Non-Motor Problems in Parkinson's Disease

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Parkinson's Disease Clinical Definition

- Bradykinesia
- Rigidity
- Tremor
  - Postural instability

Some Non-Motor Sx.

MDS-NMS	%*	NMSS	%[a]	MDS-UPDRS Part I	%*
A1. Sad or depressed	47.9	10. Sad or depressed	39.9	1.3 Depressed mood	38.9
		11. Flat moods	28.4		
A2. Difficulty pleasure	25.4	12. Difficulty pleasure	22.1		
A3. Hopeless	21.0				
A4. Negative thoughts	26.4				
A5. Felt life is not worth	12.0				
B1. Worried	54.5	9. Nervous, worried	31.1	1.4 Anxious mood	46.8
B2. Nervous	44.3	9. Nervous, worried	31.1		
B3. Panic or anxiety attacks	15.2				
B4. Worried about in public	32.1	9. Nervous, worried	31.1		
C1. Reduced motivation	38.3	7. Lost interest in surroundings	20.2	1.5 Apathy	28.7
		8. Lost interest in doing things	33.3		
C2. Reduced interest talking	28.4	8. Lost interest in doing things	33.3		
C3. Reduction in emotions	18.7	11. Flat moods	28.4		
D1. Passage or presence	21.9			1.2 Hallucinations and psychosis	17.7
D2. Illusions	15.4	13. Sees things that are not there	14.1		
D3. Hallucinations	10.7	13. Sees things that are not there	14.1		
D4. Delusions, misidentification	4.5	14. Beliefs that are not true	3.7		
E1. Increase in gambling, sex,	8.2				
E2. Increase other behaviours	6.5				
E3. Punding	4.0				
E4. Dopamine dysregulation	2.2			1.6 Features of DDS	7.0
F1. Difficulty remembering	59.0	17. Forget things	52.5	1.1 Cognitive impairment	48.0
		18. Forget to do things	36.8		
F2. Difficulty learning new	34.6				
F3. Difficulty keeping focus	45.8	16. Problems sustaining concentration	40.8		
F4. Difficulty finding words	54.0				
F5. Executive abilities	28.6				
F6. Visuospatial abilities	17.4				
G1. Lightheaded or fainted	29.6	1. Light-headedness, faintness	36.1	1.12 Light headedness on standing	33.1
G2. Dizziness or weakness	34.3	1. Light-headedness, faintness	36.1		
H1. Urinary urgency	57.2	22. Urgency	48.0	1.10 Urinary problems	63.7
H2. Urinary frequency	42.3	23. Frequency	37.7		
H3. Nocturia	41.5	24. Nocturia	50.9		
I1. Decreased sexual drive	31.4	25. Altered interest in sex	26.9		
I2. Difficulty sexual arousal	29.3	26. Problems having sex	26.3		
J1. Drooling of saliva	46.6	19. Dribbling saliva	33.3		
J2. Difficulty swallowing	30.4	20. Difficulty swallowing	28.1		
J3. Nausea, feel sick stomach	19.7				
J4. Constipation	34.6	21. Constipation	33.1	1.11 Constipation problems	48.0
K1. Insomnia	51.4	5. Difficult falling/staying asleep	49.0	1.7 Sleep problems	62.6
K2. REM sleep behavior	46.8				
K3. Dozed off or fallen asleep	48.3	3. Doze off or fall sleep	46.0	1.8 Daytime sleepiness	72.3
K4. Restlessness	37.1	6. Restlessness	33.3		
K5. Periodic limb movements	38.3				
K6. Snoring, gasping, breathing	13.2				
L1. Muscle, joint or back pain	67.4	27. Pain	29.6	1.9 Pain and other sensations	64.9
L2. Deep or dull aching pain	28.6	27. Pain	29.6		
L3. Pain due to dystonia	20.9				
L4. Other types of pain	14.4				
M1. Weight loss	10.7	29. Change in weight	14.2		
M2. Impaired olfaction	57.0	28. Change in ability to taste/smell	54.7		
M3. Physical fatigue	55.0	4. Fatigue or lack of energy	51.2	1.13 Fatigue	64.9
M4. Mental fatigue	32.3	4. Fatigue or lack of energy	51.2		
M5. Excessive sweating	21.4	30. Excessive sweating	17.2		

PD: Neuropsychiatric

- Depression*
- Dementia*
- Psychosis*
- Anxiety
- Punding
- Apathy
- Impulse Control Disorders
- Parkinson Personality
  - Risk avoidance, dependence

PD: Autonomic

- Low and labile blood pressure*
- G.I.
  - –Constipation*, Sialorrhea*
- Bladder dysfunction
- Sweats
- Sexual Dysfunction

PD: Sleep / Wake

- Excessive Daytime Sleepiness*
- Insomnia*
- REM Behavior Disorder (RBD)*
- Periodic Limb Movements of Sleep
- Nocturia

Other P.D. Symptoms (Misc.)

- Shoulder pain, neck pain
- Weight loss
- Olfaction loss
- Vague vision problems
- Psoriasis / Dermatitis

Neuropsychiatric

- Psychosis
- Dementia
- Depression

PD Psychosis - Epidemiology

- Most PD patients will develop PDP
  - 72% in 1 longitudinal study
- Methodist Clinic
  - 250 consecutive patients surveyed
    - Age: 68.6±7.0, Age PD onset, 62.7±10.5, 35.2% female
    - **82 (32.8%) - active psychosis**

PD Psychosis

- Visual hallucinations
- Paranoid delusions
  - Infidelity, persecutory
- Risk factors:
  - Age, dementia, medications, gait/balance, RBD
- Main risk factor for NHP

Screening and Diagnosing PDP

Question 1: Illusion*
In the past month, have you misinterpreted something that you saw or heard; for example, thought a lamp was a person? ____ Yes. ____No. ____Not now, but I have experienced this before

Question 2: Sense of Presence*
In the past month, have you sensed that someone or something was around you, but nothing was actually there? ____ Yes. ____No. ____Not now, but I have experienced this before

Question 3: Hallucinations*
In the past month, have you __seen, __heard, __ smelled, or __ physically felt things that you or other people around you did not think were real? ____ Yes. ____No. ____Not now, but I have experienced this before

Question 4: Delusions*
In the past month, have you had thoughts or believed things that others did not think or believe to be true; for example, someone was cheating or harming you, or being unfaithful to you? ____ Yes. ____No. ____Not now, but I have experienced this before

Who completed this?
____Patient in person ____Caregiver in person
____Patient via telemedicine ____Caregiver via telemedicine

* "Illusion", "Sense of Presence", "Hallucinations", "Delusions" do not appear on the questionnaire.

- Patients often will not report psychosis
  - Embarrassed
  - Poor insight

Koneru *et al* in prep

Psychosis Pathophysiology

- IT’S COMPLICATED ???
- Relatively specific to Lewy body pathology
- Some evidence of serotonergic / 5-HT2 pathology

