Review article

Pharmacological interventions for daytime sleepiness and sleep disorders in Parkinson's disease: Systematic review and meta-analysis

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ABSTRACT

Background: Daytime sleepiness and sleep disorders are frequently reported in Parkinson's disease (PD). However, their impact on quality of life has been underestimated and few clinical trials have been performed.
Objectives: We aimed to assess the efficacy and safety of pharmacological interventions for daytime sleepiness and sleep disorders in PD.
Methods: Systematic review of randomized controlled trials comparing any pharmacological intervention with no intervention or placebo for the treatment of daytime sleepiness and sleep problems in PD patients.
Results: Ten studies (n = 338 patients) were included. Four trials addressed interventions for excessive daytime sleepiness. Meta-analysis of the three trials evaluating modafinil showed a significant reduction in sleepiness, as assessed by the Epworth Sleepiness Scale (ESS) (-2.24 points, 95% CI -3.90 to -0.57, $p < 0.05$). In one study, treatment with caffeine was associated with a non-significant improvement of 1.71 points in ESS (95% CI, -3.57 to 0.13). The six remaining trials assessed interventions for insomnia and REM sleep Behaviour Disorder (RBD). Single study results suggest that doxepin and YXQN granules might be efficacious, while pergolide may be deleterious for insomnia and that rivastigmine may be used to treat RBD in PD patients. However, there is insufficient evidence to support or refute the efficacy of any of these interventions. No relevant side effects were reported.
Conclusions: Whilst providing recommendations, this systematic review depicts the lack of a body of evidence regarding the treatment of sleep disorders in PD patients; hence, further studies are warranted.

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1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, with its prevalence estimated at about 1% amidst people over 60 years of age [1–3]. Apart from the classical motor signs, there is a full constellation of nonmotor features [4] that greatly impairs patients' quality of life [5].

One paramount group of such features includes sleep disorders. Indeed, PD is the neurodegenerative disorder in which sleep is most often disrupted [6]. Accordingly, in the largest survey of nonmotor

symptoms of PD [7], 21.2% of patients complained of excessive daytime sleepiness (EDS), 36.9% referred insomnia, 29.6% suffered from behavioral sleep disturbances and 15.2% from restless legs syndrome (RLS).

With disease progression there are specific symptoms of PD that may interfere with global sleep quality, including nocturia, difficulty turning over in bed, dream enactment, hallucinations, dyskinesias, pain and dystonia [8]. All these phenomena were reported to be detrimental for sleep quality when compared with a control group of similar age without PD [9]. Furthermore, it is worth mentioning that the classic factor correlated with disturbed sleep in PD is the duration of L-dopa therapy [10–13]. However, it is widely agreed that sleep disorders in PD have a multifactorial etiology, namely, nighttime motor deterioration, psychiatric

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disorders, drug effects and concomitant obstructive sleep apnea syndrome [14].

Despite the significant prevalence of daytime sleepiness/sleep dysfunction and their harmful effect on quality of life, few clinical trials in this field have been conducted and, therefore, only scarce recommendations for the pharmacological management of these symptoms are available [15,16].

Consequently, the primary aim of this review was to evaluate the efficacy and safety of pharmacological interventions for the management of both daytime sleepiness and nocturnal sleep problems in PD. We also addressed the methodological quality of the trials.

2. Methods

2.1. Search strategy and selection criteria

Relevant trials were identified by searching the following electronic databases: MEDLINE/PubMed and EMBASE (both from 1966, last updated: December 2014). "Parkinson's disease" and synonyms were cross-referenced with "sleep", "nighttime" and "somnolence", related terms (e.g., "nocturnal", "daytime", "sleepiness" and "drowsiness"), and names and acronyms of commonly used scales to assess daytime sleepiness and sleep quality in PD. The search strategy also included: reference lists of identified trials and review articles on non-motor symptoms of PD; contacting in person with other researchers in the field; and, when necessary, contacting authors of published trials for further information and unpublished data. No restrictions were applied to publication status, language or blinding.

2.2. Study selection

Search results were reviewed by two independent reviewers (TMR and ACC) and discrepancies were solved by discussion. Studies eligible for this review were: (1) randomised controlled trials (RCTs), including crossover trials; (2) of patients with a clinical diagnosis of idiopathic PD; (3) of patients with either daytime sleepiness or a nocturnal sleep problem, both defined according to validated sleep rating scales, or in the absence of such definition, trials in which a clear and explicit definition was stated were also eligible; (4) comparing any pharmacological therapy with no intervention or placebo control. No restrictions were applied to age, duration of PD, concomitant therapies and duration of treatment. Non-pharmacological strategies (e.g. behavioural approaches) were excluded. No restrictions were applied to dosages or administration routes.

2.3. Data extraction and quality assessment

Two reviewers (TMR and ACC) independently assessed whether the studies fulfilled the inclusion criteria, performed the data extraction and quality assessment, according to the criteria described in the Cochrane Handbook for Reviewers [17]. Discrepancies on any of these were resolved by discussion with a third reviewer (JJF).

Sources of bias were looked for, including: (1) selection bias; (2) performance bias; (3) attrition bias; (4) detection bias; (5) selective reporting of results. Each potential source of bias was classified as one of three of the following levels of bias: A) low risk of bias; B) unclear risk of bias; C) high risk of bias.

2.4. Quantitative data synthesis

Statistical analyses were performed with Cochrane Review Manager 5.3. The primary outcome measure was quantified as the change in value of validated daytime sleepiness/sleep quality scales (e.g., Epworth Sleepiness Scale [ESS], Pittsburgh Sleep Quality Index [PSQI], SCOPA-sleep daytime sleepiness/nighttime sleep subscale or Parkinson's Disease Sleep Scale [PDSS]).

