



## Doxepin and cognitive behavioural therapy for insomnia in patients with Parkinson's disease – A randomized study



S. Rios Romenets<sup>a</sup>, L. Creti<sup>b</sup>, C. Fichten<sup>b</sup>, S. Bailes<sup>b</sup>, E. Libman<sup>b</sup>, A. Pelletier<sup>c</sup>, R.B. Postuma<sup>a,\*</sup>

<sup>a</sup> Department of Neurology, McGill University, Montreal General Hospital, Montreal, Quebec, Canada

<sup>b</sup> Department of Psychiatry, McGill University, Jewish General Hospital, Montreal, Quebec, Canada

<sup>c</sup> Neuroepidemiology Research Unit, Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada

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### ABSTRACT

**Introduction:** Although a variety of pharmacologic and non-pharmacologic treatments are effective for insomnia in the general population, insomnia in Parkinson's disease differs in important ways and may need different treatments. No studies have conclusively demonstrated effective insomnia treatments in Parkinson's disease.

**Methods:** We conducted a three-arm six-week randomized pilot study assessing non-pharmacologic treatment (cognitive behavioural therapy with bright light therapy) or doxepin (10 mg daily), compared to an inactive placebo in Parkinson's patients with insomnia. Sleep outcomes included insomnia scales, clinical global impression, sleep diaries and actigraphy. Secondary outcomes included motor severity, fatigue, depression and quality of life.

**Results:** 18 patients were randomized, 6 to each group. Compared to placebo, doxepin improved the Insomnia Severity Index ( $-9 \pm 5.4$  vs.  $-2 \pm 3.9$ ,  $p = 0.03$ ), the SCOPA-night score ( $-5.2 \pm 1.5$  vs.  $-2.3 \pm 2.8$ ,  $p = 0.049$ ), the Pittsburgh Sleep Quality Index-sleep disturbances subscale ( $-0.5 \pm 0.5$  vs.  $0.2 \pm 0.4$ ,  $p = 0.02$ ), and both patient and examiner-rated clinical global impression of change ( $1.7 \pm 0.8$  vs.  $0.5 \pm 0.8$ ,  $p = 0.03$  and  $1.4 \pm 0.5$  vs.  $0.3 \pm 0.5$ ,  $p = 0.003$ ). On secondary outcomes doxepin reduced the fatigue severity scale ( $p = 0.02$ ) and improved scores on the Montreal Cognitive Assessment ( $p = 0.007$ ). Non-pharmacological treatment reduced the Insomnia Severity Index ( $-7.8 \pm 3.8$  vs.  $-2.0 \pm 3.9$ ,  $p = 0.03$ ), and the examiner-reported clinical global impression of change ( $p = 0.006$ ), but was associated with decline in Parkinson Disease Questionnaire-39. There were no changes in other primary and secondary outcomes, including actigraphy outcomes. Adverse events were comparable in all groups.

**Conclusion:** Doxepin and non-pharmacologic treatment substantially improved insomnia in Parkinson's disease. These potential benefits must be replicated in a full confirmatory randomized controlled trial.

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### 1. Introduction

One of the most common non-motor manifestations in Parkinson's disease (PD) is insomnia, which affects up to 60% of patients [1]. Insomnia can have multiple adverse consequences. Aside from the primary frustration associated with long sleepless nights, insomnia can result in daytime fatigue, excessive daytime somnolence [2], and impairment in attention and executive functioning [3]. Insomnia can also cause severe caregiver stress if patients need

assistance while awake. Although some studies have shown potential [4,5], no treatment has been conclusively demonstrated as effective for insomnia in PD.

There are a variety of pharmacologic and non-pharmacologic treatments for insomnia that are effective in the general population [6–8]. However, insomnia in PD may differ in important ways from non-PD patients. Insomnia in PD can be related to motor manifestations (tremor, pain, etc), co-morbid non-motor conditions (nocturia, depression, hallucinations, etc), and anti-parkinsonian medications. Unlike the general population, PD insomnia is related to degeneration of brainstem sleep regulatory centers [9]. Finally, insomnia differs in its presentation – PD patients mainly have problem with sleep maintenance/sleep fragmentation and early awakenings, rather than trouble with sleep initiation [10]. Most pharmacologic agents target sleep initiation;

\* Corresponding author. Department of Neurology, L7-312 Montreal General Hospital, 1650 Cedar Ave., Montreal, Quebec, Canada H3G1A4. Tel.: +1 514 934 8026; fax: +1 514 934 8265.

