Management of Sleep Disorders in Parkinsonian Syndromes

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Disclosures

- Research support: National Institutes of Health, USA

- Consultant: Retrophin, Jazz, Acorda, Wilson's Therapeutics

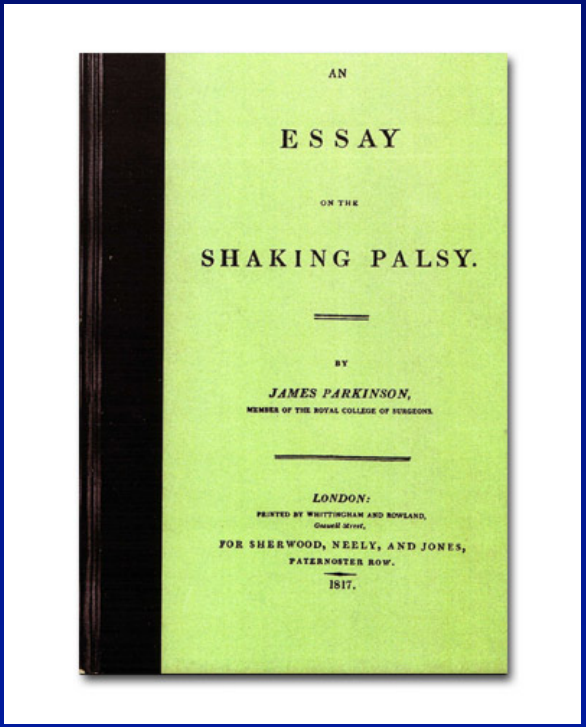
Learning Objectives

- To understand the epidemiology and etiology of sleep disorders in parkinsonism
- To discuss diagnostic approaches for sleep disorders in parkinsonism
- To discuss treatment approaches for sleep disorders in parkinsonism

SLEEP IN PARKINSON'S DISEASE

"In this stage, the sleep becomes much disturbed. The tremulous motion of the limbs occur during sleep, and augment until they awaken the patients, and frequently with much agitation and alarm."

"…when exhausted nature seizes a small portion of sleep, the motion becomes so violent as not only to shake the bed-hangings, but even the floor and sashes of the room."


AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:

PRINTED BY WHITTINGHAM AND ROWLAND,

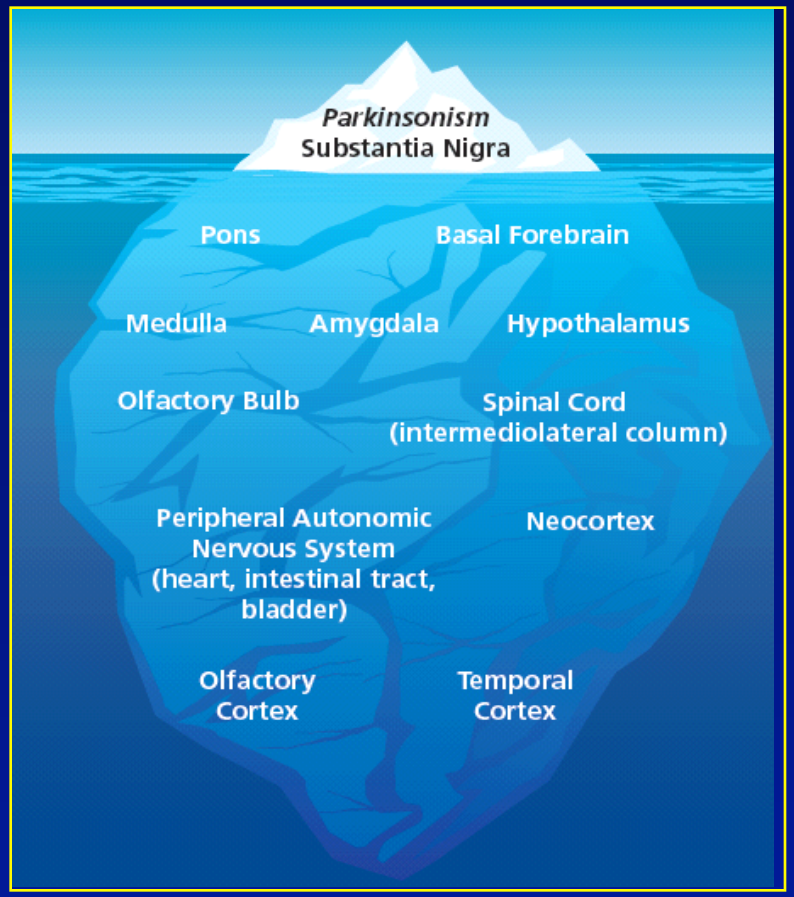
Goswell Street,

FOR SHERWOOD, NEELY, AND JONES,

PATERNOSTER ROW.

1817.

James Parkinson 1817



Adapted from Langston, 2006

Study of sleep dysfunction in PD
- challenges -

- Under-diagnosed and under-reported problem
- Heterogeneous population
- Etiology of sleep dysfunction in PD
  - Co-existent primary sleep disorders
  - Primary neurodegenerative process of PD
  - Influence of PD symptoms / signs / medications on sleep and alertness

Influence of clinical and demographic variables on quality of life in patients with Parkinson's disease

Karen Herlofson Karlsen, Jan P Larsen, Elise Tandberg, John G Mæland

J Neurol Neurosurg Psychiatry 1999;66:431–435

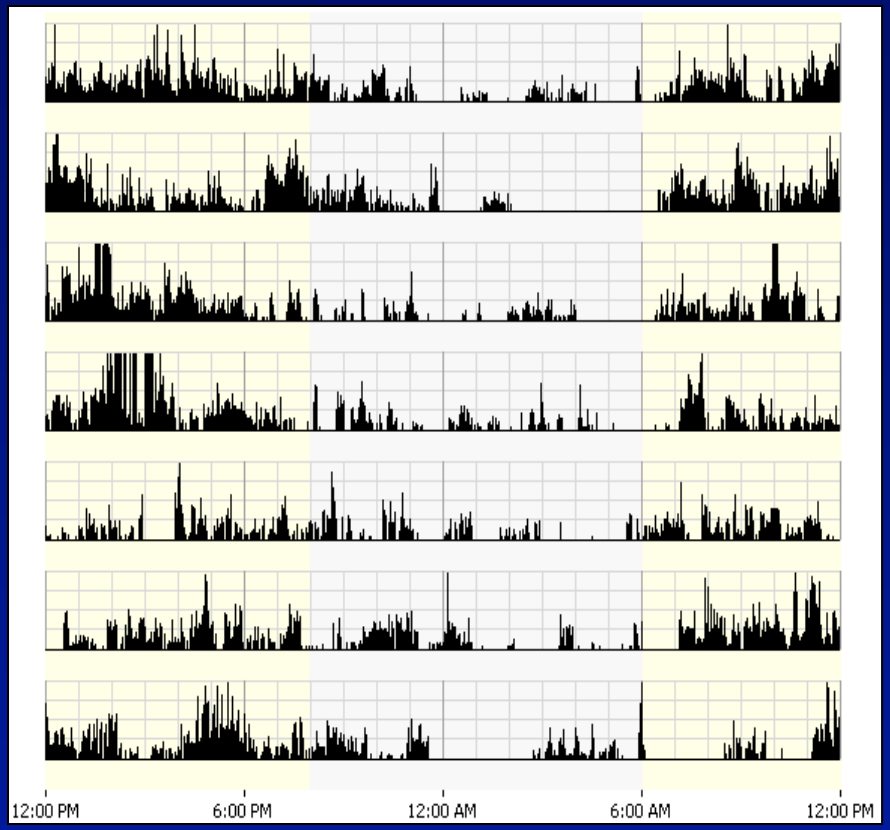
	Emotional reactions		*Energy*		*Pain*		*Physical mobility*		*Sleep*		*Social isolation*		*Total NHP*	
	Mean (SD)	% *With problems*	*Mean (SD)*	% *With problems*	*Mean (SD)*	% *With problems*	*Mean (SD)*	% *With problems*	*Mean (SD)*	% *With problems*	*Mean (SD)*	% *With problems*	*Mean (SD)*	% *With problems*
Parkinson's disease n=233	13.1 (17.0)	53	26.3 (33.3)	46	22.0 (24.6)	67	41.2 (31.7)	80	27.2 (28.4)	73	20.4 (23.6)	53	137.1 (97.3)	93
Healthy elderly n=100	6.3 (13.5)	27	10.0 (21.2)	22	13.5 (22.5)	9	11.1 (16.2)	41	19.4 (28.4)	49	10.8 (17.6)	34	67.6 (83.7)	76

