“Waking up” to sleep problems

PUK Edinburgh Research Interest Group

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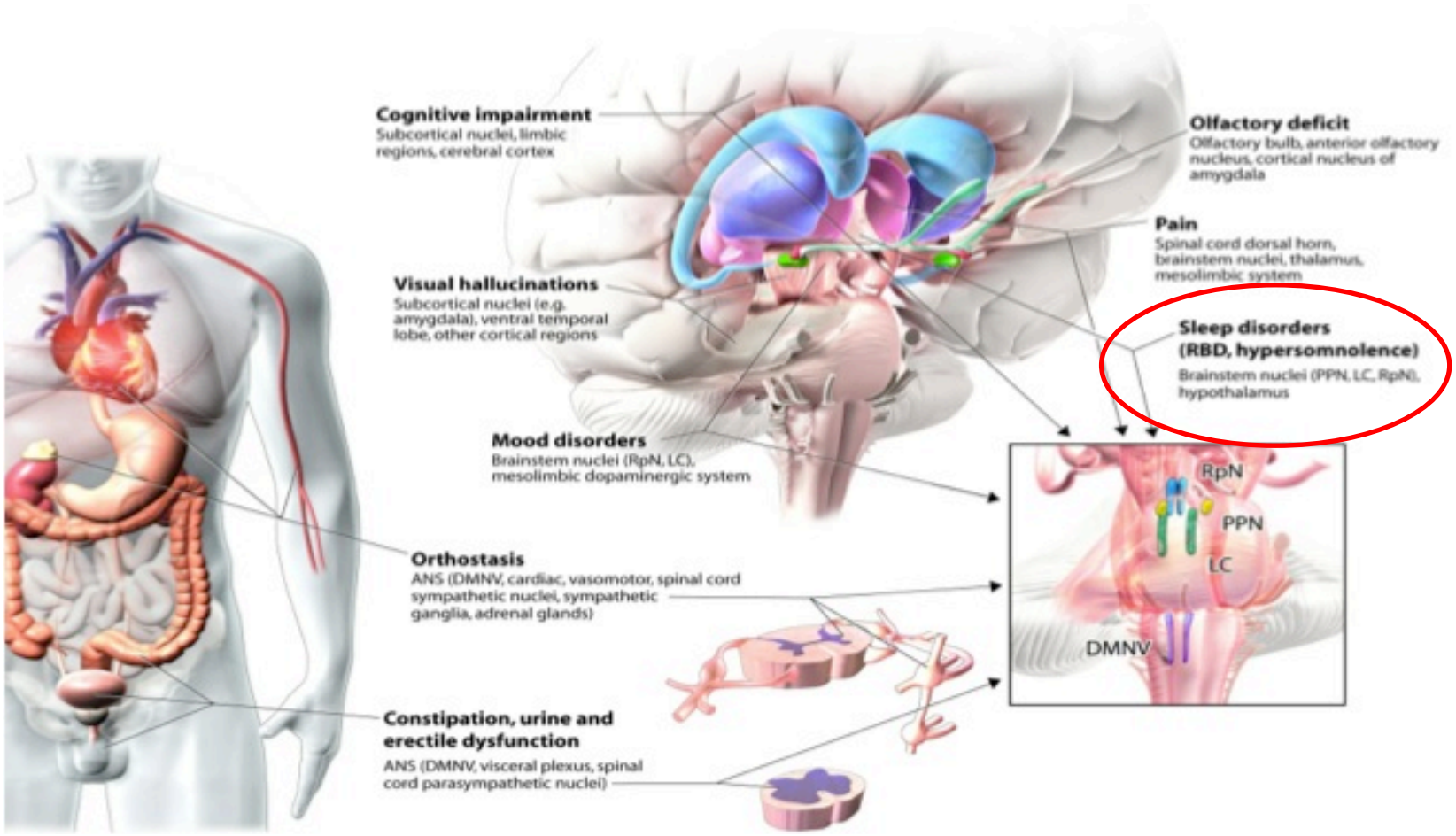
Sleep problems in PD

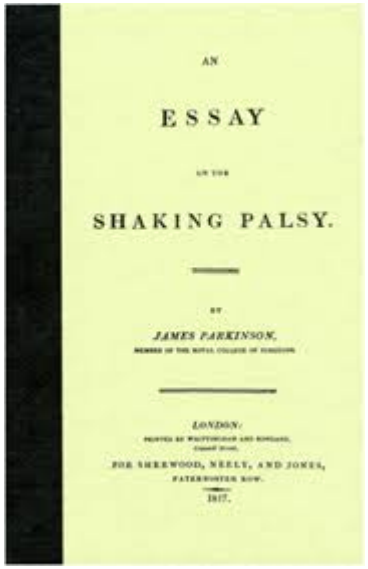
- Why care?
- Causes
- Treatment

Not just a motor disease



Early observations

"… 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"


AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

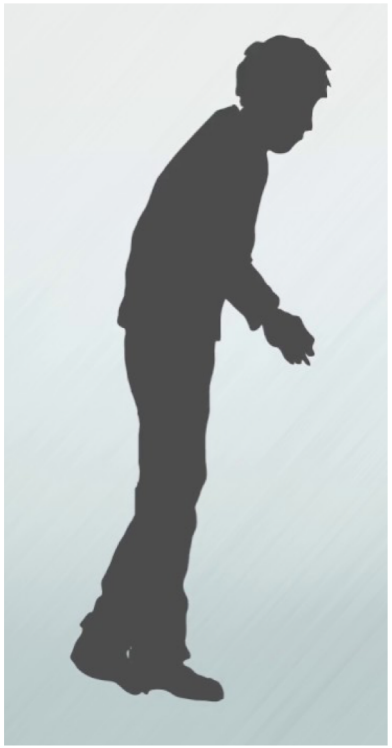
LONDON:

FOR SHERWOOD, NEELY, AND JONES,

1817.