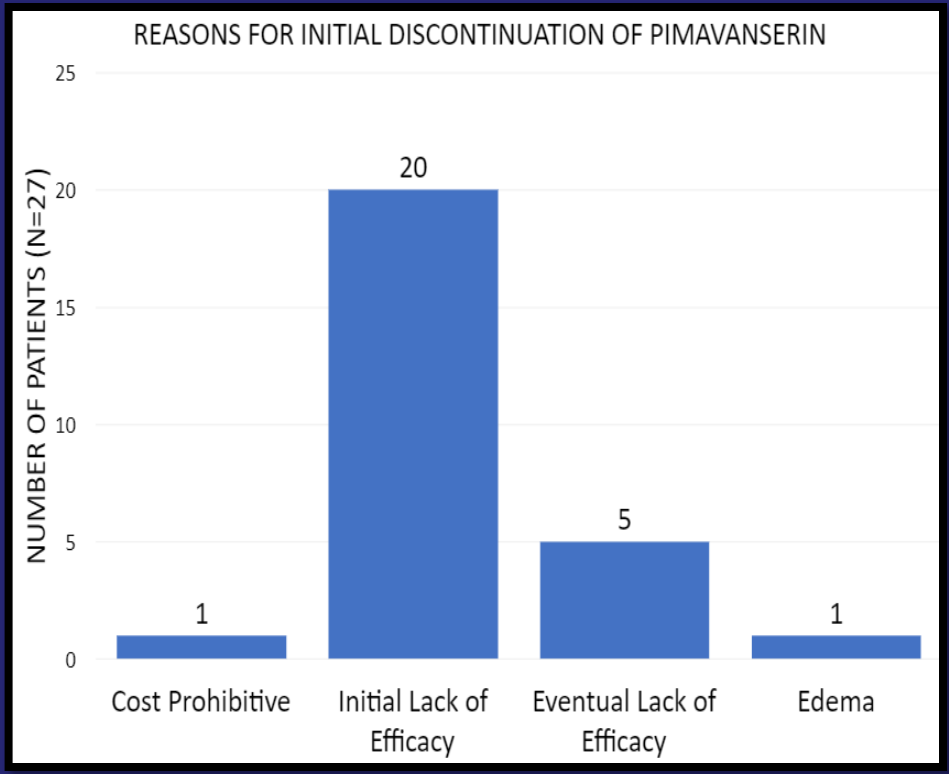
Initial Treatment of Psychosis

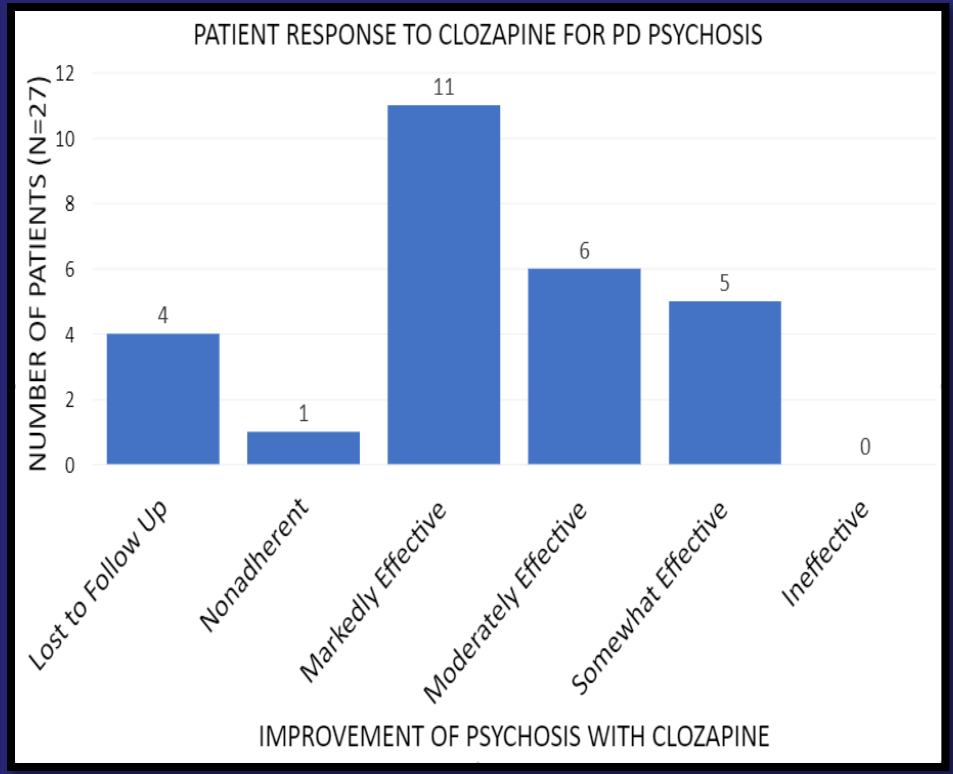
- Evaluate for other causes
  - Infection, dehydration
- Reduce PD medications
  - Amantadine > dopamine agonists > L-dopa adjunct medications > L-dopa
- Reduce other medications
  - Opioids, anti-histamines, quinolones

Treatment of Psychosis (Don't Block Dopamine)

- Pimavanserin (34mg)*
- Clozapine (12.5-100 mg)
- Quetiapine (25 - 400 mg)
- Olanzapine (1.25 - 5 mg)
- Risperidone (1 - 2 mg)
- Ziprasidone (20-80 mg)
- Aripiprizole (?)
- Ondansetron (8 - 32 mg)

Clozapine Results in Patients who Failed Pimavanserin, N=27





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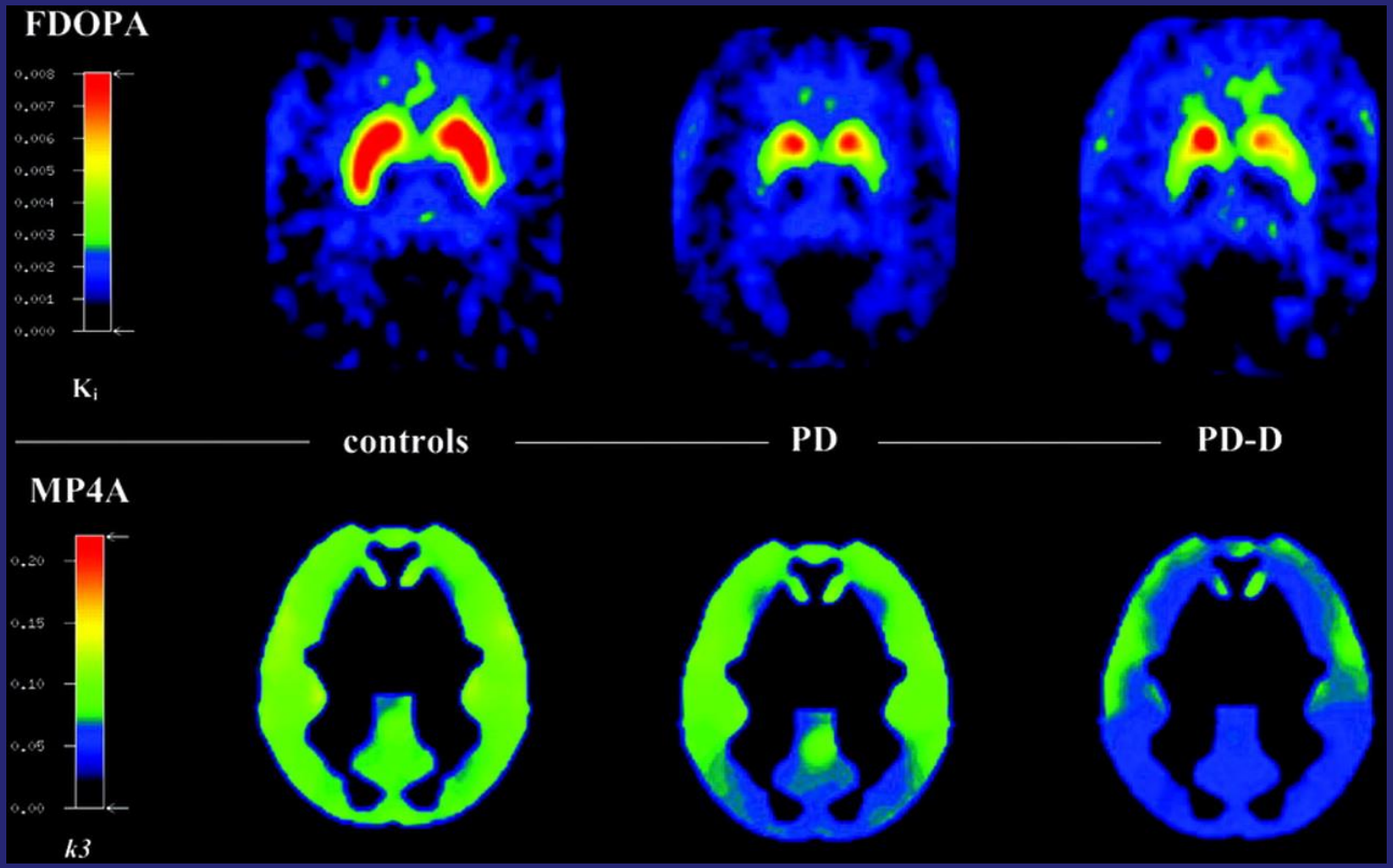
Dementia Patterns in PD

- Impaired memory
  - Retrieval, not amnestic
- Executive dysfunction
  - Problem solving, sequencing, set shifting
- Attention
  - Reaction times, vigilance
- Language preserved

Emre, M. 2003

PD Dementia Correlates with Acetylcholine Loss



Treatment of Dementia

Intervention		Efficacy	Safety	Practice implications
Drug class/intervention strategy	Drug/intervention			
Dementia				
Acetylcholinesterase inhibitors	**Donepezil**	Insufficient evidence	Acceptable risk without specialized monitoring[a]	*Possibly useful*[b]
	Rivastigmine	Efficacious	Acceptable risk without specialized monitoring[a]	Clinically useful
	Galantamine	Insufficient evidence	Acceptable risk without specialized monitoring[a]	*Possibly useful*[c]
N-methyl-D-aspartate (NMDA) antagonists	Memantine	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
Nondementia cognitive impairment				
Acetylcholinesterase inhibitors	**Rivastigmine**	*Insufficient evidence*	*Acceptable risk without specialized monitoring*[d]	*Investigational*
Monoamine oxidase B (MAO-B) inhibitors	**Rasagiline**	*Insufficient evidence*	*Acceptable risk without specialized monitoring*	*Investigational*
Nonpharmacological Interventions	**Transcranial direct-current stimulation (T-DCS)**	*Insufficient evidence*	*Insufficient evidence*	*Investigational*
	Cognitive rehabilitation	*Insufficient evidence*	*Insufficient evidence*	*Investigational*

