Sleep Disorders in Parkinson's Disease

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Sleep Disturbances in Parkinson's Disease

- Present in nearly all patients with Parkinson's disease (PD)[1]
- Emerge early in the disease course[1]
- Correlate with the disease severity (UPDRS III, S&E)
- Under recognized and ineffectively treated [2]
- Negatively impact the quality of life [3]
- Lead to early institutionalization and higher caregiver burden[1,4]

Sleep in Parkinson's Disease

Sleep Parameters	Controls (n= 10)	PD patients (n= 10)
Time in bed (min)	482.8 ± 3.1	475.1 ± 10.0
Total sleep time (min)	382.2 ± 38.3	307.6 ± 82.2*
Sleep efficiency (%)	83.1 ± 7.8	72.1 ± 17.0*
No. of awakenings	13.6 ± 3.8	25.9 ± 10.6*
Wake time (% SPT)	18.3 ± 8.3	34.0 ± 15.1*

* Significantly different from controls at P < 0.05

No difference between groups in sleep-onset latency, REM latency, stage 1 or 2, SWS, or REM.

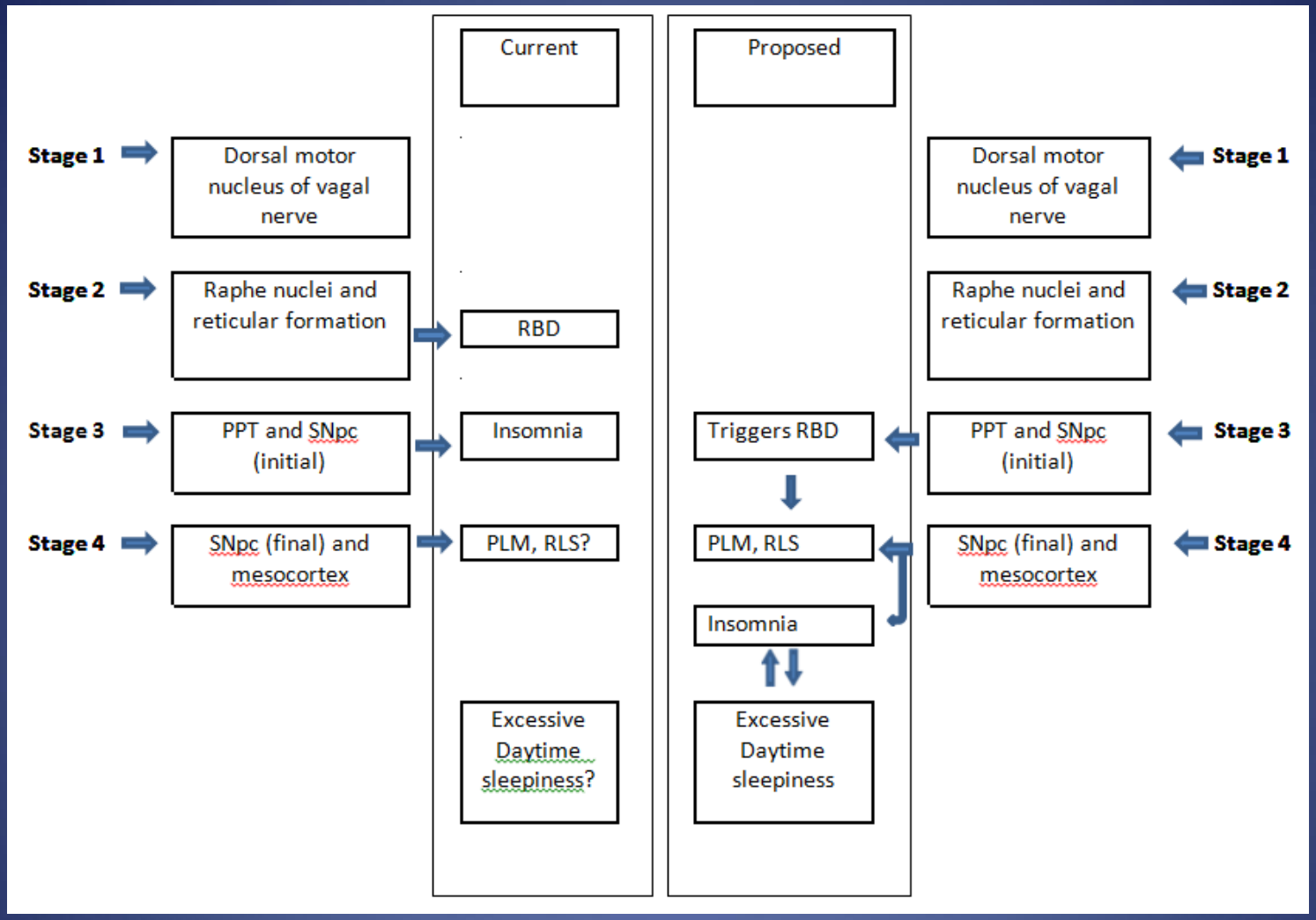
Adapted from: Adler CH, Thorpy MJ. Sleep issues in Parkinson's Disease. Neurology 2005;64(Suppl 3):S12-S20

Sleep Disorders in Parkinson's Disease

- **Why** – *do they emerge?*
- **What** – *are they?*
- **How** – *can they be managed?*

Sleep Disorders in Parkinson's Disease
The why factor

- **The etiology of sleep disorders in PD is multifactorial.**
- **Research suggests that altered sleep pattern in PD patients is due to primary degeneration/ dysfunction of nuclei involved in the control of the sleep-wake cycle and its phases[1,5]**
- **Varying degrees of circadian rhythm dysfunction is believed to underlie a significant percentage of sleep complaints in PD patients[6]**



Comparative representation of the predominant sleep disturbances in Parkinson's disease, according to the Braak staging scheme.

