

# Management of Non-Motor Symptoms

*MDS-African Section School for Young Neurologists*

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CT has received honoraria for educational lectures from UCB (Otsuka), Britannia, Abbvie, STADA, Bial, Advisor for Roche, Ono, Bial, Abbvie. UCB.

# Early Identification of Patients with Parkinson's disease

- Non-motor symptoms and other early biomarkers



**Olfactory dysfunction:**

UPSIT,  $\alpha$ -synuclein RT-QulC analysis

**Autonomic dysfunction**

nasal mucosa biopsy

**Orthostatic hypotension,**  
Constipation, reduced **gastric motility**

Urinary and erectile dysfunctions

Sleep disorders

**REM Sleep Behavior Disorder**

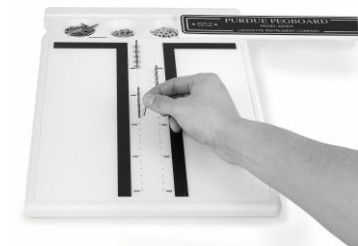
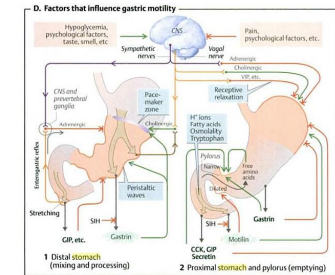
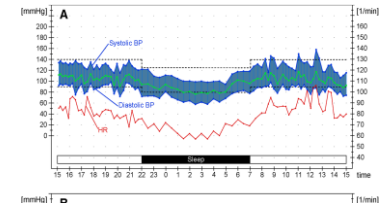
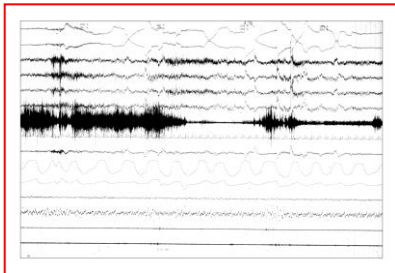
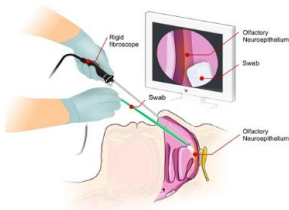
Insomnia

Excessive daytime sleepiness,

Cognitive impairments

Depression/Anxiety

Subtle motor dysfunctions



# Non-motor Symptoms in PD – Prodromal Features?

- Major features of prodromal PD include the following with various combinations:
  - Olfactory dysfunction
  - Autonomic dysfunction (Orthostatic hypotension, constipation, urinary and erectile dysfunctions)
  - Sleep and wake disorders (Insomnia, excessive daytime sleepiness, Rem Sleep Behavior Disorder (RBD))
  - Psychiatric (depression and anxiety) and cognitive impairments (MCI, dementia)
  - Subtle motor dysfunctions

*Chaudhuri and Schapira, Lancet Neurol 2009, Berg et al, Mov Disord 2015,  
Sauerbier et al Park Rel Disorders 2015,*

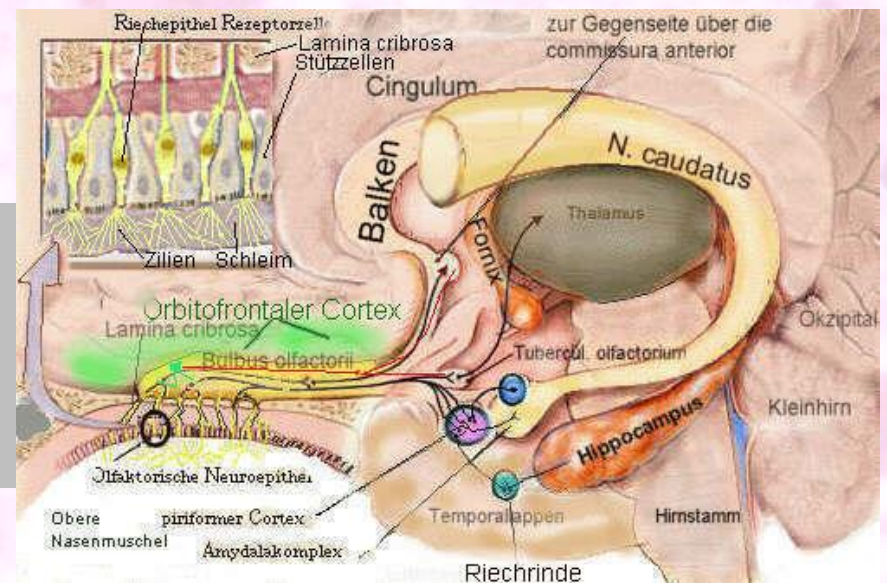


# Olfactory deficiency

## Sniffin Test

Discrimination – Threshold Identification  
pathological test if less than 9 out of 12  
samples are identified

*Ponsen et al, Olfactory testing combined with dopamine transporter imaging as a method to detect prodromal Parkinson's disease. J Neurol Neurosurg Psychiatry 2010*



# Olfactory Deficiency – Hyposmia in PD

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Hyposmia is an early sign of PD and relates to prodromal PD

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Olfaction tests are applied in patients and population to identify people at risk for PD

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Assessment using olfactory tests: Sniffin Stix or Upsit test

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Currently no medication to restore olfaction when deficient

## **CME** Update on Treatments for Nonmotor Symptoms of Parkinson's Disease—An Evidence-Based Medicine Review

Mov Disord 2019

Klaus Seppi, MD,<sup>1\*</sup> K. Ray Chaudhuri, MD,<sup>2</sup>  Miguel Coelho, MD,<sup>3</sup> Susan H. Fox, MRCP (UK), PhD,<sup>4</sup>  
Regina Katzenschlager, MD,<sup>5</sup> Santiago Perez Lloret, MD,<sup>6</sup>  Daniel Weintraub, MD,<sup>7,8</sup>  
Cristina Sampaio, MD, PhD,<sup>9,10</sup>

and the collaborators of the Parkinson's Disease Update on Non-Motor Symptoms Study Group on behalf of the  
Movement Disorders Society Evidence-Based Medicine Committee

### **Methodology used:**

electronic databases (Medline, Cochrane Library)  
and systematic checking of references from review  
articles

Inclusion criteria for studies

- pharmacological, surgical, and non-  
pharmacological

interventions to treat NMS in PD

- NMS as primary endpoint
- measured with an established rating scale or
- minimum of 20 patients
- minimum of 4 weeks treatment

**TABLE 1.** Indications of nonmotor symptoms covered by this review

- 
- Neuropsychiatric symptoms
    - Depression and depressive symptoms
    - Anxiety and anxiety symptoms
    - Apathy
    - Psychosis
    - Impulse control and related disorders
    - Dementia
    - Cognitive impairment (other than dementia; mainly mild cognitive impairment)
  - Autonomic dysfunction
    - Drooling
    - Orthostatic hypotension
    - Urinary dysfunction
    - Erectile dysfunction
    - Gastrointestinal dysfunction
    - Excessive sweating
  - Disorders of sleep and wakefulness
    - Sleep fragmentation and insomnia
    - Rapid eye movement sleep behavior disorder
    - Excessive daytime sleepiness
  - Others
    - Pain
    - Fatigue
    - Olfactory dysfunction
    - Ophthalmologic dysfunction
-

# The neuropsychiatry of Parkinson's disease: advances and challenges (1)

## **Panel 1:**

**Correlates or risk factors for the presence of neuropsychiatric signs and symptoms in patients with Parkinson's disease**

### **Risk increasing with younger age at Parkinson's disease onset**

- Depression
- Anxiety
- Impulse control disorders

### **Risk increasing with older age at Parkinson's disease onset**

- Apathy
- Psychosis

### **Female sex**

- Depression
- Anxiety
- Psychosis
- Compulsive buying and eating

### **Male sex**

- Apathy
- Compulsive sexual behaviour

### **Risk increasing with disease duration**

- Depression
- Psychosis



# The neuropsychiatry of Parkinson's disease: advances and challenges (2)

## **Dopamine replacement therapy**

- Impulse control disorders
- Psychosis

## **Cognitive impairment**

- Depression
- Anxiety
- Apathy
- Psychosis

## **Disorders of sleep or wakefulness**

- Depression
- Anxiety
- Psychosis

## **Pre-existing personality traits**

- Impulse control disorders

## **Autonomic dysfunction**

- Anxiety
- Psychosis

## **Visual disturbance**

- Psychosis

## **Parkinson's disease-related pain**

- Depression
- Anxiety

*Weintraub et al, Lancet Neurol 2022*

# Depression in PD

- **Different Symptoms in PD depression compared with Major Depressive Disorder without PD:**  
*(Leentjens et al 2003)*
  - Depressive Mood
  - Anhedonia
  - Loss of activities
  - Loss of interest in social environment
  - (Apathy)

# Depression and Anxiety in PD

Weintraub D, et al, Lancet Neurol 2020.