Sleep in Parkinson's disease

- Excessive daytime sleepiness (EDS)
- Nocturnal sleep disturbances
- Prevalence – varies widely
    - Definition of sleep disturbance
    - Method of ascertainment
    - Study population
- As many as 80-90% of PD patients have some disturbance of sleep patterns

Nocturnal sleep disturbances in PD

- Insomnia
- Sleep disordered breathing
- RBD
- RLS / PLM
- Other causes
    - Recurrent symptoms of PD, depression, nocturia, pain etc.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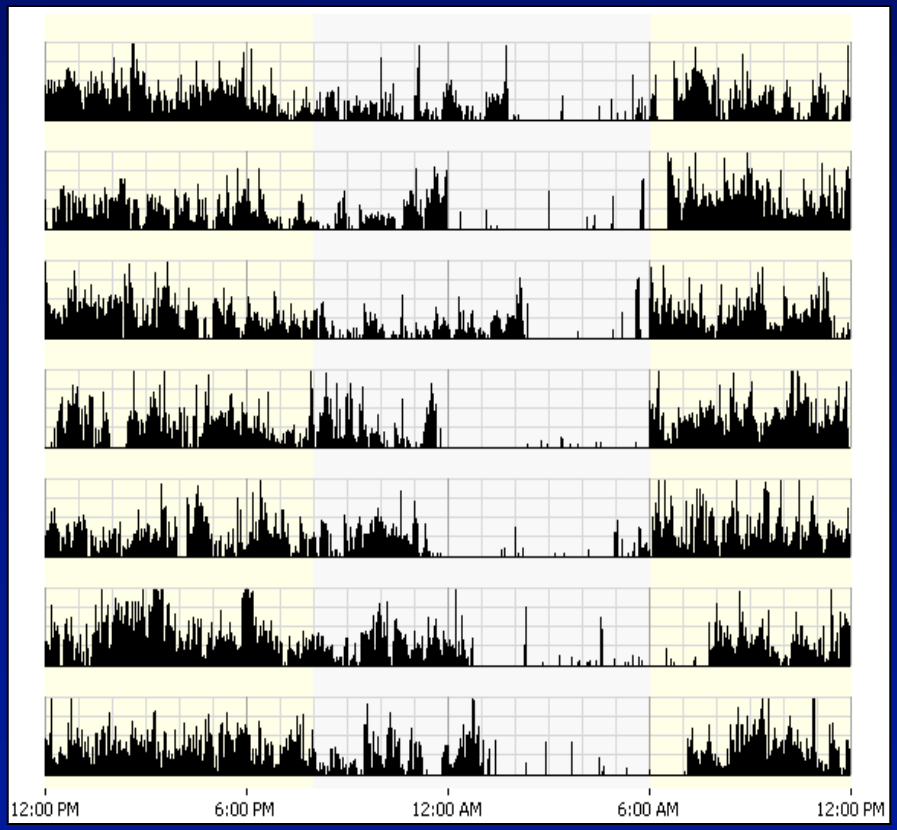
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Insomnia
- management -

- No Selegiline or Amantadine late in the day
- Minimize fluid intake before bedtime
- Diuretics earlier in the day
- Bedside commode
- Anticholinergics for nocturia
- Management of depression / psychiatric co-morbidities
- Identification of co-existent sleep disorders

The *Movement* Disorder Society Evidence-Based Medicine Review Update: Treatments for the Non-Motor Symptoms of Parkinson's Disease

Klaus Seppi, MD,[1*] Daniel Weintraub, MD,[2] Miguel Coelho, MD,[3] Santiago Perez-Lloret, MD, PhD,[4] Susan H. Fox, MRCP (UK), PhD,[5] Regina Katzenschlager, MD,[6] Eva-Maria Hametner, MD,[1] Werner Poewe, MD,[1] Olivier Rascol, MD, PhD,[4] Christopher G. Goetz, MD,[7] and Cristina Sampaio, MD, PhD[8*]

Movement Disorders, Vol. 26, No. S3, 2011

TABLE 9. Conclusions on drugs to treat disorders of sleep and wakefulness in PD

	Efficacy	Safety	Practice implications
Insomnia			
Controlled-release formulation of levodopa/carbidopa	*Insufficient evidence*	*Acceptable risk without specialized monitoring*	*Investigational*
Pergolide	*Insufficient evidence*	*Acceptable risk with specialized monitoring*	*Not useful*
Eszopiclone	*Insufficient evidence*	*Acceptable risk without specialized monitoring*	*Investigational*
Melatonin 3–5 mg	*Insufficient evidence*	*Acceptable risk without specialized monitoring*	*Investigational*
Melatonin 50 mg	*Insufficient evidence*	*Insufficient evidence*	*Investigational*
Excessive daytime somnolence and the sudden onset of sleep			
Modafinil	*Insufficient evidence*	*Insufficient evidence*	*Investigational*

- Eszopiclone – *Menza et al. Mov Disord 2010*
- Melatonin – *Medeiros et al. J Neurol 2007*
- Sodium oxybate – *Ondo et al. Arch Neurol 2008*
- Rotigotine – *Trenkwalder at al. Mov Disord 2011*

A controlled trial of antidepressants in patients with Parkinson disease and depression

Menza et al. *Neurology 2009*

Depression in Parkinson's disease: Symptom Improvement and Residual Symptoms Following Acute Pharmacological Management

Dobkin et al. *Am J Geriatr Psychiatry 2011*

A randomized, double-blind, placebo-controlled trial of antidepressants in Parkinson disease

Richard et al. *Neurology 2012*

RBD in PD

RBD

Diagnostic Criteria

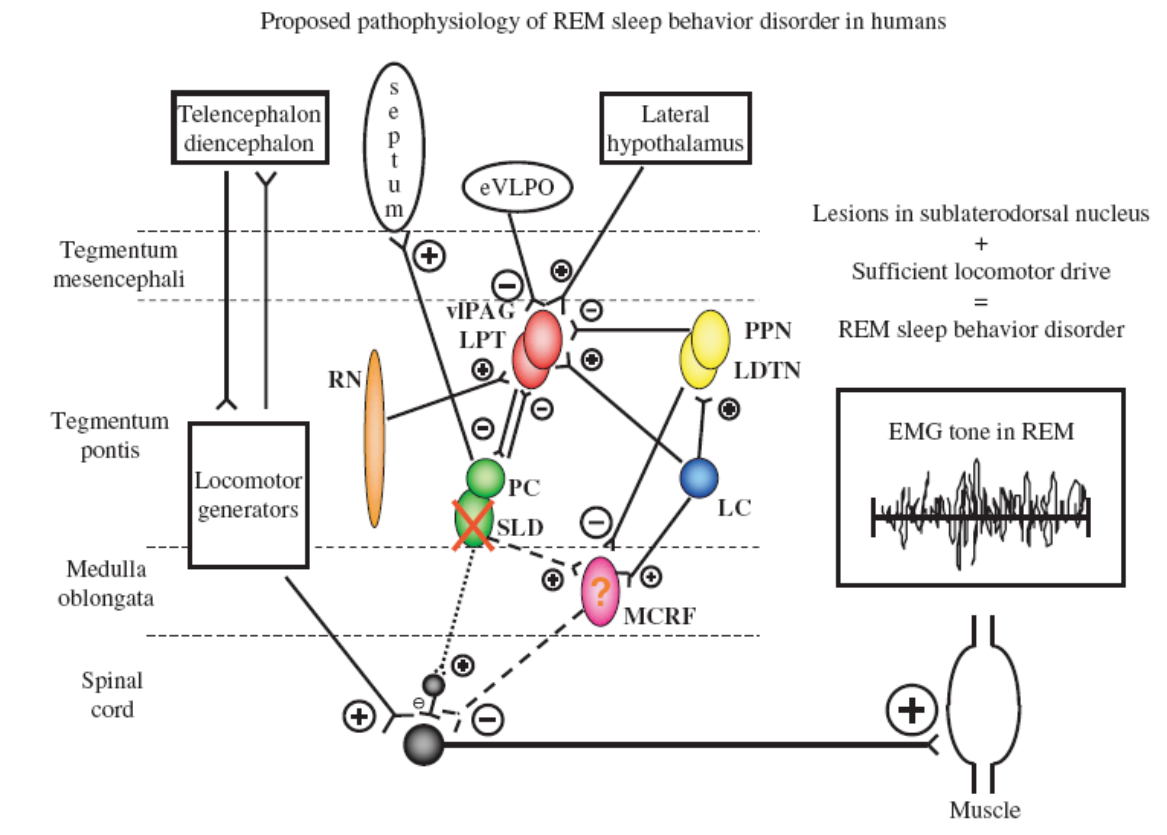
A. Repeated episodes of sleep related vocalization and/or complex motor behaviors.