Adapted from: Lima M. (2013). Sleep disturbances in Parkinson's disease: The contribution of dopamine in REM sleep regulation. Sleep Medicine Reviews, 17, 367-375

Sleep Disorders in Parkinson's Disease
The why factor

- Dopaminergic signaling is critical in arousal mechanisms.[7]
- Dopamine modulates pineal gland function,[8] and along with melatonin, is involved in non- photic and photic entrainment of the biological clock.[9,10,11]
- Phase advance in melatonin secretion in PD patients on levodopa[12]
- Patients with PD had blunted circadian rhythms of melatonin secretion compared with controls (↓amplitude, ↓24 hr. AUC) [6]
- Melatonin is beneficial in sleep disturbances in PD patients.[13]

Sleep Disorders in Parkinson's Disease

Secondary Factors

- Pharmacological agents.
- Nocturnal motor symptoms e.g. tremor, akinesia, dystonia
- Nocturia
- Depression
- Cognitive Impairment with nocturnal psychosis
- Poor sleep hygeine
- Chronic inadequately controlled pain
- Normal aging

PD Medications and Sleep

- **Levodopa**
  - Increases REM latency
  - Reduces REM duration
  - REM rebound with withdrawal
  - Improves sleep in monkey model [78]
- **Dopamine Agonists**
  - Insomnia (low dose)
  - Daytime sleepiness, Sleep attacks
  - Variable nocturnal effects
- **Selegiline**
  - Sleep onset insomnia
- **Rasagiline**
  - Improves subjective sleep quality[79]
- **Anticholinergics**
  - Daytime- Sedation
  - Nocturnal- Alertness, ↓ REM
- **Amantadine**
  - Nightmares, Insomnia
  - Improves nocturia
- **Antidepressants**
  - SSRI, SNRI - RBD, RLS, PLMs
  - Tricyclics- Sedation
- **Benzodiazepines**
  - Daytime sleepiness
  - ↓ REM, improve RBD
  - REM rebound with withdrawal

Classification of Sleep Disturbances in PD

Pure Sleep Disorders:

- Insomnia - sleep initiation, sleep maintenance
- REM Sleep Behavior Disorder (RBD)
- Restless leg syndrome (RLS)
- Periodic Limb Movements of Sleep (PLMD)
- Sleep-related breathing disorders
- Parasomnias

Medications related:

- Excessive daytime sleepiness and sleep attacks
- Insomnia
- Nocturnal psychosis
- Vivid dreams

PD related nocturnal symptoms:

- Nocturnal and/or early morning bradykinesia, dystonia and tremor
- Nocturnal confusion and psychosis associated with cognitive impairment
- Nocturia or hyperhidrosis- drenching sweats

Insomnia

- Insomnia occurs in 30-80% of patients with PD [2,1]
- Most common types reported are sleep fragmentation and early awakenings as compared to age matched controls.[14]
- PD pathophysiology, symptomatology, medications, lack of exercise, poor sleep hygiene are all contributing factors.

- Treatment
  - Optimizing PD treatment
  - Good sleep hygeine
  - Melatonin 3 mg 1-2 hours before bedtime[15]
  - Judicious use of hypnotics (Zolpidem, Temazepam) or sedating anti-depressants (Mirtazapine, Amitriptyline, Trazodone)

Excessive Daytime Sleepiness

- Excessive sleepiness (EDS) is seen in up to 50% of PD patients and is linked to cognitive impairment.[16]
- Sleep attacks similar to those of narcolepsy effect up to 4% of the PD patients, however prevalence varies across studies from 0-30%.[1]
- PD pathophysiology, nocturnal sleep disruption , circadian dysrhythmia[6], depression, dementia and medications are all contributing factors.
- Reduced hypocretin levels in CSF and loss of hypocretinergic neurons in post mortem histologic analysis[17] link PD to narcolepsy.
- In double blind RCTs, EDS was seen in 32.4% of patients on Pramipexole compared to 17.3% on levodopa (*p <0.01)* and in 27.4% on ropirinole vs 19.1% on levodopa (*p=NS).* [18, 19] D3 agonists cause EDS, in contrast D1 agonists increase arousals.[20, 21]

Excessive Daytime Sleepiness

- **Management: (General Principles)**
  - Good Sleep hygeine
  - Minimize dopaminergic medication load
  - Treat depression (Bupropion) [22]
  - Treat sleep apnea, Circadian dysrhythmia
  - Ensure safety (assess driving risk)

- **Stimulants:**
  - Modafinil (200-400 mg/day), improved ESS scores [23, 24, 25]
  - Methylphenidate [26], Caffeine (also neuroprotective?) [27]

Restless Legs Syndrome (RLS) and Periodic Limb Movements of Sleep (PLMS)