The secondary outcome measures were: 1) Subjective improvement in frequency, duration or intensity of any daytime sleepiness episodes or sleep problem associated with PD; 2) Changes in quality-of-sleep assessments; 3) Subjective improvement in morning akinesia; 4) Objective improvement in morning akinesia; 5) Changes in the subjective evaluation of clinical status by clinicians; 6) Changes of quality-of-life assessments; 7) Number of dropouts after randomization; 8) Tolerability as measured by withdrawal from trials; 9) Safety as measured by the incidence and type of adverse effects, serious adverse effects and adverse effects leading to withdrawal.

Continuous data was analyzed by using the mean and standard deviation (SD) values for each trial and by calculating the effect size (average mean difference) and the 95% confidence. When possible, results of each trial were combined using standard meta-analytic methods to estimate an overall effect for pharmacological intervention versus no intervention or placebo. Since all outcomes were continuous variables, weighted mean differences were used. When combining outcome data from different studies was not possible, we gave a descriptive summary of the results.

2.5. Heterogeneity and publication bias

We initially assessed heterogeneity by inspection of graphical presentations and by using a statistical test for heterogeneity.

For the estimation of potential asymmetry we built a funnel plot to demonstrate the precision of included trials. We used a (Peto) fixed-effect model throughout the review, except in the event of significant heterogeneity between the trials (if $p < 0.10$), in which case we would have used the random-effects model.

2.6. Sensitivity analysis

To evaluate the impact of our quality criteria on the outcome of the meta-analysis, we performed a sensitive analysis in which only RCTs with a parallel design were included. Also, given that in one study [18] the SD of change from baseline was not reported, this value was calculated from the baseline and final SD values and from an imputed correlation coefficient, as instructed in the Cochrane's Handbook for Reviewers [17]. Therefore, sensitivity analyses were performed in which different values for the correlation coefficient were imputed and also in which we assumed the variability reported in a different study [19].

3. Results

3.1. Description of studies

Our search yielded 2734 reports after duplicate removal. After screening, 142 potentially relevant reports were identified, of which only 10 complied with the pre-defined inclusion criteria for this review (Fig. 1). The two main reasons for exclusion were: lack of a placebo/no treatment control group or not having a clearly defined diagnosis of daytime somnolence/sleep dysfunction as an inclusion criterion. Of these trials (including a total of 338 patients), four addressed the treatment of EDS, whereas the remaining six addressed the treatment of a sleep dysfunction (n = 5 for Insomnia and n = 1 for REM Behaviour Disorder [RBD]). Table 1 summarizes the studies included in this review.

Records identified through database searching (n=5058)

Records identified through other sources (n=21)

Records after duplicates removed (n=2734)

Records excluded (n=2592)

Full-text articles assessed for eligibility (n=142)

Studies excluded (n=126), articles (n=132)

Lack of daytime somnolence/sleep dysfunction definition (n=39)

Also including patients without the diagnosis of PD (n=3)

Non-pharmacological intervention (n=21)

Lack of randomization (n=1)

Lack of control with placebo/no treatment (n=50)

Observational study (n=11)

Case Report (n=7)

Studies included in Qualitative Synthesis (n=10)

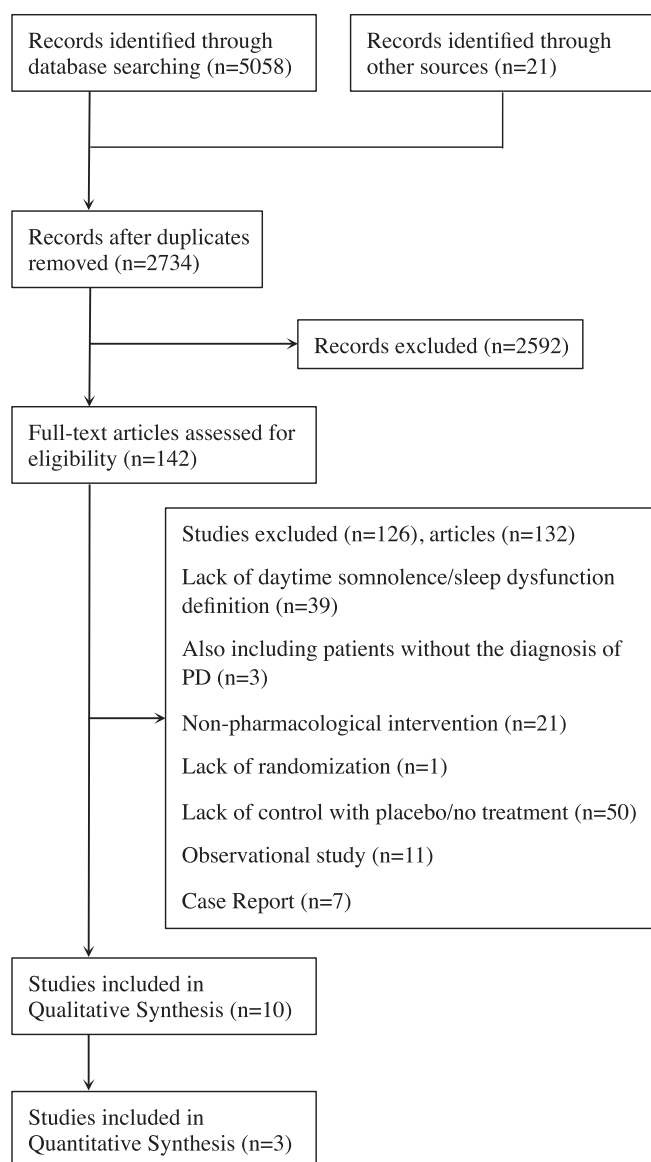Studies included in Quantitative Synthesis (n=3)

Fig. 1. Flow diagram depicting the subsequent stages of (1) searching for relevant reports; (2) abstract screening the reports for potential candidates; and (3) assessing the full-texts of those reports to select the studies that comply with the pre-defined inclusion criteria. The reasons for exclusion are stated.