B. 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.

C. Polysomnographic recording demonstrates REM sleep without atonia (RWA)

D. The disturbance is not better explained by another sleep disorder, mental disorder, medication, or substance use.

American Academy of Sleep Medicine,
International Classification of Sleep Disorders, 3rd ed., 2014



B. F. Boeve *et al.*
Brain (2007), **130**, 2770–2788

	Prevalence of RBD and REM sleep without atonia
Synucleinopathies	
Parkinson's disease	15–34%[48,85,86] 58% have REM sleep without atonia[48]
Multiple-system atrophy	Nearly all cases[92,94]
Pure autonomic failure	Some cases[96]
Dementia with Lewy bodies	Very common[5,59,61,84,97]
Parkinsonism with parkin mutations	Several cases[87]
Tauopathies	
Progressive supranuclear palsy	Few cases[5,11,102] Several have REM sleep without atonia[9,35,36,100–102]
Alzheimer's disease	Rare[104] Few cases have REM sleep without atonia[104]
Corticobasal degeneration	Few have REM sleep without atonia[105–107] One developed RBD[107]
Pick's disease	None
Pallidopontonigral degeneration	None[108]

Table: **The frequency of RBD in neurodegenerative disorders**

Jean-François Gagnon, Ronald B Postuma, Stéphanie Mazza, Julien Doyon, Jacques Montplaisir
Lancet Neurol 2006; 5: 424–32

Delayed emergence of a parkinsonian disorder in 38% of 29 older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder

Carlos H. Schenck, MD; Scott R. Bundlie, MD; and Mark W. Mahowald, MD

Neurology 1996 46:388-93.

29 iRBD aged > 50 after 12.7±7.3 years ⟶ PS 38% (1996) ⟶ 81%

Rapid-eye-movement sleep behaviour disorder as an early marker for a neurodegenerative disorder: a descriptive study

Alex Iranzo, José Luis Molinuevo, Joan Santamaría, Mónica Serradell, María José Martí, Francesc Valldeoriola, Eduard Tolosa

Lancet Neurol 2006 5: 572–77

44 RBD after 11.5 years: 45% PD/DLB/MSA/MCI

ARTICLES

Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behavior disorder

Neurology 2009 72:1296–1300

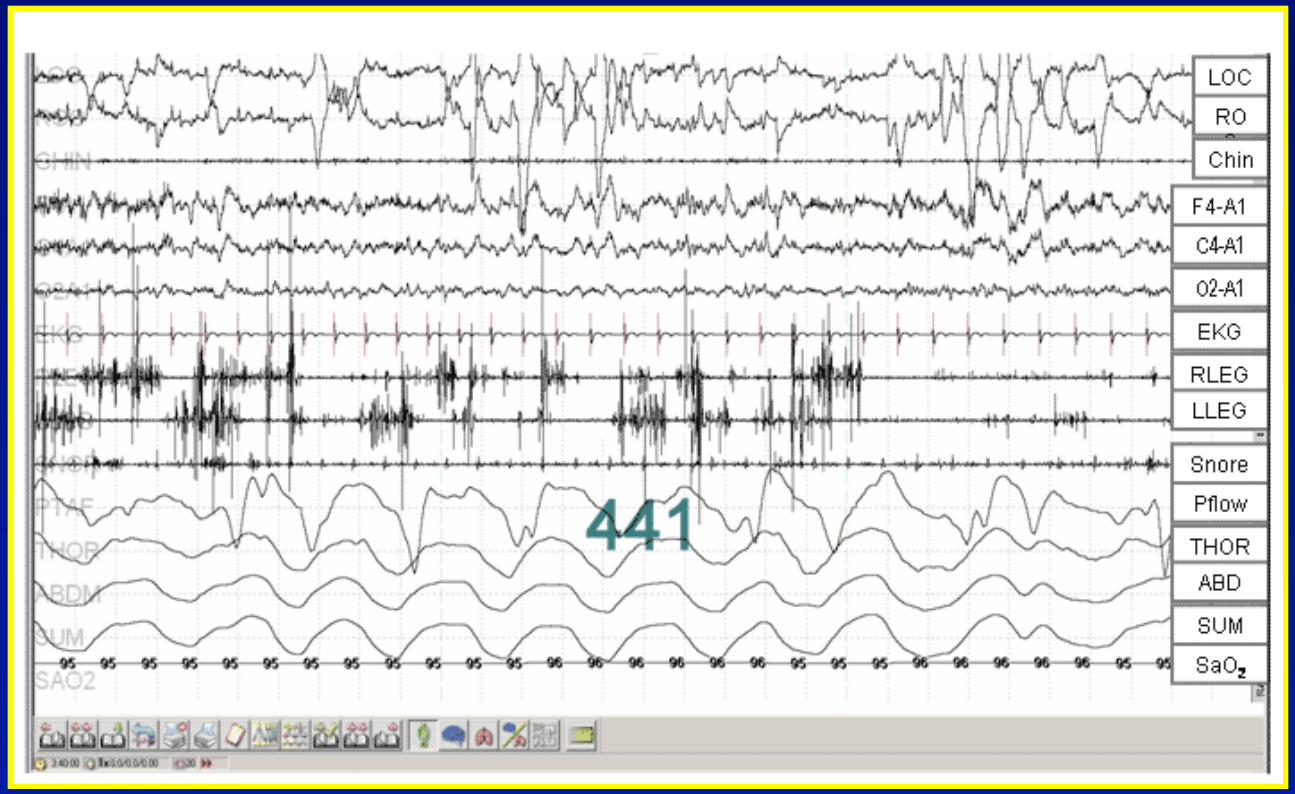
R.B. Postuma, MD: J.F. Gagnon, PhD;M. Vendette, BSc; M.L. Fantini, MD; J. Massicotte-Marquez, PhD; J. Montplaisir, MD,PhD

93 Patients

- 5-Year Risk 17.7%
- 10-Year Risk 40.6%
- 12-Year Risk 52.4% for Parkinson Syndrome or MCI