James Parkinson 1817

Spectrum of sleep disorders



REM sleep behaviour disorder

Sleep disordered breathing

Restless legs/periodic limb movements

Excessive daytime sleepiness

Insomnia and sleep maintenance issues

Different causes

=

Different treatment

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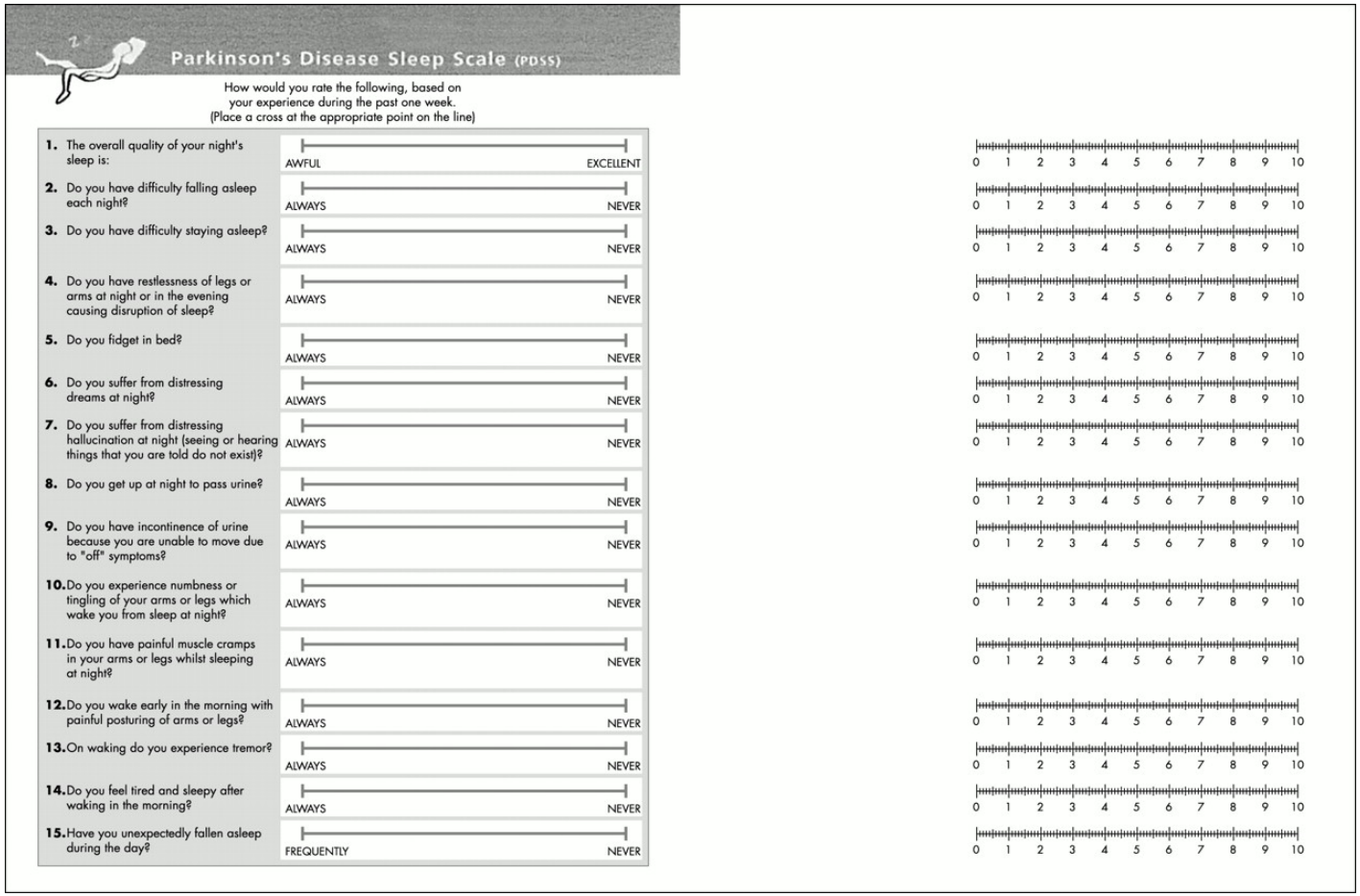
Assessment tools



