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Sleep disturbance and impulsive-compulsive behaviours in Parkinson's disease.

Sean S. O'Sullivan, Clare Loane, Andrew D. Lawrence, Andrew Evans ...+2 more authors

Institutions: University College London

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Sean S O'Sullivan, Clare M Loane, Andrew D Lawrence, Andrew H Evans, Paola Piccini, Andrew J Lees

Title Page
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Sean S. O'Sullivan, MRCPI [1,2], Clare M. Loane, MSc [2], Andrew D. Lawrence, PhD [3], Andrew H. Evans, MD [4], Paola Piccini, PhD [2], Andrew J. Lees, FMedAcadSci [1]

[1] Reta Lila Weston Institute of Neurological Studies, University College London, UK.

[2] Division of Clinical Neurosciences and MRC Clinical Sciences Centre, Faculty of Medicine, Hammersmith Hospital, Imperial College London, London, UK

[3] Wales Institute of Cognitive Neuroscience, School of Psychology, Cardiff University, UK

[4] Department of Neurology, Royal Melbourne Hospital, Victoria, Australia

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Corresponding author:

Professor Andrew J Lees

Reta Lila Weston Institute of Neurological Studies, UCL

1 Wakefield Street,

London, WC1N 1PJ

United Kingdom

Email address: alees@ion.ucl.ac.uk

Telephone number: Tel: 004420 76794191 Fax number: 004420 7679 4236

Dr Sean S. O'Sullivan and Clare M. Loane completed the statistical analysis

Other authors' emails:

sosulliv@ion.ucl.ac.uk

c.loane@imperial.ac.uk

lawrencead@Cardiff.ac.uk

andrewhevans@yahoo.com

paola.piccini@imperial.ac.uk

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Abstract

Objectives: Impulsive-compulsive behaviours (ICBs) in Parkinson's Disease (PD) have been anecdotally linked with impaired sleep. We investigate measures of sleep in PD patients with and without ICBs, and in healthy controls.

Methods: We compare Parkinsonian features, measures of depression, anxiety and mania, and sleep disturbance in 30 PD patients with ICBs (PD+ICB), 62 PD patients without ICBs (PD - ICB), and 48 healthy controls.

Results: PD+ICB patients had younger age of PD onset, took more dopamine replacement therapy (DRT), had worse sleep, and elevated anxiety, depression and mania scores. Using multiple linear regression analyses, the total anxiety and depression scores, and presence of ICBs were the only variables associated with poorer sleep in PD.

Conclusions: PD+ICB patients may show enhanced psychomotor effects of DRT that may in turn contribute to poor sleep quality. Sleep disturbance should be specifically queried in PD+ICB patients.

Introduction

Although Parkinson's disease (PD) is defined by bradykinesia, rigidity and tremor at rest, a fragmented sleep pattern with insomnia is a common complaint, affecting approximately 66% of patients in one study.[1]

Impulsive-compulsive behaviours (ICBs) are increasingly recognized as a complication of dopamine replacement therapy (DRT), including pathological gambling (PG), hypersexuality (HS),compulsive shopping (CS), binge eating (BE), punding, and the dopamine dysregulation syndrome (DDS) .[2] [3] [4] Although the aetiology of ICBs remains to be clarified, a "global sensitization" of appetitive behaviours has been proposed.[3]

Anecdotal evidence links ICBs, DRT and impaired sleep. For example, DRT induces restlessness, insomnia, nightmares and vivid dreaming, [3] [5] and dopamine is now known to play a prominent role in promoting wakefulness.[6] This study is the first to specifically investigate sleep disturbances in PD patients with ICBs and tests the hypothesis that higher levels of DRT, ICB diagnosis and/or mood, are related to sleep disturbance.

Methods

Outpatients attending a specialist PD clinic were assessed by the lead author for the presence of ICBs in a semi-structured interview using proposed criteria.[3] [2] [4] REM sleep behaviour disorder (RBD) was identified during the clinical interview, according to International Classification of Sleep Disorders criteria.[7] Patients were screened using the Mini-Mental State Examination (MMSE) and 15 who scored

below 26 were excluded because of the requirement to complete self-report scales.