E-mail addresses: [ronpostuma@hotmail.com](mailto:ronpostuma@hotmail.com), [ron.postuma@mcgill.ca](mailto:ron.postuma@mcgill.ca) (R.B. Postuma).

any benefits on sleep maintenance are usually related to longer half-lives, with resultant potential for adverse daytime effects.

All of these differences imply that treatments designed for the general population may be ineffective or inappropriate in PD. We therefore designed a pilot randomized study to test the tolerability and effectiveness of two treatment strategies. The first was a non-pharmacologic strategy consisting of combination of cognitive behavioural therapy, sleep hygiene and bright light therapy. The second was to use doxepin, a tricyclic antidepressant with selective histaminergic antagonistic action at low doses that may be particularly effective in sleep maintenance insomnia in elderly adults [11,12].

## 2. Methods

This was a three-arm six-week pilot study assessing non-pharmacologic treatment (cognitive behavioural therapy/bright light therapy) or doxepin 10 mg at bedtime, compared to an inactive placebo. The study was approved by the research ethics board of the McGill University Health Center. Written informed consent was obtained from all participants. This trial was registered with [clinicaltrials.gov](http://clinicaltrials.gov) # NCT01489982.

## 3. Participants

Patients were eligible for inclusion if they had idiopathic PD and suffered from insomnia (minimum SCOPA-sleep nocturnal subscore  $\geq 7$  [13]). The insomnia must have been persistent for at least 6 months. All subjects spoke either English or French. Exclusion criteria included frequent (i.e.  $>2$  per week) use of sedative medications at night (including sedating antidepressants), untreated restless legs syndrome, night shift work or other occupational causes of abnormal sleep pattern, insomnia related to suboptimal dopaminergic therapy, other reversible causes of insomnia detected upon baseline clinical interview, premenopausal women not using effective methods of birth control, dementia (defined according to PD dementia criteria), change in dopaminergic therapy over the preceding three months, Hoehn and Yahr  $>4$  (i.e. nonambulatory), use of non-selective MAO-inhibitors or rasagiline (due to potential doxepin contraindication), hypersensitivity to doxepin, untreated narrow angle glaucoma or severe urinary retention. We did include patients with REM sleep behavior disorder, considering that this condition does not cause insomnia. Patients were recruited from movement disorders clinics of the McGill University Health Center.

## 4. Intervention

Patients were randomized to one of three interventions: non-pharmacologic treatment, pharmacologic treatment, and placebo. The non-pharmacologic treatment arm included three key interventions: sleep hygiene training, cognitive behavioural therapy, and bright light therapy. Cognitive behavioural therapy (CBT) and sleep hygiene was instituted at the Department of Psychiatry of the Jewish General Hospital, Montreal. Interventions took place in a group setting and consisted of 6 weekly sessions of 90 min, with 2 patients per group. Light therapy was administered daily for duration of 30 min. If a patient had predominantly sleep maintenance insomnia, this was provided in the evening, 30 min before bedtime (to improve sleep maintenance by delaying melatonin secretion and therefore shifting the circadian rhythm later in the day). If a patient had sleep onset insomnia/circadian phase delay, light was given in the morning. Light boxes were provided by the Litebook Company (Litebook®). Light intensity was 10,000 lux with a head-to-light distance of 20 cm. The pharmacologic treatment was doxepin 10 mg at bedtime. The inactive/placebo intervention was 30 min of light therapy, using red light below the threshold

required to entrain light cycles (no placebo capsules were given). Patients were informed that some forms of light therapy were expected to be less active, but were not told what type of condition was inactive.