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Depression in PD

- Difficult to assess
- Mimics Sx of PD
- Low rates of suicidality
- May respond best to dopaminergics
- Norepinephrine RI may be better than Serotonin RI

Intervention				
Drug class/ intervention strategy	Drug/intervention	Efficacy	Safety	Practice implications
Dopamine Agonists	Pramipexole	Efficacious	Acceptable risk without specialized monitoring	Clinically useful
	Pergolide	Insufficient evidence	Acceptable risk with specialized monitoring	Not useful
	Rotigotine	*Unlikely efficacious*	*Acceptable risk without specialized monitoring*	*Investigational*
Monoamine oxidase B (MAO-B) inhibitors	**Rasagiline**	*Insufficient evidence*	*Acceptable risk without specialized monitoring*	*Investigational*
	Selegeline	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
	Moclobemide	Insufficient evidence	Acceptable risk with specialized monitoring[a]	Investigational
Tricyclic antidepressants	Nortriptyline	Likely efficacious	Acceptable risk without specialized monitoring[b]	Possibly useful
	Desipramine	Likely efficacious	Acceptable risk without specialized monitoring[b]	Possibly useful
	Amitriptyline	Insufficient evidence	Acceptable risk without specialized monitoring[b]	*Possibly useful*[c]
Selective serotonin reuptake inhibitors/selective serotonin norepinephrine reuptake inhibitors	Citalopram	Insufficient evidence	Acceptable risk without specialized monitoring[e]	*Possibly useful*[d]
	Sertraline	Insufficient evidence	Acceptable risk without specialized monitoring[e]	*Possibly useful*[d]
	Paroxetine	insufficient evidence	Acceptable risk without specialized monitoring[e]	*Possibly useful*[d]
	Fluoxetine	Insufficient evidence	Acceptable risk without specialized monitoring[e]	*Possibly useful*[c]
	Venlafaxine	*Efficacious*	*Acceptable risk without specialized monitoring*[e]	*Clinically useful*
Other antidepressants	Atomoxetine	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
	Nefazodone	Insufficient evidence	Unacceptable risk	Not useful
Alternative therapies	'Ω-3 fatty acids	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
Nonpharmacological interventions	**rTMS**	*Insufficient evidence*	*Acceptable risk without specialized monitoring*[f]	*Possibly useful (short term)*
	CBT	*Likely efficacious*	*Insufficient evidence*[g]	*Possibly useful*

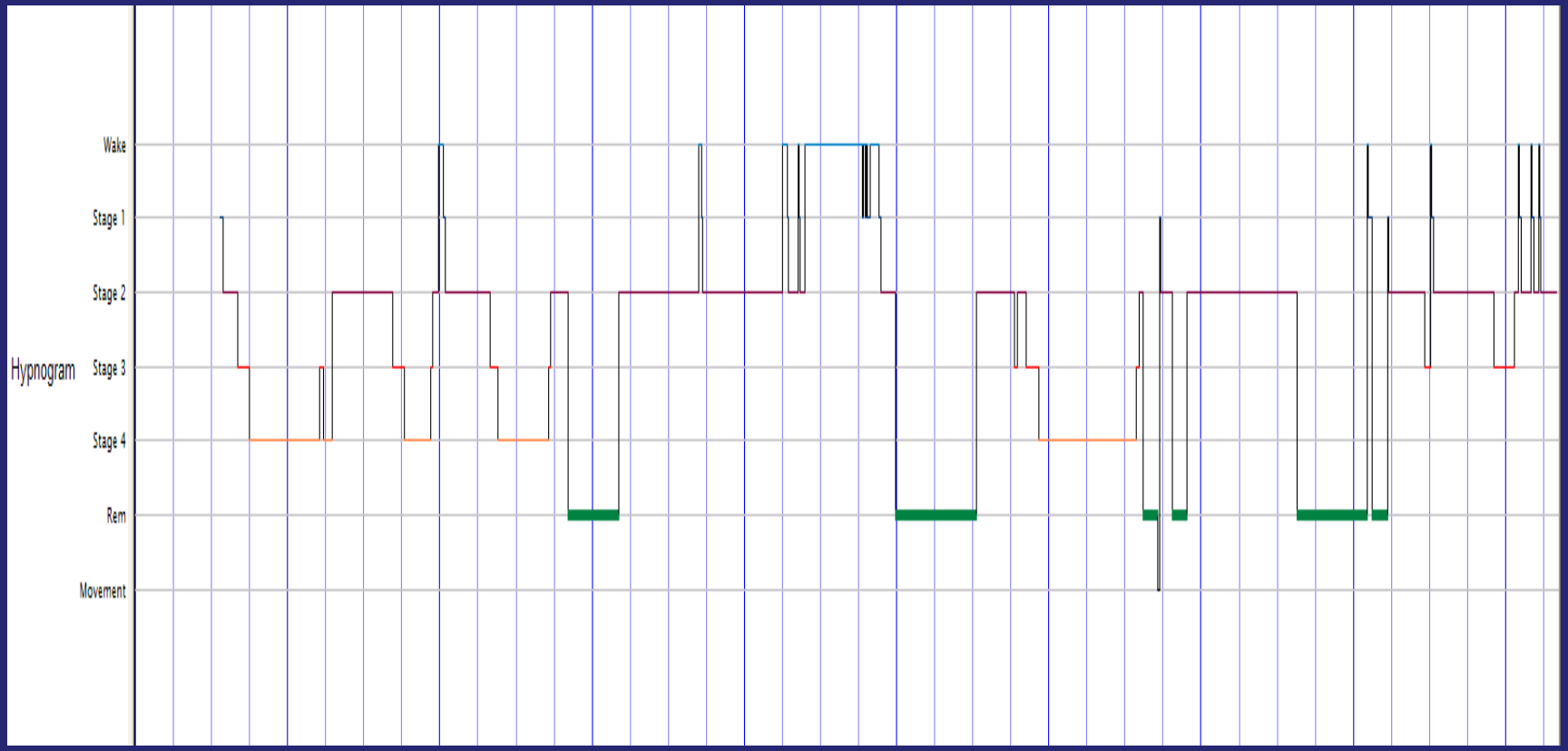
PD Sleep / Wake Issues

- REM Behavior Disorder (RBD)
- Insomnia
- Excessive Daytime Sleepiness

Rapid Eye Movement Behavioral Disorder (RBD)

Parasomnia: vigorous movements c/w dream content, associated with loss of REM atonia

Sleep Hypnogram



REM Behavioral Disorder requires:

-Lack of REM sleep atonia (physiologic)

-Dream content that precipitates body movement (psychological)

Male > Female Prevalence

- Not predicted by testosterone
- May result from dream content

	Male (n=75)	Female (n=45)
Defense from attack	18.7%	0.0%
Aggression	9.3%	0.0%
Work Related	32.0%	6.3%
Sports/Adventure	17.3%	4.4%
Domestic	32.0%	66.7%