The Unified PD Rating Scale (UPDRS) part 3 was rated in the "on" state by the treating physician. Calculation of a daily L-dopa equivalent dose (LED) dose for each patient was based on theoretical equivalence of dopamine agonists to L-dopa.[4] Healthy controls without PD or dementia were identified from partners or friends of participating patients attending the outpatient department.

Questionnaires. Participants who provided written informed consent to protocols approved by the UCLH Trust local ethics committee were given a series of questionnaires to complete in their own time and return in a reply-paid envelope. These included the PD Sleep Scale (PDSS),[8] the Mood Disorder Questionnaire (MDQ),[9] and The Hospital Anxiety and Depression Scale (HADS).[10]. The MDQ is a patient-completed bipolar disorder screen, with 73% sensitivity and 90% specificity in the identification of bipolar spectrum disorders.[9]

Data analysis. Data were analyzed with SPSS 14, SPSS Inc., Chicago, IL. Medians/means were compared using Krusall-Wallis, Mann–Whitney *U* tests (MWU), one-way analyses of variance (ANOVA), or Student *t* test where appropriate. Post-hoc multiple comparisons within a variable using ANOVA were corrected by the Bonferroni method. Kolmogorov-Smirnof tests showed that PDSS and MDQ scores were not normally distributed. Levene's test showed that all variables tested exhibited homogeneity of variance. Univariate correlations between PDSS score and variables such as total anxiety score of HADS, total depression score of HADS, total score of the MDQ symptoms, daily L-dopa amounts used, and daily LED of dopamine

agonists used were made using Spearman's or Pearson's correlation as appropriate.

Factors were entered in a multiple linear regression model to identify clinical features that were independently associated with total PDSS scores. Backward entry method was used, with the probability for stepwise removal set at 0.1. To check the consistency of the model a forward approach with a probability of stepwise entry of 0.05 was also used. Variables entered in the statistical model with total PDSS score as the dependent variable included age, gender, combined total anxiety + depression score of HADS (due to significant univariate correlation between the two HADS subscales, these results were not entered separately), total score of the MDQ symptoms, daily L-dopa amounts used, daily LED of dopamine agonists used, and the presence of documented ICBs.

Results

Participant demographics and PD history

One hundred and thirty three patients with PD received questionnaires, and 41 either did not consent or did not return the questionnaires. Thirty patients who completed the questionnaires were identified as ICBs (PD+ICB), and many of these exhibited more than one ICB. These included 15 with punding, 12 with hypersexuality, 11 with pathological gambling, 8 with compulsive shopping and 8 with binge eating. Forty eight healthy controls were also included. (Table 1). Antidepressant and/or anxiolytic

were used in 28.6% of PD+ICB (28.6%), and 16.1% of PD-ICB patients, (Chi-square = 1.2, df = 1, p=0.28,).

Table 1. Participant details, sleep and mood results

	PD total group	PD + ICB	PD – ICB	Healthy controls	Statistic (P value)
N	92	30	62	48	
M:F	70:22	24:6	46:16	39:9	χ^2=0.88, df = 2, (p=0.6)
Age	64.4 ± 9.9	58.9 ± 8.5* ‡	66.4 ± 9.7* †	57.9 ± 10.6†‡	ANOVA F (2,134) = 11.6, (p <0.0005) * 0.003 †<0.0005 ‡ = 1.0
Age PD onset.	52.3 ± 12.7	46.2 ± 10.1*	55.8± 12.0*	N/A	* t=3.6, df = 66, (p= 0.001)
Duration of PD (years)	10.5 ± 6.7	11.5 ± 5.9*	9.5 ± 7.0*	N/A	*t= 1.2, df = 67, (p= 0.2)
H + Y on medications Median (interquartile range)	2 (2-3)	3 (2.1-3)*	2 (2-3)*	N/A	* MWU = 67, *(p = 0.04)
Current L-dopa dose/day (mg)	597 ± 443	701 ± 508*	543 ± 399*	N/A	* t=-1.4, df = 73, (p= 0.16)
Current DA LEU dose/day (mg) Median (interquartile range)	90, (0-262)	201, (0-284)*	0, (0-201)*	N/A	* MWU = 555, (p= 0.12)
Combined L-dopa + DA LEU/day (mg).	764 ± 548	981 ± 651*	645 ± 443*	N/A	*t=-2.5, df = 75,(p= 0.018)
RBD diagnosed	19/55 (34.5%)	7/18* (38.9%)	12/37* (32.4%)	Not included	* χ^2=0.03, df = 1, (p=0.9)
HADS anxiety score	15.0 ± 3.6	16.9 ± 3.9¥†	14.3 ± 3.2¥*	13.9 ± 3.9*†	ANOVA F (2,128) = 6.9 (p=0.001) * = 1.0 ¥ = 0.005 † = 0.002
HADS depression score	13.2 ± 3.1	14.5 ± 3.5¥†	12.8 ± 2.7¥*	9.9 ± 2.9†*	ANOVA F (2,129) = 23.7 (p <0.0005) *= <0.0005 ¥ = 0.053 †<0.0005
Mania symptom score Median (interquartile range)	3, (1-7)	6, (3-8) †¥	3, (1-6) *¥	2, (0-5) *†	Kruskall-Wallis Chi Square = 13, df = 2, (p= 0.002) * MWU (p=0.6) ¥ MWU (p=0.002) † MWU (p=0.001)

