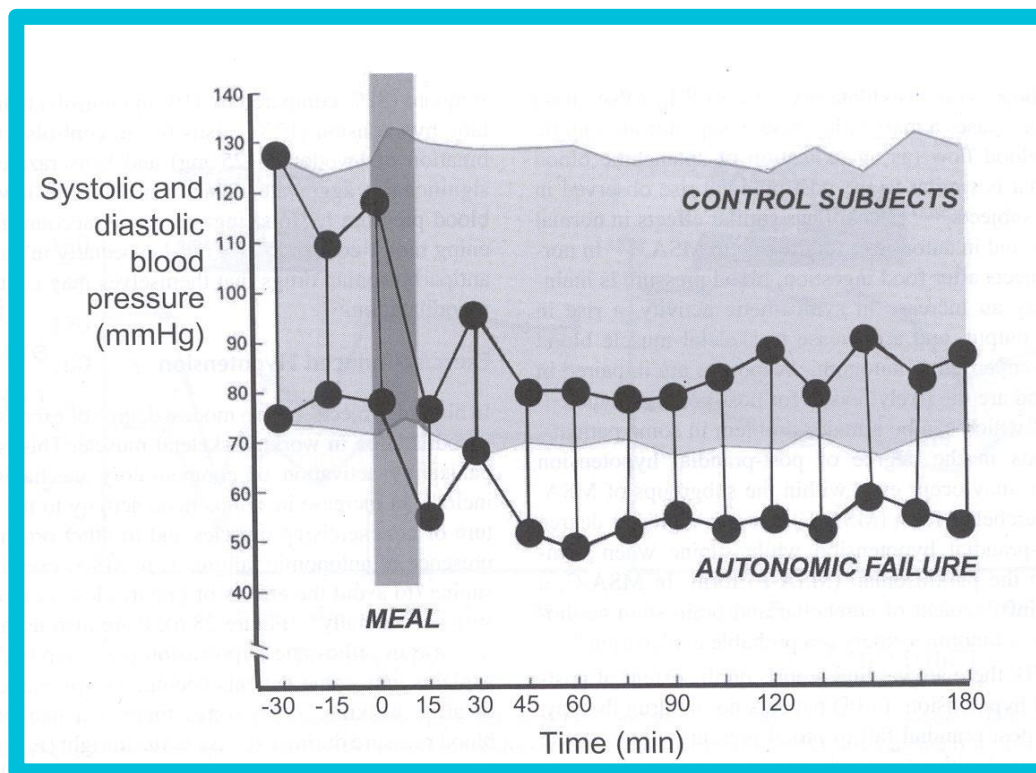
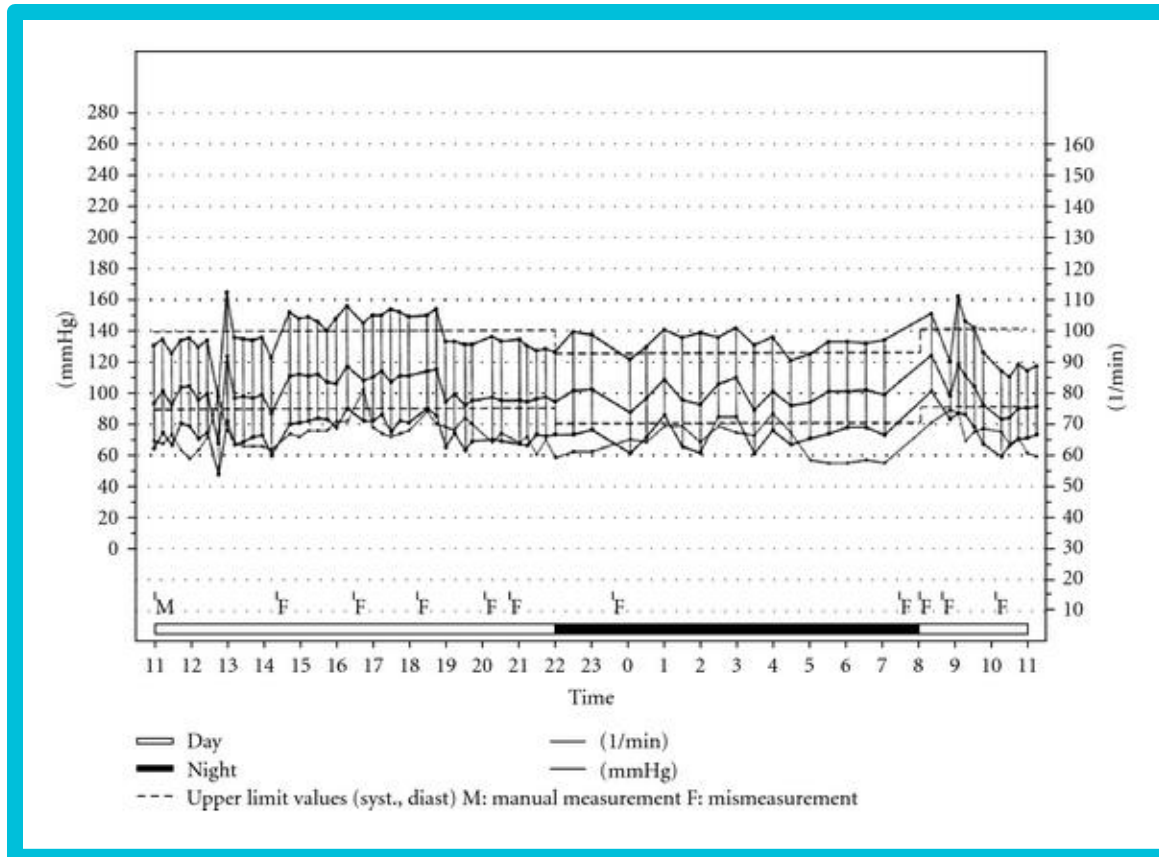


FIGURE 28.4 Systolic and diastolic blood pressure before and after a standard meal while remaining horizontal, to avoid the effects of gravity, in normal subjects (controls, stippled area) and in a patient with autonomic failure. Blood pressure does not change in normal subjects after a meal. In the patient, it rapidly falls to around 80/50 mmHg and remains low over three hours. (From Mathias, 2002.³)

Iodice V, Low D, Vichayanrat E, Mathias CJ. Cardiovascular autonomic dysfunction in Parkinson's disease and parkinsonian syndromes. In: Pfeiffer RF, Wszolek ZK, Ebadi M. Parkinson's Disease. CRC Press: Boca Raton, 2013.