Borek, 2006

Clinical RBD in PD

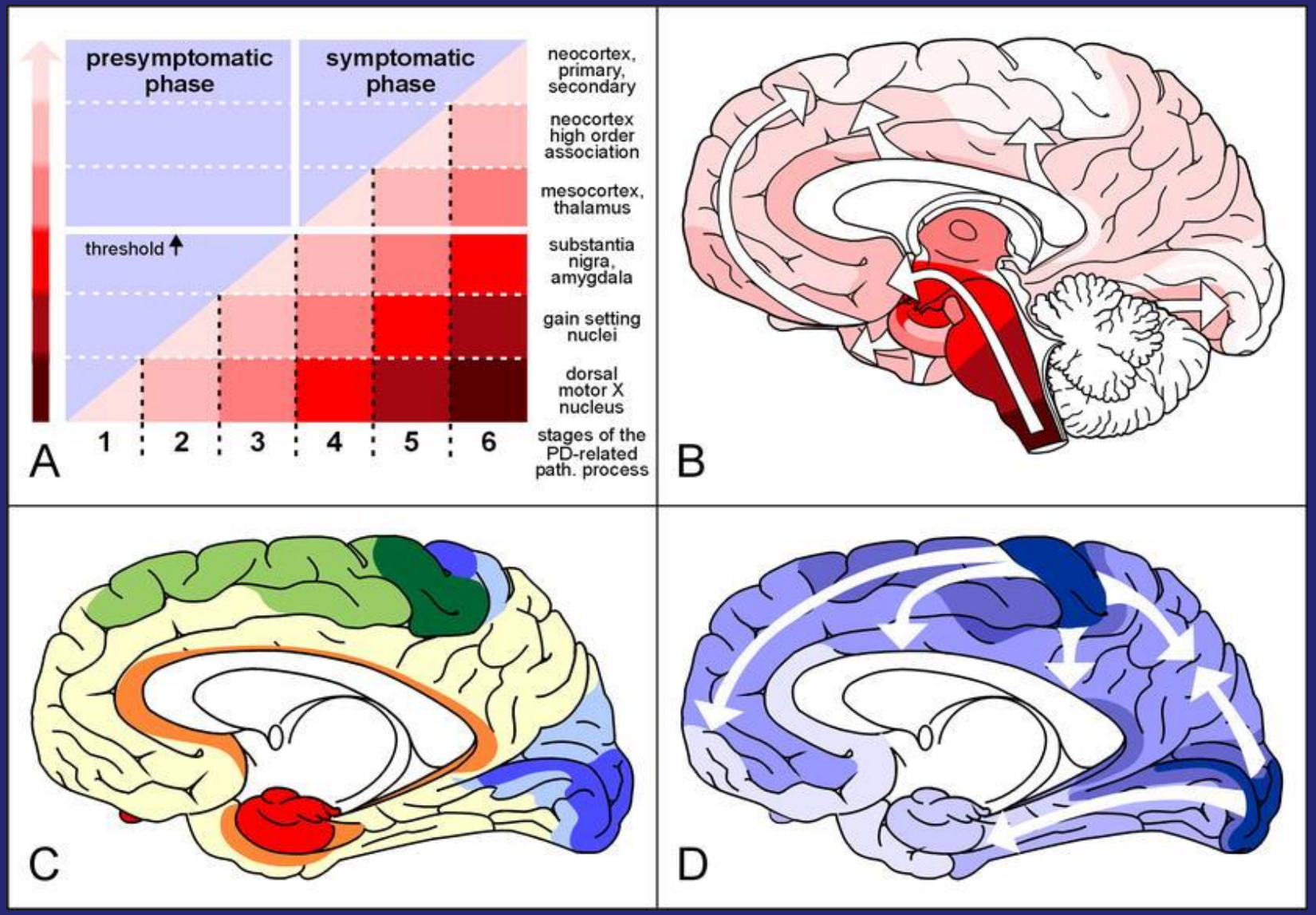
- Correlates with [1]
  - Male sex
  - Dopaminergic medications
- Correlates with longer duration and higher dose of L-dopa, not DA [4]
- Worse in non-tremor dominant PD [2]
- Worse side moves more during RBD [3]
- Movement better (faster) than when awake [3]
- Assoc. with cognitive impairment and non-motor [5]
- Pathology usually DLB [6]

1 Gjerstad 2008, 2 Kumru H 2007, 3 De Cock VC 2007 4 Ozekmekci, S 2005, 5 Gagnon, 2008, 6 Boeve 2003

RBD Becomes Parkinsonism

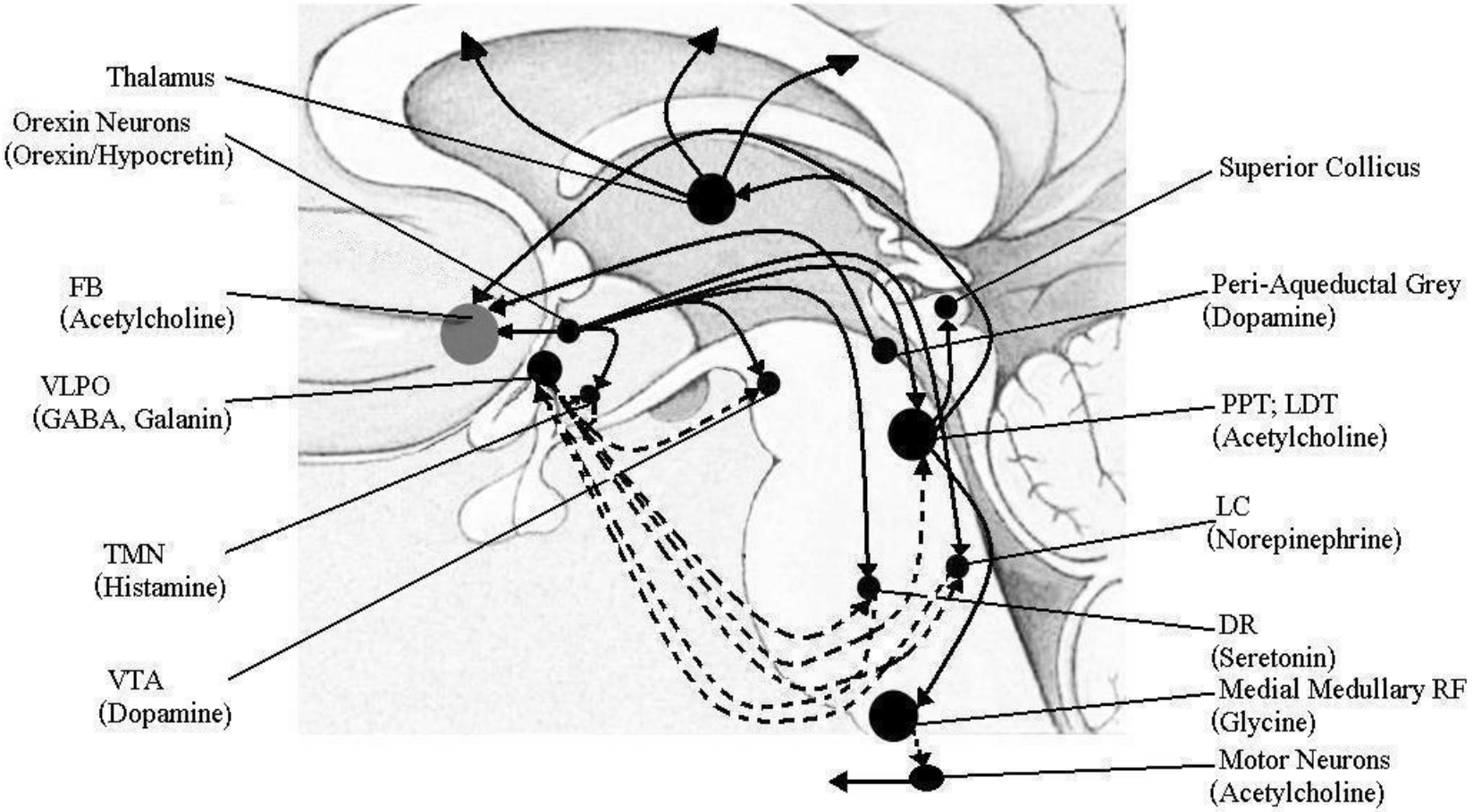
	-N / Sex -Age RBD Dx -Age RBD Onset	Duration of F/U	Outcome	Update
Schenck 1996	-N=29, 29 M -64.4 (5.8) -55.4 (8.7)	3.7 years after RBD Dx	11 (38%) Park, AD	65% p. 13.3 y
Iranzo 2006	-N=44, 39 M -67.8 (5.3) -60.8 (6.8)	4.1 (2.1) y	20 (45%) PD 9, DLB 6, MSA 1, Dem 4	28 (64%) PD 10, DLB 8, MSA 1, Dem 9
Britton 2009	N=93, 75 M 65.4 (9.3)	4.8 (3.6)	26 (28%) PD 14, MSA 1 DLB 7, AD 4	

Braak PD Pathology Staging



1C

REM Sleep


Thalamus
Orexin Neurons
(Orexin/Hypocretin)
FB
(Acetylcholine)
VLPO
(GABA, Galanin)
TMN
(Histamine)
VTA
(Dopamine)
Superior Collicus
Peri-Aqueductal Grey
(Dopamine)
PPT; LDT
(Acetylcholine)
LC
(Norepinephrine)
DR
(Seretonin)
Medial Medullary RF
(Glycine)
Motor Neurons
(Acetylcholine)

Treatment of RBD (often not needed)

- Benzodiazepines:
  - Clonazepam
- Melatonin
- Acetylcholinesterase inhibitors:
  - donepezil

Nocturnal Sleep and Excessive Daytime Sleepiness

Polysomnogram Data in PD

- Reduced sleep efficiency +++
- Fractionated sleep +++
- REM atonia ++
- PLMS ++
- Nocturia ++
- Reduced slow wave sleep +
- Sleep apnea +/-