Means are compared with t-tests, except where indicated
All values are mean +/- SD except where indicated
ANOVA = analysis of variance. Post-hoc multiple comparisons within a variable using ANOVA were corrected by the Bonferroni method.

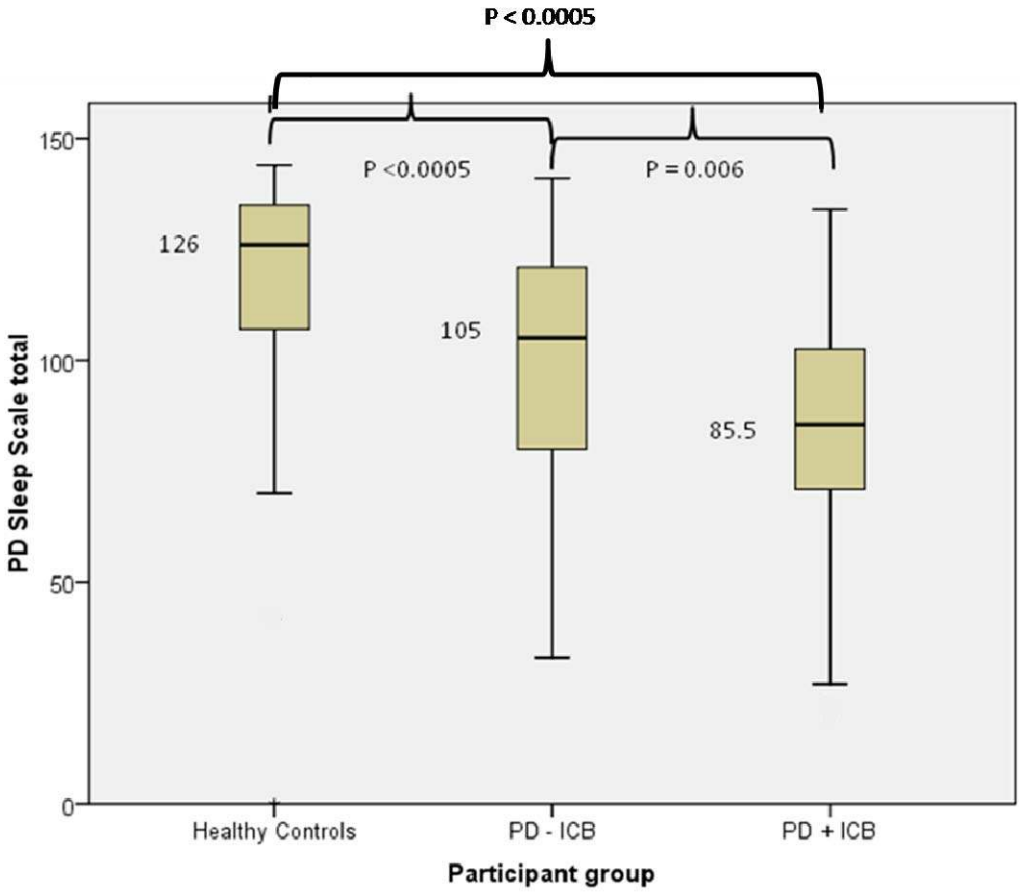
MWU =Mann Whitney U test
SD = Standard deviation
df = degrees of freedom

Sleep disturbance, mood and ICBs

PD patients had worse sleep scores than healthy controls ($p < 0.0005$), and the PD + ICB group had worse sleep than the PD-ICB ($p = 0.006$). Figure 1. Of the 92 PD patients included, the presence or absence of RBD was elicited in 55 (60%), with the vast majority of the remainder being unclassifiable due to the lack of witnessed sleep behaviours. (Table 1).

