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

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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 ± 5.4 vs. -2 ± 3.9, $p = 0.03$), the SCOPA-night score (-5.2 ± 1.5 vs. -2.3 ± 2.8, $p = 0.049$), the Pittsburgh Sleep Quality Index-sleep disturbances subscale (-0.5 ± 0.5 vs 0.2 ± 0.4, $p = 0.02$), and both patient and examiner-rated clinical global impression of change (1.7 ± 0.8 vs. 0.5 ± 0.8, $p = 0.03$ and 1.4 ± 0.5 vs. 0.3 ± 0.5, $p = 0.003$). 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 ± 3.8 vs. -2.0 ± 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.

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;

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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 # 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, pre-menopausal 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 wakening.
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