3.1.1. Excessive daytime sleepiness (EDS)

The 4 included studies on the treatment of EDS in PD patients enrolled a total of 137 patients [18—21] (baseline characteristics were available for 133 patients: 72% males (n = 96), mean age 65.3 years) and covered two pharmacological interventions: modafinil [18—20] and caffeine [21]. All 4 trials were randomised, placebo-controlled and double-blind; only one of these was multicentre [21]. Two of the trials had a crossover design [19,20], whereas the remaining two [18,21] had a parallel design. However, the report of one of the crossover trials [19] only presents the results of the first crossover period, because there was a significant carry-over effect; essentially, this created a parallel design of 10 patients per treatment group. The inclusion criteria were very consistent throughout these trials and a clinical diagnosis of EDS according to ESS was required. These trials were small (sample size ranges from 15 to 61 participants) and short-term (median duration from randomization to last follow-up was 6 weeks). In all 4 trials, the study drug or placebo was administered orally.

Except for Hogl [20], all studies defined the change in ESS as the primary outcome. The remaining scales and tests used as secondary outcomes varied widely across the four trials (as described in Table 1). Worthy of note, apart from subjective scales, some trials used objective outcomes, such as the Maintenance of Wakefulness Test (MWT) [20] and the Multiple Sleep Latency Test (MSLT) [18].

3.1.2. Sleep dysfunction

3.1.2.1. Insomnia.
For insomnia, we included 5 RCTs enrolling 189 patients [22—26] (baseline characteristics were available for 170 patients: 61% males (n = 103), mean age 63.3 years), which addressed five distinct pharmacological interventions: the dopamine receptor agonist, pergolide [22]; melatonin [23]; a ligand of the benzodiazepine allosteric site of GABA$_A$ receptors, eszopiclone [24]; a tricyclic antidepressant, doxepin [25]; and Yang-Xue-Qing-Nao (YXQN) granules [26]. All were randomised, controlled trials, but one was not double-blind [25] and only two were multicentre [23,24]. All trials had two-arms (intervention and placebo), with the exception of Dowling [23] and Rios-Romenets [25]. Dowling [23] included a placebo arm and two arms for melatonin in different doses (5 mg and 50 mg), whereas Rios-Romenets [25] included one pharmacological arm (the doxepin arm), one non-pharmacological intervention arm (sleep hygiene training, cognitive behavioral therapy and bright light therapy) and a sham intervention (exposure to 30 min of light therapy). The definition of insomnia varied considerably: Comella [22], Menza [24] and Pan [26] defined it as at least 2—3 awakenings per night occurring at least 3 nights per week; Dowling [23] only required a subjective complaint of unsatisfactory nighttime sleep, although patients were excluded in the second phase of screening if they had a sleep efficiency > 80% or ≥ 7 h of total nighttime sleep time actigraphically measured; finally, Rios-Romenets [25] defined insomnia using SCOPA-sleep nocturnal subscore. These trials were also small (sample size ranges from 20 to 70 participants) and short-term (median duration from randomization to last follow-up was 7.5 weeks).

Regarding the interventions, all trials used an oral route of administration (as described in Table 1). Only 2 studies clearly stated the primary outcomes [24,25]. With the exception of Menza [24], all studies used actigraphy, although the specific actigraphic outcome measures varied. The remaining scales and tests used as secondary outcomes also varied substantially.

3.1.2.2. REM sleep behaviour disorder (RBD).
For RBD, we included one trial of 12 patients [27] (91% males, mean age 67.7 years, mean disease duration of 9.2 years), which attempted to determine the effectiveness of rivastigmine in reducing the frequency of RBD episodes in patients with PD (Table 1). The primary outcome is clearly identified as the reduction in RBD episode frequency according to the bed partner's diary. This was the only outcome measured, except for a subset of 4 patients, who repeated Polysomnography (PSG) during rivastigmine treatment.

3.2. Methodological quality

3.2.1. Excessive daytime sleepiness (EDS)
Globally, the methodological quality of the trials assessing pharmacological interventions for EDS was good (Fig. 2A). With one exception [20], the method of randomization was clearly described. The allocation concealment methods were also clearly described and, thus, rated as being at a low risk of bias, except for Adler [19], in which the treatment sequence was randomised in blocks. Blinding of participants and personnel involved in the trials was evaluated to be at low risk of bias in all studies. The baseline

Table 1
Description of studies included in the systematic review.