No participants had a diagnosis of bipolar mood disorder. 30% of PD + ICB, 3.2% of the PD-ICB, (Chi-square = 13.8, df = 1, $p < 0.0005$), and 4.2% of healthy controls scored above the recommended cut-off for bipolar spectrum disorder on the MDQ.[9] No clinical differences were seen when comparing PD patients with and without RBD.

Figure: PD Sleep Scale total scores



Median scores are compared with Mann Whitney U tests. Lines denote the median values; box denotes specific interquartile range. Maximum and minimum scores are indicated by the upper and lower markers, respectively. Lower scores are associated with worse sleep quality.

Predictors of sleep disturbance in PD

In the combined PD group, there was a negative correlation between sleep impairment (total PDSS score) and anxiety (Pearson Correlation coefficient = -0.39, $p<0.00005$), and depression (Pearson Correlation coefficient = -0.34, $p=0.001$). No correlations were seen between PDSS totals and variables such as age, gender, or DRT amounts. In all univariate analyses, the non-significant correlation coefficients were all $< |0.22|$) Using multiple linear regression analyses, the presence of ICBs ($p=0.045$) and combined HADS anxiety + depression totals ($p=0.068$) were the only variables associated with sleep disturbance in PD ($p=0.004$).

Discussion

PD patients with ICBs have poorer sleep quality, compared to PD patients without ICBs and healthy controls. Several clinical differences were found between the PD + ICB and PD-ICB groups including age and medication use but are unlikely to account for the observed poor sleep quality. PD + ICB patients were on average 8 years younger at time of study despite a similar PD duration in both groups. The exclusion of patients scoring <26 on the MMSE might disproportionately exclude older patients,

those with a longer history or those in who decisions to reduce DRT have been made because of cognitive or psychotic problems. Previous studies have found that age does not correlate with PDSS scores,[11] but normal aging is accompanied by decreased ability to initiate and maintain sleep, and a decrease in the proportion of the more restorative slow-wave sleep and rapid eye movement sleep.[12] Age differences alone therefore, cannot explain why the PD+ICB group have a poorer quality of sleep than PD-ICB patients.

PD+ICB patients had higher rates of mood disturbance, which could potentially directly impact sleep quality. In PD, the association between sleep disturbances and mood disorders is well established.[13] [14] PD patients had increased anxiety and depression than controls, with PD+ICB more so than PD-ICB. Consistent with previous reports,[14] we found a correlation between poor sleep scores and depression and anxiety severity.

The PD + ICB patients had higher MDQ scores than the PD-ICB patients; although the MDQ has not been validated for use in PD. None of the included PD participants fulfilled diagnostic criteria for bipolar mood disorder. However, in our study 29% of PD + ICB, 3.2% of the PD – ICB group, and 4.2% of healthy controls scored above the recommended cut-off for bipolar spectrum disorder.[9] A recent large study of bipolar disorders including sub-threshold bipolar disorder found a lifetime prevalence of 4.4% amongst the general population.[15] The increased frequency of manic

symptoms in the PD patients may relate to medication-effects which have been recognised since the introduction of L-dopa.[16] An association between medication-induced hypomania and pathological gambling in PD has been described,[2] in contrast with patients developing ICBs after being treated with dopaminergic medications for restless legs syndrome, where none describe medication-induced mania.[17] As with any work involving multiple comparisons, caution is required regarding the risk of false positive results.