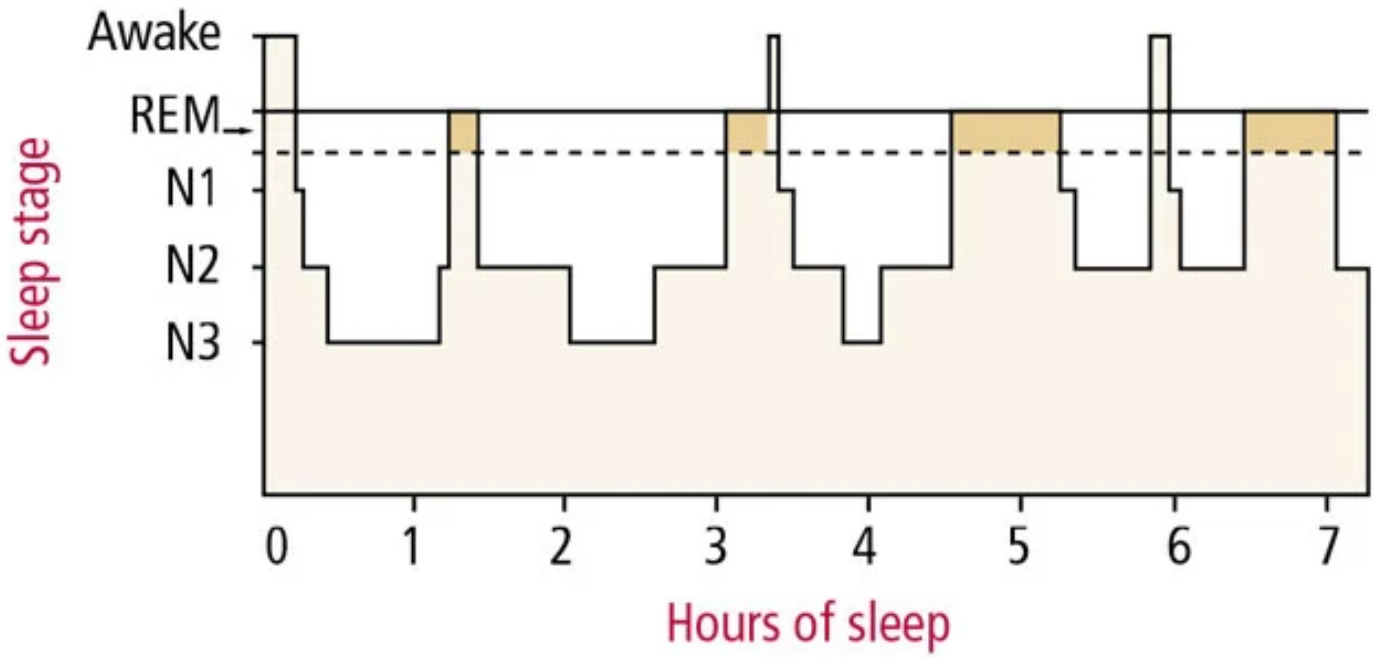
Parkinson's Disease Sleep Scale (PDSS)

How would you rate the following, based on your experience during the past one week.
(Place a cross at the appropriate point on the line)

1. The overall quality of your night's sleep is:	AWFUL	EXCELLENT
2. Do you have difficulty falling asleep each night?	ALWAYS	NEVER
3. Do you have difficulty staying asleep?	ALWAYS	NEVER
4. Do you have restlessness of legs or arms at night or in the evening causing disruption of sleep?	ALWAYS	NEVER
5. Do you fidget in bed?	ALWAYS	NEVER
6. Do you suffer from distressing dreams at night?	ALWAYS	NEVER
7. Do you suffer from distressing hallucination at night (seeing or hearing things that you are told do not exist)?	ALWAYS	NEVER
8. Do you get up at night to pass urine?	ALWAYS	NEVER
9. Do you have incontinence of urine because you are unable to move due to "off" symptoms?	ALWAYS	NEVER
10. Do you experience numbness or tingling of your arms or legs which wake you from sleep at night?	ALWAYS	NEVER
11. Do you have painful muscle cramps in your arms or legs whilst sleeping at night?	ALWAYS	NEVER
12. Do you wake early in the morning with painful posturing of arms or legs?	ALWAYS	NEVER
13. On waking do you experience tremor?	ALWAYS	NEVER
14. Do you feel tired and sleepy after waking in the morning?	ALWAYS	NEVER
15. Have you unexpectedly fallen asleep during the day?	FREQUENTLY	NEVER