## 5. Outcomes

Since the validity and responsiveness to change of insomnia scales has not been fully defined in PD [14], there is no clear single scale choice. Therefore, we used several insomnia scales. Two scales were chosen as primary outcomes: the SCOPA sleep [13] (a disease-specific scale for PD which includes a nocturnal component for insomnia and a daytime component for somnolence) and the Insomnia Severity Index [15] (a non-disease-specific scale that has been validated in clinical trials).

Other insomnia outcome measures included:

1. Parkinson's Disease Sleep Scale (PDSS) [16]
2. Daily Sleep Diary, assessing sleep onset, sleep duration, daytime naps, and night waking.
3. Pittsburgh Sleep Quality Index (PSQI) [17]
4. Clinical Global Impression of Change (CGI-C), completed by both the examiner and the patient, with insomnia as the target symptom, scored from -3 (severe worsening) to +3 (dramatic improvement) [18]
5. Actigraphy [19], including total time in bed, total sleep duration, sleep efficiency, and wake after sleep onset (Actiwatch Spectrum and Actiwatch 2, Respironics).
6. Sleep Hygiene Index (SHI) [20]
7. Dysfunctional Beliefs and Attitudes about Sleep – brief version (DBAS-16) [21]
8. Krupp Fatigue Severity Scale (FSS) [22]
9. Epworth Sleepiness Scale (ESS) [23]
10. Beck Depression Inventory (BDI) [24]
11. Disease severity, assessed with the Unified Parkinson Disease Rating Scale (UPDRS)
12. Parkinson's Disease Questionnaire-39 (PDQ-39) [25]
13. Adverse events and side effects of treatment, via a structured interview.
14. Montreal Cognitive Assessment (MoCA) [26]

## 6. Randomization and analysis

Patients were randomized to one of three initial treatment groups: CBT/BLT, doxepin or inactive/placebo (red light). Randomization was done with a block design (block size = 9). Because CBT/BLT is a group therapy, randomization of one patient to CBT/BLT led to automatic assignment of the subsequent two patients to the non-pharmacologic arm. The placebo condition was not disclosed as an inactive placebo, but treatment assignment was not otherwise blinded.

Statistical analysis compared each active treatment to placebo using *t*-tests for continuous variables and chi-squared tests for categorical variables. All patients who received intervention were analyzed (see Results section). We estimated effect of treatment (i.e. placebo vs. CBT/BLT and placebo vs. doxepin) on the SCOPA-night scale and ISI (change from baseline) without adjusting for age and gender because of small numbers of participants.

## 7. Results

Twenty PD patients signed informed consent. Two patients withdrew from the study before intervention was provided, one from the placebo group because of health problems during Week 1

**Table 1**  
Baseline characteristics.

	Placebo, n = 6	CBT/BLT, n = 6	Doxepin, n = 6
Age	69.5 ± 10.5	64.5 ± 16.3	65.3 ± 10.5
Sex (% male)	83%	100%	50%
Disease duration	5.2 ± 4.4	5.2 ± 1.8	4.8 ± 3.6
Levodopa dose (mg)	678.3 ± 183.3	566.7 ± 267.7	433.3 ± 242.1
Primary insomnia outcomes			
SCOPA sleep-total	24.3 ± 8.3	26.5 ± 5.6	25.0 ± 3.5
SCOPA-night	10.0 ± 3.0	12.7 ± 1.4	11.0 ± 2.2
SCOPA-daytime	9.2 ± 6.4	9.3 ± 4.0	8.3 ± 2.3
Insomnia severity index	14.7 ± 6.1	19.9 ± 3.7	16.5 ± 5.4
Sleep quality			
PSQI	13.2 ± 3.2	14.7 ± 2.9	12.0 ± 2.6
PDSS	86.5 ± 23.4	91 ± 19.1	87.7 ± 10.2
Daytime functioning			
Krupp fatigue severity Scale	34.0 ± 16.6	44.5 ± 4.9	46.5 ± 10.9
Epworth sleepiness scale	11.2 ± 7.0	9.0 ± 3.4	13.8 ± 4.8
Beck depression inventory	8.2 ± 3.7	7.8 ± 6.7	12.0 ± 7.5
Insomnia beliefs and behavior			
Sleep hygiene index	24.0 ± 5.9	21.8 ± 3.4	25.3 ± 5.0
DBAS-16	91.2 ± 32.7	83.7 ± 15.6	82.3 ± 33.6
Disease severity			
PDQ-39	24.0 ± 18.1	27.2 ± 14.8	43.5 ± 16.2
UPDRS-total	32.8 ± 14.5	32.8 ± 16.3	30.9 ± 7.6
UPDRS III	22.1 ± 9.1	22.6 ± 12.8	18.3 ± 7.6
Cognitive functioning			
MoCA	26.8 ± 2.6	24.0 ± 1.4,	24.8 ± 3.6
		<b>p = 0.04</b>	