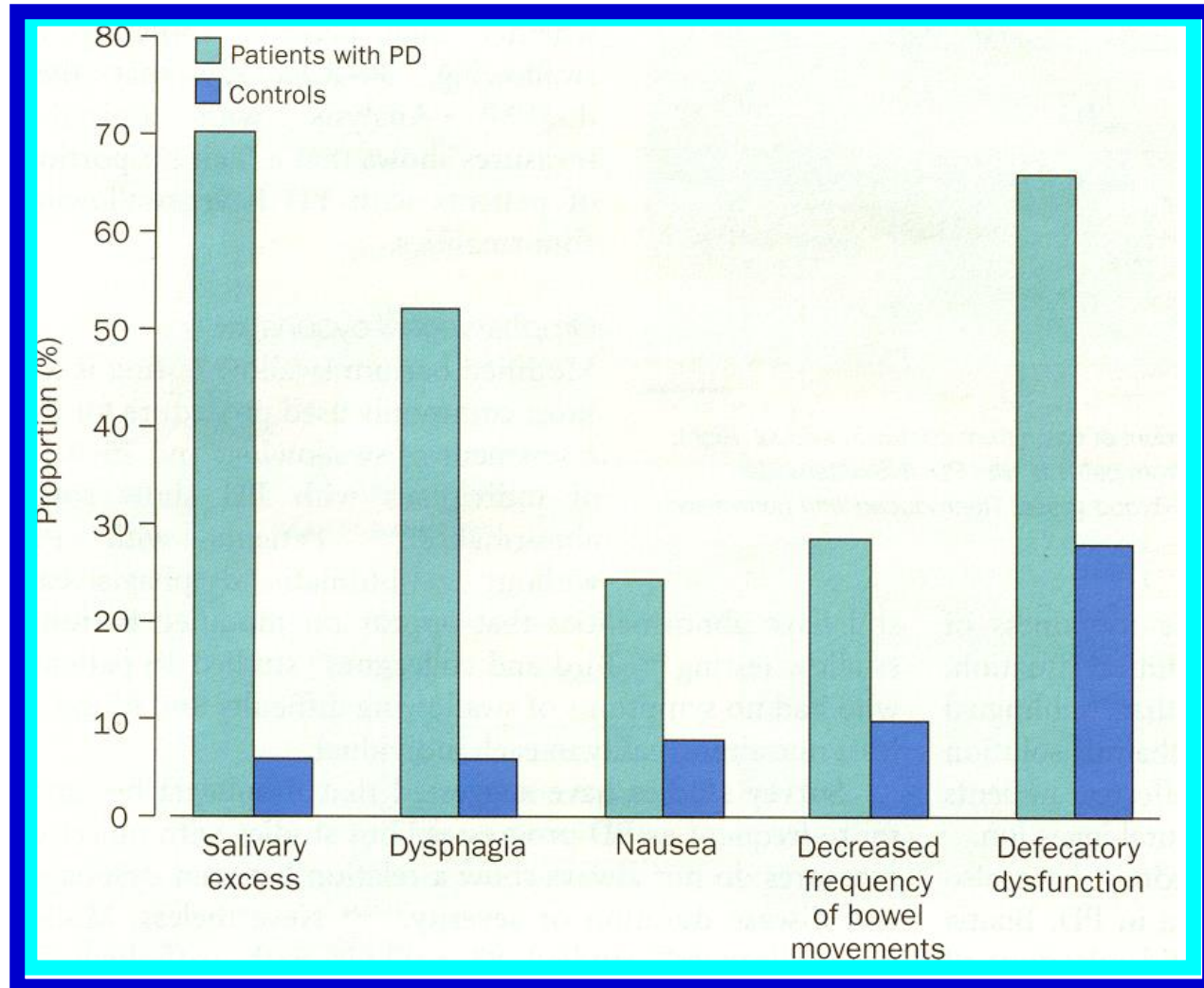
“Nondipping” in PD



Sommer S, et al. Parkinson's Dis 2011;doi:10.4061/2011/897586

Gastrointestinal Dysfunction

Gastrointestinal Symptoms



Edwards LL, Pfeiffer RF, Quigley EM, Hofman R, Balluff M. *Mov Disord* 1991;6:151-156.