Broen MP. Prevalence of anxiety in Parkinson's disease: a systematic review and meta-analysis. Mov Disord 2016;

Daly J et al Progression of neuropsychiatric symptoms over time in an incident Parkinson's disease cohort (ICICLE-PD). Brain Sci 2020; 10: 78.

Most frequent neuropsychiatric symptoms in **early PD**

Can occur **at any disease stage** and increase with age

In **advanced disease** about 60% experience depressive symptoms

Anxiety presents mostly as generalized anxiety disorder

Depressive symptoms occur during off-periods in **advanced PD**

Depressive symptoms occur during dopamine agonist withdrawal syndrome

**TABLE 2.** Interventions to treat depression, including depressive symptoms in PD

Intervention		Efficacy	Safety	Practice implications
Drug class/ intervention strategy	Drug/intervention			
Dopamine Agonists	Pramipexole	Efficacious	Acceptable risk without specialized monitoring	Clinically useful
	Pergolide	Insufficient evidence	Acceptable risk with specialized monitoring	Not useful
	<b>Rotigotine</b>	<i>Unlikely efficacious</i>	<i>Acceptable risk without specialized monitoring</i>	<i>Investigational</i>
Monoamine oxidase B (MAO-B) inhibitors	<b>Rasagiline</b>	<i>Insufficient evidence</i>	<i>Acceptable risk without specialized monitoring</i>	<i>Investigational</i>
	Selegeline	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
	Moclobemide	Insufficient evidence	Acceptable risk with specialized monitoring <sup>a</sup>	Investigational
Tricyclic antidepressants	Nortriptyline	Likely efficacious	Acceptable risk without specialized monitoring <sup>b</sup>	Possibly useful
	Desipramine	Likely efficacious	Acceptable risk without specialized monitoring <sup>b</sup>	Possibly useful
	Amitriptyline	Insufficient evidence	Acceptable risk without specialized monitoring <sup>b</sup>	<i>Possibly useful<sup>c</sup></i>
Selective serotonin reuptake inhibitors/selective serotonin norepinephrine reuptake inhibitors	Citalopram	Insufficient evidence	Acceptable risk without specialized monitoring <sup>e</sup>	<i>Possibly useful<sup>d</sup></i>
	Sertraline	Insufficient evidence	Acceptable risk without specialized monitoring <sup>e</sup>	<i>Possibly useful<sup>d</sup></i>
	<b>Paroxetine</b>	insufficient evidence	Acceptable risk without specialized monitoring <sup>e</sup>	<i>Possibly useful<sup>d</sup></i>
	Fluoxetine	Insufficient evidence	Acceptable risk without specialized monitoring <sup>e</sup>	<i>Possibly useful<sup>c</sup></i>
	<b>Venlafaxine</b>	<i>Efficacious</i>	<i>Acceptable risk without specialized monitoring<sup>e</sup></i>	<i>Clinically useful</i>
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	<b>rTMS</b>	<i>Insufficient evidence</i>	<i>Acceptable risk without specialized monitoring<sup>f</sup></i>	<i>Possibly useful (short term)</i>
	<b>CBT</b>	<i>Likely efficacious</i>	<i>Insufficient evidence<sup>g</sup></i>	<i>Possibly useful</i>

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- Many antidepressant agents are possibly useful
- Venlafaxine and pramipexole are the only „clinically useful“ antidepressant agents

#### Practical Management:

- Start with a dopamine agonist if indicated because of PD
- If no improvement, start with an antidepressant

# The Movement Disorder Society Nonmotor Rating Scale: Initial Validation Study

K. Ray Chaudhuri, DSc, FRCP, MD,<sup>1\*</sup>  Anette Schrag, FRCP, PhD,<sup>2</sup>  Daniel Weintraub, MD,<sup>3,4</sup>  
Alexandra Rizos, MSc,<sup>1</sup> Carmen Rodriguez-Blazquez, PhD,<sup>5</sup> Eugenia Mamikonyan, MS,<sup>3</sup> and  
Pablo Martinez-Martin, MD, PhD<sup>5</sup>

## SCORING

### Average Frequency / Duration: (percentages denote days per week or hours per week)

- 0: Never  
1: Rarely ( $\leq 10\%$  of time)  
2: Sometimes (11-25% of time)  
3: Frequently (26-50% of time)  
4: Majority of time ( $\geq 51\%$  of time)

### Average Severity:

- 0: Not present (only if frequency = 0)  
1: Minimal (no distress or disturbance to patient or caregiver)  
2: Mild (minor distress or disturbance to patient or caregiver)  
3: Moderate (considerable distress or disturbance to patient or caregiver)  
4: Severe (major distress or disturbance to patient or caregiver)

### Calculations:

- Item Total** = Frequency multiplied by severity  
**Subscale Total** = Sum of all Item totals for that Subscale  
**MDS-NMS Total Score** = Sum of totals for Subscales A-M

## International Parkinson and Movement Disorder Society – Non-Motor Rating Scale (MDS-NMS)

RATER-ADMINISTERED VERSION

Rate symptoms over past 4 weeks

### A. Depression:

1. Felt sad or depressed? .....  
2. Had difficulty experiencing pleasure? .....  
3. Felt hopeless? .....  
4. Had negative thoughts about yourself? .....  
5. Felt that life is not worth living? .....

Frequency (0-4)      Severity (0-4)      Frequency x severity

Subscale A Total		

### B. Anxiety:

1. Felt worried? .....  
2. Felt nervous? .....  
3. Had panic or anxiety attacks? .....  
4. Been worried about being in public or in social situations? .....

Subscale B Total		

### C. Apathy:

1. Had a reduced motivation to start day-to-day activities? .....  
2. Had a reduced interest in talking to people? .....  
3. Had a reduction in experiencing emotions? .....

Subscale C Total		

### D. Psychosis:

1. Sensed things or people in margins of visual field?  
(passage or presence phenomena) .....  
2. Visually misinterpreted an actual object? (illusions) .....  
3. Seen, heard, felt, tasted or smelled things that other people did  
not? (hallucinations) .....  
4. Believed things to be true that others did not?  
(e.g., delusions of persecution, jealousy or misidentification) .....

Subscale D Total		

# Non-Motor Symptoms

## Comparison of assessment

MDS-NMS

NMSS

MDS-UPDRS Part

- Prevalence rates for NMS using the MDS-NMS are higher than on other scales used and increase with higher disease severity.

**TABLE 1** Percentage of symptoms measured by MDS-NMS, NMSS and MDS-UPDRS Part I

MDS-NMS	% <sup>a</sup>	NMSS	% <sup>a</sup>	MDS-UPDRS Part I	% <sup>a</sup>
A1. Sad or depressed	47.9	10. Sad or depressed	39.9	1.3 Depressed mood	38.9
A2. Difficulty pleasure	25.4	11. Flat moods	28.4		
A3. Hopeless	21.0	12. Difficulty pleasure	22.1		
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		

<sup>a</sup>Percentages are computed as the proportion of scores  $\geq 1$  in each item.