RBD – diagnosis

Polysomnography



Proposed cut-off values for RBD detection

Authors	Investigated EMG measures	Proposed Cut-off scores	Investigated muscles	Epoch duration	Scoring system
Ferri 2008, 2010	REM atonia index	0.8	chin	N/A	semiautomatic
Montplaisir 2010	Phasic EMG activity Tonic EMG activity Leg movements	15% 30 % 24	chin chin tibialis anterior	2 20 N/A	manual scoring
SINBAR (Frauscher 2012)*	Any EMG activity Phasic EMG activity SINBAR EMG activity Tonic EMG activity Any EMG activity Phasic EMG activity SINBAR EMG activity	18 % 16 % 32 % 10 % 15 % 11 % 27 %	chin chin chin + FDS chin chin chin chin + FDS	3 3 3 30 30 30 30	manual scoring

Frauscher & Högl, in Sleep and Circadian Rhythms in Parkinson's Disease. Videnovic, Högl (eds.), Springer 2015

RBD – diagnosis

Questionnaires

Author	Questionnaire	Characteristics	Sensitivity	Specificity
Stiasny-Kolster et al., Mov Disord (2007)	RBD Screening Questionnaire	- 10 items with 13 questions - yes / no answers - max score =13	96%	56%
Li et al., Sleep Med(2010)	RBDQ-HK	- 13 questions - assesses for life time and recent (1year) occurrence	82%	87%
Boeve et al., Sleep Med (2011)	Mayo Sleep Questionnaire	- contains an introductory question about RBD, followed by 5 subsequent questions about RBD symptoms	98%	74%
Postuma et al., Mov Disord (2012)	Single-Question Screen for RBD	- single question	94%	87%
Frauscher et al., Mov Disord (2012)	Innsbruck RBD Inventory	- 5 questions - yes / no / do not know answers	91%	86%
Frauscher et al., Mov Disord (2012)	RBD summary question (from Innsbruck RBD Inventory)	- single question	74%	93%

Frauscher & Högl, in Sleep and Circadian Rhythms in Parkinson's Disease. Videnovic, Högl (eds.), Springer 2015

RBD – treatment

Protective measures

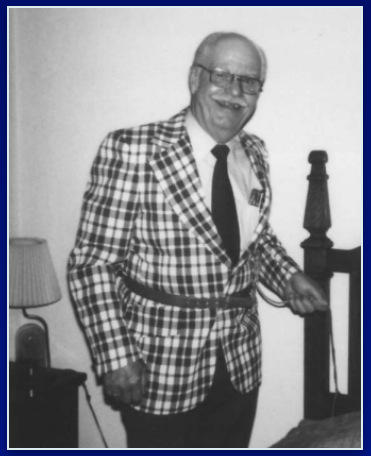


TABLE 3. Therapy of REM sleep behavior disorder

Drug (dose)	Level of evidence	Benefit	Side effect
Melatonin (3–15 mg)	2: One double-blind placebo-controlled study, small groups ($n < 50$)[87,88]	82% of positive responders. Reduction of phasic and tonic muscle activity in PSG.	Rare: morning headache, morning sleepiness, hallucinations.
Clonazepam (0.5–2 mg)	4: Open studies, large groups ($n > 300$)[89–91]	73% with complete control of RBD, 17% with partial control, 10% of nonresponders	In 58% of patients, residual sleepiness, confusion, memory dysfunction, impotence, falls, and sleep apnea.
Zopiclone (3.75–7 mg)	4: Open study, small group ($n = 11$)	73% of responders when used alone ($n = 9$) or in combination ($n = 2$)	Rash ($n = 1$), nausea ($n = 1$)
Rivastigmine (4.5–6 mg)	4: Open studies in patients with DLB, small group ($n = 10$)	100% of responders (little data)	No information
Donepezil (10–15 mg)	4: Open studies in patients with DLB, small group ($n = 6$)	66% of responders (little data)	No information
Pramipexole (0.5–1.5 mg)	2: One double-blind placebo-controlled study ($n = 11$)[9,93] 4: Open studies ($n = 29$)	Open series: 45% of responders Double-blind study in PD: no benefit	Hallucinations and delusions in patients with DLB.

Arnulf, Mov Dis, 2012

RLS and PD

Similarities

- dramatic response to dopaminergic agents
- aggravated by dopaminergic antagonists
- associated with PLMS

Differences

PD
- neuronal loss
- Lewy bodies
- Increased iron deposition in the SNc

RLS
- absence of neuronal loss
- absence of Lewy bodies
- depleted iron stores in dopaminergic areas

RLS and PD

Table 2. Prevalence of restless legs syndrome in Parkinson's disease.

Study	Design	Methods	Subjects (n)		Prevalence (%)		Comments	Ref.
			PD	Controls	PD	Controls		
Nomura *et al.* (2006)	Case–control	PSQI IRLSSG criteria	165	131	12	2	PSQI score was higher in PD/RLS patients compared with PD patients without RLS and controls Higher prevalence of RLS in Japanese than in Caucasians	[67]
Braga-Neto *et al.* (2004)	Cohort	Questionnaire ESS	86	NA	50	NA	RLS was investigated with a single question	[64]
Krishnan *et al.* (2003)	Case–control	IRLSSG criteria ESS	126	128	8	1	Depression was more prevalent among PD/RLS patients Lower ferritin levels in PD/RLS patients	[65]
Kumar *et al.* (2002)	Case–control	Sleep questionnaire	149	115	14	1	RLS was investigated with a single question	[66]
Ondo *et al.* (2002)	Cohort	Survey Interview IRLSSG criteria ESS	303	NA	21	NA	Lower ferritin levels in PD/RLS patients	[68]
Tan *et al.* (2002)	Cohort	IRLSSG criteria	125	NA	0	NA	RLS prevalence in PD was similar to general population	[69]
Lang *et al.* (1987)	Cohort	Survey	100	NA	17	NA	RLS prevalence in PD was similar to general population	[130]

ESS: Epworth Sleepiness Scale; IRLSSG: International Restless Legs Syndrome Study Group; NA: Not applicable; PD: Parkinson's disease; PSQI: Pittsburg Sleep Quality Index; RLS: Restless legs syndrome.

Videnovic, 2007

RLS and PD

- No prospective studies of RLS cohorts have assessed the risk for subsequent development of PD

- Confounding factors
    - Dopaminergic treatment
    - Ferritin levels
    - Sensory symptoms of PD / lower limb restlessness with motor fluctuations (akathisia, severe off states, inner tremor, dystonic postures)

RLS and PD
- treatment -

- Dopaminergic medications
- Benzodiazepines
- Anticonvulsants
- Opioids

Sleep disordered breathing and PD

- Initial reports in postencephalitic parkinsonism
- Early studies reported higher prevalence of SDB in PD compared with the general population
- Epidemiological data are somewhat limited
  - Affects up to 50%
  - In 20% moderate to severe OSA
- Obstructive, central, and mixed apneas may be equally represented in PD
- PD patients with OSA have normal BMI
- No clear relationship between OSA and disease duration, severity, and medication regimen

Arnulf et al, 2002, Chotinaiwattarakul et al, 2011, Diederich et al, 2005, Noradina et al, 2010

TABLE 1. *Frequency of sleep apnea of varying severity in PD patients and controls*

	AHI < 1.5	AHI 1.5–4.9	AHI 5–14.9	AHI 15-29.9	AHI ≥ 30
PD patients	18 (32.7%)	13 (23.6%)	16 (29.1%)	6 (10.9%)	2 (3.6%)
SHHS controls	1691 (27.6%)	1598 (26.1%)	1751 (28.6%)	719 (11.7%)	373 (6.1%)