- Prevalence of RLS in PD varies from 0-50% [28, 29, 30]
- Majority of patients with RLS have PLMS that occur at 20-40 sec intervals and last 0.5-5 seconds [31]
- PLMS may effect one or both legs, arms and torso.[2]
- RLS can cause sleep initiation insomnia while PLMS can cause sleep fragmentation.
- **Etiologic relationship between PD and RLS/PLMD is unclear.**
- Functional imaging (SPECT and PET) has provided conflicting evidence on the relationship between RLS/PLMD and dopamine neuronal and receptor abnormalities. [32,33,34,35,36,37,38]
- RLS may result from reduced dopaminergic cell function secondary to local iron deficiency, rather than depletion of dopaminergic cells.[39]

2012 Revised IRLSSG Essential Diagnostic criteria for RLS

All must be met

1. An urge to move the legs usually but not always accompanied by or felt to be caused by uncomfortable or unpleasant sensations in the legs.
2. The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting.
3. The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching at least as long as the activity continues.
4. The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day.
5. The occurrence of the above features is not solely accounted for as symptoms primarily due to another medical or behavioral condition.

Allen RP, Picchietti DL, Garcia-Borreguero D Ondo WG, Walters AS, Winkelman JW, Zucconi M, Ferri R, Trenkwalder C Lee HB; Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria - history, rationale, description, and significance. Sleep Med.2014 Aug;15(8):860-73

RLS and PLMS

- **Diagnosis:**
  - Careful history, Polysomnography
- **Treatment:**
  - Ropirinole and Pramipexole are FDA approved and are generally considered the first line agents. [41]
  - Rotigotine transdermal patch (1-3 mg / 24 hours) [41] has shown sustained efficacy for up to 5 years [42] and lower rate of augmentation (2.7%) as compared to other DAs or L-Dopa [43]
  - Gabapentin enacarbil (600 mg) is also FDA approved for RLS.
  - Pregabalin has similar efficacy as DAs without producing augmentation [44]
  - Opioids and Benzodiazepines are other treatment options. [45, 46]

REM Sleep Behavior Disorder (RBD)

- RBD is a parasomnia characterized by vivid and enacted dreams.[1]
- The pathophysiology of RBD involves functional depression or destruction of brainstem serotonergic or noradrenergic regions responsible for atonia of REM sleep. [47, 48]
- Diagnosis requires demonstration of recurrent complex behavior or vocalization during REM sleep using video-polysomnography accompanied by REM sleep without atonia.[49]
- Approximately 30-50% of patients with PD have RBD.[3]
- REM sleep with atonia is seen in 60% [50]
- RBD may predate motor symptoms of PD by several decades.
- A 40% conversion rate of RBD into a parkinsonian syndrome in one and 66% in two decades have been demonstrated.[51, 52]

REM Sleep Behavior Disorder (RBD)

- **Diagnosis:**
  - History
  - Polysomnographic Video Recording
  - IPT-SPECT may be a useful tool [53]

- **Treatment:**
  - Clonazepam (0.5 mg to 3 mg) Level B [54,55,56]
  - Melatonin (3-6 mg at bedtime) Level B [56, 57,58,59,]
  - Pramipexole (0.125mg to 1.5 mg) Level C [56]
  - ACEI, Carbamazepine, Clozapine, Desipramine Level C [56]
  - Address nocturnal safety issues

Sleep Disordered Breathing

- Prevalance figures in PD with respect to general population vary.
- Snoring and apneic episodes may be up to 3 times more common in PD (12%) than general population.[60]
- Risk factors: Male gender, age, obesity, others
- Dopamine agonists (DA) seems to enhance the risk of central SDB. Loss of normal muscle atonia may be responsible for decreased SDB severity during REM sleep in PD patients on DA [61]
- **Diagnosis:**
  - History, Polysomnogram
- **Treatment:**
  - Weight reduction, CPAP, oral devices

Nightmares, Psychosis, Hallucinations

- Nightmares/vivid dreams are reported in 30% of the PD patients. [62, 63]
- Often a prodrome of daytime hallucinations [64]
- Correlated with disease severity and L-Dopa dose [62]
- Psychosis is more common with increasing age and greater cognitive impairment [2]
- Day time hallucinations are coincident with REM sleep intrusions during awake state.[2]
- **Treatment:**
  - Reduction of antiparkinsonian medications
  - Atypical antipsychotics (Quetiapine, Clozapine)
  - Acetylcholinesterase inhibitors [65] , Mirtazapine [66, 67]
-

Nocturia

- 80% of the patients with PD have 2 or more and 33% have at least 3 episodes of urination per night. [68]
- Risk factors: disease severity and L-Dopa wearing off. [2]

- **Diagnosis:**
  - History, Urologic examination, Urodynamics
- **Management:**
  - Treat secondary cause (BPH, OSA, L-Dopa wearing off)
  - Reduce/eliminate fluids 1-2 hours before bedtime
  - Anticholinergic medications (Tolterodine, Oxybutynin ER)
  - Intra nasal Desmopressin [69]

Circadian Dysrhythmia

- Risk factors: PD, medications, poor sleep hygeine
- Circadian dysfunction may underlie EDS in PD. [70, 6]
- Delayed sleep phase can mimic insomnia, while advanced sleep pattern may appear as excessive daytime sleepiness.
- An irregular sleep pattern can present as both.