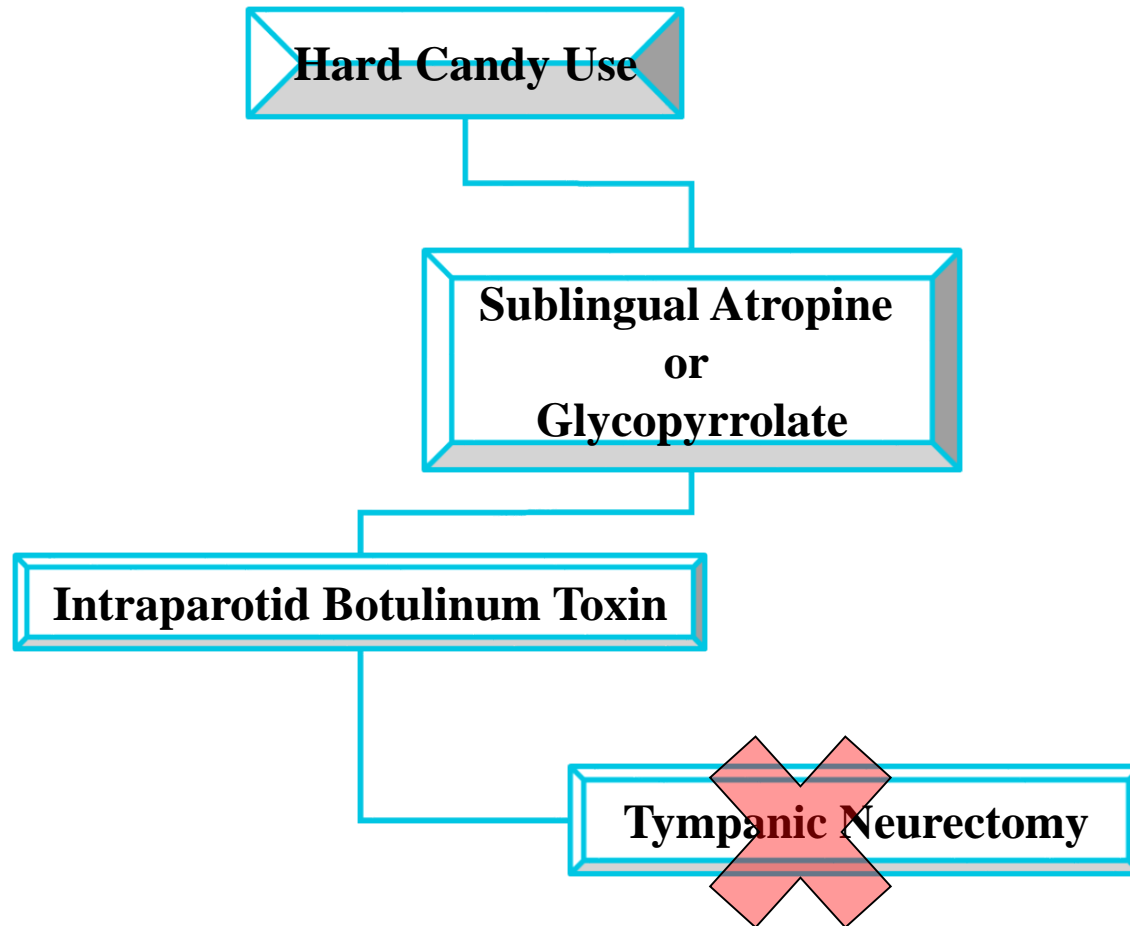
Excess Saliva in PD

- Experienced by 56-78%
- Initially nocturnal drooling
- May progress to “handkerchief” stage
- Saliva production is actually decreased
- Drooling is due to:
 - Decreased swallowing frequency
 - Decreased swallowing efficiency
 - Tendency for mouth to be open
 - Stooped posture

Pfeiffer RF. Gastrointestinal Dysfunction in Parkinson's Disease.
In: Parkinson's Disease, 2nd Edition (Pfeiffer RF, Wszolek ZK, Ebadi M, Eds), 2013, pp. 309-326.



Treatment of Salivary Excess



Dry Mouth in PD

- Saliva production actually is reduced in PD
- Causes dry mouth in some individuals
- Medications can accentuate the dryness
- May increase the risk of cavity formation
- May increase the risk of periodontal disease

Treatment of Dry Mouth

Artificial saliva products (Biotene)

- contains xylitol and glycerin

Pilocarpine (Salagen)

Cevimelene (Evoxac)

Halitosis in PD

More common in persons with PD

Multiple factors contribute

- Dry mouth
- Inadequate brushing/cleaning
- Gum (periodontal) disease
- Bacteria in the mouth
- Inadequate fluid intake

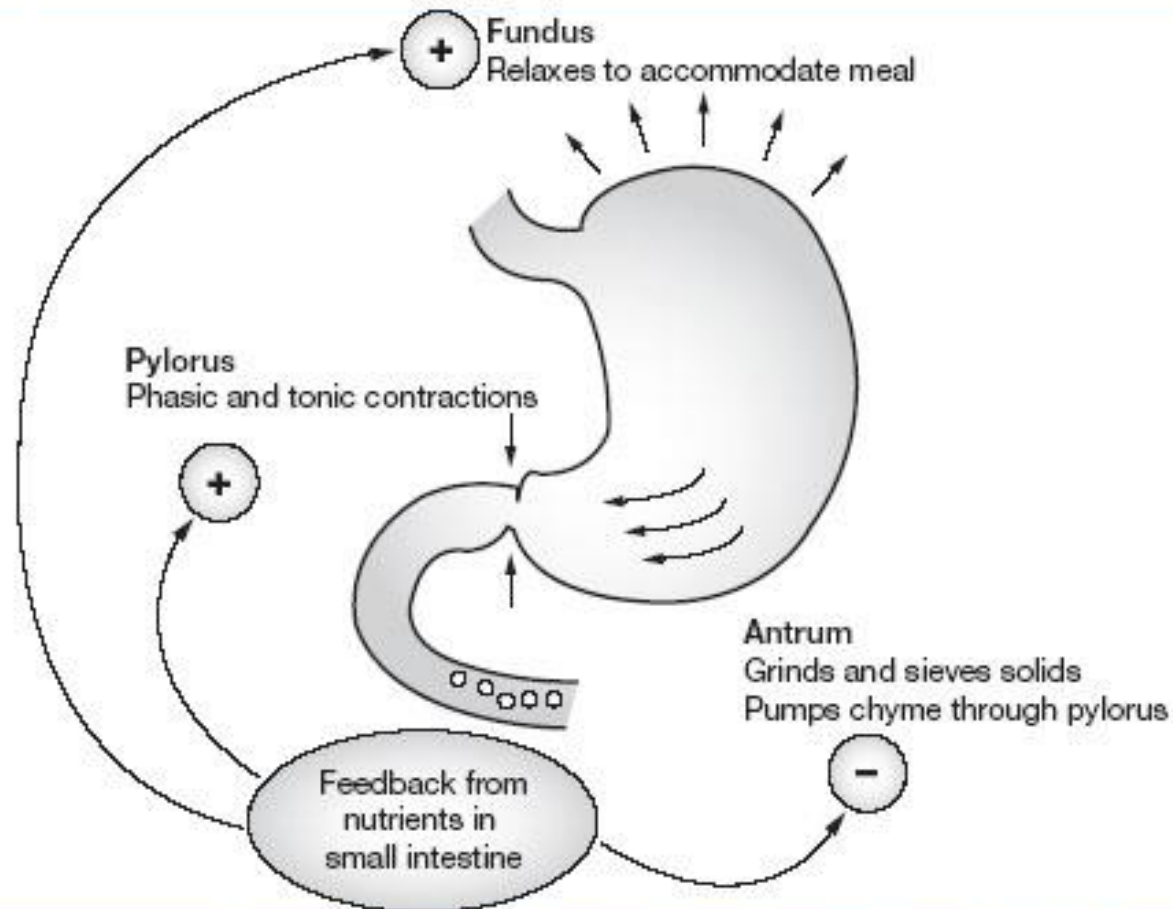
Treatment involves

- Adequate cleaning of teeth and mouth
- Alleviating dry mouth

Gastroparesis

Medscape®

www.medscape.com



Source: Nat Clin Pract Gastroenterol Hepatol © 2005 Nature Publishing Group

Raynor CK and Horowitz M. Nat Clin Pract Gastroenterol Hepatol 2005;2:454-462.