Treatment of Insomnia

Drug class/intervention strategy	Drug/intervention	Efficacy	Safety	Practice implications
Insomnia				
Levodopa	Controlled-release formulation of levodopa/carbidopa	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
Dopamine agonists	Pergolide	Insufficient evidence	Acceptable risk with specialized monitoring	Not useful
	Piribedil	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
	Rotigotine	Likely efficacious	Acceptable risk without specialized monitoring	Possibly useful
Hypnotics	Eszopiclone	Insufficient evidence	Acceptable risk without specialized monitoring[1]	*Possibly useful*[a]
Melatonin	3-5 mg	Insufficient evidence	Acceptable risk without specialized monitoring	*Possibly useful*[b]
	50 mg	Insufficient evidence	Insufficient evidence	Investigational
Nonpharmacological interventions	**Continuous positive airway pressure**[c]	*Likely efficacious*	*Acceptable risk without specialized monitoring*	*Possibly useful*

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Excessive Daytime sleepiness and “Sleep Attacks”

- First reported by James Parkinson
- Sleep attacks first reported with pramipexole
- Subsequent reports with other agonists and other PD medications
- Numerous studies demonstrate EDS

Baylor PD Sleep Survey

- 303/320 consecutive patients included
  - 11 (Not PD), 4 (unknown drugs), 2 (incomplete data)
- Age : 67.1 ± 10.7
- Duration : 9.1 ± 5.7 years
- Gender : 60.4 % male
- Hoehn and Yahr : 2.5 ± 0.9

Daytime Sleepiness in PD

- Epworth Score: 11.1 ± 5.9, 43% > 10
- Daytime sleepiness correlates with:
  - Duration of PD
  - Severity of PD
  - Male Gender
  - All dopamine agonists
    - pergolide 12.5 ± 5.4
    - ropinirole 12.1 ± 5.7
    - pramipexole 11.7 ± 5.4

Falling Asleep While Driving

- Falling Asleep : 63 / 279 (20.8 %)
- Correlates with :
  - –Age
  - –Dopamine agonists
  - –Levodopa
- Independently correlates only with levodopa
- All DA had similar % of falling asleep

Correlations of Subjective EDS

• Dopamine agonists	• ++++
• Disease severity	• +++
• L-dopa	• +++
• Older Age	• +++
• Male sex	• +++
• Dementia	• ++
• Depression	• ++
• Genetics	• +
– D2, Preprohypocretin	
• **Nocturnal sleep problems**	• **+/--**
– Snoring, PLMS	• +

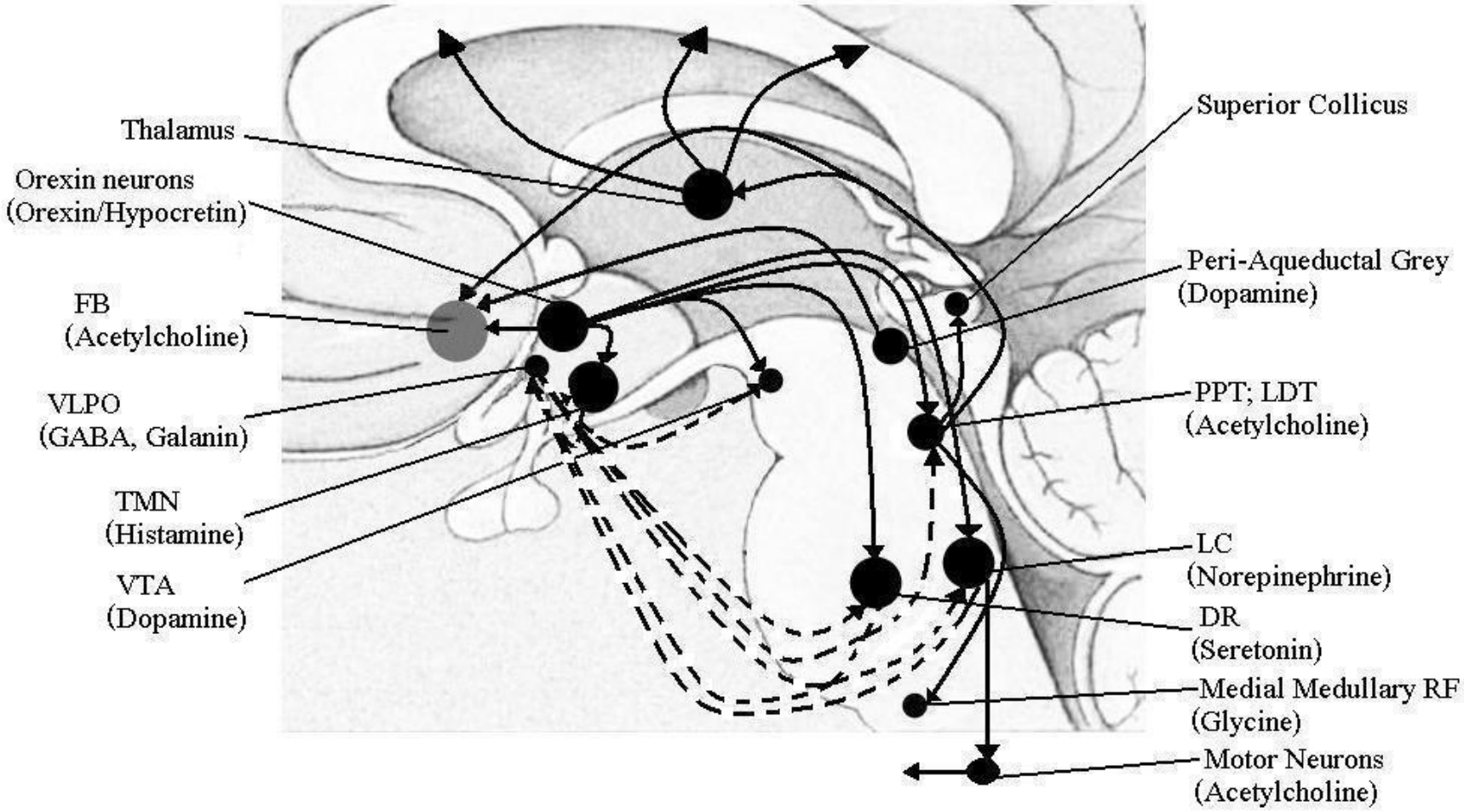
Suzuki K 2007, Ghorayeb I 2007, Hobson 2002, Ondo 2001, Homann 2002, Dagmar 2007, Braga-Neto 2002, Razmy 2004, Rissling 2005, Gjerstad M 2006, Ferreira, J 2006, Poryazova 2009