- **Diagnosis:**
  - History, Sleep diary, Actigraphy

- **Treatment**
  - Good sleep hygiene
  - Timed Bright light therapy (1000 – 7,500 Lux, 30-90 min)
  - Melatonin (1-10 mg, daytime ≤ 0.5 mg)

Diagnosis of Sleep Disorders

- **Detailed history:**
  - Include spouse, caregiver
  - Sleep diary, home videos, medication list

- **Sleep Scales:**
  - Daytime sleepiness - **Epworth Sleepiness Scale (ESS)**
  - REM Sleep Behavior Disorder- **RBDSQ**
  - Rest less leg syndrome – **RLS rating scale**
  - Overall sleep quality – **PDSS-2, PSQI**

Aspects of Nocturnal disability in Parkinson's disease measured by the Parkinson's Disease Sleep Scale

- Item 1: Overall sleep quality of nocturnal sleep
- Item 2/3: Sleep onset and maintenance insomnia
- Item 4/5: Nocturnal restless legs
- Item 6/7: Nocturnal psychosis and REM sleep behavior disorder
- Item 8/9: Nocturnal and off- related incontinence
- Item 10-13: Nocturnal akinesia and motor symptoms
- Item 10: Early morning dystonia
- Item 14: Sleep refreshment
- Item 15: Daytime sleepiness

Adapted from Chaudhuri KR & Martinez-Martin P. Clinical assessment of nocturnal disability in Parkinson's disease ; The Parkinson's Disease Sleep Scale. Neurology 2004;63(Suppl 3):S17-S20.

Parkinson's Disease Sleep Scale (PDSS-2)

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?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2) Did you have difficulty falling asleep each night?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
3) Did you have difficulty staying asleep?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
4) Did you have restlessness of legs or arms at nights causing disruption of sleep?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
5) Was your sleep disturbed due to an urge to move your legs or arms?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
6) Did you suffer from distressing dreams at night?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
7) Did you suffer from distressing hallucinations at night (seeing or hearing things that you are told do not exist)?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
8) Did you get up at night to pass urine?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
9) Did you feel uncomfortable at night because you were unable to turn around in bed or move due to immobility?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
10) Did you feel pain in your arms or legs which woke you up from sleep at night?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
11) Did you have muscle cramps in your arms or legs which woke you up whilst sleeping at night?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
12) Did you wake early in the morning with painful posturing of arms and legs?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
13) On waking, did you experience tremor?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
14) Did you feel tired and sleepy after waking in the morning?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
15) Did you wake up at night due to snoring or difficulties with breathing?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0

Diagnosis of Sleep Disorders

- **Physical Examination:**
  - BMI, neck circumference, thyroid, peripheral nerves
- **Laboratory Tests:**
  - Exclude organic causes (Iron deficiency, Thyroid dysfunction)
- **Sleep Studies:**
  - Polysomnography, MSLT
  - Video-EEG monitoring
  - Actigraphy

Suggestions for Improved Sleep

- Appropriate sleep duration
- Regular sleep and wake times
- Daily steady exercise and morning bright light exposure.
- Reduce nap frequency and duration
- Quiet, cool sleep environment.
- Hunger may disturb sleep; a light snack before bed may help
- Avoid excessive liquids, caffeinated beverages, and alcohol in the evening
- Use the bedroom only for sleep and sexual activity
- Do not stay in the bed if you are not sleepy, angry or frustrated.

Adapted from: Kutscher, S., Farshidpanah, S., Claassen, D. Sleep dysfunction and its management in Parkinson's disease. *Curr Treat Options Neurol* 2014; 16:304, 1-16.

Effects of common therapies on sleep dysfunction in PD

	Insomnia	EDS	Sleep fragmentation	RLS/PLMS	RBD	Circadian disorder	OSA
Sleep Hygiene	++	+	++	N/A	N/A	N/A	N/A
DBS	+	+/-	+	+	N/A	N/A	N/A
Physical Activity	+	+	+	N/A	N/A	+	N/A
C- PAP	N/A	++	++	N/A	N/A	N/A	++
Bright Light Therapy	+	+	+	N/A	N/A	++	N/A
Dopamine	-	-	-	+	+/-	-	N/A
Pramipexole / Ropinirole	+/-	+/-	+	++	+	-	N/A
Rotigotine	+/-	+	+	++	N/A	N/A	N/A
Clonazapam	+	-	+	+	++	N/A	-
Melatonin	++	+	N/A	+	+	+	N/A
Zolpidem / Eszopiclone	++	-	++	-	-	N/A	N/A
Quetiapine	+	+/-	+	N/A	N/A	N/A	N/A
Clozapine	+	+/-	+	N/A	N/A	N/A	N/A
Modafinil	-	++	N/A	N/A	N/A	N/A	N/A
Donepezil	+/-	+/-	-	N/A	N/A	N/A	N/A
Gabapentin/Pregabalin	++	+/-	++	++	N/A	N/A	N/A

++ FDA approval or significant evidence of efficacy in published literature. + Evidence of efficacy in published literature. +/- Evidence exists supporting positive and negative effects. – Significant evidence exists supporting adverse relationship. N/A No evidence or unknown treatment effect.