CBT, Cognitive behavioural therapy; BLT, Bright light therapy; SCOPA, Scales for Outcomes in Parkinson's disease; PSQI, Pittsburgh Sleep Quality Index PDQ-39; PDSS, Parkinson's Disease Sleep Scale; Parkinson's Disease Questionnaire-39; DBAS, Dysfunctional Beliefs and Attitudes about Sleep; UPDRS, Unified Parkinson Disease rating Scale; MoCA, Montreal Cognitive Assessment; n, number; hrs; p values reflect t-tests comparing treatment condition to placebo – only p values that demonstrate a significant difference between groups (i.e. baseline MoCA) are shown.

and another one from CBT group (during baseline assessment) because of inability to complete evaluations (i.e. unable to follow actigraphy and sleep diary instructions). These were not included in the analysis. One patient from the CBT group missed four of six sessions, but completed all evaluations – this data was included in the analysis. Of the 18 patients, 14 were men; the average age was 66.4 ± 12.4, and disease duration was 5.0 ± 3.3 years. Based on scores from the SCOPA-night and Insomnia Severity Index 16 patients had sleep maintenance insomnia and 7 had sleep onset insomnia (trouble with sleep initiation). Based on scores of SCOPA-daytime and Epworth sleepiness scale, 10 patients also reported

**Table 2**  
-Primary and secondary sleep outcomes.

	Placebo, n = 6	CBT/BLT, n = 6	p value	Doxepin, n = 6	p value
Primary insomnia outcomes					
SCOPA-night	-2.3 ± 2.8	-5.4 ± 4.3	p = 0.17	-5.2 ± 1.5	<b>p = 0.049</b>
Insomnia severity index	-2.0 ± 3.9	-7.8 ± 3.8	<b>p = 0.03</b>	-9.0 ± 5.4	<b>p = 0.03</b>
Clinical global impression (insomnia)					
CGI of change patient	3.5 ± 0.8	4.2 ± 0.4	<b>p = 0.08</b>	4.7 ± 0.8	<b>p = 0.03</b>
CGI of change examiner	3.3 ± 0.5	4.2 ± 0.4	<b>p = 0.006</b>	4.4 ± 0.5	<b>p = 0.003</b>
Sleep quality					
PSQI-total	-3.8 ± 4.5	-4.7 ± 4.3	p = 0.73	-3.7 ± 2.7	p = 0.96
PSQI-sleep disturbances	0.2 ± 0.4	-0.3 ± 0.5	p = 0.08	-0.5 ± 0.5	<b>p = 0.02</b>
PDSS-total*	10.0 ± 9.8	10.3 ± 8.3	p = 0.96	19.5 ± 20.4	p = 0.33
PDSS#1-quality of sleep*	-0.3 ± 1.0	3.8 ± 2.2	<b>p = 0.02</b>	1.7 ± 2.8	p = 0.13

CBT, Cognitive behavioural therapy; BLT, Bright light therapy; SCOPA, Scales for Outcomes in Parkinson's disease; CGI, Clinical global impression of change; PSQI, Pittsburgh Sleep Quality Index; PDSS, Parkinson's Disease Sleep Scale Parkinson's Disease; \*, indicates that increase in scores is positive improvement; p values reflect t-tests comparing treatment condition to placebo (**p < 0.05** are highlighted in bold text).