Although the PD+ICB group were using more DRT than the PD-ICB patients, notably neither the daily amount of L-dopa nor dopamine agonist medication use correlated with altered sleep scores or RBD frequency. These results suggest that it is not simply the amount of DRT that causes poor sleep quality. This finding differs from previous reviews which have suggested an association between DRT and nightmares,[18] and RBD[19]

The presence of ICBs was identified as being independently associated with sleep disturbance. This suggests that PD+ICB patients may be more sensitive to the psychomotor stimulant-arousal effects of DRT, which in turn contributes to poorer sleep. Punding behaviours, may contribute to poor sleep quality as a consequence of persistence of these stereotyped behaviours throughout the night at the expense of a normal sleep pattern.[4] However, we found no difference when comparing sleep scores in PD+ICB patients with or without punding ($p = 0.7$, MWU) This is consistent with animal models, showing an effect of dopamine on wakefulness independent of

motor stereotypies.[20] Alternatively, sleep disturbance in PD + ICB might relate to underlying impulsive personality traits, which are risk factors for developing ICBs,[21] and which are linked with insomnia independent of DRT use.[22] Sleep disruption has also been suggested to heighten psychomotor sensitization effects,[23] which could impact on the expression of ICDs in PD. Further work is needed in this area, and we conclude that sleep disturbance should be specifically queried in PD+ICB patients.

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Statement:

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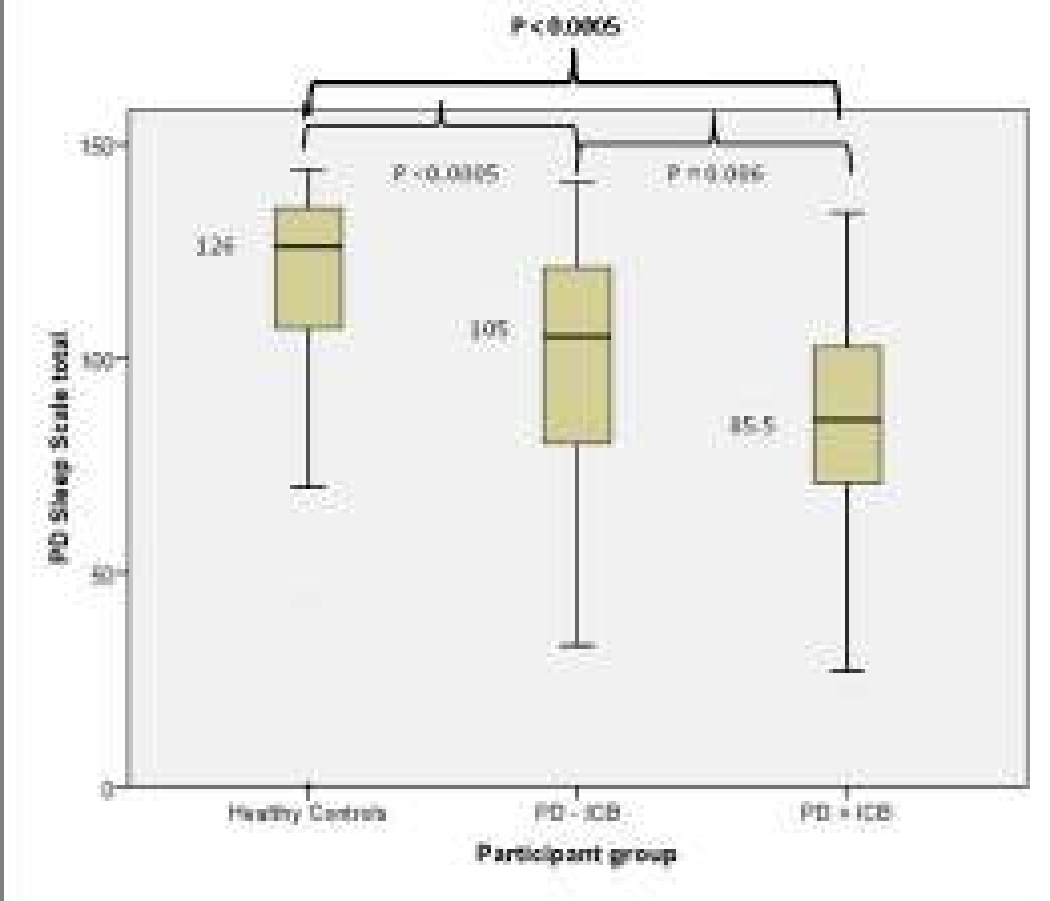
P < 0.0005
P < 0.0005
P = 0.006
126
105
85.5
150
100
50
0
PD Sleep Scale total
Healthy Controls
PD - ICB
PD + ICB
Participant group