Trotti et al, 2012

Sleep measures	Controls	Unselected PD	Sleepy PD
No.	50	50	50
Night-time sleep, min			
Total sleep period	450 ± 105	507 ± 93	449 ± 69†
Total sleep time	376 ± 77*	347 ± 108	336 ± 85
Wakefulness after sleep onset	90 ± 61*	161 ± 88	117 ± 73†
Latency to, min			
Sleep onset	30 ± 33	52 ± 52	13 ± 16†
REM sleep onset	100 ± 54	146 ± 111	116 ± 84
Sleep stages, % total sleep time			
Stage 1	7 ± 7	4 ± 5	12 ± 14†
Stage 2	54 ± 15	59 ± 14	49 ± 15†
Stage 3–4	21 ± 13	18 ± 10	27 ± 11†
REM sleep	17 ± 8	19 ± 10	12 ± 7†
Sleep fragmentation with			
Arousals/hr	25 ± 20	15 ± 11	25 ± 20†
Periodic legs movements/hr	7 ± 17	12 ± 17	10 ± 21
Patients with OSA, %	40	20	34
Apnea–hypopnea/hr	23 ± 23*	6 ± 11	17 ± 16†
Apnea/hr	10 ± 15	4 ± 9	8 ± 12
Obstructive, %	67 ± 36	73 ± 41	80 ± 31
Central and mixed, %	23 ± 33	18 ± 31	9 ± 17
Minimum oxygen saturation	84 ± 8*	88 ± 8	85 ± 6

Cochen De Cock et al, 2010

Sleep disordered breathing and PD
- treatment -

- Positional therapy
- Weight loss
- Nasal positive airway pressure therapy (nPAP)
- Dental appliances
- Surgery

Continuous Positive Airway Pressure Improves Sleep and Daytime Sleepiness in Patients with Parkinson Disease and Sleep Apnea

Ariel B. Neikrug, MS[1]; Lianqi Liu, MD[2]; Julie A. Avanzino[2]; Jeanne E. Maglione, MD, PhD[2]; Loki Natarajan, PhD[3]; Lenette Bradley, BS[2]; Alex Maugeri[2]; Jody Corey-Bloom, MD, PhD[4]; Barton W. Palmer, PhD[1,2,5]; Jose S. Loredo, MD[6]; Sonia Ancoli-Israel, PhD[1,2,6,7]

[1]San Diego State University and University of California, San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA; [2]Department of Psychiatry, University of California San Diego, San Diego, CA; [3]Department of Family and Preventive Medicine, University of California San Diego, San Diego, CA; [4]Department of Neurosciences, University of California San Diego, San Diego, CA; [5]Veterans Medical Research Foundation, San Diego, CA; [6]Department of Medicine, University of California San Diego, San Diego, CA; [7]Veterans Affairs Center of Excellence for Stress and Mental Health, San Diego, CA

Study Objectives: Obstructive sleep apnea (OSA), common in Parkinson disease (PD), contributes to sleep disturbances and daytime sleepiness. We assessed the effect of continuous positive airway pressure (CPAP) on OSA, sleep, and daytime sleepiness in patients with PD.
Design: This was a randomized placebo-controlled, crossover design. Patients with PD and OSA were randomized into 6 w of therapeutic treatment or 3 w of placebo followed by 3 w of therapeutic treatment. Patients were evaluated by polysomnography (PSG) and multiple sleep latency test (MSLT) pretreatment (baseline), after 3 w, and after 6 w of CPAP treatment. Analyses included mixed models, paired analysis, and within-group analyses comparing 3 w to 6 w of treatment.
Setting: Sleep laboratory.
Participants: Thirty-eight patients with PD (mean age = 67.2 ± 9.2 y; 12 females).
Intervention: Continuous positive airway pressure.
Measurements: PSG outcome measures: sleep efficiency, %sleep stages (N1, N2, N3, R), arousal index, apnea-hypopnea index (AHI), and % time oxygen saturation < 90% (%time SaO_2 < 90%). MSLT outcome measures: mean sleep-onset latency (MSL).
Results: There were significant group-by-time interactions for AHI ($P < 0.001$), % time SaO_2 < 90% ($P = 0.02$), %N2 ($P = 0.015$) and %N3 ($P = 0.014$). Subjects receiving therapeutic CPAP showed significant decrease in AHI, %time SaO_2 < 90%, %N2, and significant increase in %N3 indicating effectiveness of CPAP in the treatment of OSA, improvement in nighttime oxygenation, and in deepening sleep. The paired sample analyses revealed that 3 w of therapeutic treatment resulted in significant decreases in arousal index ($t = 3.4$, $P = 0.002$). All improvements after 3 w were maintained at 6 w. Finally, 3 w of therapeutic CPAP also resulted in overall decreases in daytime sleepiness ($P = 0.011$).
Conclusions: Therapeutic continuous positive airway pressure versus placebo was effective in reducing apnea events, improving oxygen saturation, and deepening sleep in patients with Parkinson disease and obstructive sleep apnea. Additionally, arousal index was reduced and effects were maintained at 6 weeks. Finally, 3 weeks of continuous positive airway pressure treatment resulted in reduced daytime sleepiness measured by multiple sleep latency test. These results emphasize the importance of identifying and treating obstructive sleep apnea in patients with Parkinson disease.
Keywords: Continuous positive airway pressure, daytime sleepiness, obstructive sleep apnea, Parkinson disease, sleep disorders, sleep quality
Citation: Neikrug AB; Liu L; Avanzino JA; Maglione JE; Natarajan L; Bradley L; Maugeri A; Corey-Bloom J; Palmer BW; Loredo JS; Ancoli-Israel S. Continuous positive airway pressure improves sleep and daytime sleepiness in patients with Parkinson disease and sleep apnea. *SLEEP* 2014;37(1):177-185.

EDS in PD
- Frucht report -

- Eight PD patients
- Age 54 – 83
- Stage 2
- PD duration – 6.4 yrs
- “sleep attacks” while driving, causing MVA
- All on pramipexole (1-4.5 mg)
- One had similar episode on ropinirole (16 mg)

Frucht et al. Neurology, 1999

EDS in PD
- Frucht report -

- Increased interest in sleep dysfunction in PD
- Lead to controversial guidelines for driving
- Physician responsibility to report those at risk ?
- Should PD patients treated with DA be permitted to drive?

Sleep attack

"events of overwhelming sleepiness that occur without warning or with a prodrome that is sufficiently short or overpowering to prevent the patient form taking appropriate protective measures"

"Unintended sleep episode"

"Sudden onset sleep" (SOS)

EDS in PD

- 20 – 60% PD patients
- EDS – prodromal feature of PD ??
- Associations with:
  - Age
  - DA dose
  - Disease severity
  - Autonomic dysfunction
  - Cognitive dysfunction
- Disconnect: *subjective vs objective sleepiness*

Sleep Attacks, Daytime Sleepiness, and Dopamine Agonists in Parkinson's Disease

Sebastian Paus, MD,[1] Hans Michael Brecht, MD,[2] Jürgen Köster, PhD,[2] Gert Seeger, MD,[3] Thomas Klockgether, MD,[1] and Ullrich Wüllner, MD[1]*

[1]*Department of Neurology, University of Bonn, Bonn, Germany*
[2]*Boehringer Ingelheim Pharma KG, Ingelheim, Germany*
[3]*Central Institute of Mental Health, Mannheim, Germany*

	All patients	No sleep attacks	Sleep attacks w/wo warning	Sleep attacks w/o warning
No. patients	2,952	2,372	177	91
Age, yr (mean ± SD)	69.3 ± 8.6	68.9 ± 8.6	69.9 ± 8.4	69.3 ± 8.4
Male/female (%)	60.7/38.7	60.0/39.5	69.9/31.1[a]	70.3/29.7[a]
Male/female ratio	1.52	1.56	2.22	2.37
Duration of PD, yr (mean ± SD)	9.2 ± 6.6	8.7 ± 6.4	11.9 ± 7.1[b]	12.2 ± 8.1[b]

[a]$P < 0.05$ (*t*-test vs. patients without sleep attacks).
[b]$P < 0.001$ (Wilcoxon–Mann-Whitney test vs. patients without sleep attacks).
PD, Parkinson's disease.