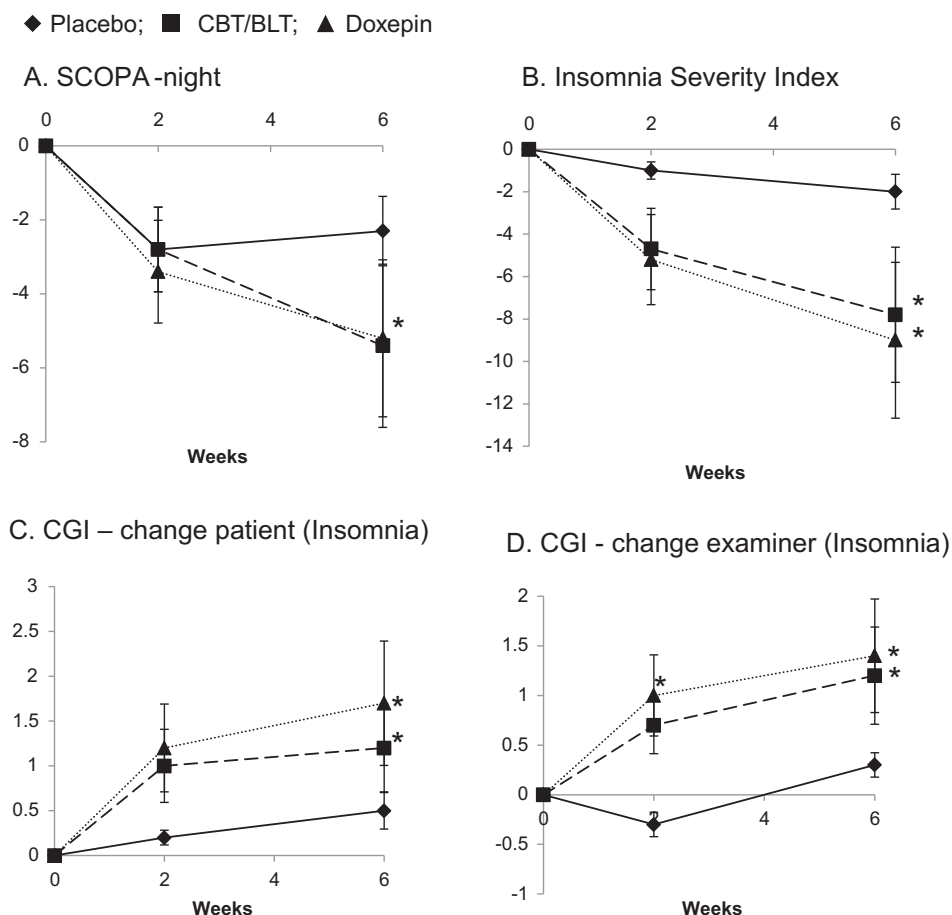
excessive daytime somnolence. There were no significant differences between groups in age, sex, disease duration, levodopa dose, disease severity, or primary and secondary sleep outcomes (Table 1). Patients in the CBT group had lower baseline MoCA scores than the other two groups. Seventeen patients were taking levodopa (average dose = 564 ± 237 mg), 12 were taking dopamine agonists, 2 were taking COMT inhibitors, and 14 were taking MAO-inhibitors. Two patients were on antidepressants (non-sedating antidepressants), 2 took medications for REM sleep behavior disorder (1 melatonin, 1 clonazepam) and 6 patients (two from each group) were taking prn hypnotics as rescue therapy (all ≤2/week). All 18 patients completed the trial.