RESEARCH ARTICLE

## The Movement Disorder Society Nonmotor Rating Scale: Initial Validation Study

K. Ray Chaudhuri, DSc, FRCP, MD,<sup>1\*</sup> Anette Schrag, FRCP, PhD,<sup>2</sup> Daniel Weintraub, MD,<sup>3,4</sup>  
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Pablo Martinez-Martin, MD, PhD<sup>5</sup>

<b>MDS-NMS Score Sheet – Non Motor Fluctuations</b> Subscore “Change” = Sum of all “degree of change” items Subscore “Time” = Time spent in non-motor “Off” state MDS-NMS NMF Total Score = Subscore “Change” multiplied by Subscore “Time”	
<b>NON-MOTOR FLUCTUATIONS (optional)</b>	<b>Typical degree of change from “On” to “Off” period</b>
1. Depression	
2. Anxiety	
3. Thinking or cognitive abilities	
4. Bladder symptoms	
5. Restlessness	
6. Pain	
7. Fatigue	
8. Excessive sweating	
<b>Subscore “Change”</b>	
<b>Subscore “Time”</b>	
<b>MDS-NMS NON-MOTOR FLUCTUATIONS TOTAL SCORE</b>	



# Prevalence of Non-Motor Symptoms and Non-Motor Fluctuations in Parkinson's Disease Using the MDS-NMS

Carmen Rodríguez-Blázquez, PhD,<sup>1,2</sup> Anette Schrag, MD, FRCP, PhD,<sup>3</sup> Alexandra Rizzo, MSc,<sup>4</sup> K. Ray Chaudhuri, MD, DSc, FRCP,<sup>4</sup> Pablo Martínez-Martin, MD, PhD,<sup>2,4</sup> and Daniel Weintraub, MD,<sup>5</sup>

NMFluctuation is evident from mild to severe PD graded by HY stage

RODRIGUEZ-BLAZQUEZ C. ET AL.

RESEARCH ARTICLE

**TABLE 5** Percentage of patients with NMF by severity level

Severity levels*	NMF items							
HY	1	2	3	4	5	6	7	8
Mild (N = 105)	36.2	59.0	52.4	23.8 **	42.9	37.1	69.5	9.5
Moderate (N = 47)	48.9	66.0	68.1	19.1 **	42.6	42.6	63.8	23.4
Severe (N = 13)	46.2	76.9	46.2	53.8	30.8	38.5	76.9	23.1
p***	0.306	0.382	0.146	0.035	0.701	0.818	0.621	0.053
<b>CISI-PD</b>								
Mild (N = 59)	33.9	47.5 **	44.1 **	16.9	39.0	35.6	61.0	5.1 **
Moderate (N = 96)	43.8	70.8 **	64.6 **	27.1	44.8	38.5	72.9	19.8 **
Severe (N = 10)	50.0	70.0	50.0	50.0	30.0	60.0	70.0	20.0
p***	0.395	0.012	0.040	0.060	0.572	0.341	0.300	0.037
<b>MDS-UPDRS Part IV</b>								
Mild (N = 97)	31.3	50.0	45.8	20.8	37.5	39.6	60.4	8.3 **
Moderate (N = 125)	45.9	68.4	60.2	25.5	42.9	38.8	75.5	16.3 **
Severe (N = 9)	44.4	67.6	67.6	44.4	44.4	22.2	88.9	44.4
p***	0.235	0.095	0.209	0.323	0.810	0.599	0.082	0.021

Percentages are computed as the proportion of scores  $\geq 1$  in each item.

NMF items: 1. Depression, 2. Anxiety, 3 Thinking or cognitive abilities, 4. Bladder symptoms, 5. Restlessness, 6. Pain, 7. Fatigue, 8. Excessive sweating.

\*Parkinson's disease severity levels according to *Expert Rev Neurother* 2018;18:41–50 [Ref. 26].

\*\*significant differences between levels.

\*\*\*chi-squared test;

CISI-PD, clinical impression of severity index of Parkinson's Disease; HY, Hoehn & Yahr stage; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Scale; NMF, non-motor fluctuations

# Non-Motor Symptoms ....

...are not only  
a sign of early  
PD

But progress  
in advanced  
PD

and in motor  
fluctuations

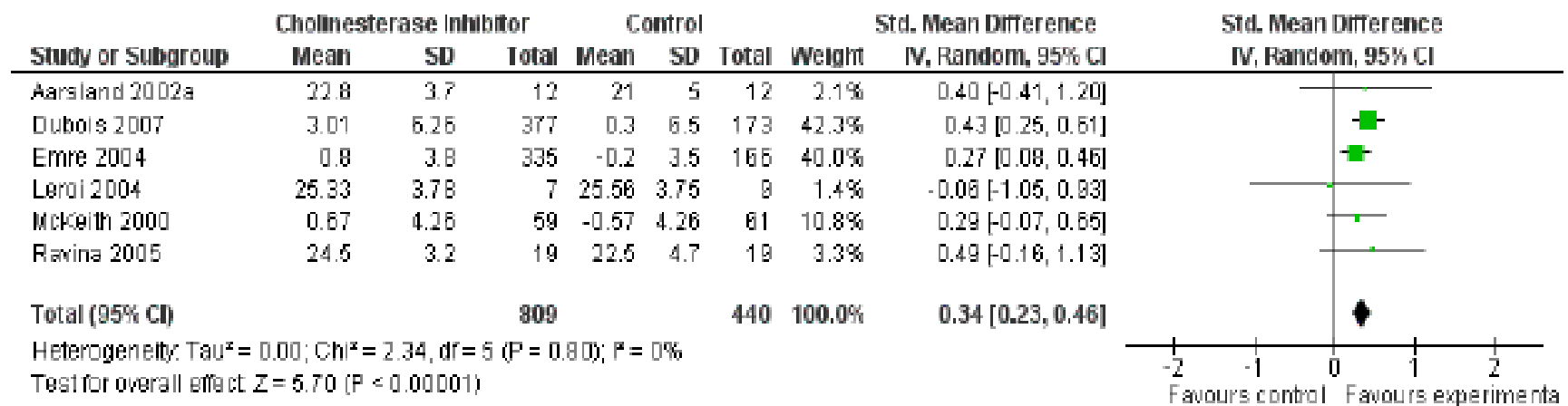
**DEMENTIA**

# Cholinesterase inhibitors for dementia with Lewy bodies, Parkinson's disease dementia and cognitive impairment in Parkinson's disease (Review)

*Cochrane Database of Systematic Reviews 2012, Issue 3. Art. No.: CD006504.*

Rolinski M, Fox C, Maidment I, McShane R

**Figure 2. Forest plot of comparison: 2 Cognitive function, outcome: 2.3 Combined: MMSE or ADASCog.**



AEs more common in rivastigmine groups

# PD Dementia

DRUG/ INTERVENTION	Efficacy	Safety	Practice implications
<b>Donepezil</b>	Insufficient evidence <sup>#</sup>	acceptable risk	Investigational
<b>Rivastigmine</b>	Efficacious	acceptable risk	Clinically useful
<b>Galantamine</b>	Insufficient evidence	acceptable risk	Investigational
<b>Memantine</b>	Insufficient evidence	acceptable risk	Investigational
<b>Exercise</b>	<i>Not Yet Assessed (positive in some measures)</i>		
<b>Cognitive Therapy</b>	<i>Not yet Assessed (variable studies)</i>		

# conflicting outcomes in studies

Seppi et al, EBM Recommendations MovDisord 2019

# Autonomic dysfunction

Urinary dysfunction

Constipation – gastric emptying dysfunction

Orthostatic hypotension

# Urinary Dysfunction

- ***Bladder dysfunction.***
- Urinary dysfunction in PD includes nocturia, and **increased frequency and urgency of micturition**
- associated with detrusor hyper-reflexia.
- Micturition regulation is dependent on the autonomic arc of the sacral spinal cord segments
- tonically facilitated by the pontine micturition centre
- the storage function is facilitated by the hypothalamus, cerebellum, frontal cortex and basal ganglia
- **Bladder hyperreflexia in PD is thought to be related to loss of the inhibitory role of the basal ganglia.**

# Overactive Bladder

DRUG	efficacy	safety	practice implications
<b>Oxybutynin</b>	insufficient evidence	insufficient evidence	investigational
<b>Tolteradine</b>	insufficient evidence	insufficient evidence	investigational
<b>Flavoxate</b>	insufficient evidence	insufficient evidence	investigational
<b>Propiverine</b>	insufficient evidence	insufficient evidence	investigational
<b>Prazosin</b>	insufficient evidence	insufficient evidence	investigational
<b>Desmopressin</b>	insufficient evidence	insufficient evidence	investigational
Solifenacin succinate	<i>Not yet assessed (negative study)</i>		
Transcutaneous tibial nerve stimulation	<i>Not yet assessed (positive study)</i>		



# Constipation **Definition:**

- *Physician definition:* reduction in the frequency of bowel movements <3 times per week
- *Patients definition:* difficulty passing stool, hard stool consistency, feelings of abdominal cramping, and feelings of incomplete stool passage

[Treatments for Constipation: A Review of Systematic Reviews](#)

Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2014 Nov 17.