Study/year	Design	Participants	Experimental intervention	Comparator group	Duration of treatment	Primary outcome	Other outcomes	Results
Hogl 2002 [20]	RDBCPC-SC trial	15 patients IPD; ESS ≥ 10 and with subjective complaint of EDS	Modafinil, 100 −200 mg/day, po, single-dose in the morning	Placebo similar in color, size and shape	2 weeks with 2 weeks of washout	Not stated	ESS; MWT; BDI; UPDRS; H&Y; sleep log	**Beneficial:** improved daytime sleepiness according to ESS, but latency to sleep in the MWT was not significantly altered.
Adler 2003 [19]	RDBCPC-SC trial [a]	21 patients IPD; ESS ≥ 10	Modafinil, 200 mg/day, po, single dose 30−45 min after breakfast	Placebo similar in color, size and shape	3 weeks with 1 week of washout	ESS	Motor fluctuation diaries; EDSRS; modified FAI; FSS; EDFRS; UPDRS; H&Y; S&E; timed tapping test; CGI; sleep diaries; patient-reported number of "sleep attacks"	**Beneficial:** modestly effective for the treatment of excessive daytime sleepiness, with few side effects.
Comella 2005 [22]	RDBPPC-SC trial	26 patients IDP; LD treated; complaining of at least 3 awakenings/ night occurring at least 3 nights/week	Pergolide, titrated over 4 weeks to a maximum of 1 mg/day, po, single-dose at bedtime	Placebo similar in color, size and shape	6 weeks	Not stated	Actigraphy (sleep latency, sleep time, sleep efficiency and movement and fragmentation index); UPDRS	**Harmful:** worsened actigraphic measures of sleep efficiency and sleep fragmentation; side effects were more frequent versus the placebo group.
Dowling 2005 [23]	RDBCPC-MC trial	43 patients IDP; presenting with subjective complaint of unsatisfactory nighttime sleep	Melatonin, 5 mg/day and 50 mg/day, po, single-dose 30 min before bedtime	Placebo similar in color, size and shape	2 weeks with 1 week of washout	Not stated	Actigraphy (sleep start, sleep end, actual sleep time, actual sleep percent, actual wake time and actual wake percent); UPDRS; modified H&Y; PSQI; GDSS; SSS; ESS	**Beneficial:** 5 mg improved sleep quality and daytime sleepiness, according to GDSD; 50 mg increased total nighttime sleep time.
Ondo 2005 [18]	RDBPPC-SC trial	40 patients IPD; ESS ≥ 10	Modafinil, 200 −400 mg/day, po, bid (upon waking and at lunch)	Placebo similar in color, size and shape	4 weeks	ESS	UPDRS; FSS; Hamilton Depression Scale; MOS SF-36; MSLT; sleep survey; motor fluctuation diaries; UPDRS; global impressions	**Neutral:** failed to significantly improve ESS scores and performance in the MSLT; it did not alter motor symptoms and was well tolerated.
Menza 2010 [24]	RDBPPC-MC trial	30 patients ≥2 awakening/ night at least 3 nights/week OR TST < 6.5 h OR sleep latency ≥ 30 min at least 3 nights/week	Eszopiclone, 2 −3 mg/day, po, single-dose at bedtime	Placebo similar in color, size and shape	6 weeks	Patient-reported TST	Patient-reported WASO and number of awakenings; SII; 10-point Likert for QoL, ability to function and daytime alertness; PDQ-8; UPDRS;	**Beneficial (?):** did not increase TST, but reduced the number of awakenings and improved quality of sleep; produced no significant differences in

Study	Design	Patients	Intervention	Control	Duration	Primary outcome	Other measures	Results
							CGI; FSS; MCBF; CES-D	measures of daytime functioning.
Di Giacopo 2012 [27]	RDBCPC-SC	12 patients IPD; RBD refractory to melatonin (up to 5 mg/day) and clonazepam (up to 2 mg/day)	Rivastigmine, 4.6 mg/day, cutaneous patch	Identical looking cutaneous patch	3 weeks with 1 week of washout	Episode frequency (bed partner's diary)	PSG	**Beneficial:** significantly reduced the mean frequency of RBD episodes and was well tolerated.
Postuma 2012 [21]	RDBPPC-MC trial	61 patients IPD; ESS ≥ 10	Caffeine, 200−400 mg/day, po, bid (upon waking and at lunch)	Placebo similar in color, size and shape	6 weeks	ESS	UPDRS; CGI; FSS; PSQI; BDI; PDQ-39; MOS SF-36.	**Beneficial (?):** provided equivocal borderline improvement in excessive somnolence - ESS score change was significant on PP, but not on ITT analysis.
Rios Romenets 2013 [25]	RDBPNTC-SC trial	20 patients SCOPA-sleep nocturnal subscore ≥ 7 and the insomnia must had persisted for ≥ 6 months	Doxepin, 10 mg/day, po, single-dose at night	Sham light intervention (exposure to 30 min of light therapy)	6 weeks	SCOPA-sleep and ISI	PDSS; patient-reported sleep onset and duration, daytime naps and night awakenings; PSQI; CGI; actigraphy (total time in bed, total sleep duration, sleep efficiency, WASO); SHI; DBAS-16; FSS; ESS; BDI; UPDRS; PDG-39; MOCA	**Beneficial:** significantly improved insomnia, as assessed by SCOPA-sleep, ISI, PSQI and CGI.
Pan 2013 [26]	RDBPPC-SC trial	70 patients IPD; LD treated; ≥ 3 awakenings/night for at least 3 nights/week attributable to PD symptoms	YXQN granules, 4 g/day, po, 3x/day	Granules similar in color, size and shape	12 weeks	Not stated	Actigraphy (daytime, evening and nocturnal activity); UPDRS; PDSS	**Beneficial:** significant improvements on actigraphically measured evening activity and PDSS scores were observed.