Gastroparesis Symptoms

- Reduced appetite
- Early satiety (fullness after a few bites)
- Nausea
- Vomiting (sometimes undigested food)
- “Heartburn” (gastroesophageal reflux)
- Abdominal bloating and distension
- Weight loss

Pfeiffer RF. Gastrointestinal Dysfunction in Parkinson's Disease.

In: Parkinson's Disease, 2nd Edition (Pfeiffer RF, Wszolek ZK, Ebadi M, Eds), 2013, pp. 309-326.

Rozenberg A, et al. Gastric Dysfunction in Parkinson's Disease.

In: Parkinson's Disease and Nonmotor Dysfunction, 2nd Edition (Pfeiffer RF, Bodis-Wollner I, Eds), 2013, pp. 145-154.



Dopamine antagonists

- Domperidone - Not available in the USA; rising concern for cardiotoxicity
- Metoclopramide (Reglan) - Do **NOT** use in PD – crosses the BBB

Motilin agonists

- Erythromycin - Effective acutely when given iv; not ideal for long term use

Histamine H₂ antagonist/cholinomimetics

- Nizatidine (Axid) - Only one small pilot study

Ghrelin agonists

- Relamorelin (RM-131) - Still experimental; positive reports in diabetic GP

Serotonin 5-HT₄ agonists (increase ACh release)

- Cisapride and tegaserod withdrawn
- Mosapride, prucalopride, and renzapride not available
- RQ-10 - currently experimental; clinical trial underway

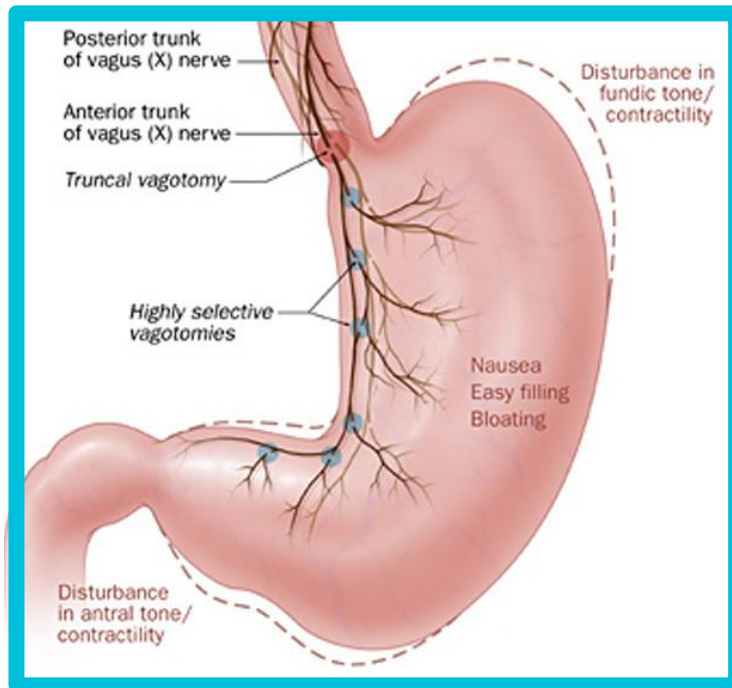
Doi H, et al. Nizatidine ameliorates gastroparesis in Parkinson's disease: a pilot study. *Mov Disord* 2014;29:562-566.

Pfeiffer RF. Gastrointestinal and Swallowing Disturbances in Parkinson's Disease.

In: *Parkinson's Disease: Non-Motor and Non-Dopaminergic Features* (Olanow CW, Stocchi F, Lang AE, Eds.). 2011, pp. 257-273.

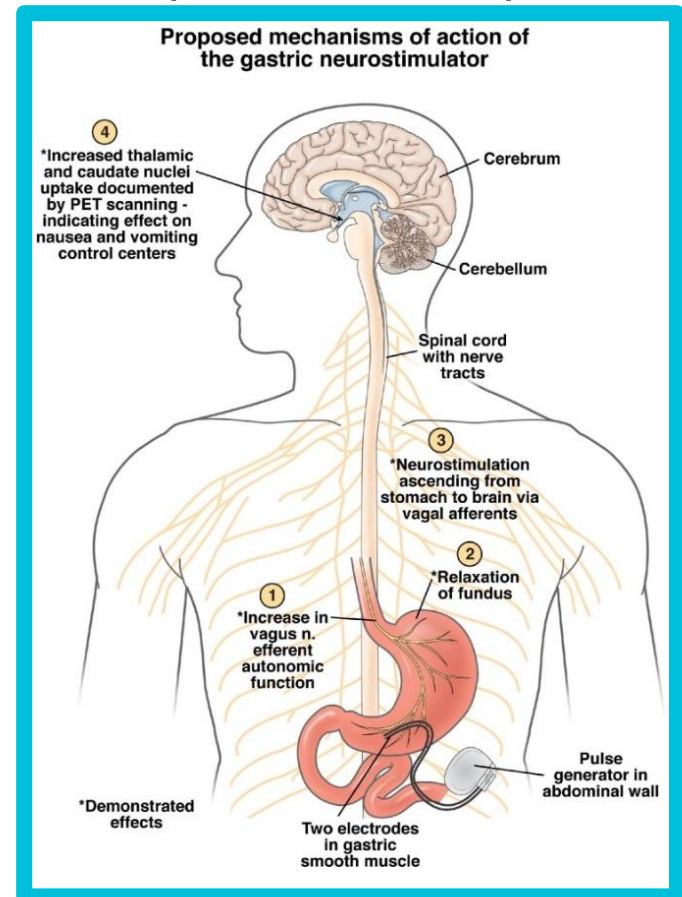
Treatment: Possible Approaches

Botulinum toxin injections of the pyloric sphincter



Gil R, Hwynn N, Fabian T, Joseph S, Fernandez HH. Parkinsonism Relat Disord 2011;17:285-287.
Triadafilopoulos G, Gandhi R, Barlow C. Parkinsonism Relat Disord 2017;44:33-37.

Gastric pacemaker implantation



Reddymassu, SC, Sarosiek I, McCallum RW. Clin Gastroenterol Hepatol 2010;8:117-124.