PMID: 25535635 **Free Books & Documents**

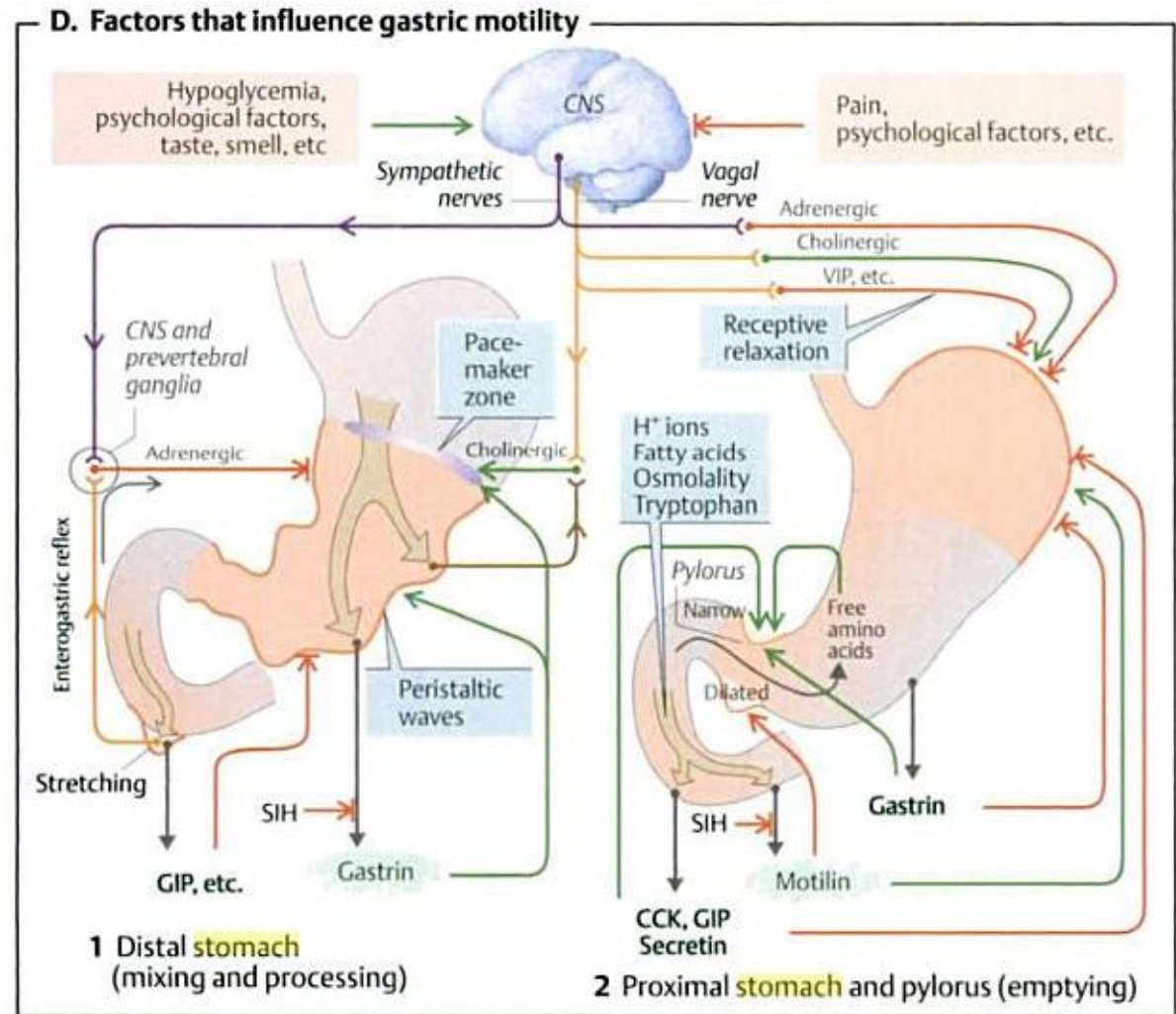
# Constipation

## Dysfunction of gastric emptying

## Dysphagia

## Sialorrhea

## Weight loss



[Treatments for Constipation: A Review of Systematic Reviews](#)

Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2014 Nov 17.

PMID: 25535635 [Free Books & Documents](#)

# Constipation

DRUG	efficacy	safety	practice implications
<b>Macrogol</b>	likely efficacious	acceptable risk	possibly useful
<b>Lubiprostone</b>	likely efficacious	insufficient evidence	investigational
Nizatidine (Histamine H2-receptor antagonist and a cholinomimetic)	<i>Not Yet Assessed (positive outcome)</i>		
Probiotics and prebiotic fiber	<i>Not Yet Assessed (positive outcome)</i>		

# **Possible Reasons for Weight Loss in Parkinson Disease**

Schapira et al, 2017

Hyposmia, impaired hand–mouth coordination

Difficulty chewing, dysphagia, intestinal hypomotility,

Depression, decreased reward processing of dopaminergic mesolimbic regions

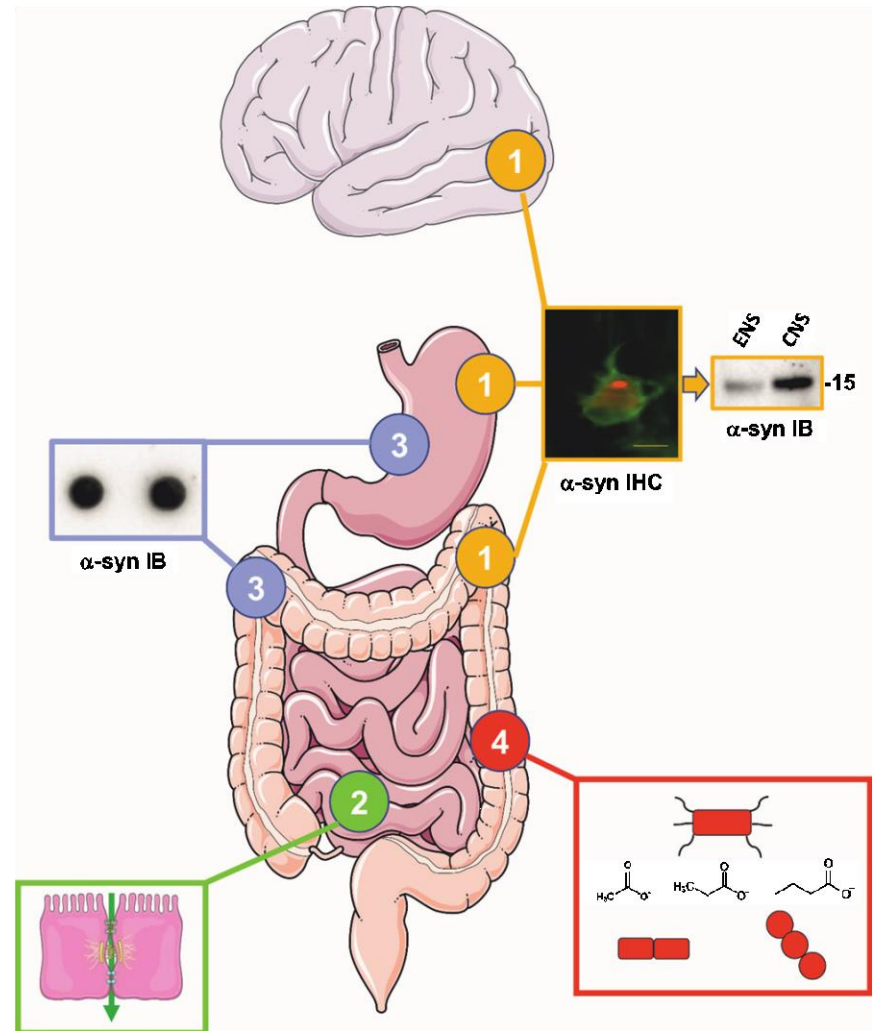
Nausea and anorexia as the side effects of medication