0 1 2 3 4 5 6 7 8 9 10

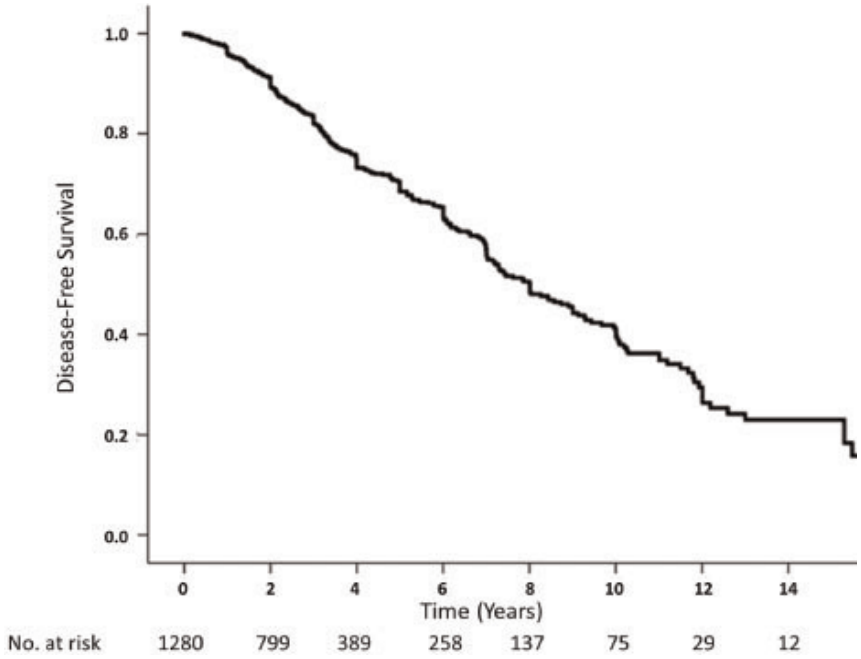
Sleep structure



REM sleep behaviour disorder

Courtesy of Birgit Högl, Innsbruck

RBD as earliest marker of Parkinson's



Three-quarters of people 'convert' to Parkinson's, Multiple System Atrophy or Dementia with Lewy bodies

Postuma et al, Brain 2019

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Treatment of RBD

Minimise risk of injury (to PwP and bed partner)

- Moving furniture
- Placing cushions next to bed
- (Partner sleeping in another bed)

Melatonin – up to 8mg

Clonazepam – up to 2mg

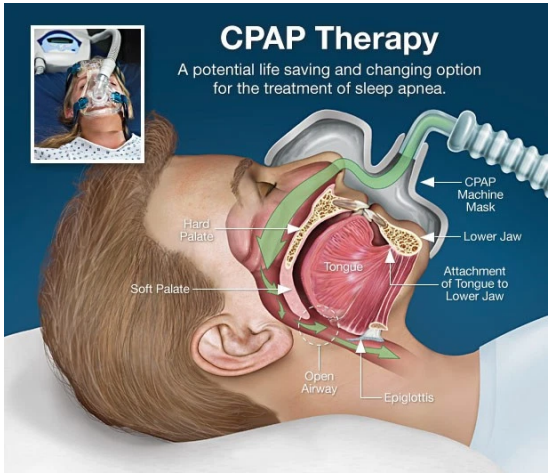
Obstructive sleep apnoea

Nosy, interrupted breathing due to airflow obstruction

Prevalence figures vary, but probably not more common in PD

Treatment

- Avoid sleep on back
- Weight loss
- Dental appliances
- Continuous positive airway pressure therapy (CPAP)
- (Surgery)



Restless legs syndrome

Intense urge to move the legs, particularly in the evening or during periods of inactivity, which is relieved by moving and only returns when the movement stops

Not an involuntary movement. Not the same as muscle cramp

Associated with periodic limb movements of sleep

Common in diabetes, renal disease and other medical conditions

Treatment

- Iron replacement (ferritin >50ng/mL)
- Avoid certain medications (antidepressants, antihistamines)
- Dopamine replacement medications (beware ‘augmentation’)
- Pregabalin

Excessive daytime sleepiness

Feeling of sleepiness that impairs alertness and ability to stay awake

Causes difficulties with activities of daily living (including driving accidents)

One questionnaire study reported that 11% of 5210 PwPs with a driving licence had caused a road traffic accident and more common in those with EDS

Due to disease (loss of orexin neurones), aggravated by dopamine agonists

Treatment

- Address night-time sleep issues
- Consider reduction in dopaminergic drugs
- Take naps
- Modafinil
- Bright light therapy