Abbreviations. BDI. Beck Depression Inventory. CES-D. Centre for Epidemiological Studies Depression Scale. CGI. Clinical Global Impression. DBAS-16. Dysfunctional Beliefs and Attitude about Sleep − brief version. EDFRS. Excessive Daytime Fatigue Rating Scale. EDS. Excessive Daytime Sleepiness. EDSRS. Excessive Daytime Sleep Rating Scale. ESS. Epworth Sleepiness Scale. FAI. Fatigue Assessment Inventory. FSS. Fatigue Severity Scale. GSDS. General Sleep Disturbance Scale. H&Y. Hoehn and Yahr. IDP. Idiopathic Parkinson's Disease. ISI. Insomnia Severity Index. LD. Levodopa. MCFB. Multidimensional Caregiver Burden Inventory. MoCA. Montreal Cognitive Assessment. MOS SF-36. Medical Outcome Survey Short Form-36. MSLT. Multiple Sleep Latency Test. MWT. Maintenance of Wakefulness Test. PDSS. Parkinson's Disease Sleep Scale. Po. Per os. PSQI. Pittsburgh Sleep Quality Index. PDQ-8. Parkinson's Disease Questionnaire-8. PDQ-39. Parkinson's Disease Questionnaire-39. PSG. Polysomnography. QoL. Quality of Life. RBD. REM Behavior Disorder. RDBCPC-MC. Randomized, Double-Blind, Crossover, Placebo-Controlled, Multi-Center. RDBCPC-SC. Randomized, Double-Blind, Crossover, Placebo-Controlled, Single-Center. RDBPNTC-SC. Randomized, Double-Blind, Parallel, No Treatment-Controlled, Single-Center. RDBPPC-MC. Randomized, Double-Blind, Parallel, Placebo-Controlled, Multi-Center. RDBPPC-SC. Randomized, Double-Blind, Parallel, Placebo-Controlled, Single-Center. SCOPA-sleep. Scales for Outcomes in Parkinson's Disease Sleep. S&E. Schwab & England Activities of Daily Living scale. SHI. Sleep Hygiene Index. SII. Sleep Impairment Index. SSS. Stanford Sleepiness Scale. TST. Total Sleep Time. UPDRS. Unified Parkinson's Disease Rating Scale. WASO. Wake After Sleep Onset. YXQN. Yang-Xue-Qing-Nao.

[a] However, only the results of the first crossover period were presented, because there was a carry-over effect; essentially, this created a parallel design study of 10 patients per treatment group.
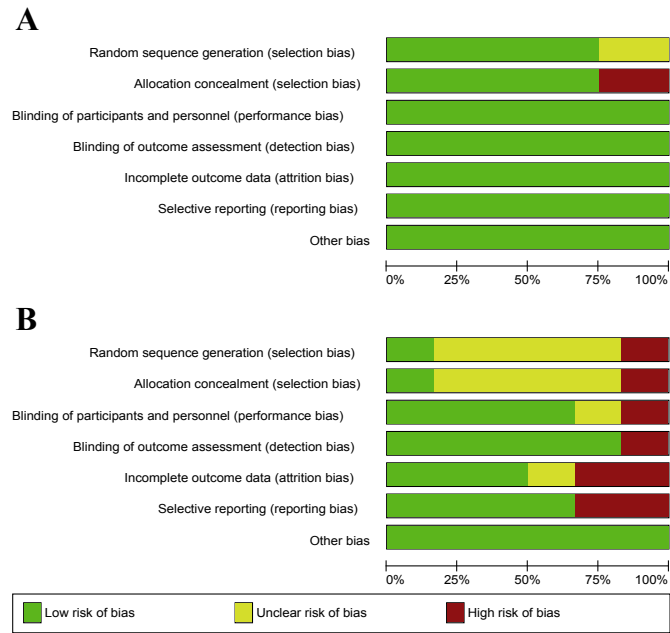
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A

B

Fig. 2. Review authors' judgments about the risk of six different sources of bias in the studies included in this review, according to the guidelines presented in the Cochrane Handbook for Reviewers [17]. Results are presented as the percentage for each type of bias across all included studies for (A) EDS and (B) sleep dysfunction.

characteristics of the study population were similar between trials and were well matched between study arms. One exception is a baseline imbalance in the estimated caffeine intake in Postuma [21], which would likely favor the intervention. Missing data is addressed by all studies and dealt with appropriately; hence, risk of attrition bias was rated as low.

3.2.2. Sleep dysfunction

Overall, the methodological quality of this set of trials is worse (Fig. 2B). Only two studies [23,26] provided a clear description of the randomization method; Comella [22], Menza [24] and Di Giacopo [27] were assessed to be at an unclear risk of selection bias; Rios-Romenets [25] was assessed to be at high risk because randomization was performed with a block design, in which the random assignment of one patient to the non-pharmacological arm implied that the subsequent two patients were assigned to this arm as well. Only one study [26] described an adequate allocation concealment process; with one exception [25], the remaining studies had an unclear risk of selection bias. Blinding of participants and personnel involved in these trials was assessed to be at a low risk of bias in the majority of the studies. For one study [27] the risk of performance bias was unclear since all the patients that repeated PSG were on rivastigmine. Rios Romenets [25] was considered to be

at high risk of selection, performance and detection bias; although the placebo intervention was not disclosed as inactive, treatment assignment was not otherwise blinded, since no placebo pills were used.

The baseline characteristics of the study population varied between trials and were not well matched between study arms in one study [22], whilst this could not be excluded in two other studies [23,24]. The number of dropouts was considerable across these trials (n = 27/189, average 14%, range 2–37%).

All studies summarized the reasons for missing data and the risk of attrition bias was considered to be low, with 3 exceptions [22,23,27]. Comella trial [22] had an uneven number of withdrawals (4 from pergolide *vs* 0 from placebo arm) and the analysis was performed per protocol. The reasons for the 3 dropouts on melatonin were unclear in Dowling trial [23]. In Di Giacopo [27], the risk of attrition bias was also considered to be high, given the high percentage of dropouts (17%). Finally, the reporting bias was considered to be low for all trials, except for two: Comella [22] did not report one of the pre-specified outcomes (sleep time) and Rios-Romenets [25] did not report any data from the sleep diaries (included in the study protocol).