Increased energy requirements

Progression of degenerative process

## 4 Major issues to be addressed for the gut in PD

1. Alpha-synuclein deposits are observed in the ENS of PD patients
2. initial alpha-synuclein aggregation in enteric nerve terminals through extrinsic factors, facilitated by intestinal hyperpermeability.
3. conflicting results. There is therefore a critical need to develop alternative techniques to detect alpha-synuclein aggregates in the gut.
4. Changes of composition of the gut microbiom in PD



*Scheperjans et al, „The gut and PD: hype or hope?“  
J Park Dis 2018*

# Orthostatic hypotension

## <90mmHg systolic BP

### Recommendations active standing

#### Recommendations

- Manual intermittent determination with sphygmomanometer of BP supine and during active standing for 3 minutes is indicated evaluation when OH is suspected
- Continuous beat-to-beat non invasive pressure measurement may be helpful in cases of doubt

class

I

level

B

#### Diagnostic criteria

- **The test is diagnostic when there is a symptomatic fall in systolic BP from a baseline value  $\geq 20$ mmHg or diastolic BP  $\geq 10$ mmHg, or a decrease in systolic BP to  $<90$ mmHg** **I** **C**
- The test should be considered diagnostic when there is an asymptomatic fall in systolic BP from baseline value  $\geq 20$ mmHg or diastolic BP  $\geq 10$ mmHg, or a decrease in systolic BP to  $<90$ mmHg **IIa** **C**

<sup>A</sup>Class of recommendation

<sup>B</sup>Level of evidence

BP=blood pressure,; OH=orthostatic hypotension

Orthostatic hypotension:

1. Systolic BP fall  $\geq 20$ mmHg, or
2. Diastolic BP fall  $\geq 10$ mmHg, or
3. Orthostatic syst. BP  $< 90$ mmHg

*Moya et.al, ESC Syncope guidelines 2009*

# Orthostatic Hypotension

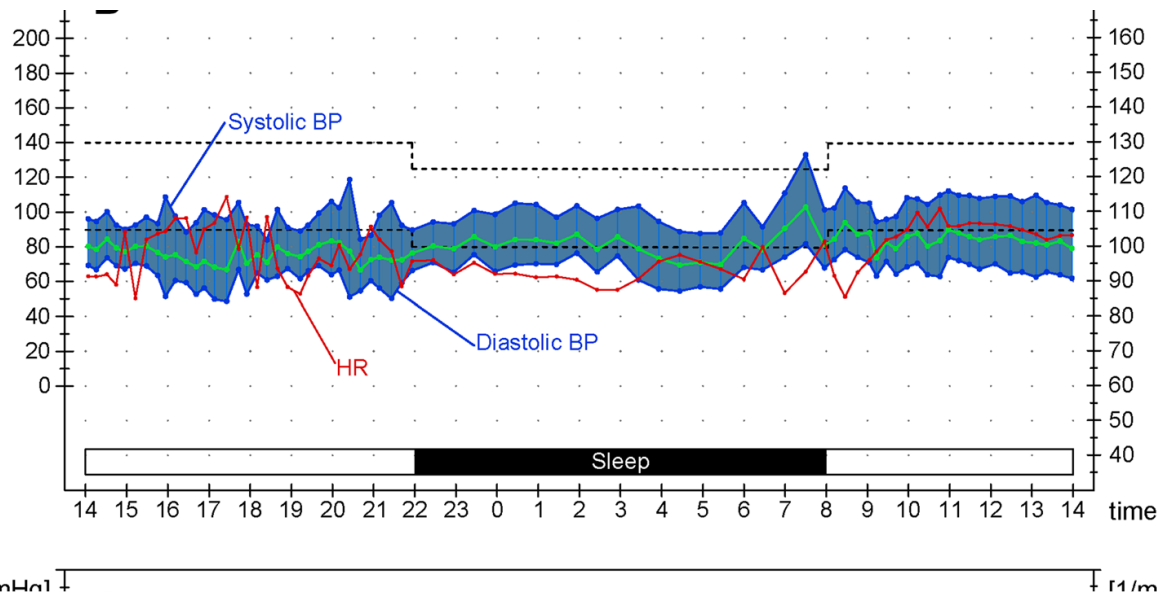
Orthostatic Hypotension Questionnaire Symptom assessment (OHSA)  
Graded on a Likert scale with a minimum of 0 (none) and a maximum of 10

English version

1. Dizziness, lightheadedness, feeling faint, or feeling like you might black out
2. Problems with vision (blurring, seeing spots, tunnel vision, etc.)
3. Weakness
4. Fatigue
5. Trouble concentrating
6. Head/neck discomfort

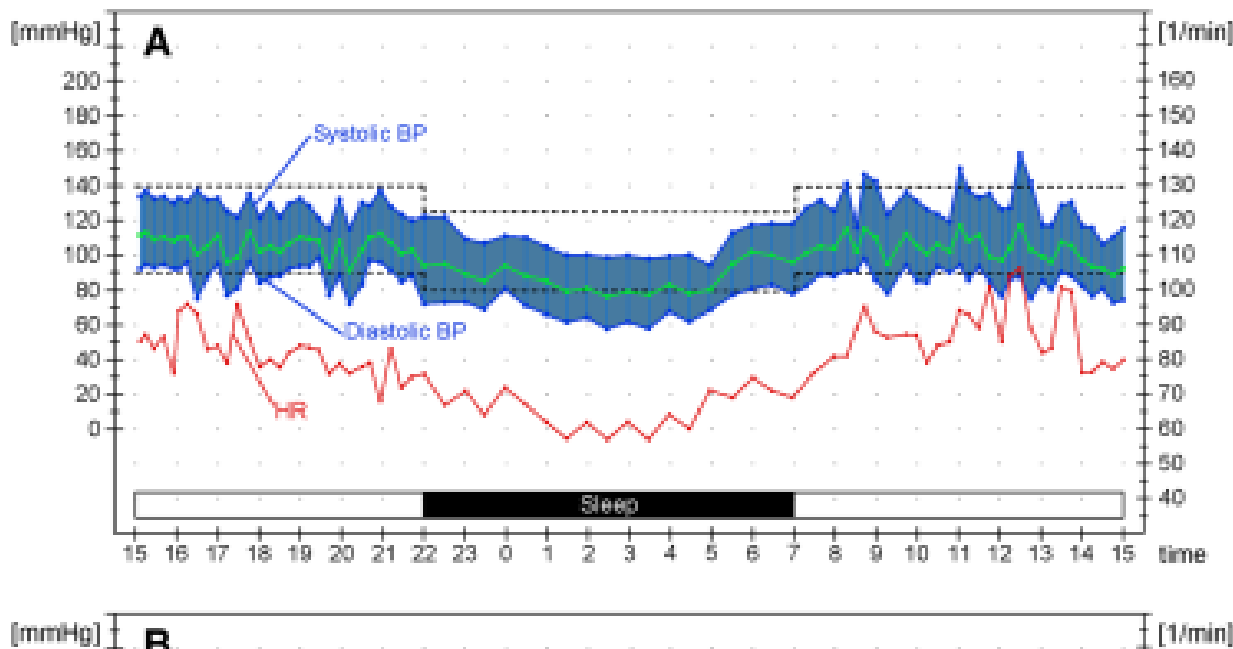
**Definition: Orthostatic hypotension:**

1. Systolic BP fall  $\geq 20\text{mmHg}$ , or
2. Diastolic BP fall  $\geq 10\text{mmHg}$ , or
3. Orthostatic syst. BP  $< 90\text{mmHg}$



**Fig. 1** Nocturnal blood pressure (BP) profiles at 24 h-ambulatory BP monitoring  
**a** Physiological nocturnal dipping profile (mean nocturnal BP falls by  $\geq 10\%$  with respect to daytime BP),

**c** rising profile (mean nocturnal BP increases with respect to daytime BP), in a patient with cardiovascular autonomic failure.  
 Note: severe hypotension occurring in the early morning.