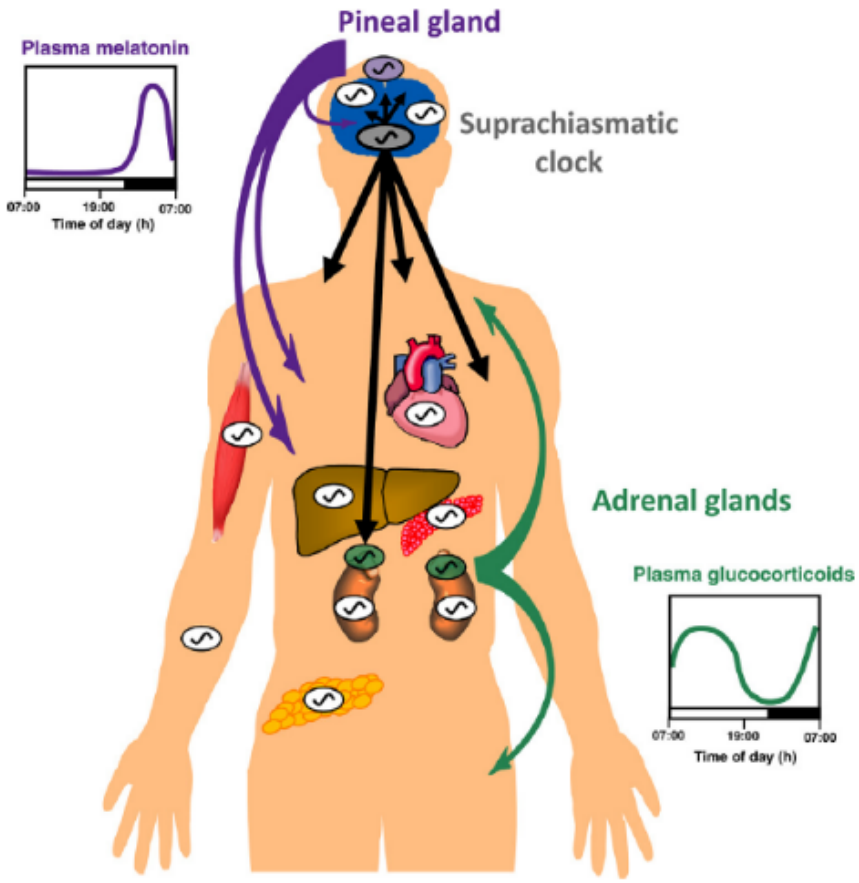
Insomnia

Sleep parameter	Controls	PD	*p*-value (Univariate analysis[a])	*p*-value (Multivariate analysis[b])
Total sleep time (min) ↓	340.2±84.6	277.1±104.4	<0.001	0.010
Sleep efficiency (%) ↓	76.6±18.3	59.4±22.0	<0.001	0.001
Sleep onset latency (min)	19.2±29.1	40.3±68.6	0.082	0.133
REM latency (min) ↑	128.2±79.8	177.0±104.1	0.013	0.007
% stage 1 sleep ↑	13.0±8.8	21.3±16.7	0.010	0.017
% stage 2 sleep	48.0±11.2	46.0±16.4	0.665	0.849
% deep sleep	21.6±10.7	23.1±17.3	0.881	0.466
% REM sleep ↓	17.1±6.9	8.5±7.4	<0.001	<0.001
Arousal index (/hr)	13.4±8.5	12.9±8.5	0.898	0.506
PLMI (/hr)	10.7±21.5	10.3±18.1	0.595	0.549
AHI (/hr)	12.2±13.1	12.5±15.6	0.302	0.999
MSL (min) ↑	9.5±4.2	12.5±5.6	0.002	0.010

PD patients have reduced and fragmented sleep, as well as excessive daytime sleepiness

Yong et al, PLoS ONE 2011

Disturbed body clock?