MSLT Data

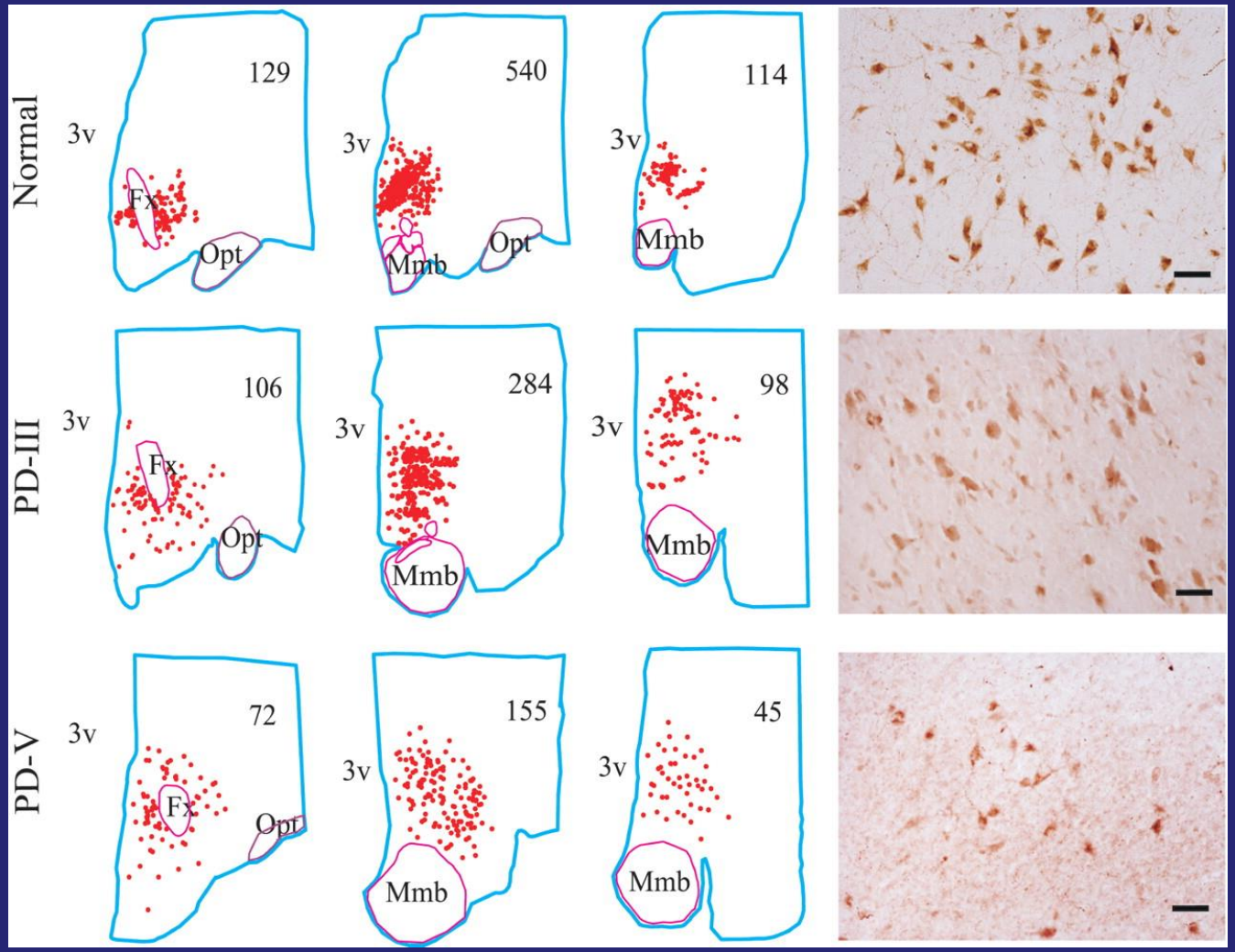
	Epworth	Sleep latency	SOREM
Arnulf 02 (N=54)	14.3 (4.1)	6.3 (0.6)	39% of pt. had ≥2 ep.
Ondo 04 (N=40)	15.1	5.1 (4.9)	9/148 ep.
Razmy 04 (N=80, DA)	6.6 (4.9)	12.1 (5.1)	NR
Rye 00 (N=27)	NR	11.0 (6.1) 40/134 < 5	6/27 subjects 13/108 ep.
Monaca, 06 (N=36)	13.0 (5.8)	10.0 (5.5)	10/36 had ≥ 2 ep.
Poryazova, 10 (N=30)	>10 in 57%	11/30 had <5	0

1A

Wakefulness



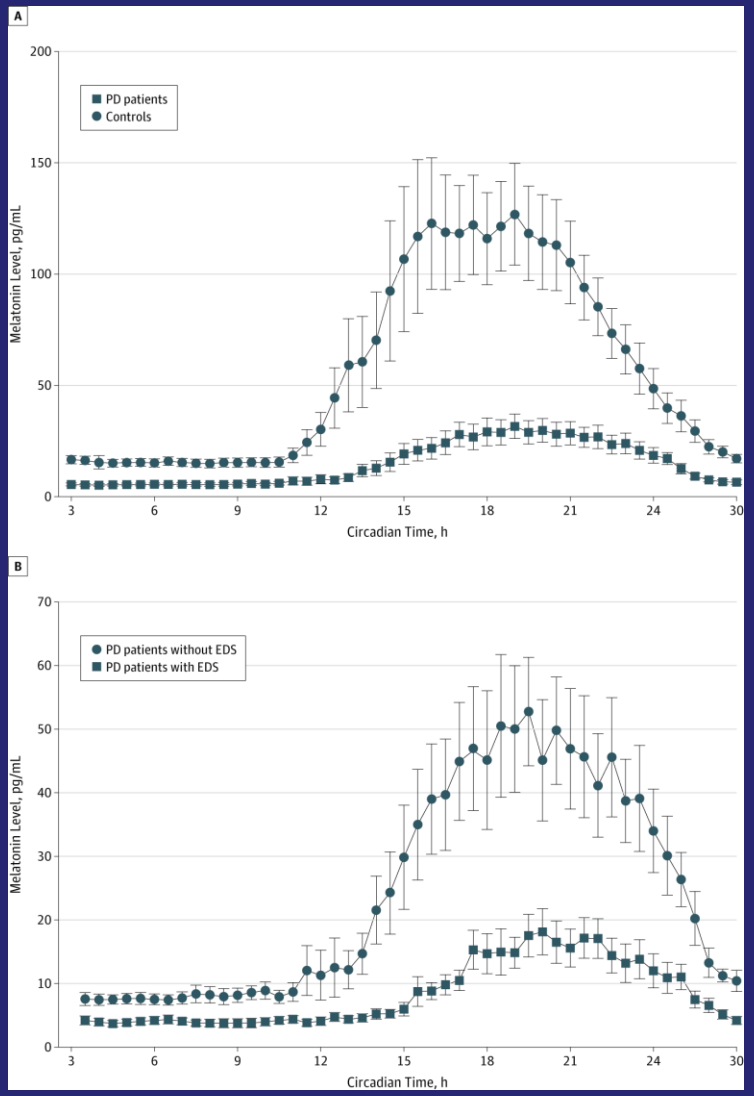
Reduced Hypocretin Cells in PD



Thannickal, T. C. et al. Brain 2007 130:1586-1595

Altered Circadian Biology

- Flattened diurnal cortisol curve
- Reduced and flattened body temperature
- Flattened melatonin



Videnovic A JAMA Neurol 2014

EDS Etiology

- Caused by PD and dopaminergic medications
  - Reduce catecholamines, hypocretin, altered chronobiology
  - Dopaminergics may have unknown soporific properties and/or alter circadian rhythms
- Some physiologic / pathologic similarities to narcolepsy
- Probably not associated with nocturnal sleep problems

Management of Daytime Sleepiness

- Not effective
  - Melatonin, STN DBS
- Possibly effective
  - Optimize nocturnal sleep
  - Minimize offending agents
  - Stimulant medications
  - Histamine-3 inverse agonists
  - Modafinil / Armodafinil
  - Sodium Oxybate

PD: Autonomic

- Low and labile blood pressure
- G.I.
  - –Constipation
  - – Sialorrhea

Autonomic Dysfunction in PD

	PD	Control	*p* Value
Total no. (%) of NMS	8.4 (4.3)	2.8 (2.6)	<0.001[b]
Gastrointestinal tract, n (%)			
Sialorrhea	89 (56.0)	6 (6.1)	<0.001[b]
Dysphagia	32 (20.1)	3 (3.0)	<0.001[b]
Nausea	15 (9.4)	4 (4.0)	0.142
Constipation	67 (42.1)	7 (7.1)	<0.001[b]
Bowel incontinence	9 (5.7)	5 (5.1)	1.000
Incomplete bowel emptying	51 (32.1)	12 (12.1)	<0.001[b]
Hyposmia	71 (44.7)	10 (10.1)	<0.001[b]
Weight change (unexplained)	36 (22.6)	19 (19.2)	0.536
Urinary tract, n (%)			
Urinary urgency	74 (46.5)	19 (19.2)	<0.001[b]
Nocturia	42 (26.4)	17 (17.2)	0.095
Sexual function, n (%)			
Sexual dysfunction	33 (20.8)	10 (10.1)	0.026
Impaired libido	28 (17.6)	7 (7.1)	0.016
Cardiovascular, n (%)			
Orthostatic symptoms	53 (33.3)	11 (11.1)	<0.001[b]
Falls	37 (23.3)	4 (4.0)	<0.001[b]
Lower limb swelling	29 (18.2)	11 (11.2)	0.157

Khoo et al. Neurology 2013;80:276-281

Causes of Orthostatic Hypotension (OH)

NON-NEUROGENIC

Causes include:

- Hypovolemia
- Cardiac insufficiency
- Impaired venous return

NEUROGENIC

Causes include:

- Primary autonomic failure
- Autonomic neuropathies

IATROGENIC

Causes include use of:

- Vasodilators
- Antihypertensives
- Some antidepressants

OH in PD - peripheral autonomic failure

Goldstein DS, Sharabi Y. *Circulation.* 2009;119(1):139-146.

Autonomic Nervous System Maintains Blood Pressure by Releasing Norepinephrine

Standing results in the pooling of ~500-1000 mL of blood in the lower extremities and splanchnic circulation

- **Decrease in venous return to heart**
- **Reduction in cardiac output**

Triggering of venous and arterial baroreceptors

↓

Sympathetic activation
(increased norepinephrine)

↓

- Venoconstriction and increased venous return
- Increased heart rate
- Increases blood pressure

. Freeman R. *N Engl J Med*. 2008;358(6):615-624; Low PA, Singer W. *Lancet Neurol*. 2008;7(5):451-458.
. Isaacson SH. *Vasc Health Risk Manag*. 2014;10:169-176.