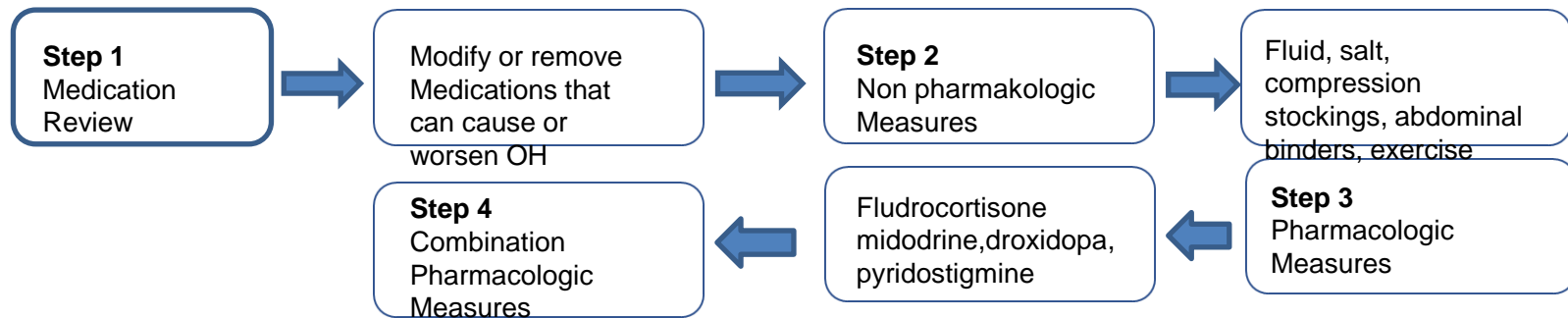
# Orthostatic hypotension

## Stepwise approach

**Table 4** Proposed grading Scale for nOH [27]

Grade	Attributes
1	Infrequent symptoms/unrestricted standing time AND mild OH [20-30 mmHg drop in SBP during supine-to-standing test]
2	≥5 min standing time (but not unrestricted) AND [> 30 mmHg drop in SBP OR moderate impact ADL]
3	<5 min standing time AND [> 30 mmHg drop in SBP OR severe impact on ADL]
4	<1 min standing time AND [> 30 mmHg drop in SBP OR incapacitated]
<ul style="list-style-type: none"> <li>A patient with grade 3 or 4 nOH should be treated by a healthcare provider with experience in managing nOH</li> </ul>	

*SBP* systolic blood pressure, *ADL* activities of daily living



# Orthostatic Hypotension

DRUG	efficacy	safety	practice implications
<b>Fludrocortisone</b>	insufficient evidence	insufficient evidence	investigational
<b>Domperidone</b>	insufficient evidence	insufficient evidence	investigational
<b>Midodrine<sup>1</sup></b>	insufficient evidence	insufficient evidence	investigational
<b>Dihydroergotamine</b>	insufficient evidence	insufficient evidence	investigational
<b>Etilefrine hydrochloride</b>	insufficient evidence	insufficient evidence	investigational
<b>Indomethacine</b>	insufficient evidence	insufficient evidence	investigational
<b>Yohimbine</b>	insufficient evidence	insufficient evidence	investigational
<b>L. Threo-DOPS<sup>2</sup></b>	insufficient evidence#	insufficient evidence	investigational

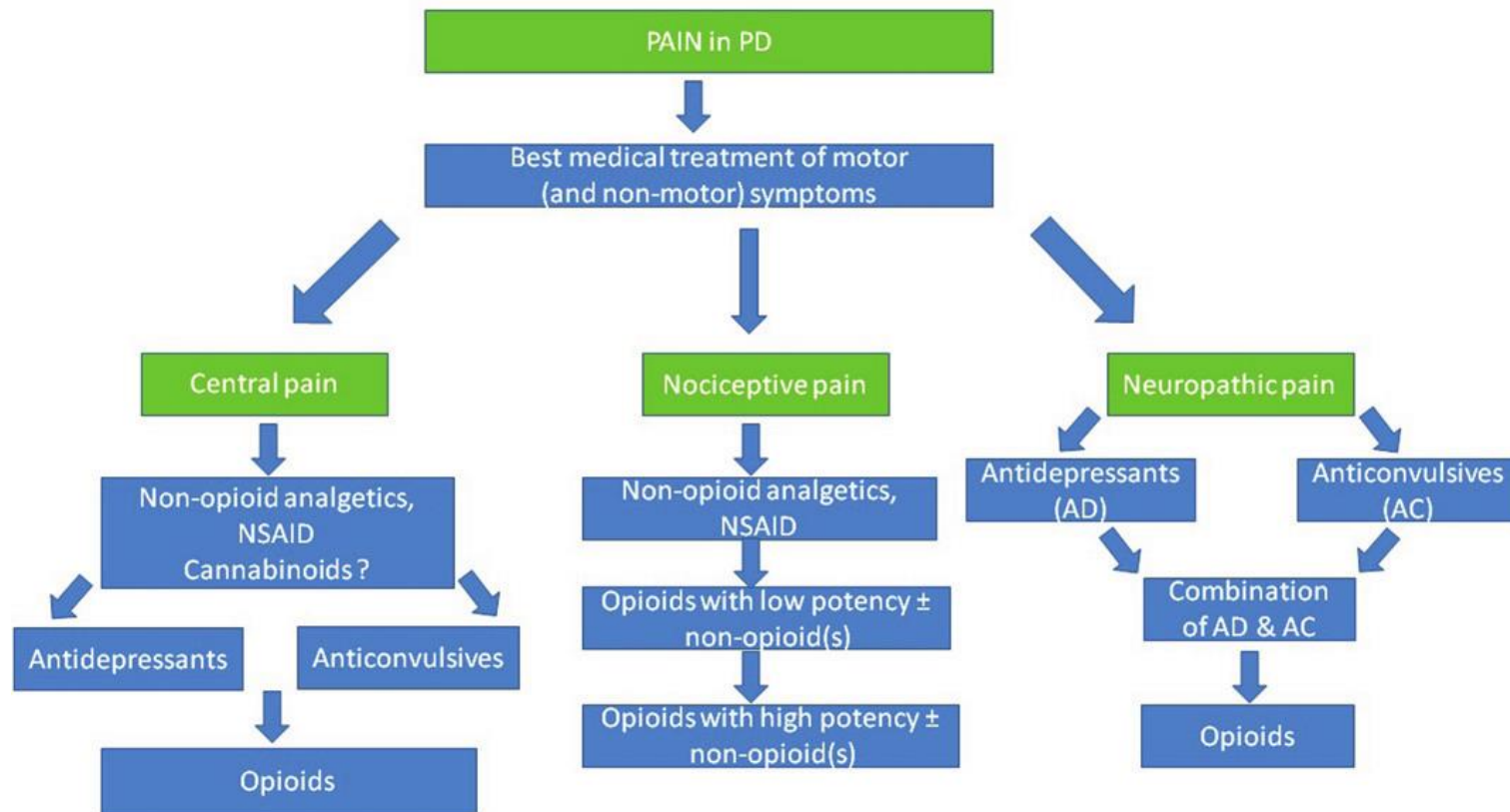
Seppi et al, EBM Recommendations MovDisord 2019

<sup>1</sup> Ongoing: **Treatment of Orthostatic Intolerance in Patients With Parkinson's Disease Using Midodrine** NCT02365012 ; 2 weeks

<sup>2</sup> Ongoing **Sustained Effect of Droxidopa in Symptomatic Neurogenic Orthostatic Hypotension (RESTORE)** NCT02586623 ; 36 wk duration