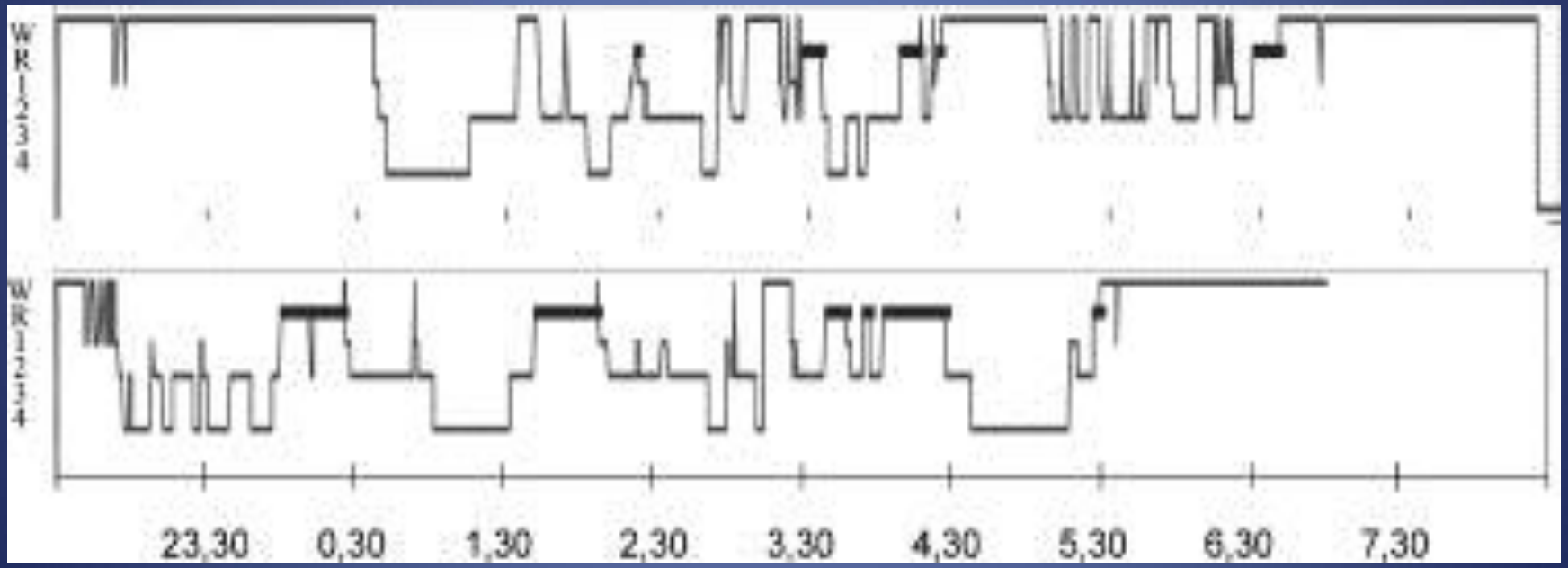
Adapted from: Kutscher, S., Farshidpanah, S., Claassen, D. (2014).Sleep dysfunction and its management in Parkinson's disease. *Curr Treat Options Neurol* 16:304, 1-16.

DBS and Sleep in Parkinson's Disease

- STN-DBS has been shown to increase sleep time, stage N3 sleep and reduce nocturnal arousals. [73] Class III
- PLM, apnea-hypopnea index and REM sleep behavior disorder were unaffected by STN DBS. [73]
- In a case series of 53 PD patients unilateral STN DBS improved subjective sleep quality up to 6 months post-operatively. [74]
- Improvement could be secondary to improved parkinsonism and or medication reduction. [75, 76]
- Stimulation of pedunculopontine nucleus (PPT) improved sleep quality and excessive daytime sleepiness [77] Class III

DBS and Sleep in Parkinson's Disease

Sleep histograms of Patient 3 at T1 (upper panel) evaluation, and 3 months after surgery (T2) (lower panel). The x-axis shows time, and the y-axis shows sleep stages; NREM sleep is shown as open bars, and REM sleep as filled bars. Three months after STN DBS the sleep appears better organized (more continuous and efficient) than at pre-surgical evaluation



Adapted from: Alessandro Cicolin et al. Effects of deep brain stimulation of the subthalamic nucleus on sleep architecture in parkinsonian patients. Sleep Medicine, Volume 5, Issue 2, 2004, 207 – 210

Summary

- Sleep disturbances are common in patients with Parkinson's disease.
- Sleep dysfunction increases morbidity and reduces the quality of life.
- Early screening and aggressive management is warranted.
- Careful history is the most useful diagnostic exercise.
- Good sleep hygiene and medication modification are generally the most useful therapeutic strategies.
- Co-morbid conditions e.g. depression and pain should be aggressively sought and treated.
- Safety aspects e.g. driving (EDS) and risk of injuries (RBD) should be fully addressed.
- Improved sleep may lead to improved cognition, mood, motor function and hence overall function.