Circumventing Gastroparesis

Bypassing the stomach

- Levodopa/carbidopa intestinal gel
- Subcutaneous apomorphine
- Rotigotine



Small Intestinal Bacterial Overgrowth in PD

- Not well-studied in PD
- Present in 54% of PD patients in one study
- Is characterized by:
 - Increased bacterial density in the small intestine
 - Presence of colonic-type bacterial species in the small intestine
- Results in malabsorption
 - Might explain weight loss in PD
- Impaired GI motility favors its occurrence

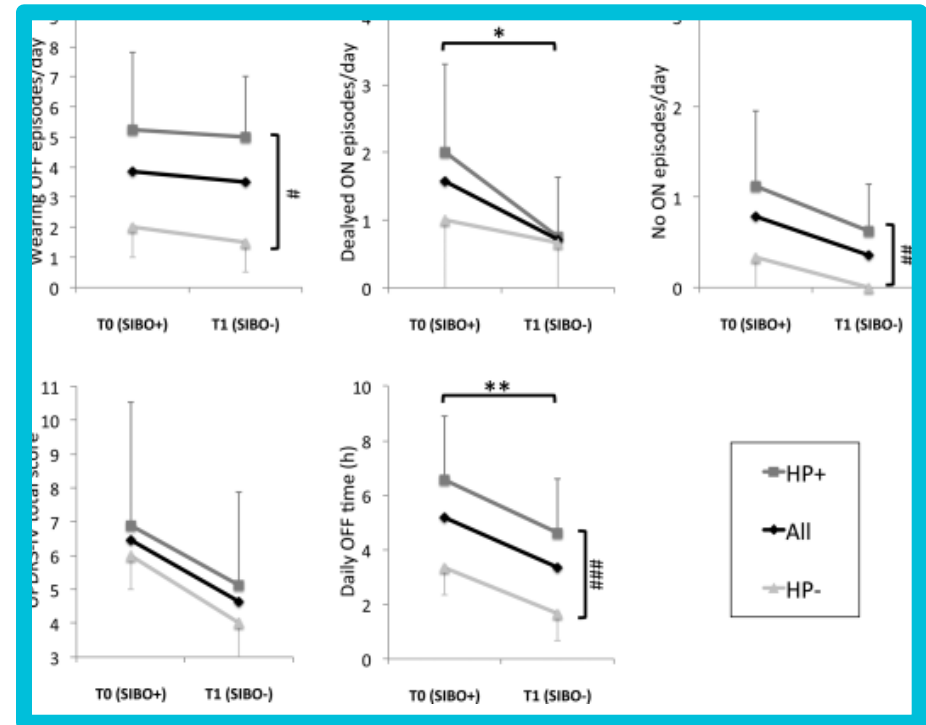
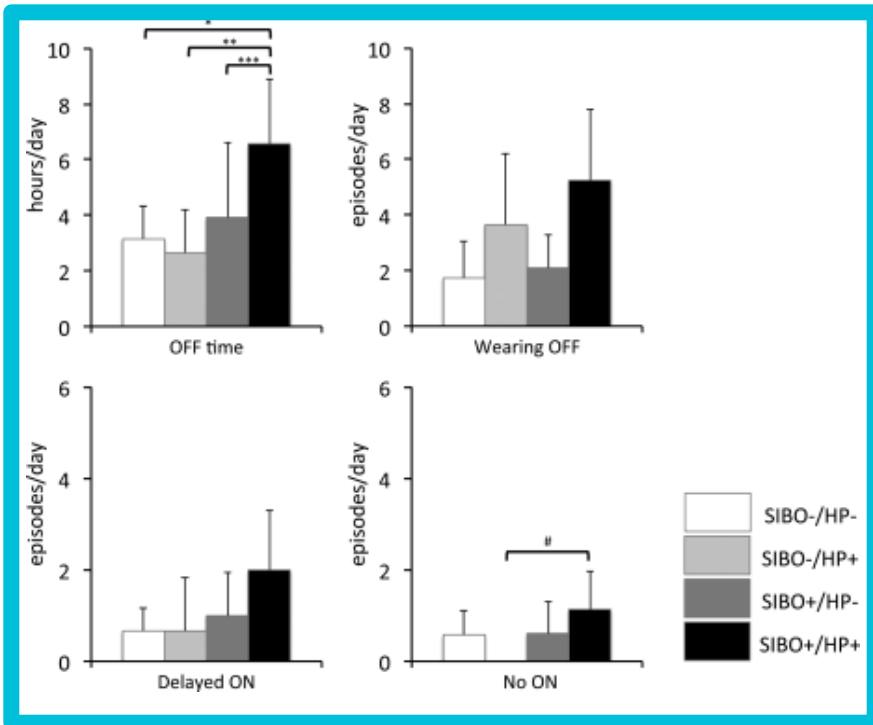
Gabrielli M, et al. *Mov Disord* 2011;26:889-892

Small Intestinal Bacterial Overgrowth in PD

Prevalence of gastrointestinal symptoms in patients with Parkinson's disease affected by SIBO versus those without SIBO

	SIBO positive, % (n = 26)	SIBO negative, % (n = 22)	OR (CI)
Abdominal discomfort	30.8	27.3	ns
Bloating	69.2	31.8	2.07 (1.42–16.40)
Flatulence	65.4	36.4	1.74 (1.01–10.83)
Constipation	73.1	81.8	ns
Diarrhea	19.2	9.1	ns

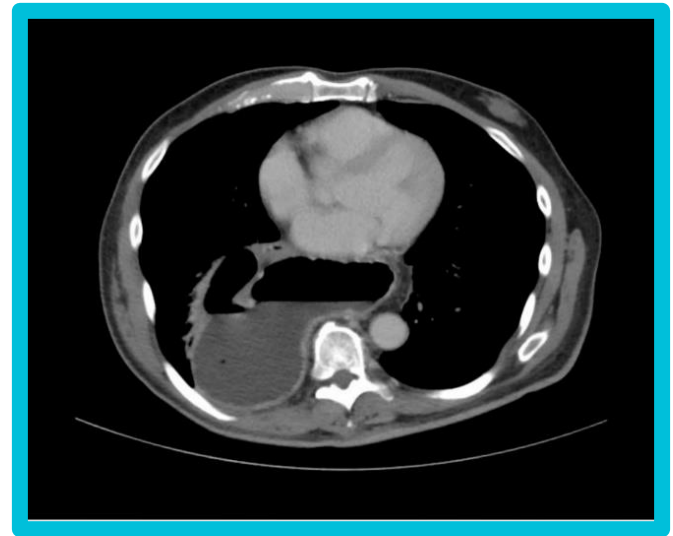
Small Intestinal Bacterial Overgrowth in PD



Fasano A, Bove F, Gabrielli M, et al. *Mov Disord* 2013;28:1241-1249.