# 2 weeks duration only

# Management of Pain in PD



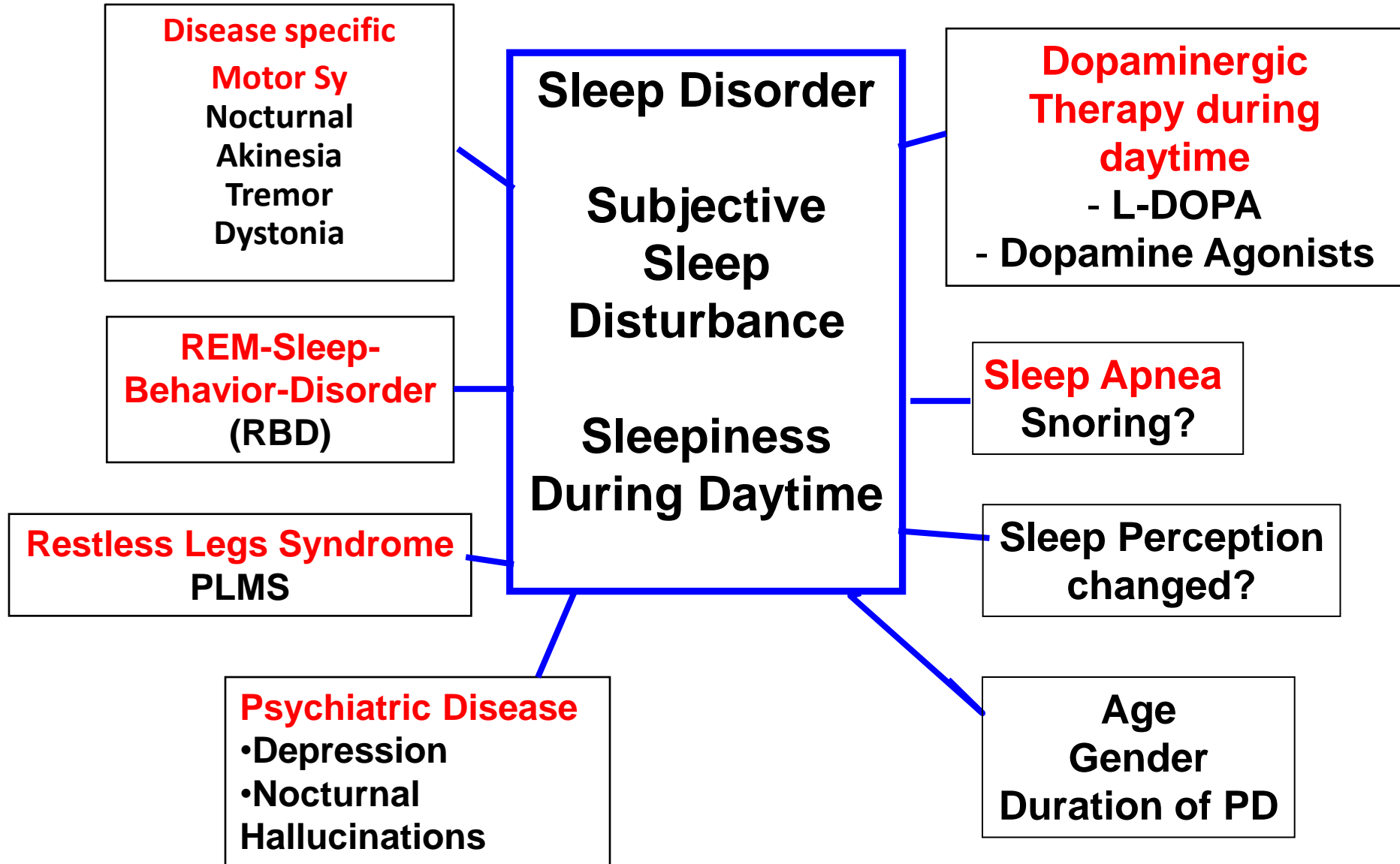
Modified according to WHO three-steps pain treatment scheme

Table 1

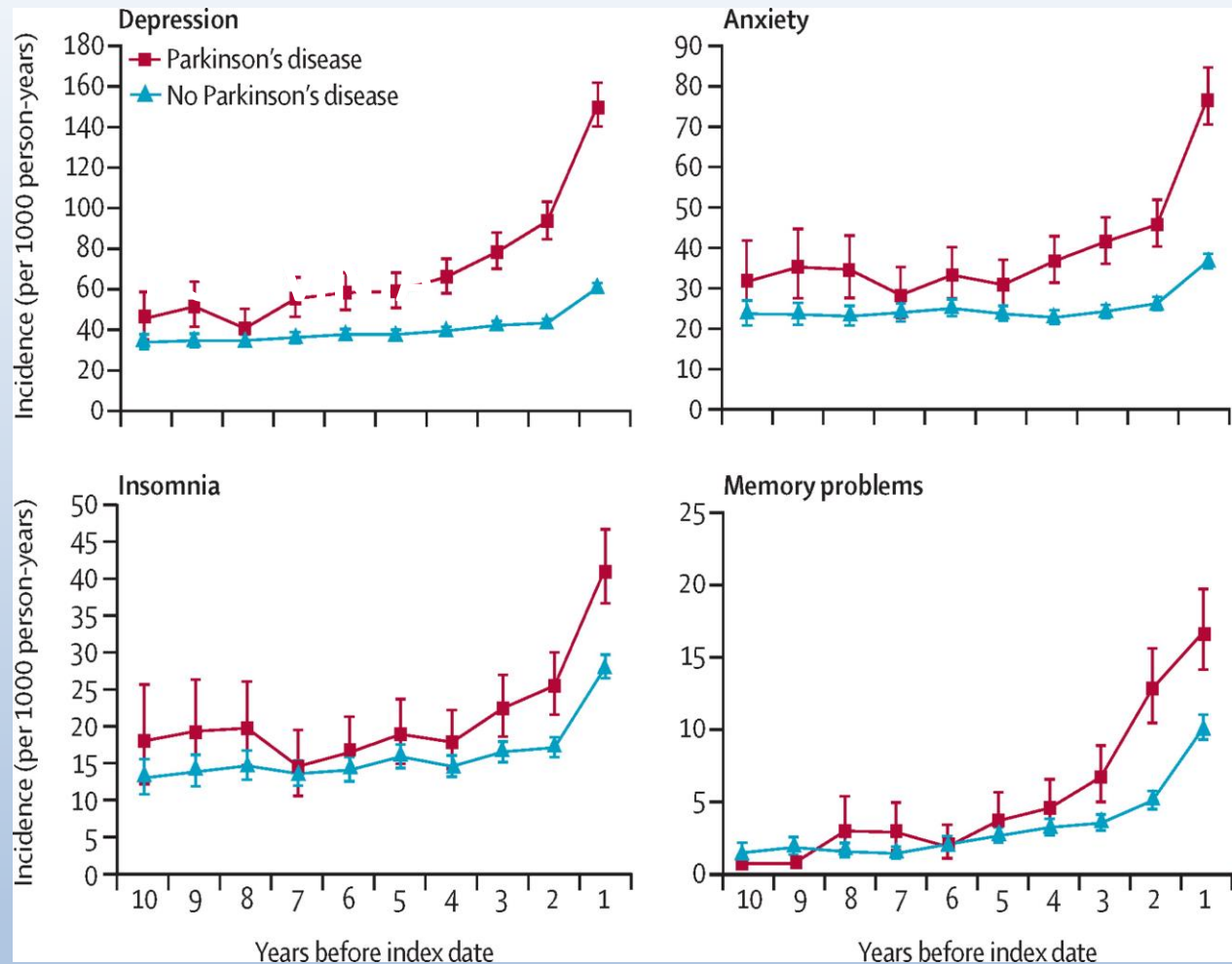
Shows larger randomized controlled trials (RCT) of antiparkinsonian drugs and opioids assessing the effect on pain in PD patients