## 8. Doxepin

At week 6, several insomnia outcomes revealed significant improvements in the Doxepin group when compared to placebo. On the primary measures, scores on the Insomnia Severity Index (ISI) improved (-9 ± 5.4 vs. -2 ± 3.9, p = 0.03) and the SCOPA-night scale also improved (-5.2 ± 1.5 vs. -2.3 ± 2.8, p = 0.049). On secondary sleep measures, there was no significant change in the total PDSS or PSQI, although the PSQI-sleep disturbances subscale improved significantly (0.5 ± 0.5 vs. 0.2 ± 0.4, p = 0.02). Patient and examiner-rated CGI-change scores also improved significantly (1.7 ± 0.8 vs. 0.5 ± 0.8, p = 0.03 and 1.4 ± 0.5 vs. 0.3 ± 0.5, p = 0.003, respectively) (Table 2, Fig. 1). Daytime fatigue scores (FSS) significantly improved when compared to placebo (-17.7 ± 14.3 vs. 0 ± 5.8, p = 0.02), but scores on other sleepiness measures did not change compared to placebo. On non-sleep secondary outcomes, cognitive functioning (MoCA) improved significantly in the Doxepin group compared to placebo (2.2 ± 1.9 vs. -1.2 ± 1.3, p = 0.007) (Table 3). There were no differences among groups on other sleep variables including depression (BDI), difficulty in daily living (PDQ-39), sleep hygiene (SHI), dysfunctional sleep beliefs (DBAS-16), and disease severity (UPDRS) (Tables 2 and 3 and Supplemental).

## 9. Non-pharmacological treatment

At 6 weeks, for primary insomnia outcomes, the insomnia severity (ISI) scores showed significant improvement in the non-pharmacological treatment group compared to placebo (-7.8 ± 3.8 vs. -2.0 ± 3.9, p = 0.03). However, there was no change in the SCOPA-night score. On secondary sleep outcomes, the examiner-rated CGI-change improved significantly (1.2 ± 0.4 vs. 0.3 ± 0.5, p = 0.006) with a non-significant trend towards improvement in the patient-rated CGI-Change (4.2 ± 0.4 vs. 3.5 ± 0.8, p = 0.08) (Table 2, Fig. 1). None of the other insomnia frequency measures (total PDSS, PSQI) changed. Of the sleep quality



**Fig. 1.** Change in outcomes in CBT/BLT, Doxepin vs placebo. (A) SCAles for Outcomes in Parkinson's disease (SCOPA), (B) Insomnia Severity Index (ISI), (C,D) Clinical Global Impression (CGI)-Change. Shown are the changes in primary outcomes of interest in Cognitive Behavior Therapy (CBT)/Bright light therapy (BLT), Doxepin and placebo over the 6-week trial. Baseline values are set at 0. Error bars indicate standard error. \*Significant difference from placebo,  $p < 0.005$ . ◆Placebo; ■CBT/BLT; ▲Doxepin.

items, only the PDSS sleep quality question improved ( $3.8 \pm 2.2$  vs.  $-0.3 \pm 1.0$ ,  $p = 0.02$ ). The PSQI sleep quality subscale did not show significant improvement. On non-sleep secondary outcomes there was deteriorating in total UPDRS and the ADL component of the PDQ-39 in the non-pharmacological treatment group compared to placebo ( $5.5 \pm 3.7$  vs.  $-7.2 \pm 12.3$ ,  $p = 0.04$ ;  $13.2 \pm 6.6$  vs.  $-4.5 \pm 13.2$ ,  $p = 0.01$ ; respectively) (Table 3). There were no differences in any of the measures of daytime sleepiness or fatigue, depression (BDI), sleep hygiene (SHI), dysfunctional sleep beliefs

(DBAS-16), and cognitive functioning (MoCA) (Tables 2 and 3 and Supplemental).

## 10. Adverse events

All three interventions were well tolerated. Overall, 4 (22%) patients reported adverse events: 3 patients on doxepin and 1 patient using the light box. One patient taking doxepin reported mild fatigue, another reported transient mild nausea during