3.3. Effects of intervention

3.3.1. Excessive daytime sleepiness (EDS)

3.3.1.1. Efficacy data. Modafinil significantly reduced EDS as assessed by ESS. As showed in the Forest Plot (Fig. 3), the overall mean difference (MD) was 2.24 points (95% CI, − 3.90 to − 0.57). No significant heterogeneity was found ($\chi 2 = 2.45$, df = 2, p = 0.29). Since the SD of change from baseline was not available for Ondo [18], this value was calculated from the reported values of baseline and final SD and from an imputed Correlation Coefficient (CC) (0.5), as recommended by the Cochrane Collaboration [17]. Therefore, we also conducted a sensitivity analysis to determine whether this result would be robust to other imputed CC values, and also to the exclusion of Hogl [20] (the only crossover trial in the meta-analysis). We found that the significant reduction of ESS was robust to different CC imputed, but not when Hogl [20] was excluded (Table 2).

Postuma [21] found a non-significant 1.71-point improvement in the caffeine group on intention-to-treat analysis (95% CI − 3.57, 0.13). On per protocol analysis, a significant reduction in ESS points was found (− 1.97 points, 95% CI − 3.87, − 0.05). Positive results were also noted in outcomes not directly related to sleep.

3.3.1.2. Adverse effects. Adverse events in modafinil group were reported in 19 out of 41 patients, compared to 10 out of 40 patients in the placebo arms. All trials reported that the side effects were mild and none of them led to study withdrawal. Also, no differences were found between the side effects reported by caffeine and placebo arms, in Postuma [21].
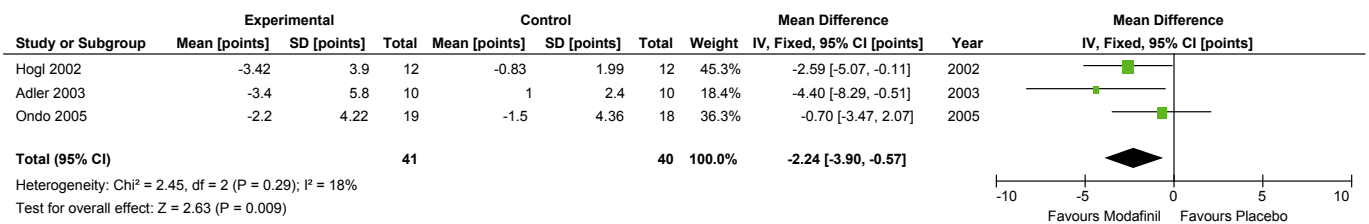

Study or Subgroup	Experimental Mean [points]	SD [points]	Total	Control Mean [points]	SD [points]	Total	Weight	Mean Difference IV, Fixed, 95% CI [points]	Year	Mean Difference IV, Fixed, 95% CI [points]
Hogl 2002	-3.42	3.9	12	-0.83	1.99	12	45.3%	-2.59 [-5.07, -0.11]	2002	
Adler 2003	-3.4	5.8	10	1	2.4	10	18.4%	-4.40 [-8.29, -0.51]	2003	
Ondo 2005	-2.2	4.22	19	-1.5	4.36	18	36.3%	-0.70 [-3.47, 2.07]	2005	
Total (95% CI)			41			40	100.0%	-2.24 [-3.90, -0.57]		

Heterogeneity: Chi² = 2.45, df = 2 (P = 0.29); I² = 18%
Test for overall effect: Z = 2.63 (P = 0.009)

Fig. 3. Forest Plot of ESS results in modafinil vs. placebo trials. The standard deviation (SD) of change from baseline for both arms of Ondo's trial [18] was not available. Therefore, we calculated the SD from the reported values of baseline and final SD and from an imputed Correlation Coefficient (0.5), as recommended by the Cochrane Collaboration [17]. CI. Confidence Interval. SD. Standard Deviation.

Table 2
Results of the sensitivity analysis.

Modafinil group		Placebo group		Including Hogl [20]		Excluding Hogl [20]	
CC imputed	SD calculated[b]	CC imputed	SD calculated[b]	Weight of Ondo [18] in the MA	MD, IV, Fixed, 95% CI [points]	Weight of Ondo[18] in the MA	
1.0	1.7	1.0	1.1	83.80%	− 1.09 [− 1.93, − 0.25]	94.70%	− 0.90 [− 1.79, − 0.00]
0.5	4.22	0.5	4.36	36.30%	− 2.24 [− 3.90, − 0.57]	66.40%	− 1.94 [− 4.20, 0.31]
0	5.71	0	6.06	23.20%	− 2.55 [− 4.38, − 0.72]	51.20%	− 2.51 [− 5.22, 0.21]
− 0.5	6.89	− 0.5	7.38	17.10%	− 2.70 [− 4.60, − 0.80]	41.60%	− 2.86 [− 5.83, 0.11]
− 1	7.9	− 1	8.5	13.50%	− 2.79 [− 4.73, − 0.84]	35.10%	− 3.10 [− 6.24, 0.03]
0.34[a]	4.73	0.88[a]	2.31	43.50%	− 2.06 [− 3.63, − 0.49]	72.80%	− 1.71 [− 3.74, 0.32]

Abbreviations. CC. Correlation Coefficient. CI. Confidence Interval. MA. Meta-Analysis. MD. Mean Difference. SD. Standard Deviation.

[a] CC for the Modafinil and the Placebo groups calculated from the respective samples from Adler [19], according to the instructions in the Cochrane's Handbook for Reviewers [17].

[b] SD for change from baseline was calculated from the values of baseline and final SD in Ondo [18] and from an imputed CC, as instructed in the Cochrane's Handbook for Reviewers.[17].

3.3.2. Sleep dysfunction

3.3.2.1. Efficacy data.
After treatment, the pergolide group had a reduction in median sleep efficiency of 7% vs. the placebo group with a reduction of − 0.6% (p = 0.049). Therefore, nighttime pergolide was concluded to worsen sleep activity [22].