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Orthostatic Hypotension

- Occurs in 58% of persons with PD
  - Produces symptoms in 20%
  - Without symptoms in 38%
- Medications may magnify
  - Unknown why dopaminergics lower BP

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

OH Symptom Correlate with absolute lower BP, not drop in BP

	OR	95% CI		P value
Standing SBP	0.9713	0.9559	0.9857	**0.0002**
Change in SBP	0.9934	0.9718	1.0152	0.5517
Standing DBP	0.9524	0.9225	0.9815	**0.0020**
Change in DBP	0.9855	0.9470	1.0242	0.4613

Heisler J (in prep)

Comparison “On” and “Off” State

variables	Off	On	pval
Age	69 (65 to 72)	67.5 (63.8 to 72)	7E-04
DBP_Change	1.5 (-2 to 8)	1 (-3 to 7)	0.3127
dbp_seated	80 (75.8 to 85.2)	78 (70.8 to 83)	0.0069
dbp_standing	80 (71.8 to 83)	78 (67.8 to 81.2)	0.0659
HR_Change	-2 (-7 to 1)	-2 (-7 to 2)	0.7569
MAP_Change	4.8 (0.7 to 13)	6 (0 to 10.8)	0.3465
MAP_Sitting	103.2 (93.7 to 109.8)	98.8 (87.7 to 102.5)	0.0055
MAP_Standing	96.7 (88.6 to 104.1)	94 (83.9 to 99)	0.0226
Puls_Pres_Sitting	62 (49 to 76)	56 (47 to 69)	0.103
Puls_Pres_Standing	50.5 (41 to 59.5)	45.5 (40 to 57)	0.0323
pulse_seated	74 (67.5 to 87)	78 (67 to 88.2)	0.9299
pulse_standing	77 (68.5 to 91)	78 (73 to 89)	0.9705
SBP_Change	11 (4 to 19.2)	14 (1 to 20.2)	0.6043
sbp_seated	145.5 (129 to 159)	136.5 (120.8 to 148)	0.0149
sbp_standing	132 (115.8 to 143.5)	124 (111 to 136)	0.0148

OH Treatment: (Non-pharmacological)

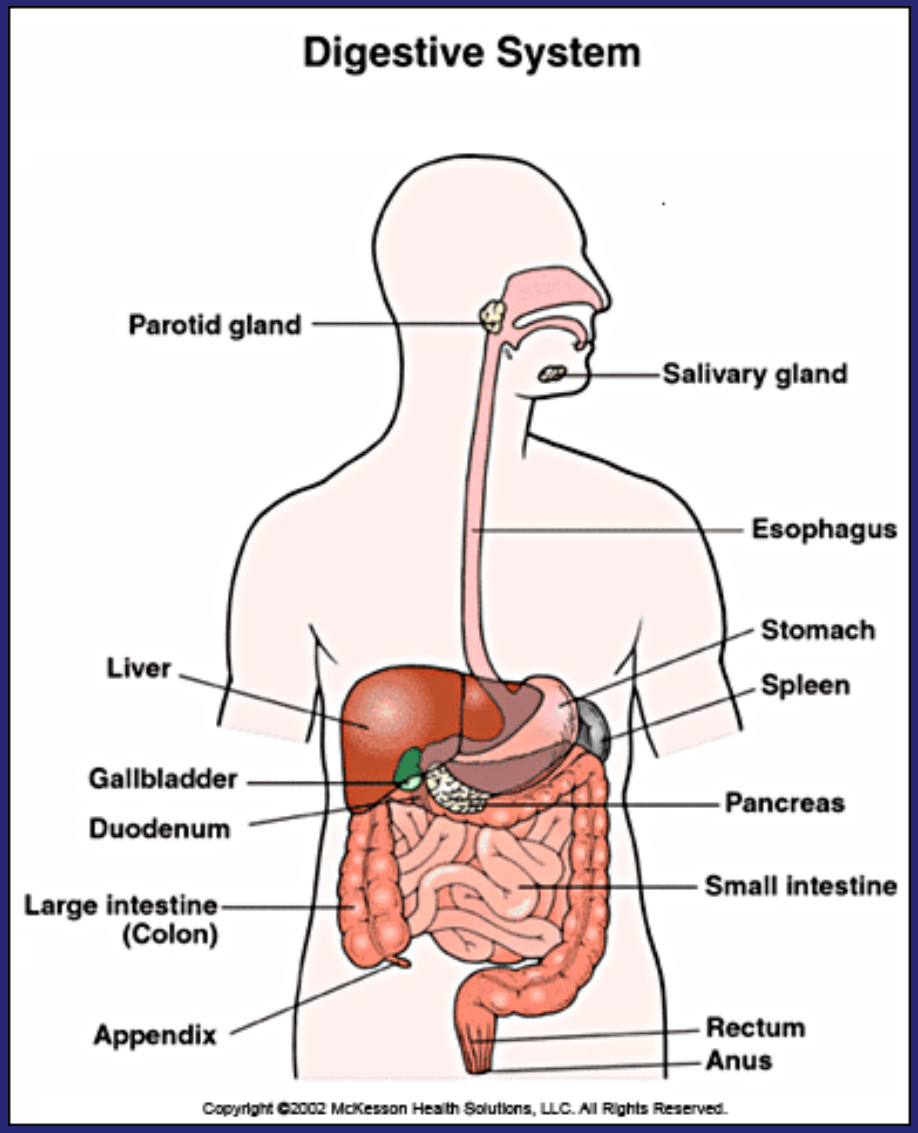
- Increased water ingestion
- Increased salt ingestion
- Get up slowly, bounce, dip head
- Pressure stockings (waist high)
- Abdominal band/binder
- Avoid large meals (carbohydrates)
- Head of bed elevation
  - Eat just before bed

OH: Pharmacological Measures

- Droxidopa*: norepinephrine precursor
- Fludrocortisone
- Midodrine: alpha-1 agonist
- Pyridostigmine
- Others (with less supportive evidence)
  - Octreotide
  - Blood
  - Desmopressin
  - Caffeine
  - Domperidone

Gastrointestinal Abnormalities

- Saliva
- Swallowing
- Stomach Problems
- Small Intestine Problems
- Colon Problems
- Anal Dysfunction



Sialorrhea in PD

- Experienced by 56-78%
- Initially nocturnal drooling
- 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.

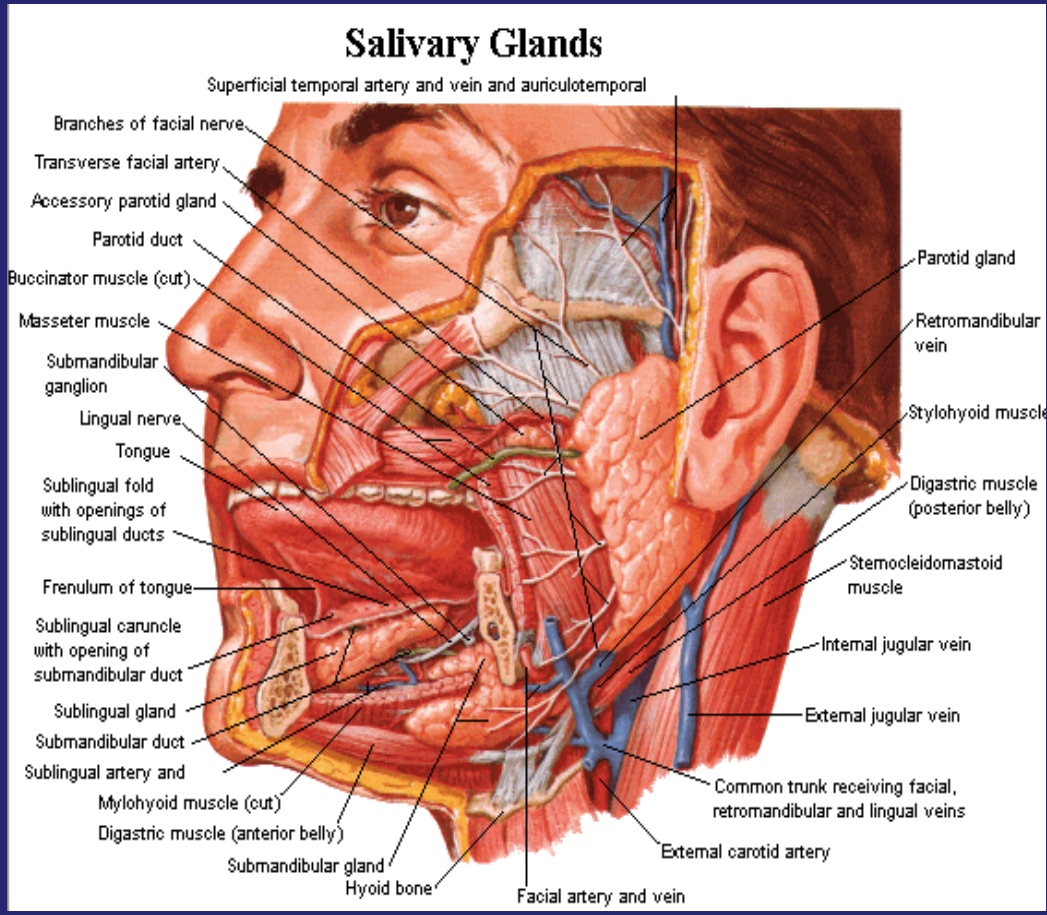
Treatment of Sialorrhea

- Gum and hard candy
  - Make swallowing more "conscious
- PD medications
- Anticholinergic drugs
  - Avoid systemic drugs such as trihexyphenidyl or benztropine
  - Glycopyrrolate avoids central (brain-related) side effects but not peripheral
  - Sublingual atropine ophthalmic solution
  - Botulinum toxin

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.