		Multiple DA + L-dopa	DA + L-dopa	DA mono	L-Dopa mono	No L-dopa no DA
Patients, n (%)	2,952	109 (3.7)	1869 (63.3)	131 (4.4)	769 (26.1)	71 (2.5)
Sleep attacks w/wo warning	177	10	137	7	22	1
Prevalence	6.0%	9.2%	7.3%	5.3%	2.9%	1.4%
Age (yr)	mean ± SD	70.5 ± 8.0	69.6 ± 8.0	58.6 ± 7.8	74.5 ± 7.4	85
Male/female	%/%	50.0/50.0	76.6/22.4	42.9/57.1	36.6/63.6	100/0
Ratio		1.00	3.28	0.75	0.57	
Duration of PD	mean ± SD	13.1 ± 6.5	12.1 ± 6.4	9.0 ± 8.0	11.4 ± 10.6	3.5

PD, Parkinson's disease; DA, dopamine agonist; mono, monotherapy; L-dopa; levodopa.

Driving in Parkinson's Disease: Mobility, Accidents, and Sudden Onset of Sleep at the Wheel

Charlotte Meindorfner, MSc,[1] Yvonne Körner, MSc,[1]* Jens Carsten Möller, MD,[2] Karin Stiasny-Kolster, MD,[2] Wolfgang Hermann Oertel, MD,[2] and Hans-Peter Krüger, PhD[1]

[1]*Center for Traffic Sciences, Department of Psychology, University of Würzburg, Würzburg, Germany*
[2]*Department of Neurology, Philipps-University, Marburg, Germany*

- 5,210 PD subjects with a driving license
- 390 (8%) experienced sudden-onset sleep at the wheel
  - 57% had warning signs of sleepiness
  - 26% had "sleep attacks"
- ESS – SOS
  - ESS ≥ 10: 77% specificity; 74% sensitivity

EDS in PD
- etiology -

- Complex medication regimens
- Primary neurodegeneration of PD
- Co-existent sleep disorders
- Age related changes in sleep architecture

Somnolence in PD
- medication adverse effect in efficacy trials -

- Levodopa
  - Lesser, 1979 13.3%
  - PSG, 2000 17.3%
  - Rascol, 2000 19.1%
- Ropinirole
  - Adler, 1997 36.2%
  - Rascol, 2000 27.4%
- Pramipexole
  - Shannon, 1997 18.3%
  - PSG, 2000 32.4%

EDS – intrinsic to PD itself?

J. Sleep Res. (2000) **9**, 63–69

FAST TRACK

Daytime sleepiness in Parkinson's disease

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Parkinson's disease and sleepiness: An integral part of PD

I. Arnulf, E. Konofal, M. Merino–Andreu, J. L. Houeto, V. Mesnage, M. L. Welter, L. Lacomblez, J. L. Golmard, J. P. Derenne and Y. Agid

Neurology 2002;58;1019-1024

Assessment of sleepiness and unintended sleep in Parkinson's disease patients taking dopamine agonists

Thomas Roth[a,*], David B. Rye[b], Leona D. Borchert[c], Cindy Bartlett[d], Donald L. Bliwise[b], Charles Cantor[e], Jay M. Gorell[a], Jean P. Hubble[f], Bruno Musch[c], C. Warren Olanow[g], Charles Pollak[f], Matt B. Stern[e], Ray L. Watts[b]

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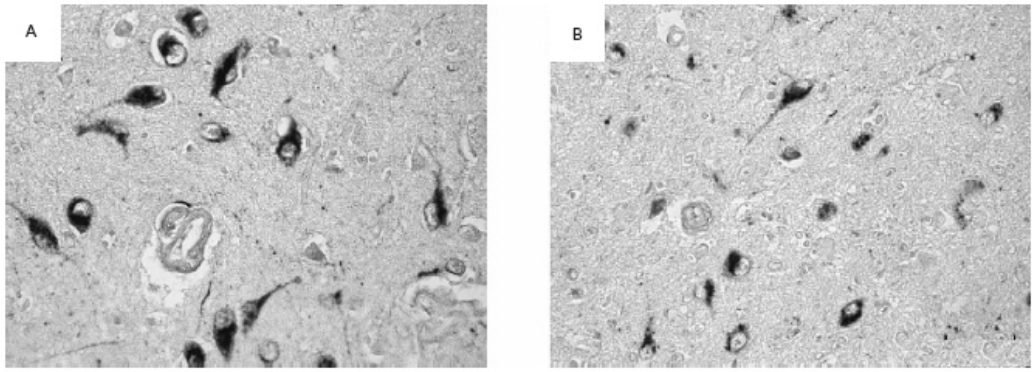
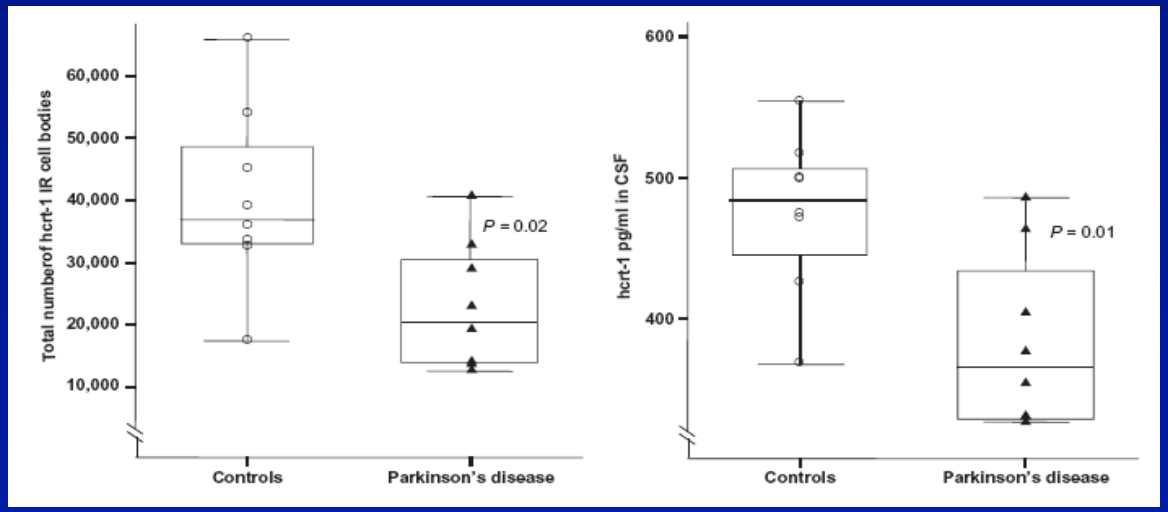
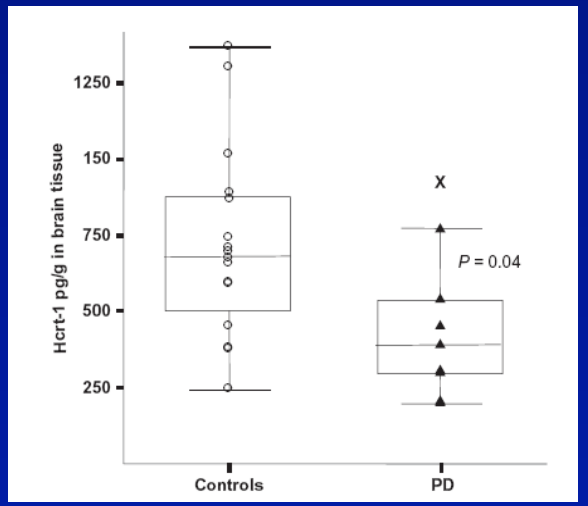
Hypocretin (orexin) loss in Parkinson's disease

Rolf Fronczek,[1,2] Sebastiaan Overeem,[1,3] Sandy Y. Y. Lee,[2] Ingrid M. Hegeman,[1] Johannes van Pelt,[4] Sjoerd G. van Duinen,[5] Gert Jan Lammers[1] and Dick F. Swaab[2]