**Table 3**  
Other selected sleep and non-sleep outcomes.

	Placebo, n = 6	CBT/BLT, n = 6	p value	Doxepin, n = 6	p value
Daytime functioning					
Krupp fatigue severity scale	0 ± 5.8	-0.5 ± 6.2	$p = 0.88$	-17.7 ± 14.3	<b><math>p = 0.02</math></b>
Epworth sleepiness scale	-2.3 ± 3.2	-1.3 ± 5.2	$p = 0.69$	-1.3 ± 2.3	$p = 0.55$
Beck depression inventory	-1.0 ± 5.9	-0.7 ± 2.5	$p = 0.91$	-2.2 ± 2.5	$p = 0.65$
Insomnia beliefs and behavior					
Sleep hygiene index	-0.2 ± 2.1	-1.0 ± 3.2	$p = 0.62$	-1.5 ± 3.4	$p = 0.44$
DBAS-16	-18.0 ± 22.3	-13.5 ± 23.5	$p = 0.7$	-1.7 ± 23.0	$p = 0.2$
Disease severity					
PDQ-39-total	-4.5 ± 13.2	13.2 ± 6.6	<b><math>p = 0.01</math></b>	-9.7 ± 14.2	$p = 0.5$
Total UPDRS	-7.2 ± 12.3	5.5 ± 3.7	<b><math>p = 0.04</math></b>	-5.7 ± 5.5	$p = 0.79$
UPDRS Part III	-5.0 ± 9.0	2.1 ± 2.4	$p = 0.09$	-2.0 ± 4.8	$p = 0.48$
Cognitive functioning					
MoCA	-1.2 ± 1.3 (n = 6)	-1.0 ± 2.6 (n = 3)	$p = 0.9$	2.2 ± 1.9 (n = 5)	<b><math>p = 0.007</math></b>

CBT, Cognitive behavioural therapy; BLT, Bright light therapy; SCOPA, SCAles for Outcomes in Parkinson's disease; PDQ-39, The Parkinson's Disease Questionnaire-39; DBAS, Dysfunctional Beliefs and Attitudes about Sleep; UPDRS, Unified Parkinson Disease rating Scale; MoCa, Montreal Cognitive Assessment; p values reflect t-tests comparing treatment condition to placebo ( $p < 0.05$  are highlighted in bold text).

treatment initiation and a third reported transient orthostatic dizziness. One CBT patient fell asleep while using the light therapy, causing a small burn of his face, without severe consequences.

## 11. Discussion

In this pilot study, we have found some significant benefits of doxepin 10 mg at bedtime upon insomnia in PD. CBT plus BLT also showed some evidence of benefit upon insomnia.

Although there are a variety of medications for insomnia in the general population, options for PD patients are limited. The most widely used treatments of insomnia in non-PD populations are the non-benzodiazepine hypnotics, such as eszopiclone, zolpidem, and zaleplon. They decrease latency to sleep initiation, increase duration of sleep, and reduce episodes of awakening [27]. A recent controlled trial with eszopiclone showed improvement of quality of sleep and sleep maintenance in PD patients [4], without improvement in total sleep time or several other insomnia measures. One important limitation of current pharmacologic treatments is that they were primarily designed for persons with difficulty falling asleep – any benefit upon sleep maintenance depends on long half-life with potential for daytime sedation. We chose low-dose doxepin as a pharmacologic treatment based upon two studies, which suggested that it was especially effective for sleep maintenance insomnia in elderly persons [11,12]. In these studies sleep efficiency during the final third of the night was significantly increased at all 3 doses ( $p < 0.0001$ ) compared with placebo. These sleep maintenance benefits were not associated with significant next-day residual sedation (relative to placebo) or other adverse side effects. However, until now doxepin had not been tested in patients with PD.

Our non-pharmacologic strategy consisted of a combination of CBT, sleep hygiene training, plus BLT. CBT is an effective non-pharmacological intervention that is widely used for adults with insomnia [7]. Goals of CBT include alteration of patient's dysfunctional beliefs and misconceptions about sleep and insomnia [8]. Sleep hygiene measures consist of simple recommendations that promote good sleep habits, and were included in our CBT program. Large-scale RCTs have suggested that CBT may have better long-term effects on insomnia than pharmacological treatments [6]. Although originally developed to treat seasonal depression [28], BLT has also been used to treat sleep disturbances. BLT regulates circadian cycle by stabilizing secretion of melatonin, the regulator of the circadian light/dark cycle. Studies have suggested that melatonin secretion decreases with PD progression and perhaps with levodopa therapy [29].