Thank you

References

1. Lima M. Sleep disturbances in Parkinson's disease: The contribution of dopamine in REM sleep regulation. *Sleep Medicine Reviews*, 2013; 17, 367-375.
2. Adler, C. & Thorpy, M. Sleep Issues in Parkinson's disease. *Neurology* 64 (Suppl 3), 2005; S13-S20
3. Schrempf W, Brandt MD, Storch A, Reichmann H. Sleep disorders in Parkinson's disease. J Parkinsons Dis. 2014;4(2):211-21
4. Chaudhuri KR, Yates L, Martinez-Martin P. The non-motor symptom complex of Parkinson's disease: a comprehensive assessment is essential. Curr Neurol Neurosci Rep.2005 Jul;5(4):275-83.
5. Kalaitzakis ME, Gentleman SM, Pearce RK. Disturbed sleep in Parkinson's disease: anatomical and pathological correlates. Neuropathol Appl Neurobiol. 2013 Oct;39(6):644-53
6. Videnovic A, Noble C, Reid KJ, Peng J, Turek FW, Marconi A.Circadian melatonin rhythm and excessive daytime sleepiness in Parkinson disease. JAMA Neurol.2014 Apr;71(4):463-9
7. Lu J, Jhou TC, Saper CB. Identification of Wake-Active Dopaminergic Neurons in the Ventral Periaqueductal Gray Matter. *The Journal of Neuroscience* 2006;26(1):193–202
8. Santanavanich C, Chetsawang B, Ebadi M, Govitrapong P. Effects of D1- and D2-dopamine receptor activation on melatonin synthesis in bovine pinealocytes. 2003;35(3):169-176. .
9. Zisapel N. Melatonin-dopamine interactions: from basic neurochemistry to a clinical setting. *Cell Mol Neurobiol* 2001;21(6):605-616.
10. Doyle SE, Grace MS, McIvor W, Menaker M. Circadian rhythms of dopamine in mouse retina: the role of melatonin. Vis Neurosci 2002;19(5):593-601.
11. Tosini G. Melatonin circadian rhythm in the retina of mammals. Chronobiol Int. 2000 Sep;17(5):599-612
12. Bordet R, Devos D, Brique S, Touitou Y, Guieu JD, Libersa C, Destée A. Study of circadian melatonin secretion pattern at different stages of Parkinson's disease. Clin Neuropharmacol. 2003;26:65-72
13. Dowling GA, Mastick J, Colling E, Carter JH, Singer CM, Aminoff MJ. Melatonin for sleep disturbances in Parkinson's disease. Sleep Med 2005;6(5):459-466.

References

14. Tranberg E, larsen JP, Karlsen K. Excessive daytime sleepiness and sleep benefit in Parkinson's disease: a community-based study. *Mov Disord* 1999;14:922-927.
15. Kunz D, Bes F. Melatonin as a therapy in REM sleep behavior disorder patients: an open-labeled pilot study on the possible influence of melatonin on REM-sleep regulation. *Mov Disord* 1999;14:507-511.
16. Goldman JG, Stebbins GT, Leung V, Tilley BC, Goetz CG. Relationships among cognitive impairment, sleep, and fatigue in Parkinson's disease using the MDS-UPDRS. Parkinsonism Relat Disord. 2014 Aug 13. pii: S1353-8020(14)00296.
17. Thannickal TC, Lai YY, & Seigel JM. Hypocretin (orexin) cell loss in Parkinson's disease. Brain 2007;18:287-293
18. Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE, for the 056 Study Group. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. *N Engl J Med* 2000;342:1484-149
19. Holloway RG, Shoulson I Fahn S, et al, for the Parkinson's Study Group. Pramipexole vs levodopa as initial treatment for Parkinson disease: a 4-year ramdomized controlled trail. *Arch Neurol* 2004;61:1044-1053.
20. Bagetta G, De Sarro G, Priolo E, & Nistico G. Ventral tegmental area: Site through which dopamine D-2 receptors agonist evoke behavioral and electrocortical sleep in rats. *Br J Pharmacol* 1988;95:860-866.
21. Bagetta G, De Sarro G, Oriolo E, & Nistico G. Dopamine D-2 receptors in the ventral tegmental area mediate behavioral and electrocortical sleep of dopaminergic drugs in rats. *Pharmacol Res Commun* 1988;20:1091-1092.
22. Goetz CG, Tanner CM, Klawans HL, Buperion in Parkinson's disease. Neurology 1984;34:1092-1094
23. Adler CH, Caviness JN, Hentz JG, Lind M,&Tiede J (2003) Randomized trial of modafinil for treating subjective daytime sleepiness in patients with Parkinson's disease. *MovDisord*, 18, 287-293.
24. Hauser RA, Wahba MN, Zesiewicz TA, & McDowell, Anderson W (2000) Modafinil treatment of pramipexole associated somnolence. *Mov Disord*, 15, 1269-1271.
25. Hogl B, Saletu M, Brandauer E, Glatzl S, Frauscher B, Seppi K, Ulmer H, Wenning G, & Poewe W (2002) Modafinil for the treatment of daytime sleepiness in Parkinson's disease: A double-blind, randomized, crossover, placebo-controlled polygraphic trial. *Sleep*, 25, 905- 909.