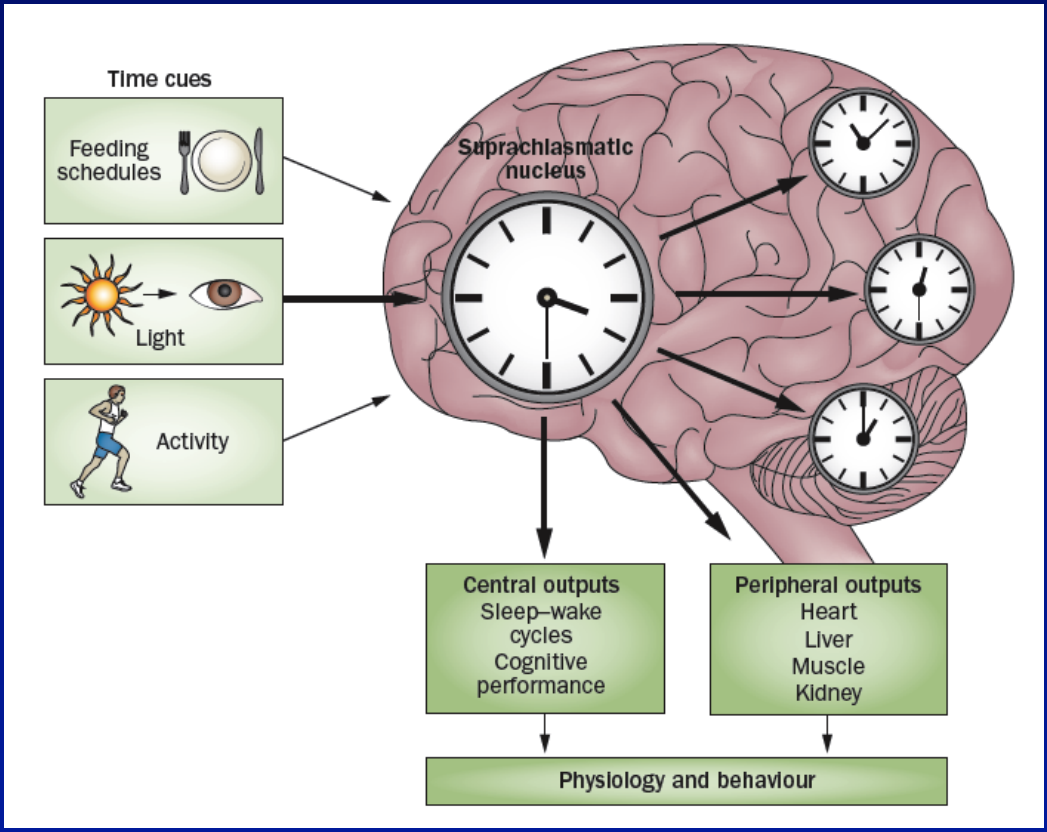
EDS in PD
- assessment -

- History
- Collateral history form spouse / caregiver
- Review of the medication regimen
- Screen for primary sleep disorders
- MSLT
- Parkinson’s Disease Sleep Scale - PDSS
- ESS
- SCOPA – SLEEP Scale

EDS in PD
- treatment -

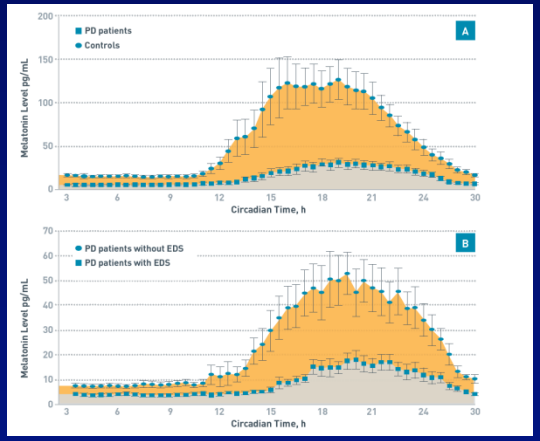
- Sleep hygiene
- Co-existent sleep disorder
- Adjustment of the medication regimen
- Stimulants
- Modafinil
- Light therapy
- Melatonin ?
- Sodium oxybate ?
- Deep brain stimulation ?
- Atomoxetine ?
- Caffeine ?