Levodopa Dose Failure

- Competition with protein for intestinal absorption
- Dysphagia with vallecular sequestration of levodopa tablet
- Hiatal hernia with impaired gastric emptying
- Gastroparesis
- Helicobacter pylori infection
- Small intestinal bacterial overgrowth



Sato H, Yamamoto T, Sato M, Furusawa Y, Murata M. *Case Rep Neurol* 2018;10:101-107.

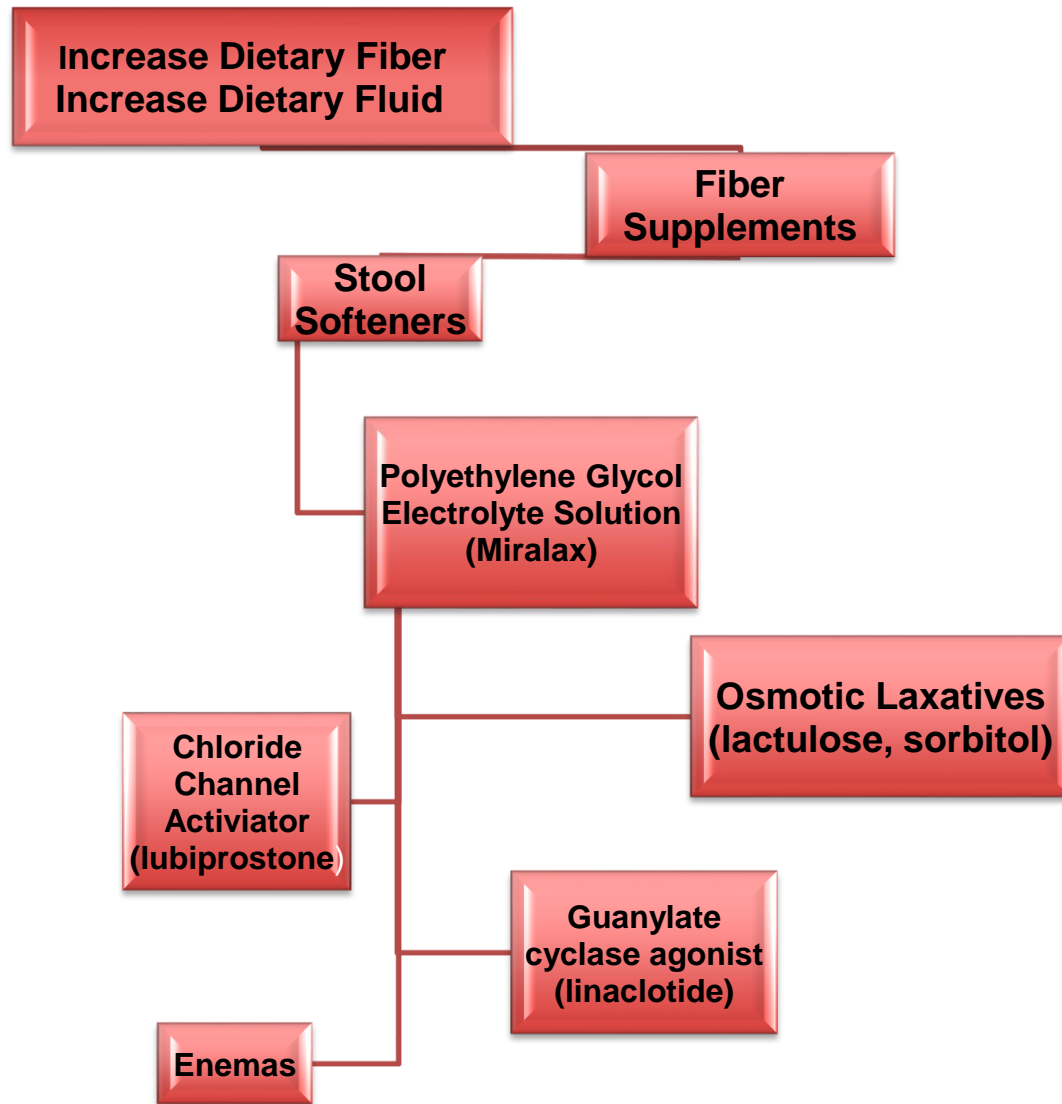
Staisch J, Bakis J, Nutt J. *Parkinsonism Relat Disord* 2018;50:130-131.

Fasano A, Visanji NP, Liu LW, Lang AE, Pfeiffer RF. *Lancet Neurol* 2015;14:625-639.

What Causes Constipation in PD?

- Colon transit time is prolonged in PD
- Slowing occurs in 80% of PD patients
- Average CTT in PD is twice as long:
44 hours vs. 20 hours (Edwards et al.)
- Other investigators report much longer times

Treatment of Colonic Dysmotility



Defecatory Dysfunction

- Develops in 66% of PD patients
- Characterized by:
 - Increased straining
 - Painful defecation
 - Incomplete emptying

Normal Defecation

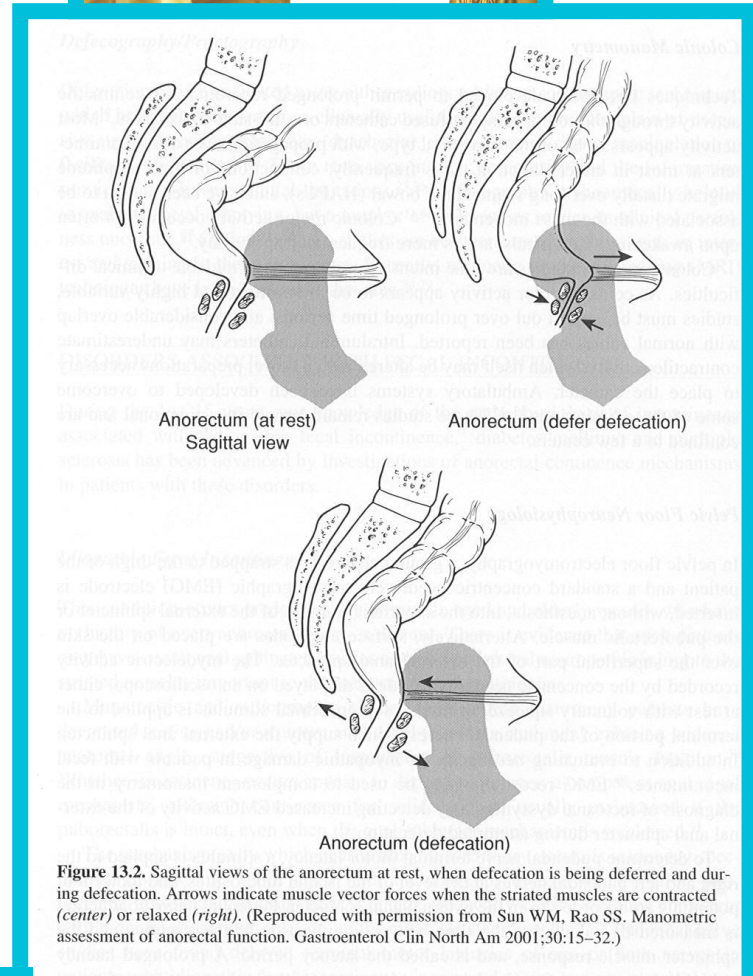
Relaxation of:

- Internal anal sphincter
- External anal sphincter
- Puborectalis

Contraction of:

- Abdominal wall muscles
- Diaphragm
- Glottic muscles

Sun WM, Rao SS. *Gastroenterol Clin North Am* 2001;30:15-32.



Treatment of Defecatory Dysfunction

- Dopaminergic medications
 - Apomorphine injections
 - Conventional DA agonists
 - Levodopa
- Botulinum toxin
 - External anal sphincter
 - Puborectalis
- Biofeedback techniques

Mathers SE, et al. Arch Neurol 1989;46:1061-1064.

Edwards LL, et al. Ann Neurol 1993;33:490-493.

Albanese A, et al. Mov Disord 1997;12:764-766.

Albanese A, et al. Am J Gastroenterol 2003;98:1439-1440.

Pfeiffer RF. Gastrointestinal Dysfunction in Parkinson's Disease.

In: Parkinson's Disease, 2nd Edition (Pfeiffer RF, Wszolek ZK, Ebadi M, Eds), 2013, pp. 309-326.

Pfeiffer RF. Intestinal Dysfunction in Parkinson's Disease.

In: Parkinson's Disease and Nonmotor dysfunction, 2nd Edition (Pfeiffer RF, Bodis-Wollner I, Eds), 2013, pp. 155-171



Urinary Dysfunction



Irritative Urinary Symptoms

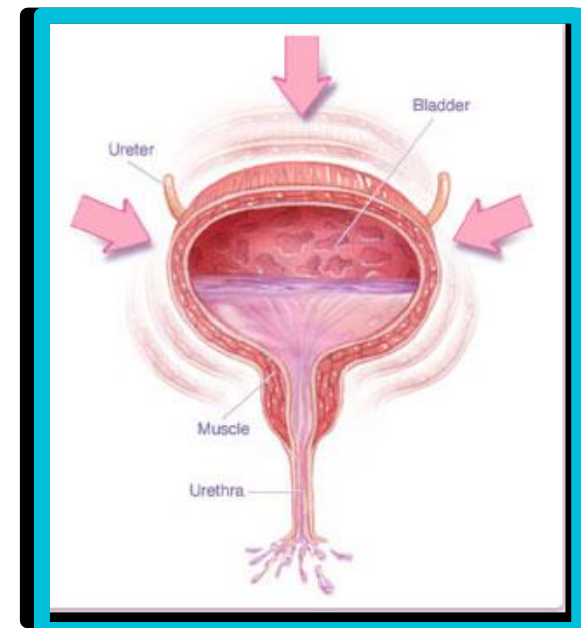
The most common urinary problem in PD

- Occurs in 53-83% of affected persons

Consists of overactive bladder contraction

Characteristics include:

- Frequent urination
- Night-time urination
- Urination of small amounts
- Urinary urgency
- “Urge” type incontinence



Irritative Symptoms: Treatment

Anticholinergic drugs (older)

- Are nonselective muscarinic blockers
- Cross the blood-brain barrier
 - Oxybutynin
 - Tolterodine

Anticholinergic drugs (newer)

- More selective (M3 receptor)
- Do not cross the blood-brain barrier
 - Trospium
 - Darifenacin
 - Solifenacin