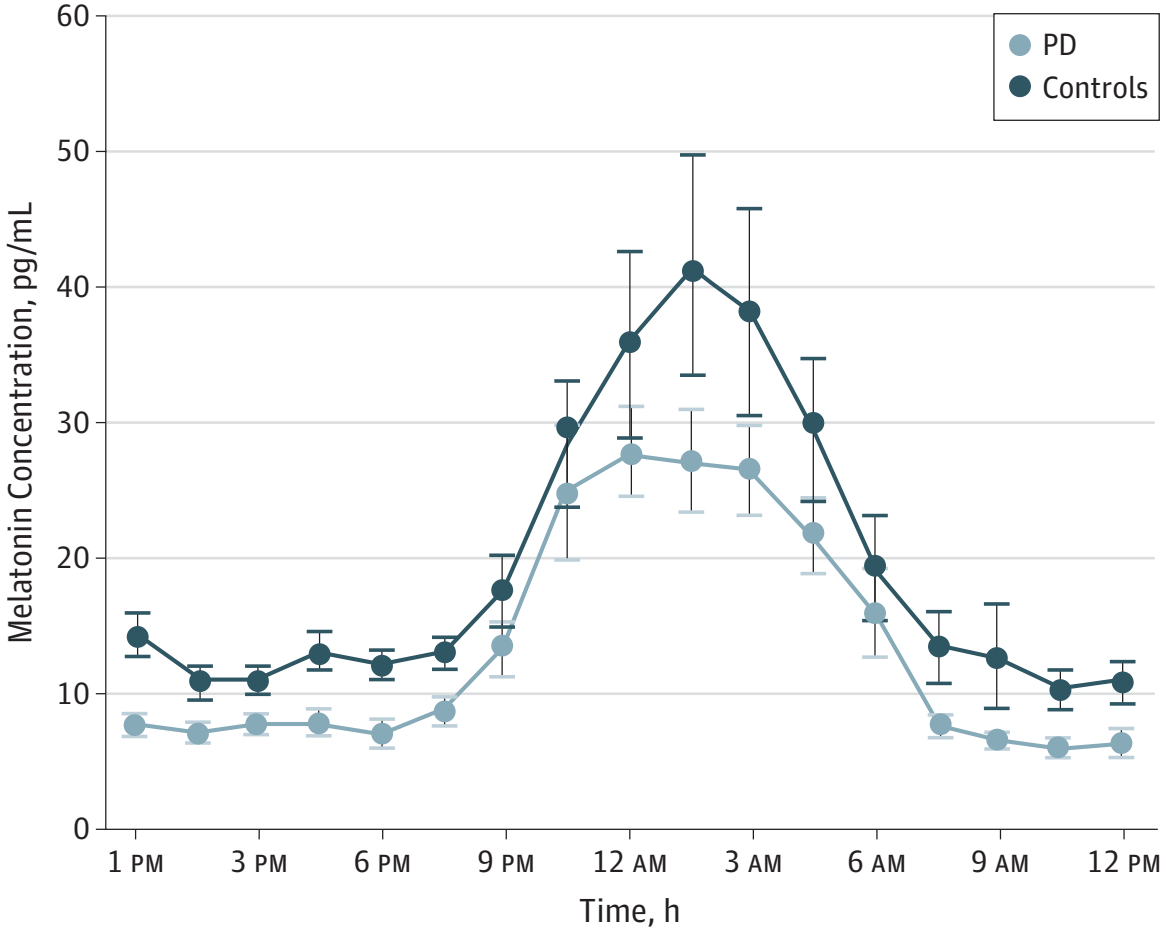


Suprachiasmatic nucleus (SCN) synchronises circadian oscillations

Endocrine profiles (such as melatonin and cortisol) can be used as surrogate markers of the central 'clock' since their rhythmic output is generated by the SCN

Clock genes form the molecular machinery of the cellular clock. Peripheral clock gene expression can be readily measured in peripheral blood cells.

Blunted melatonin rhythm



PARKINSON'S UK
CHANGE ATTITUDES.
FIND A CURE.
JOIN US.

LOTTERY FUNDED

Breen et al, JAMA Neurol 2014

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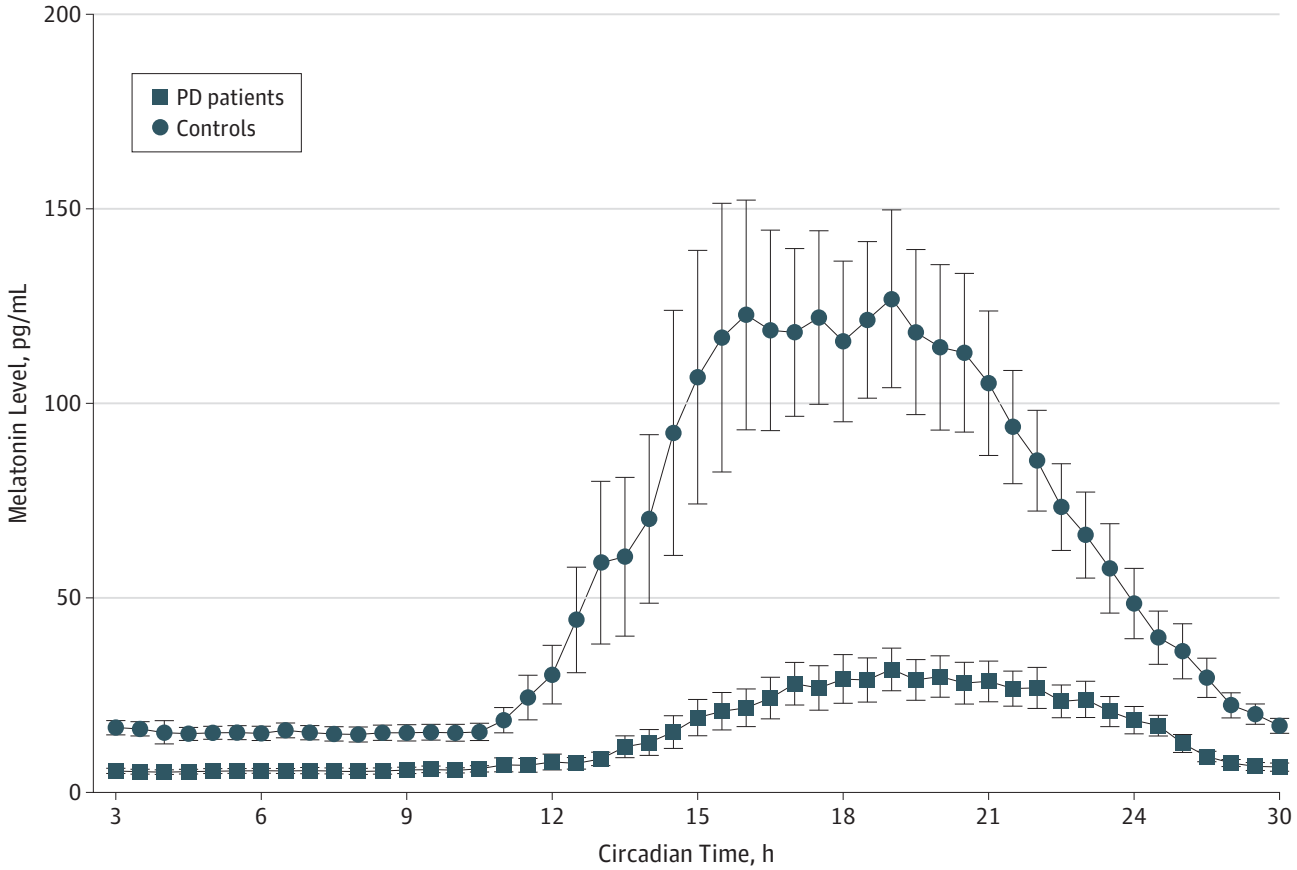
Blunted melatonin rhythm