Dowling [23] reported that treatment with 50 mg of melatonin significantly increased nighttime sleep time (p < 0.05), which corresponded to a mean increase of only 10 min. However, neither the General Sleep Disturbance Scale (GSDS), nor actigraphic measurements corroborated this benefit.

In Menza [24] trial, the benefit of eszopiclone failed to reach statistical significance on the primary outcome. However, significant differences were noted on sleep-related secondary outcomes.

Rios-Romenets [25] showed that, after doxepin, there were significant improvements in insomnia outcomes, as assessed by SCOPA-sleep and Insominia Severity Index (ISI) (p = 0.049 and p = 0.03, respectively). Outcomes related to quality of life and cognitive functioning also showed significant improvement.

Through actigraphy, Pan [26] showed that YXQN granules increased physical activity during the diurnal period, whilst reducing activity levels during the nocturnal period. Accordingly, a significant improvement was also noted on PDSS.

Finally, Di Giacopo [27] reported that rivastigmine significantly reduced the frequency of RBD episodes (p = 0.012).

3.3.2.2. Adverse effects.
Pergolide was associated with increased frequency of adverse effects (90% on pergolide vs. 33% on placebo; p < 0.05). The most commonly reported were nausea, light-headedness and worsened constipation. Menza [24] reported sedation during the day while on eszopiclone, however at a lower frequency than on placebo. Rios-Romenets [25] stated that 50% of patients on doxepin reported adverse effects vs. 0 patients on the sham light intervention. These included mild fatigue, mild nausea and orthostatic dizziness.

Di Giacopo [27] reported two adverse effects occurring in 2 patients during rivastigmine treatment (orthostatic hypotension and asthenia), which caused both patients to drop out. No significant side effects were reported while on melatonin [23] or YXQN granules [26].

4. Discussion

The main finding of this review was that modafinil improves daytime sleepiness of PD patients, based on a pooled analysis of three trials. The significance found on the meta-analysis was not robust to all sensitivity analyses. We could not perform any other pooled analysis, since each trial addressed a different pharmacological intervention. Single trial results suggested that: (1) caffeine might be effective for the treatment of EDS; (2) doxepin and YXQN granules might be efficacious, while pergolide may be deleterious for insomnia; and (3) rivastigmine may be effective for RDB in PD patients. However, given the small number of participants included and the methodological flaws in these studies, as well as the possibility of publication bias, we consider that there is insufficient evidence to support or refute their efficacy.

The overall methodological quality of the studies included for daytime somnolence was good. In contrast, the methodological quality of the trials for nocturnal sleep problems was poor.

4.1. Clinical implications

Daytime sleepiness is known to increase the risk of accidents [28,29] and to generate a social handicap [30]. Moreover, people who suffer from insomnia have been shown to have lower quality of life than good sleepers within both healthy and chronically ill populations [31,32]. Importantly, poor quality of sleep in PD patients has also been associated with depression and increased burden in caregivers [33,34]. Trials of insomnia in non-PD populations suggest that improvements in sleep are associated with improvements in quality of life [35,36]. Overall, this was not observed in the trials here included, which could, nonetheless, be due to the fact that the trials were underpowered.

For some included trials, even when an improvement upon sleep outcomes was found, its clinical significance may be questionable (for instance, the 10 min increase in total sleep time while on melatonin). The availability of good quality evidence for minimal clinically important differences (MCID) for these outcomes would help the interpretation of these findings. However, such sort of evidence is also lacking.

EASE-PD [37] and RECOVER [38] trials reported that, while on ropinirole and rotigotine respectively, both motor function and sleep disturbances in PD patients were improved. However, for these trials, a formal diagnosis of daytime somnolence or sleep disturbance was not an inclusion criterion, unlike the trials included in this review. Yet, the trials herein included found no differences in motor outcomes even when sleep outcomes improved (except for caffeine, which seemed to improve motor function [21]).

With the exception of pergolide and caffeine, the risks of metabolic or cardiovascular effects over a long period of exposure to the remaining pharmacological interventions, specifically in patients with PD, are unknown. Furthermore, none of the included trials included a health economics analysis of the pharmacological intervention.

We defined rigorous criteria for study inclusion in this systematic review, since we were aiming to gather and review the best quality data available and, hopefully, to produce strong recommendations. However, as we may have excluded data with clinical usefulness, we revised excluded studies with moderate to large cohorts [39—56] (for details and reasons for exclusion of these studies, please see Supplemental Table 1). Most of these studies were excluded because a specific recruitment of patients with daytime somnolence/sleep dysfunction was not undertaken. Indeed, for these studies, sleep and daily somnolence scales were a means to evaluate drug adverse effects or were part of a battery of outcomes aiming to assess non-motor symptoms. Furthermore, if the objective of the trial was not to improve EDS or sleep problems, but rather to ameliorate a different comorbidity (e.g., depression or psychosis), the interpretation of any observed improvements in daytime sleepiness or sleep quality may be misleading.

There are a few specific guidelines for the pharmacotherapy of EDS and sleep problems in PD patients [15,16,57,58]. The Movement Disorder Society (MDS) evidence-based medicine review [57] concludes that there is insufficient data to recommend any specific drug for the long-term treatment of sleep-related problems in PD patients. The EFNS/MDS-European Section provides further clinical guidance [58]. Namely, it recommends that improving nocturnal sleep by reducing nocturnal akinesia, discontinuing sedative drugs and decreasing the dosage of dopamine agonists may be beneficial when managing daytime somnolence in PD patients. However, for the remaining sleep disorders, physicians usually follow the recommendations available for the general population.