Beta-3 adrenergic agonist drugs

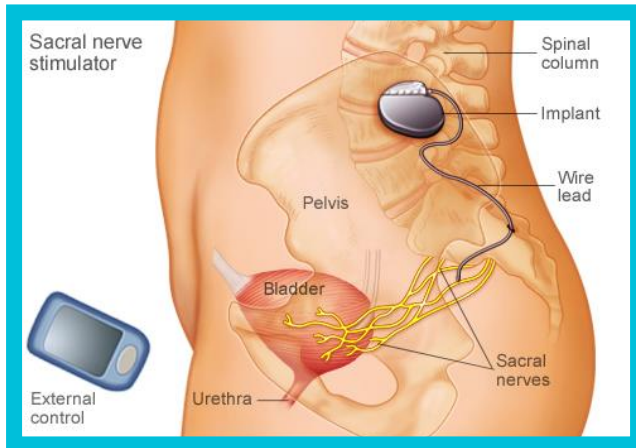
- Mirabegron



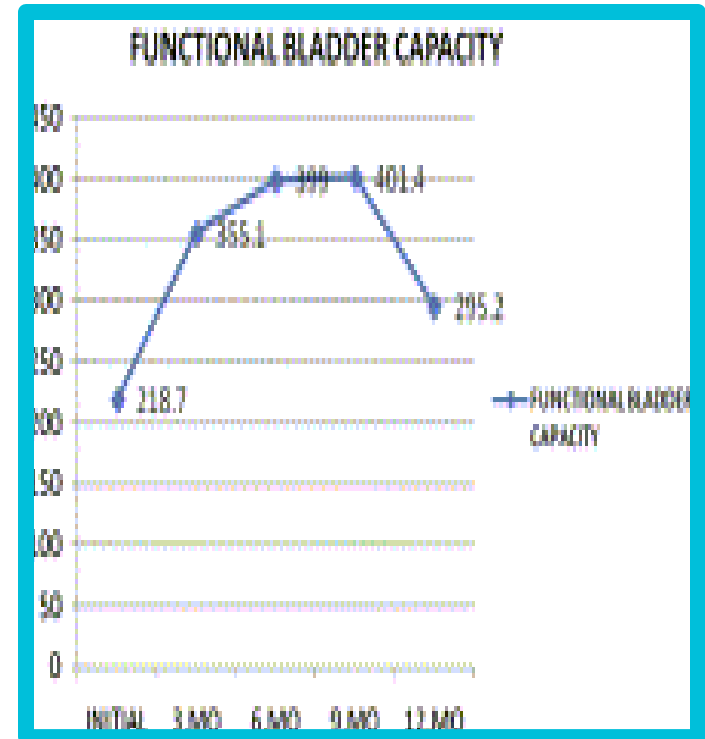
Irritative Symptoms: Treatment

Botulinum toxin injections
Detrusor muscle

Sacral nerve stimulator



Wallace PA, Lane FL, Noblett KL.
Am J Obstet Gynecol 2007;197:96.e1-5



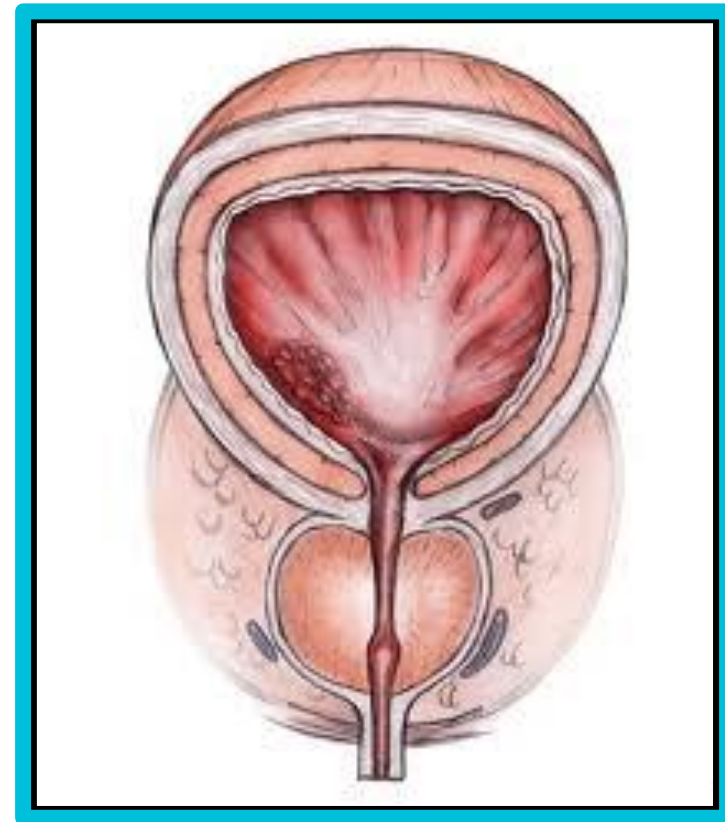
Kulaksizoglu H, Parman Y.
Parkinsonism Relat Disord
2010;16:531-534

Obstructive Urinary Symptoms

Less common urinary problem in PD
Causes 23-36% of urinary symptoms
Characteristics include:

- Hesitancy
- Weak urinary stream

May develop overflow incontinence



Obstructive Symptoms: Treatment

Alpha-1 adrenergic antagonists

- Terazosin
- Doxazosin
- Tamsulosin

5-Alpha-reductase inhibitors

- Dutasteride
- Finasteride

Parasympathomimetic agent

- Bethanecol

Intermittent catheterization



Sexual Dysfunction



Reduced or impaired function

- In men
 - Erectile dysfunction (39-79%)
 - Decreased desire (44-84%)
 - Decreased orgasm (87%)
- In women
 - Reduced vaginal sensitivity (?%)
 - Decreased desire (71-83%%)

Treatment of Sexual Dysfunction

Erectile dysfunction

- PDE5-inhibitors
 - sildenafil, tadalafil, vardenafil
- Sublingual apomorphine
- Intrapenile injections of vasoactive drugs
 - alprostadil, papaverine

Decreased libido

- Testosterone

Inadequate lubrication

- Lubricants



Thermoregulatory Dysfunction

Thermoregulatory Dysfunction

Has not received wide attention in PD

Probably more common than recognized

Two primary manifestations:

- Hyperhidrosis
- Hyperthermia/Hypothermia



Hyperhidrosis in PD

Present in over 50% of persons with PD

Primarily involves the head and neck

Consists of sudden, drenching sweats

Typically occurs in two situations:

- As a “wearing-off” phenomenon
- During episodes of dyskinesia

But may occur in persons on no medication

Treatment of Hyperhidrosis

- Adjustment of dopaminergic therapy
 - To reduce “off” time
 - To reduce dyskinesia
- Subthalamic DBS
- Botulinum toxin injections*
 - *If sweating is localized to armpits

Fatigue



In a recent study was the most frequent nonmotor symptom in persons with PD

- Present in 58%

In another study:

- Ranked as the worst PD symptom by 33%
- Named as one of their 3 most disabling symptoms by 58%



Treatment of Fatigue in PD

Modalities reported to be beneficial:

- Exercise
- Methylphenidate
- Modafinil
- Memantine
- Caffeine
- PD medications
 - Amantadine
 - Rasagiline
 - Pramipexole
 - Levodopa
- Behavioral interactions

Respiratory Dysfunction



Respiratory Dysfunction

Lower airway obstruction

Upper airway obstruction

Restrictive pulmonary abnormalities



Treatment of Respiratory Dysfunction in PD

- Adjust PD medications to reduce “off” time
- Adjust PD medications to reduce dyskinesia
- Treat anxiety if present
- Treat obstructive sleep apnea if present
- Inspiratory and expiratory muscle strength training

Nonmotor features

- are varied and multiple in PD
- may be present early in the course of PD
- may precede the development of motor features in PD
- may be the source of greater disability than motor features, especially in advanced PD
- impair quality of life throughout the course of PD
- may prompt hospitalization or institutionalization

Effective treatment often exists

QUESTIONS?

**Yes, teacher, me
has question...**



Why you so boring?





Allied Team Training for Parkinson's Disease (ATTP®)



 Professional
Education
Parkinson's Foundation

MARCH 27-30, 2019
IOWA CITY, IOWA

Resources



National Helpline

Available at
1-800-4PD-INFO or
Helpline@Parkinson.org
Mon- Friday 9 am to 8 pm ET

Podcast: Substantial Matters

New episodes every other Tuesday featuring Parkinson's experts highlighting treatments, techniques and research.

Parkinson.org/Podcast



Fact Sheets and Publications

Get the resources and information you need to start living a better life with Parkinson's.

Aware in Care Kit

Includes tools and information for people with PD to share with hospital staff during a planned or emergency hospital stay.

Parkinson.org/Awareincare