Botulinum Toxin

- Benefits:
  - 3-4 months
- Parotid and Submandibular
- Approved
  - Myobloc® (Type B)
  - Xeomin ® (Type A)

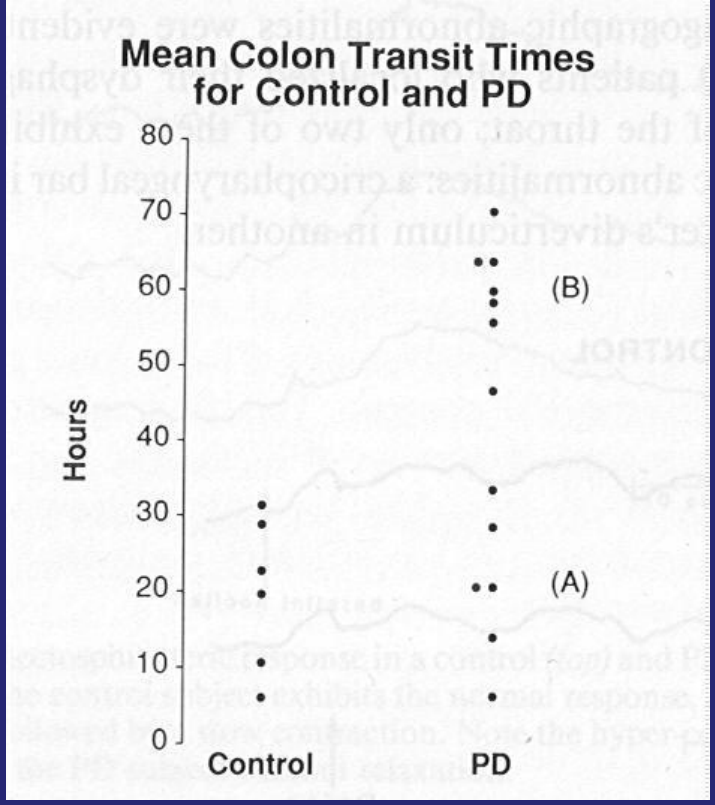


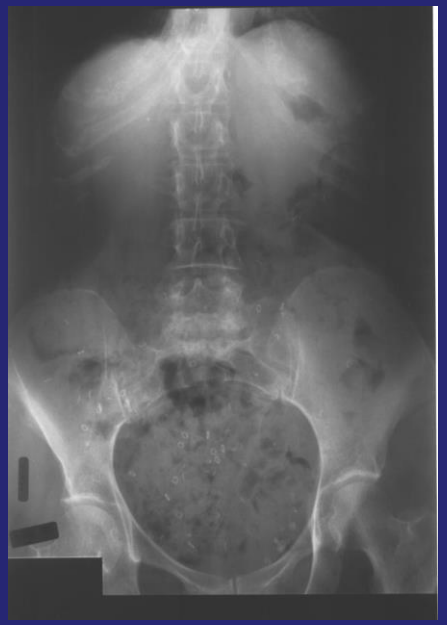
Bowel Dysfunction in PD

- Constipation (colonic inertia)
  - Decreased bowel movement frequency
- Defecatory dysfunction
  - Difficulty with the act of defecation

Slow colonic transit

- Colon transit time (CTT) is prolonged in PD
- Slowing occurs in 80% of PD patients
- Average CTT in PD is twice as long: 44 hours vs. 20 hours





Pfeiffer RF. Parkinsonism Relat Disord 2011;17:10-15.
Pfeiffer RF. In: Parkinson's Disease, 2nd
Edwards LL, et al. Am J Gastroenterol 1994;89:15-25

Defecatory Dysfunction: Pathophysiology

- Impaired motor coordination:
  - Inadequate sphincter relaxation
  - Failure of anorectal angle to open
  - Insufficient intra-abdominal pressure
  - 60-70% of constipation pts have DD
- Underlying mechanisms?:
  - Bradykinesia
  - Rigidity
  - Dystonia (off-period phenomenon)
- Testing
  - anorectal manometry
  - EMG
  - defecography

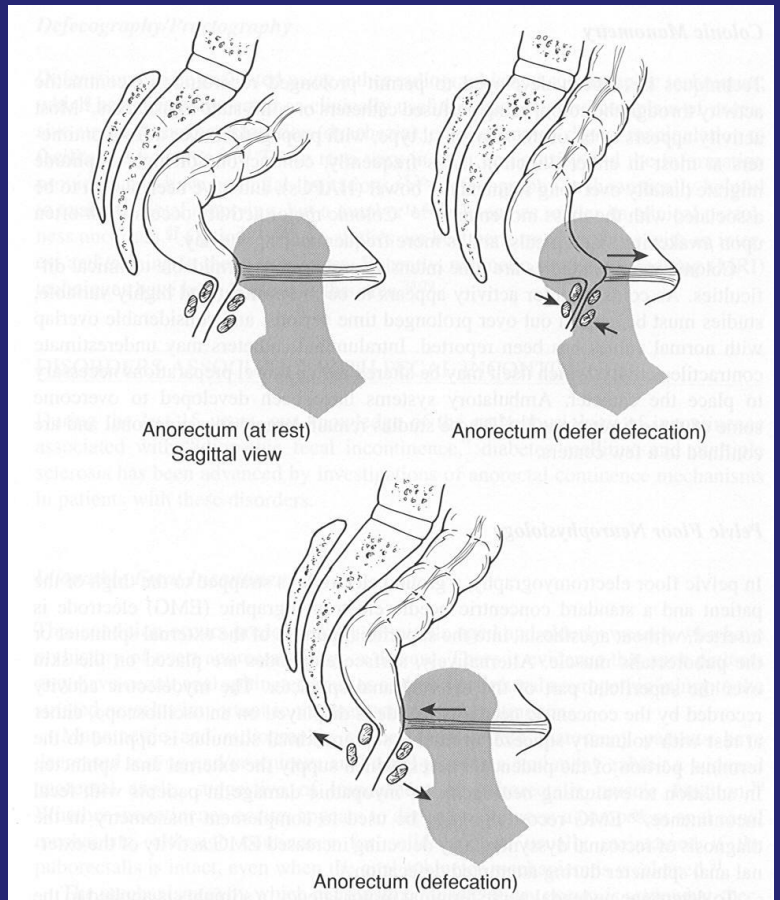


Figure 13.2. Sagittal views of the anorectum at rest, when defecation is being deferred and during defecation. Arrows indicate muscle vector forces when the striated muscles are contracted *(center)* or relaxed *(right)*. (Reproduced with permission from Sun WM, Rao SS. Manometric assessment of anorectal function. Gastroenterol Clin North Am 2001;30:15–32.)

Pfeiffer RF. Parkinsonism Relat Disord 2011;17:10-15.

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

Simple Constipation Treatments

Behavioral treatments

- Adequate fluid intake
- Increased dietary fiber
- Exercise / abdominal massage
- Regular bowel habits

Treatment - Medical

- Polyethylene glycol / Macrogol*
- Lubiprostone (Amitiza®)
- Probiotics*
- Others:
  - Linaclotide (Linzess)
  - Stool softeners
  - Magnesium based products
  - Osmotic laxatives (lactulose)

Seppi et al. Mov Disord 2011
Ondo et al. Neurology 2012
Zesiewicz et al Neurology 2010

Treatment of Defecatory Dysfunction

- Dopaminergic medications
  - Apomorphine inject
  - 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.
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Summary

- From metaphysical concepts of reality (hallucinations) to bowel movements, non-motor symptoms contribute the majority of morbidity in treated PD patients
- All have treatment options

Thank You

Questions?