References

26. Halliday AM, Nathan PW. Methylphenidate in parkinsonism. BMJ 1961;5240:1652-1655
27. Schwarzschild MA, Xu K, Oztas E, et al. Neuroprotection by caffeine and more specific $A2_A$ receptor antagonists in animal models of Parkinson's disease.Neurology 2003;61(suppl 6):S55-61.
28. Brage-Neto P, da Silva-Junior FP, Sueli Monte F, de Bruin PF, & de Bruin VM. Snoring and excessive daytime sleepiness in Parkinson's disease. *J Neurol Sci* 2004;217:41-45.
29. Ondo WG, Vuong KD, & Jackovic J. Exploring the relationship between Parkinson's disease and restless legs syndrome. *Arch Neurol* 2002;59:421-424.
30. Tan EK, Lum SY, & Wong MC. Restless legs syndrome in Parkinson's disease. *J Neurolo Sci* 2002;196:33-36
31. Trenkwalder C, Walters AS, Hening WA. Periodic lime movements and restless legs syndrome. *Neurol Clin* 1996;14:629-650.
32. Eisensehr I, Wetter TC, Linke R, et al. Normal IPT and IBZM SPECT in drug-naïve and levodopa-treated idiopathic restless legs syndrome. *Neurology* 2001;57:1307-1309.
33. Happe S, Pirker W, Klosch G, Sauter C, Zeithofer J. Periodic leg movements in patients with Parkinson's disease are associated with reduced striatal dopamine transporter binding. *J Neurol* 2003; 250:83-86
34. Michaud M, Spoucy JP, Chabli A, Lavigne G, Montplaisir J, SPECT imaging of striatal pre-and postsynaptic dopaminergic status in restless legs syndrome with periodic leg movements in sleep. *J Neurol* 2002;249:164-170.
35. Ruottinen HM, Partinen M, Hublin C, et al. An FDOPA PET study in patients with periodic leg movement disorder and restless legs syndrome. *Neurology* 2000;54:502-504
36. Trenkwalder C, Walters AS, Hening WA. Positron emission tomographic studies in restless legs syndrome. *Mov Disord* 1999;14:141-145.
37. Trenkwalder C, Walters AS, Hening WA. Periodic lime movements and restless legs syndrome. *Neurol Clin* 1996;14:629-650.
38. Turjanski N, Lees AJ, Brooks DJ. Striatal dopaminergic function in restless legs syndrome: ^{18}F-dopa and ^{11}C-raclopride PET studies. *Neurology* 1999;52:932-937.
39. Allen R. Dopamine and iron in the pathophysiology of restless legs syndrome (RLS). *Sleep Med* 2004;5:385-391.
40. Allen RP et. al; International Restless Legs Syndrome Study Group. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria - history, rationale, description, and significance. Sleep Med.2014 Aug;15(8):860-73

References

41. Kutscher, S., Farshidpanah, S., Claassen, D.Sleep dysfunction and its management in Parkinson's disease. *Curr Treat Options Neurol* 2014; 16:304, 1-16.
42. Dohin E, Hogl B, Ferini-strambi L, Schollmayer E, Fichtner A, Bauer L, et al. Safety and efficacy of rotigotine transdermal patch in patients with restless legs syndrome: a post-hoc analysis of patients taking 1-3 mg/24 h for up to 5 years. *Expert Opin Pharmacother*. 2013;14(1): 15-25.
43. Garcia-Borreguero D, Kohnen R, Silber MH, Winkelman JW, Earley CJ, Hogl B, et al. The long-term treatment of restless legs syndrome/Willis-Ekbom disease: evidence-based guidelines and clinical consensus best practice guidance: a report from the International Restless Legs Syndrome Study Group. *Sleep Med* 2013;14(7):675-684.
44. Huete B, Varona L. Insomnia during treatment with amantadine. *Rev Neurol*. 1997;25(148):2095-101Silber MH, Ehrenberg BL, Allen RP, et al., for the Medical Advisory Board of the Restless Legs Syndrome Foundation. An algorithm for the management of restless legs syndrome. *Mayo Clin Proc* 2004;79:916-922.
45. Silber MH, Ehrenberg BL, Allen RP, et al., for the Medical Advisory Board of the Restless Legs Syndrome Foundation. An algorithm for the management of restless legs syndrome. *Mayo Clin Proc* 2004;79:916-922.
46. Lesage S, Hening WA. The restless legs syndrome and periodic limb movement disorder: a review of management.*Semin Neurol* 2004;24:249-259.
47. Morrison AR. The pathophysiology of REM-sleep behavior disorder. *Sleep* 1998;21:446-449
48. Gilman S, Koeppe RA, Chervin RD, et al. REM sleep behavior disorder is related to striatal monoaminergic deficits in MSA. *Neurology* 2003;61:29-34.
49. American Academy of sleep Medicine. *International classification of sleep disorders* 2014;3rd ed. Darien, IL.
50. Gagnon JF, Bedard MA, Fantini ML, Petit D, Panisset M, Rompre S, Carrier J & Montplaisir J. REM sleep disorder and REM sleep without atonia in Parkinson's disease. *Neurology* 2002;59:585-589
51. Iranzo A, Molinuevo JL, Santamaria J, Serradell M, Marti MJ, Valldeoriola F, et al. Rapid-eye-movement sleep behavior disorder as an early marker for a neurodegenerative disorder: a descriptive study. *Lancet Neurol* 2006;5:571-577.
52. Gagon JF, Postuma RB, Mazza S, Doyon J, Montplaisir J. Rapid-eye-movement sleep behavior disorder and neurodegenerative diseases. *Lancet Neurol* 2006;5:424-432