Videnovic et al, JAMA Neurol 2014

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Blunted melatonin rhythm

RESEARCH ARTICLE

Plasma Melatonin Is Reduced in Huntington's Disease

Eirini Kalliolia, MD,[1†] Edina Silajdžić, PhD,[2†] Rajasree Nambron, MD,[1] Nathan R. Hill, PhD,[3] Anisha Doshi, MD,[1] Chris Frost, MA, DipStat,[4] Hilary Watt, MSc, CStat,[5] Peter Hindmarsh, FRCP,[6] Maria Björkqvist, PhD,[2] and Thomas T. Warner, FRCP[1*]

Melatonin Secretion Rhythm Disorders in Patients with Senile Dementia of Alzheimer's Type with Disturbed Sleep–Waking

Kazuo Mishima, Tozawa Tozawa, Kohtoku Satoh, Yasuhiro Matsumoto, Yasuo Hishikawa, and Masako Okawa

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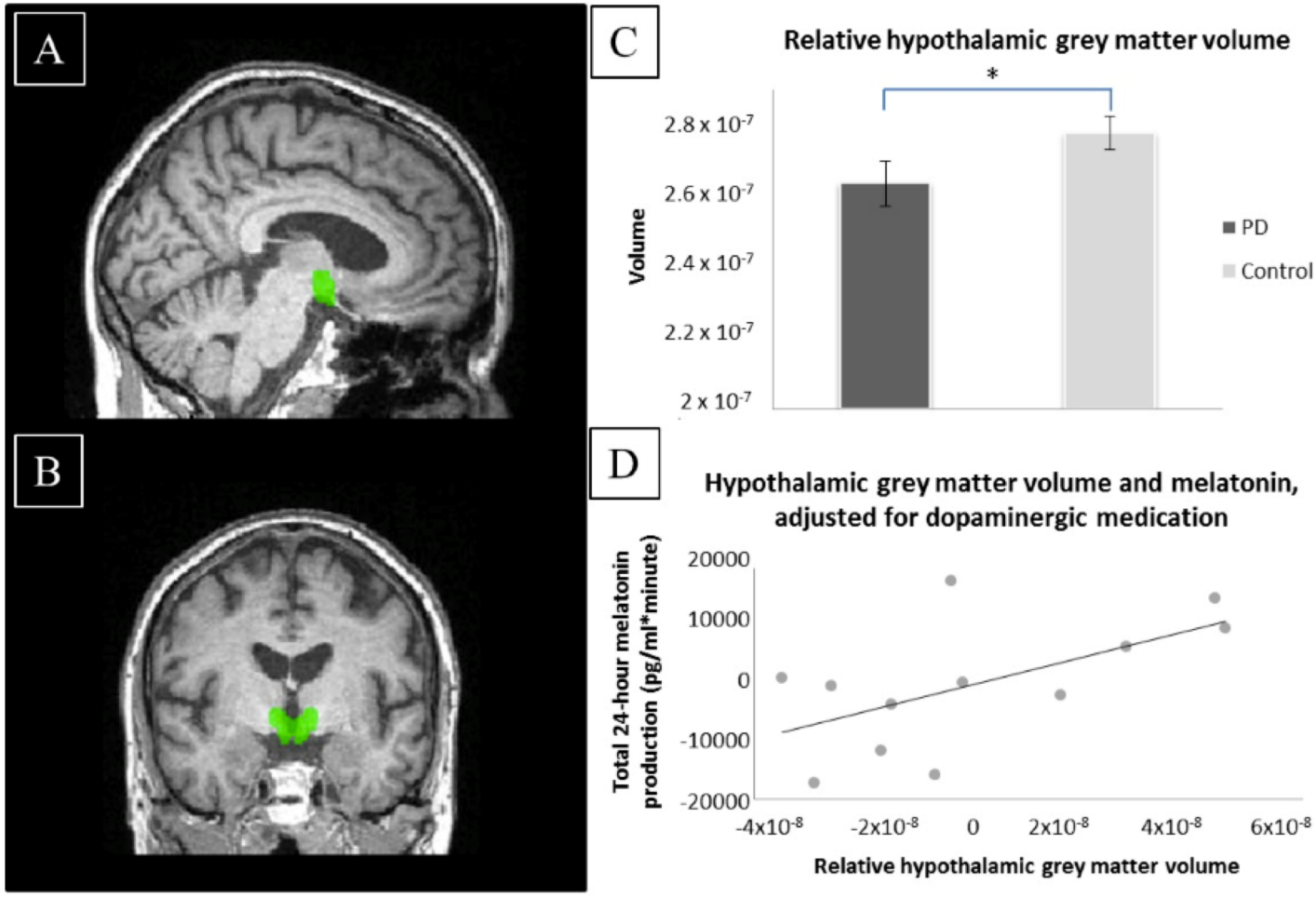
Hypothalamic volume loss



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Breen et al, Mov Disord 2016