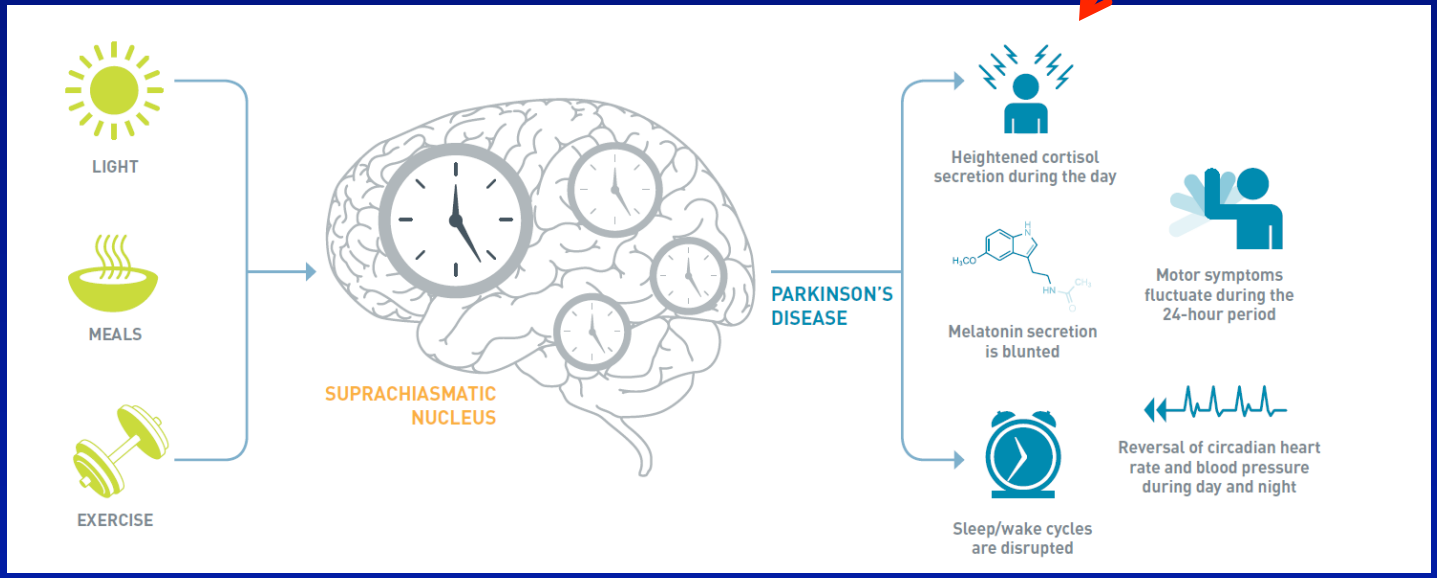
Circadian system



Videnovic et al. 2014

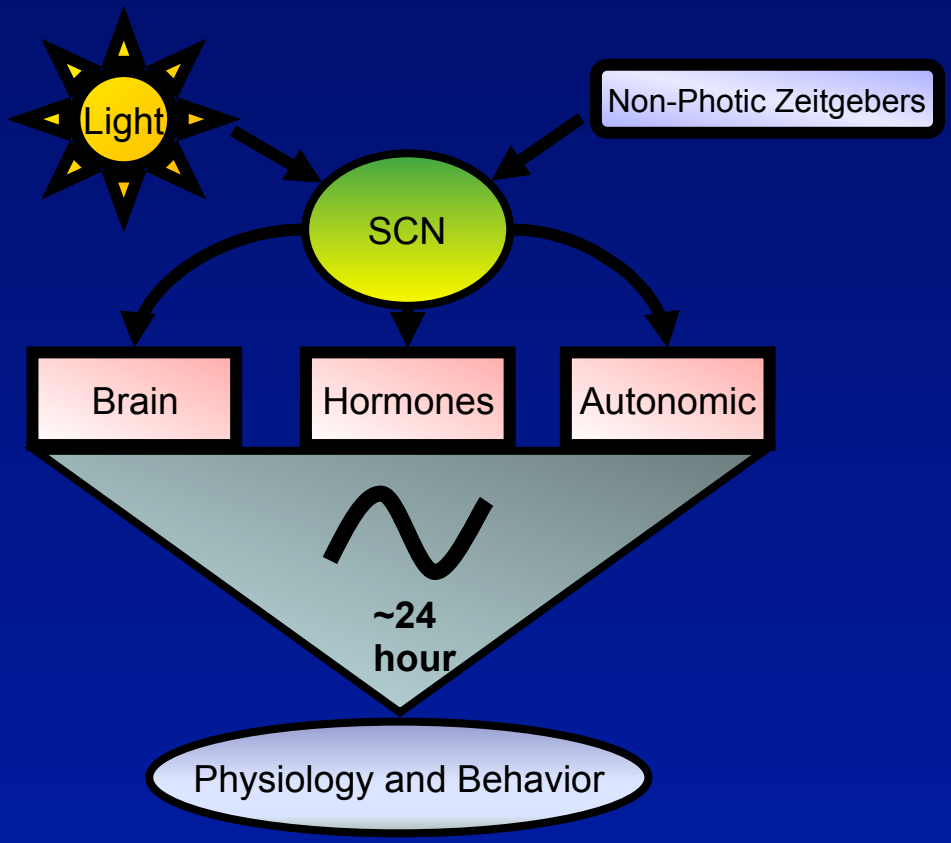
Circadian disruption in PD





Videnovic et al. 2014

Circadian-based treatment interventions for sleep/wake dysfunction



JAMA Neurology | Original Investigation

Timed Light Therapy for Sleep and Daytime Sleepiness Associated With Parkinson Disease
A Randomized Clinical Trial

Aleksandar Videnovic, MD, MSc; Elizabeth B. Klerman, MD, PhD; Wei Wang, PhD; Angelica Marconi, MS; Teresa Kuhta, DO; Phyllis C. Zee, MD, PhD

Table 2. Effects of LT on Parkinson Disease Severity, Sleep, Alertness, Depression, Fatigue, and Quality of Life

Outcome Measure[a]	Mean (SD)				*P* Value, Group/ Condition/ Interaction			*P* Value, Group/ Condition/ Interaction
	Baseline		Postintervention (Week 4)			Postwashout (Week 6)		
	Bright LT	Dim-Red LT	Bright LT	Dim-Red LT		Bright LT	Dim-Red LT	
UPDRS	39.69 (15.85)	45.07 (20.15)	35.47 (17.67)	40.02 (19.48)	.39/.001	35.94 (12.29)	40.20 (18.68)	.43/.78
I	1.75 (0.86)	2.27 (1.49)	1.40 (1.06)	1.33 (1.18)	.49/.008	1.56 (1.41)	1.87 (1.36)	.74/.07
II	10.44 (5.23)	10.40 (7.13)	8.87 (4.87)	9.53 (6.39)	.84/.03	10.13 (4.30)	10.40 (6.66)	.79/.02
III	24.75 (11.26)	29.13 (12.43)	22.67 (13.12)	25.87 (11.87)	.35/.01	21.94 (8.84)	24.60 (11.79)	.44/.52
IV	2.75 (2.24)	3.27 (2.12)	2.53 (1.85)	3.47 (2.67)	.33/.80	2.31 (1.85)	3.33 (2.64)	.22/.47
BDI	8.31 (3.63)	8.27 (4.71)	7.88 (4.53)	9.33 (10.57)	.84/.26	7.06 (5.56)	10.40 (10.49)	.94/.73
ESS	15.81 (3.10)	15.47 (2.59)	11.19 (3.31)	13.67 (4.78)	.37/<.001/.005	11.38 (4.15)	13.13 (3.56)	.10/.81
PSQI	7.88 (4.11)	8.87 (2.83)	6.25 (4.27)	7.33 (3.52)	.40/.006	5.56 (3.60)	6.00 (2.39)	.51/.08
PDSS	97.24 (22.49)	95.11 (19.86)	106.98 (19.37)	99.28 (16.94)	.4792/.001	103.23 (21.76)	100.49 (17.87)	.43/.53
FSS	41.62 (12.62)	37.00 (9.10)	37.92 (13.65)	36.53 (11.54)	.57/.48	37.07 (13.01)	39.21 (10.39)	.94/.63
PDQ-39	41.46 (19.30)	36.80 (19.72)	43.00 (14.84)	39.40 (26.17)	.49/.41	41.00 (18.68)	37.20 (27.38)	.64/.23

Table 3. Effects of LT on Self-reported Sleep Diaries

Sleep Diary Measure[a]	Mean (SD)				*P* Value, Group/ Condition/ Interaction			*P* Value, Group/ Condition/ Interaction
	Baseline		Postintervention (Week 4)			Postwashout (Week 6)		
	Bright LT	Dim-Red LT	Bright LT	Dim-Red LT		Bright LT	Dim-Red LT	
Sleep								
Duration, h	7.42 (0.99)	7.43 (1.31)	6.95 (0.95)	7.25 (1.29)	.71/.05	7.03 (0.90)	7.35 (1.29)	.43/.59
Latency, min	37 (45)	24 (16)	23 (21)	22 (10)	.42/.02	20 (16)	24 (12)	.65/.64
No. of awakenings	1.51 (1.03)	2.18 (1.09)	0.92 (0.97)	1.77 (1.08)	.02/<.001/.006	1.28 (1.13)	1.76 (1.02)	.03/.01/.004
Wake during night, min	45.18 (50.63)	38.56 (21.69)	39.74 (40.93)	31.77 (23.28)	.54/.05	40.19 (48.46)	29.53 (19.62)	.44/.89
Sleep quality	3.03 (1.01)	3.58 (0.53)	3.53 (0.91)	3.61 (0.75)	.38/<.001/.002	3.47 (0.82)	3.79 (0.43)	.54/.73
Feeling refreshed	2.93 (0.84)	3.39 (0.77)	3.03 (1.15)	3.44 (0.95)	.24/.053	3.14 (1.00)	3.65 (0.70)	.22/.08
Easily waking up	2.42 (0.65)	2.33 (1.28)	2.35 (0.62)	2.32 (1.17)	.74/.59	2.45 (0.88)	2.26 (1.14)	.69/.56
Easily falling asleep	2.32 (0.89)	2.65 (1.11)	1.83 (0.88)	2.49 (1.10)	.18/<.001/<.001	1.85 (0.82)	2.58 (1.10)	.05/.33
Dreaming	1.79 (0.78)	1.83 (0.74)	1.71 (0.70)	1.74 (0.65)	.89/.24	1.81 (0.80)	1.63 (0.62)	.91/.66

MSA

- No pronounced changes in sleep architecture
- Hypersomnolence – 25% [1]
  - Hypocretin network ?? [2,3]
  - Pontine network - LDT, PPT [4]
- Advanced sleep phase syndrome, RLS, stridor – potential contributors

PSP

- Early, worse with PSP progression
- Degeneration of pontine tegmental nuclei
- Sleep architecture [5]
  - REM sleep suppressed
  - N3 sleep decreased
  - spindles blunted
  - increased alpha activity
- Insomnia

CBS

- Limited knowledge

[1] Moreno-Lopezl et al. Arch Neurol, 2011
[2] Benarroch et al. Brain, 2007
[3] Abdo et al. Parkin Relat Dis, 2008
[4] Schmeichel et al. Neurology, 2008
[5] Montplaisir et al. Neurology, 1997

AUTONOMIC DYSFUNCTION

PRIMARY SLEEP DISORDERS

RBD

SAS

RLS / PLMS

ALERTNESS

SLEEP

MEDICATIONS

Circadian system

Homeostatic drive

PD NEURODEGENERATION

MOTOR SYMPTOMS OF PD

NEUROPSYCHIATRIC SYMPTOMS