References

53. Eisensehr I, Linke R, Noachtar S, Schwarz J, Gildehaus FJ, Tatsch K Brain. Reduced striatal dopamine transporters in idiopathic rapid eye movement sleep behaviour disorder. Comparison with Parkinson's disease and controls. 2000 Jun;123 (Pt 6):1155-60
54. Olson EJ, Boeve BF, Silber MH. Rapid eye movement sleep behaviour disorder: demographic, clinical and laboratory findings in 93 cases *Brain*. Feb 2000;123 (Pt 2):331-9
55. Gagnon JF, Postuma RB, Montplaisir J. Update on the pharmacology of REM sleep behavior disorder. *Neurology*. Sep 12 2006;67(5):742-7
56. Aurora NR et. al. Best Practice Guide for the Treatment of REM Sleep Behavior Disorder (RBD).Standards of Practice Committee. Journal of Clinical Sleep Medicine, 2010, Vol.6(1); 85-95
57. Takeuchi N, Uchimura N, Hashizume Y, et al. Melatonin therapy for REM sleep behavior disorder. *Psychiatry Clin Neurosci*. Jun 2001;55(3):267-9
58. Boeve BF, Silber MH, Ferman TJ. Melatonin for treatment of REM sleep behavior disorder in neurologic disorders: results in 14 patients.*Sleep Med*. Jul 2003;4(4):281-4
59. Kunz D, Bes F. Exogenous melatonin in periodic limb movement disorder: an open clinical trial and a hypothesis. *Sleep*. Mar 15 2001;24(2):183-7.
60. Oerlemans WG, de Weerd AW. The prevalence of sleep disorders in patients with Parkinson's disease: a self-reported, community-based survey. *Sleep Med* 2002;3:147-149.
61. Valko PO et al. Observations on sleep-disordered breathing in idiopathic Parkinson's disease. PLoS One. 2014 Jun 26;9(6)
62. Kumar S, Bhatia M, Behari M. Sleep disorders in Parkinson's disease. *Mov disord* 2002; 17:775-781
63. Sharf B, Moskovitz C, Lupton MD, et al. Dream phenomena induced by chronic levodopa therapy. *J Neural Transm* 1978;43:143-151.
64. Moskovitz C, Moses K, Klawans HL. Levodopa-induced psychosis: a kindling phenomenon. *Am J Psychiatry* 1978;135:669-675
65. Kulisevsky J, Roldan E. Hallucinations and sleep disturbances in Parkinson's Disease. Neurology.2004 Oct 26;63(8 Suppl 3):S28-30.

References

66. Godschalx-Dekker JA, Siegers HP. Reduction of parkinsonism and psychosis with mirtazapine: a case report. Pharmacopsychiatry.2014 May;47(3):81-3.
67. Tagai K, Nagata T, Shinagawa S, Tsuno N, Ozone M, Nakayama K. Mirtazapine improves visual hallucinations in Parkinson's disease: a case report. Psychogeriatrics.2013 Jun;13(2):103-7
68. Lees AJ, blackburn NA, Campbell VL. The nighttime problems of Parkinson's disease. *Clin Neuropharmacol* 1988;11:512-519
69. O. Suchowersky, S. Furtado, and G. Rohs, "Beneficial effect of intranasal desmopressin for nocturnal polyuria in Parkinson's disease," Movement Disorders, vol. 10, no. 3, pp. 337–340, 1995
70. Videnovic A, Noble C, Reid KJ, Peng J, Turek FW, Marconi A, Rademaker AW, Simuni T, Zadikoff C, Zee PC. Circadian melatonin rhythm and excessive daytime sleepiness in Parkinson disease. JAMA Neurol. 2014 Apr;71(4):463-9.
71. Chaudhuri KR & Martinez-Martin P. Clinical assessment of nocturnal disability in Parkinson's disease The Parkinson's Disease Sleep Scale. Neurology 2004;63(Suppl 3):S17-S20.
72. Chaudhari KR, Pal S, Brefel-Courbon C. 'Sleep attacks' or 'unintended sleep episodes' occur with dopamine agonists. Is this a class effect? Drug Safety 2002;25:473–483.
73. Cicolin A, Lopiano I, Zibetti M, torre E, Tavella A, Gistamacchia G, et al. Effects of deep brain stimulation of the subthalamic nucleus on sleep architecture in parkinsonian patients. *Sleep Med* 2004;5(2):207-210
74. Amara AW, Standaert DG, Guthrie S, Cutter G, Watts RL, Walker HC. Unilateral subthalamic nucleus deep brain stimulation improves sleep quality in Parkinson's disease. Parkinsonism Relat Disord. 2012 Jan;18(1):63-8
75. Lyons KE, Pahwa R, Effects of bilateral subthalamic nucleur stiumulation on sleep, daytime sleepiness, and early morning dystonia in patients with Parkinson's disease. *J Neurosurg*. 2006;104(4):502-5
76. Antonini A, Landi A, Mariani C, DeNotaris R, Pezzoli G. Deep brain stimulation and its effect on sleep in Parkinson's disease. *Sleep Med*. 2004;5(2):211-4.
77. Peppe A, Pierantozzi M, Baiamonte V, caltagirone C, Stanzione P, et al. Deep brain stimulation of pedunclopontine tegmental nucleus: role in sleep modulation in advanced Parkinson's disease patients: one-year follow-up. *Sleep*. 2012;35(12):1637-42.
78. Belaid H et. al. Sleep Disorders in Parkinsonian Macaques: Effects of l-Dopa Treatment and Pedunculopontine Nucleus Lesion. The Journal of Neuroscience, 2 July 2014, 34(27): 9124-9133
79. Michel Panisset and Sylvain Chouinard. Treatment with Rasagiline Improves the Quality of Sleep in Patients with Parkinson's Disease: Results of the Rasagiline Effect on Sleep Trial (REST) Neurology April 26, 2012. (S52.006)