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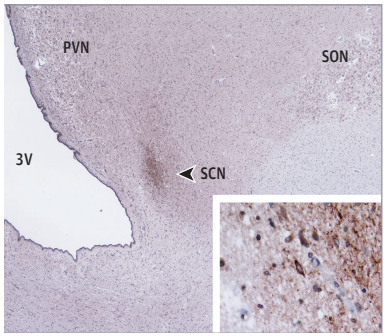
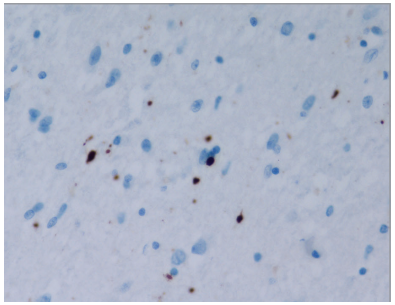
Postmortem damage

Brain bank study of PD (n=28), PSP (n=21), MSA (n=11) and controls (n=12)

Staining of the SCN for vasointestinal peptide



Staining of the SCN for α-synuclein



Variable	Control (n = 12)	PD (n = 28)	MSA (n = 11)[b]	PSP (n = 21)
Male-female sex	6:6	22:6 (*P* = .07)	7:4 (*P* = .52)	13:8 (*P* = .51)
Age at diagnosis, median (IQR), y	NA	67.1 (58.0-72.1)	63.3 (57.0-68.3)	66.5 (61.2-71.9)
Age at death, median (IQR), y	83.8 (78.2-88.0)	78.8 (75.5-83.8) (*P* = .10)	69.5 (61.6-77.7) (*P* < .001)	74.3 (69.7-81.1) (*P* < .001)
Disease duration, median (IQR), y	NA	14.3 (7.2-20.0)	5.4 (4.4-10.5) (*P* < .001)[c]	7.2 (4.5-9.1) (*P* = .002)[c]
SCN	**(n = 5)**	**(n = 13)**	**(n = 5)**	**(n = 5)**
SCN pathology, No. (%)	5 (100) Absent	4 (31) Absent, 7 (54) mild, 2 (15) moderate (*P* = .01)[d]	5 (100) Absent (*P* > .99)[d]	2 (40) Mild, 3 (60) moderate (*P* = .003)[d]
Pineal Gland	**(n = 7)**	**(n = 17)**	**(n = 6)**	**(n = 19)**
Pineal pathology, No. (%)	7 (100) Absent	15 (88) Absent, 2 (12) mild (*P* = .35)[d]	6 (100) Absent (*P* > .10)[d]	19 (100) Absent (*P* > .99)[d]
Braak stage, No. (%)	NA	3 (12) Braak stage 5, 22 (88) Braak stage 6 (*P* = .25)[e]	NA	NA
Lewy body subtype, No. (%)	NA	5 (22) Limbic, 18 (78) neocortical (*P* = .54)[f]	NA	NA

De Pablo-Fernandez, Mov Disord 2018

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Treatment

PD and medication triggers

PD TRIGGERS

Nocturnal motor dysfunction (consider Levodopa CR or Rotigitine patch)

Treat nocturia (anticholinergics)

Manage any cognitive or psychiatric co-morbidities

MEDICATION TRIGGERS

Avoid selegiline or amantadine later in the day

Avoid caffeine and alcohol (and large meals) later in the day

Avoid diuretics later in the day

Other sleep tips

Regular bed times

Dark and comfortable temperature

Suitable mattress and pillow (especially if difficulty turning)

Avoid TV or iPad before bed, avoid bright lights

Relaxation techniques

Avoid prolonged time in bed when awake

Exercise during the day (but avoid intense exercise just before bed)

Melatonin supplementation

Melatonin supplementation and the effects on clinical and metabolic status in Parkinson's disease: A randomized, double-blind, placebo-controlled trial

Reza Daneshvar Kakhaki[a], Vahidreza Ostadmohammadi[b,c], Ebrahim Kouchaki[d,e], Esmat Aghadavod[c], Fereshteh Bahmani[c], Omid Reza Tamtaji[c], Russel J.Reiter[f], Mohammad Ali Mansournia[g], Zatollah Asemi[c,*]

- 60 patients over 12 weeks
- 10mg melatonin SR
- Improvement in sleep and other measures

Prolonged-release melatonin in Parkinson's disease patients with a poor sleep quality: A randomized trial

Jong Hyeon Ahn[a,b], Minkyeong Kim[a,b], Suyeon Park[c], Wooyoung Jang[d], Jinse Park[e], Eungseok Oh[f], Jin Whan Cho[a,b], Ji Sun Kim[a,b,**], Jinyoung Youn[a,b,*]

- 34 patients with poor sleep over 4 weeks
- 2mg melatonin PR
- Improvement in sleep, NMSS and PDQ-39

Other medications commonly prescribed

Hypnotics (Eszopiclone recommended by MDS)

Benzodiazepines (e.g. Temazepam)

Antidepressant-type medications (e.g. Mirtazapine)

Sodium oxybate

New classes of medication

ARTICLE CLASS OF EVIDENCE

Daridorexant, a new dual orexin receptor antagonist, in elderly subjects with insomnia disorder

Gary Zammit, PhD,* Yves Dauvilliers, MD,* Scott Pain, MSc, Dalma Sebök Kinter, PhD, Yosef Mansour, PhD, and Dieter Kunz, PhD

Neurology® 2020;94:e2222-e2232. doi:10.1212/WNL.0000000000009475

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Thank you

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