Although some sleep variables showed improvement, the effects of CBT and BLT on insomnia in our study appeared to be less clear than with doxepin. Moreover, we found a surprising worsening in ADL scores on the PDQ-39 in the non-pharmacological treatment arm. The reason for this is unclear. Coincidence is certainly a strong possibility, although all 6 patients in the CBT group had worse scores at week 6 than week 0. Of note, PDQ-39 is a self-reported functional impact scale, which does not directly address sleep problems. It is possible that an increasing awareness of self that is implicit in the process of CBT, combined with the opportunity to compare symptoms and daily functioning provided by group therapy could have increased awareness of functional limitations. On the other hand, the CBT program itself did not focus on recognition of activities of daily living, the most assessed measure of the PDQ-39. Also, the objective UPDRS also demonstrated worsening compared to placebo, perhaps suggesting a true effect (although this may have been driven by improving scores in the placebo group). Note that our finding of motor worsening is in direct contrast to previously-published studies, which suggested

potential improvement with bright light therapy [30]. It is unclear whether this effect would be seen in a longer-duration study, or whether improvements in sleep would eventually allow these scores to return to baseline.

In contrast to relatively clear evidence of benefit on subjective measures, we did not find a statistically significant difference between groups on actigraphic measures of sleep (although doxepin values trended in a positive direction). Of interest, a recent study of eszopiclone in insomnia also failed to show any actigraphic improvement despite improvement in subjective measures of sleep [4].

Somewhat surprisingly, we found improved MoCA test scores in participants who took doxepin compared to placebo. Although doxepin's action as a tricyclic antidepressant could have suggested potential worsening of cognition, it has selective histaminergic antagonistic action at low doses without substantial anticholinergic activity. Sleep and cognitive functioning may be correlated, especially if sleep deprivation impacts attention and executive function [3]. Therefore it is possible that improvements in sleep resulted in improved cognition. The patients in the doxepin arm also had significant improvement of fatigue, independently of other non-motor symptoms such as depression and daytime sleepiness. The striking amplitude of the effect was surprising and unexplained. Mental fatigue is present in more than 50% of patients, and seems to be an independent symptom that develops parallel to the progression of the disease. It is possible that doxepin may affect predominantly mental fatigue, but a direct effect on 'physical' fatigue cannot be ruled out.

Although the clinical benefit appeared to be somewhat more robust for doxepin than for non-pharmacologic therapy, we cannot endorse superiority of pharmacologic treatment over non-pharmacologic treatment based on this study. Potential advantages of non-pharmacological treatments include absence of pharmacologic side effects and potential long-lasting benefits after treatment is completed (pharmacologic treatments generally must be continued indefinitely [4]). However, CBT can be costly, requires trained clinicians to administer [4] and also demands good cognitive functioning in participants. Also, MoCa scores at the baseline were lower in CBT group which could indicate that these patients had some subtle cognitive impairment – since successful CBT involves active cognitive participation, our effect size may have been underestimated.

Some limitations of our study should be noted. First, this was a pilot study with a small number of participants, and many of our negative findings could be related to poor power to detect differences in these variables. As this was a pilot study, no single primary outcome was delineated and no adjustment for multiple comparisons was made; therefore, all outcomes should be considered exploratory in nature. The duration of the study was relatively short – in particular, it is possible that non-pharmacological interventions require more time to produce benefits in insomnia. We did not use polysomnography as an outcome measure in this study – this is principally because polysomnography's utility in the assessment and treatment of insomnia is unclear; the artificial environment of the sleep lab may not reflect a patients' normal sleep profile and can be performed only on one night. Although the inactive therapy arm was not disclosed as placebo, our study was otherwise unblinded; it is conceivable that participants could have done independent reading about mechanisms of light therapy and thereby became fully unblinded. Finally, our non-pharmacologic strategy included both CBT and BLT (bright light therapy is used as standard therapy in the CBT program at our institution); therefore, it is impossible to determine whether each modality used alone would be effective for insomnia.

In summary, our findings suggest substantial potential benefit for doxepin for insomnia, and possible evidence for benefit with CBT plus BLT. These findings must be confirmed in full confirmatory randomized controlled trial.

## Disclosure

The authors report no conflicts of interest related to the study.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.parkreldis.2013.03.003>.

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