Treatment	Study design and applied scales for pain	Patients & Methods	Results Means with (SD), (range) or (CI)	References
Pramipexole	RCT, VAS-P	138 vs. 148 controls	–3,3 (–8.9 to 0.3) vs. –2.4 (–8.9 to 2.6) Group comparison –1.3 (–3.3 to 0.8) $p=0.19$	Barone et al. 2010 [96]
Safinamide	RCT ( <i>post hoc</i> ), PDQ-39	440 vs. 438 controls	reduction of the number of concomitant pain treatments of 23.6% [5% confidence interval (CI): 41.1%, 1.0%; $p=0.0421$ ] PDQ-39: item 37 (–0.26 vs. –0.07; $p=0.0009$ ), item 38 (0.19 vs. 0.1; $p=0.1585$ ), item 39 (–0.18 vs. –0.03; $p=0.0060$ )	Cattaneo et al. 2017 [63]
Entacapone	RCT, PDQ-39	281 vs. 274 controls	(0.04) vs. 0.1 (0.04); $p=0.9$ . SMD = 1.81, $p<0.0001$	Olanow et al. [64]
Oxycodone	RCT, KPPS	88 vs. 106 controls	5.0 (95% CI 4.5 to 5.5) versus 5.6 (5.1 to 6.0). Difference –0.6, 95% CI –1.3 to 0.0; $p=0.058$ .	Trenkwalder et al. [78]
Pardoprunox	RCT ( <i>post-hoc</i> ), VAS-P	140 vs. 133 controls	During OFF time –2.2 (2.7) vs. –1.0 (2.7), no $p$ -values given During ON time –2.3 (2.8) vs. –0.5 (3.0), no $p$ -values given	Rascol et al. [65]
Rotigotine	RCT, Likert pain scale	178 vs. 88 controls	–0.9 (SD 2.2) vs. –0.1 (SD 2.3), $p=0.004$ Difference –0.77 [–1.28 to –0.25]	Trenkwalder et al. [72]
	RCT ( <i>post-hoc</i> ), Likert pain scale	178 vs. 88 controls	‘any pain’: –0.88 [95% CI: –1.56, –0.19], $p=0.013$ ‘moderate-to-severe’ pain: (–1.38 [–2.44, –0.31], $p=0.012$ UPDRS III or PDSS-2 responders showed greater improvement in pain than non-responders	Kassubek et al. [73]

# Sleep Disturbance in Parkinson Disease - contributing factors



- Early Sleep Disorders in Pre-motor Parkinson Disease:
- insomnia complaints start about 4 years prior to diagnosis



*Schrag et al, Lancet Neurol 2015*

[The Lancet Neurology 2015 14, 57-64DOI: \(10.1016/S1474-4422\(14\)70287-X\)](https://doi.org/10.1016/S1474-4422(14)70287-X)

# Insomnia

DRUG	efficacy	safety	practice implications
Controlled-release levodopa/carbidopa	Insufficient evidence	Investigational	investigational
Eszopiclone	insufficient evidence	acceptable risk	investigational
Melatonin (3-5 and 50mg)	insufficient evidence	acceptable risk	possibly useful


Seppi et al, EBM Recommendations MovDisord 2019

# Developing Sleep Measures in PD: PDSS-2

**The Parkinson's Disease Sleep Scale:** a new instrument for assessing sleep and nocturnal disability in Parkinson's disease: 15 questions, specific for nocturnal disturbances in PD patients (2002, revised: 2011)

Establishing sleep for the first time as  
co-primary outcome measure in a PD trial

PARKINSON'S DISEASE SLEEP



## Parkinson's Disease Sleep Scale (PDSS-2)

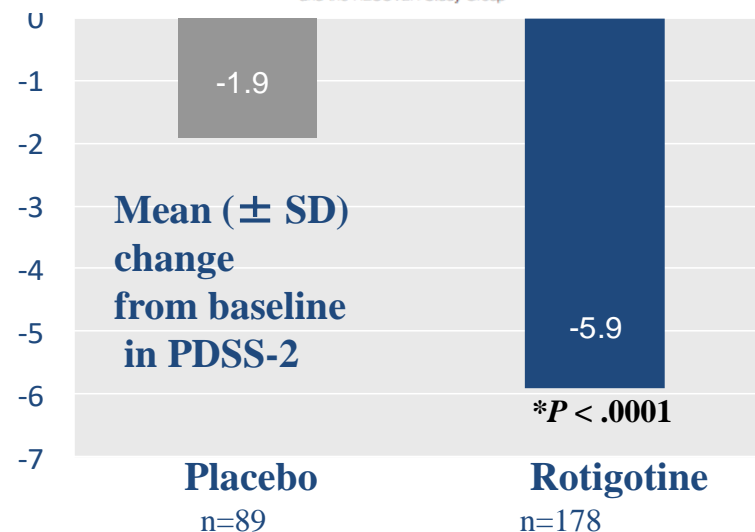
Please rate the severity of the following based on your experiences during the past week (7 days). Please make a cross in the answer box

	Very often (This means 6 to 7 days a week)	Often (This means 4 to 5 days a week)	Sometimes (This means 2 to 3 days a week)	Occasionally (This means 1 day a week)	Never
1) Overall, did you sleep well during the last week?	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
2) Did you have difficulty falling asleep each night?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0

## RESEARCH ARTICLE

### Rotigotine Effects on Early Morning Motor Function and Sleep in Parkinson's Disease: A Double-Blind, Randomized, Placebo-Controlled Study (RECOVER)

Claudia Trenkwalder, MD,<sup>1\*</sup> Bryan Kies, FCPNeuro (SA),<sup>2</sup> Monika Rudzinska, MD,<sup>3</sup> Jennifer Fine, FCP (SA) Neurology,<sup>4</sup> Janos Niki, MD,<sup>5</sup> Krystyna Honczarenko, MD,<sup>6</sup> Peter Dioszeghy, MD,<sup>7</sup> Dennis Hill, MD,<sup>8</sup> Tim Anderson, FRACP,<sup>9</sup> Vilho Myllyla, MD,<sup>10</sup> Jan Kassubek, MD,<sup>11</sup> Malcolm Steiger, FRCP,<sup>12</sup> Marco Zucconi, MD,<sup>13</sup> Eduardo Tolosa, MD,<sup>14</sup> Werner Poewe, MD,<sup>15</sup> Erwin Surmann, MSc,<sup>16</sup> John Whitesides, PhD,<sup>17</sup> Babek Boroojerdi, MD,<sup>18</sup> Kallol Ray Chaudhuri, DSc<sup>18</sup> and the RECOVER Study Group



Chaudhuri et al, JNNP 2002; Trenkwalder et al, MovDisord 2011 (PDSS-2); Trenkwalder et al Mov Disord 2011 (RECOVER) Högl et al, Mov Disord 2010;



# *Diagnostic Criteria for REM Sleep Behavior Disorder*

- Repeated episodes of sleep related vocalization and/or complex motor behaviors.<sup>1,2</sup>
- These behaviors are documented by polysomnography to occur during REM sleep or, *based on clinical history of dream enactment, are presumed to occur during REM sleep.*
- Polysomnographic recording demonstrates REM sleep without atonia (RWA).<sup>3</sup>
- The disturbance is not better explained by another sleep disorder, mental disorder, medication, or substance use.<sup>4</sup>

ICSD (intern. Classification of Sleep Disorders) 2014

# Nocturnal Akinesia: a major complaint in PD

Review article

## Getting a good night sleep? The importance of recognizing and treating nocturnal hypokinesia in Parkinson's disease

Roongroj Bhidayasiri <sup>a, b, \*</sup>, Claudia Trenkwalder <sup>c</sup>



**Fig. 1.** Serial still images demonstrating a common strategy that Parkinson's disease patients use to turn and get out of bed. A–B: Turning the head and bringing the arm across the body with the attempt to swing the leg over; C–D: Holding to the side of the bed in order to move the body to the edge. At the same time, the trunk is laterally flexed with weight bearing at the elbow; E: The patient attempted to sit up by pushing herself through the elbow on one side and pulling the bed sheet with the other hand; F: The patient successfully sat up on the edge of the bed.

# Sleep Disorders in PD:

## Treatment Options in RBD, RLS, Sleep Apnoe

- RBD:
  - Clonazepam 0.5-1 (2)mg
  - Melatonin 2-6 (10) mg
  - No efficacy of DA
- RLS:
  - Long-acting dopamine agonists such as rotigotine (EBM)
  - Opioids (off-label)
  - No Benzodiazepine
- Apnoe:
  - obstructiv, if yes, avoid lying on the back
  - CPAP-Therapy

Expert Opinion

# Summary

- Non-motor symptoms in PD occur early in the disease, even as prodromal features and biomarkers
- Individual variability of symptoms is large
- Specific assessment and recognition is necessary to improve QoL of patients
- Non-motor symptoms progress during the course of PD and may occur as severe non-motor fluctuations

# Thank you to the leaders of the African Section