Modafinil is indicated for most forms of hypersomnia [59] and, according to the pooled analysis we conducted, it is also an effective strategy for EDS in PD patients. Caffeine may also be an efficacious treatment for EDS, as showed by one study included in this review [21]. Moreover, a randomized placebo-controlled trial showed that atomoxetine could improve daytime sleepiness in PD patients with depression [55]. On the contrary, quetiapine [51] and memantine [56] do not seem to affect daytime somnolence, while pramipexole produced controversial results in PD patients [44,48].

Current guidelines for the pharmacotherapy of primary insomnias recommend that short-intermediate acting benzodiazepine receptor agonists, such as eszopiclone, be attempted first [60]. Single trial results included in this review suggest that eszopiclone [24], doxepin [25] and melatonin [23] can be effective therapies for insomnia in PD patients. However, in clinical routine, controlled-release (CR) levodopa is frequently administered to PD patients to treat nocturnal akinesia. The evidence for such practice came from randomized trials that are now around 20 years old [39—41]. The dopamine receptor agonists rotigotine [42—44], ropinirole [45—47] and pramipexole [44] were also shown to improve sleep quality in PD patients. Additionally, a large randomized placebo-controlled trial suggests that pimavaserin may improve nighttime sleep in PD patients with psychosis [53], while nortriptyline, but not paroxetine, may improve sleep quality in PD patients with clinical depression [54]. In an open-label study, tolcapone improved sleep quality [49], while the results of a retrospective study suggest that clozapine may improve sleep disturbances in PD patients [50].

Regarding the treatment of RBD, clonazepam is usually used as the first line [61]. Results from a retrospective study suggest that the response to clonazepam of PD patients with RBD is identical to the response of patients with idiopathic RBD [52]. The results from one study included in this review suggest that rivastigmine may be an effective therapy for PD patients with RBD refractory to clonazepam and melatonin [27].

Finally, ropinirole and pramipexole are FDA-approved drugs to treat RLS [62]. However, no controlled trial with PD patients suffering from RLS has tested the efficacy of these drugs.

Furthermore, during the screening phase of this review, we found that a wide range of non-pharmacological interventions have been attempted to treat either EDS or sleep dysfunction in PD patients, including deep brain stimulation [63,64], transcranial magnetic stimulation [65,66], behavioural/educational therapy [67], bright light therapy [68,69], tactile touch and rest to music [70], continuous-positive airway pressure [71] and active theatre [72]. However, even if we had not limited our review to pharmacological interventions, we found no trials of non-pharmacological interventions that would otherwise fulfill our inclusion criteria, mostly because they had no control group or lacked a clear definition of daytime somnolence or nocturnal sleep problem.

4.2. Quality of the evidence

This review provides the most robust information available, however it has some limitations. Firstly, crossover trials were included, thus, carry-over bias cannot be excluded; this may be particularly important, since duration of effect for most interventions is unclear. To address this issue, we performed a sensitivity analysis that only included parallel studies. Secondly, the protocol of the review excluded non-pharmacological therapies and, thus, clinically relevant interventions might not have been mentioned.

Regarding the methodological quality of the included trials, it was often inadequate, particularly of the trials included for sleep dysfunction. Among the 10 included trials, only 4 [18,19,21,26] provided clear information on the randomization method. Some had high or unbalanced dropout rates between arms and only 3 trials [18,21,24] reported data using intention-to-treat analysis. Since follow-up periods were short, the positive results have to be considered alongside the possibility of a honeymoon effect [73], which could be inflating the effect in favor of the pharmacologic intervention for the treatment period.

Amidst the 5 trials included for insomnia, only 1 trial [25] defined the diagnosis of insomnia using a validated and recommended sleep scale for PD. All the 4 trials included for EDS assessed daytime somnolence using the ESS and 3 of 4 defined it as the primary outcome. On the contrary, the 6 trials included for sleep dysfunction depict that there is no consensual strategy to assess the quality and maintenance of sleep in PD patients. Actigraphy, which was used by 4 of 6 trials, has not been validated for PD patients, as it lacks the ability to distinguish between nocturnal activity due to wakefulness and activity due to motor symptoms or other sleep disorders. Only 2 of 6 trials included for sleep dysfunction [25,26] used sleep scales recommended by the Movement Disorder Society Sleep Scale Task Force (MDS-SSTF) [74] to evaluate efficacy. None of the neurophysiological approaches used (PSG, MSLT and MWT) have been validated for PD.

Moreover, all included trials had small sample sizes and were of very short duration, which ultimately hampers the possibility of drawing any definitive conclusions regarding the efficacy or safety of any of the pharmacological interventions tested.

4.3. Implications for research

This review clearly showed that the treatment of sleep disorders in PD is in need of a larger and better body of evidence. Future trials need to ensure that their designs fulfill the requirements of a methodologically sound, large randomized controlled trial, which includes valid sample size calculations. Also, trials should be of sufficient length to assess the long-term effects of treatments. Trials should only include patients diagnosed with PD and with a sleep disorder and only use PD-validated outcomes. Furthermore, data

should be analyzed according to intention-to-treat principles and reporting should follow the CONSORT guidelines [75].

In summary, additional research is needed to understand the exact clinical effect of the interventions included in this review, as well as potential variables that may influence their effect and duration, including concomitant medications, disease duration and psychiatric and cognitive factors.

Author's roles

Tiago Martins Rodrigues (TMR) and Joaquim J. Ferreira (JJF) were involved in the conception and organization of the research project. TMR and Ana Castro Caldas (ACC) executed the research project. All authors contributed to the design of the statistical analysis, which was performed by TMR and subsequently reviewed by ACC and JJF. TMR wrote the first draft of the manuscript, which was subsequently reviewed by all authors.

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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.2016.03.002.

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