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# The effect of melatonin on sleep quality and daytime sleepiness in Parkinson's disease: A systematic review and meta-analysis of randomized placebo-controlled trials

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ABSTRACT

*Background:* Sleep disturbances are common in Parkinson's disease (PD), significantly impacting quality of life. Melatonin may help, but evidence regarding dosage, formulation, and treatment duration remains inconclusive.
*Objective:* To quantitatively analyze the effect of melatonin on sleep quality and daytime sleepiness in patients with PD.
*Methods:* We comprehensively searched multiple databases up to February 2025, selecting relevant randomized controlled trials (RCTs). RevMan software was used for analysis. Subgroup analyses included treatment duration (4 weeks vs. 8–12 weeks), dose (≤4 mg vs. >4 mg), and formulation (immediate-release vs. prolonged-release).
*Results:* Five RCTs (206 patients) were included. Doses ≤4 mg showed no significant improvement in total Pittsburgh Sleep Quality Index (PSQI) scores (MD = −1.26, 95 % CI: −2.72 to 0.20). Doses >4 mg demonstrated a stronger effect (MD = −2.90, 95 % CI: −4.02 to −1.78). Short-term use (4 weeks) significantly improved PSQI scores (MD = −2.43, 95 % CI: −3.98 to −0.88), whereas longer treatment (8–12 weeks) showed a non-significant effect (MD = −1.24, 95 % CI: −3.15 to 0.67). Immediate-release formulations significantly improved PSQI scores (MD = −2.20, 95 % CI: −3.32 to −1.08), while prolonged-release formulations showed no significant effect (MD = −0.61, 95 % CI: −4.15 to 2.93). Melatonin modestly reduced excessive daytime sleepiness measured by the Epworth Sleepiness Scale (ESS) (MD: −0.97, 95 % CI: −1.81, −0.14).
*Conclusion:* Melatonin may improve sleep quality and reduce daytime sleepiness in PD patients, particularly with short-term use of immediate-release formulations.

## 1. Introduction

Parkinson's disease (PD), the second most prevalent neurodegenerative disorder, is characterized by the progressive degeneration of dopaminergic neurons in the substantia nigra, leading to the hallmark motor symptoms of tremor, rigidity, and bradykinesia [1].

However, as the disease advances, non-motor symptoms become increasingly prominent, often diminishing patients' quality of life more profoundly than motor manifestations [2–4]. Among these non-motor symptoms, sleep disturbances are particularly pervasive, affecting a substantial majority of patients. Research suggests that 60–98 % of PD patients experience some form of sleep disorder, exacerbating disease symptoms and further impairing cognitive function and overall well-being [5–8]. Sleep disturbances in this patient population can be broadly categorized into two groups: disturbances in sleep and disturbances in wakefulness. Sleep-related disturbances include insomnia, restless leg syndrome (RLS), rapid eye movement sleep behavior disorder (RBD), sleep apnea, and parasomnias, while wakefulness-related disturbances encompass excessive daytime sleepiness (EDS) and sleep attacks [9].

The pathophysiology underlying these disturbances is multifactorial and complex, with neurodegeneration disrupting key neurotransmitters

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involved in sleep regulation, such as norepinephrine, serotonin, dopamine, GABA, and acetylcholine [10]. In addition to PD-related impairments in brain and neurotransmitter function, several other factors contribute to sleep-related issues. These include dopaminergic medications that may alter sleep regulation, polypharmacy in elderly patients, coexisting comorbidities, as well as PD-related symptoms like nocturnal akinesia and genetic predispositions to specific sleep disorders [11,12].

Melatonin, a neurohormone primarily secreted by the pineal gland, plays a crucial role in regulating circadian rhythms [13]. First identified in 1958 by dermatologist Aaron Lerner, melatonin has numerous regulatory and protective functions, including synchronizing sleep cycles, shielding against oxidative stress, modulating energy metabolism, supporting immune function, and delaying the aging process [14–16]. However, its production decreases with age, typically declining by 10–15 % every decade after the age of 35 [17].

Alterations in melatonin production have been observed in a variety of neurodegenerative diseases, including Parkinson's disease [18]. In PD patients, there is a marked reduction in both the quantity and regularity of melatonin secretion, disrupting circadian rhythms and contributing to the sleep disturbances commonly seen in this population [19].

Evidence suggests that melatonin supplementation may offer potential therapeutic benefits by improving sleep quality, reducing sleep onset latency, and better synchronizing sleep-wake cycles [20]. However, despite the potential benefits, the clinical application of melatonin in PD remains somewhat contentious due to mixed results from existing research.

Therefore, we conducted this systematic review and meta-analysis to evaluate the impact of melatonin on sleep quality and daytime sleepiness in individuals with PD, aiming to provide a comprehensive and evidence-based assessment of melatonin's potential therapeutic benefits in this patient population. Our analysis focused on randomized, parallel-group, placebo-controlled clinical trials that measured sleep quality using the Pittsburgh Sleep Quality Index (PSQI) and daytime sleepiness using the Epworth Sleepiness Scale (ESS), both widely validated assessment tools in sleep medicine. Additionally, we performed subgroup analyses examining the effects of dosage, treatment duration, and formulation variations to offer a clearer understanding of how these factors may influence melatonin's efficacy in improving sleep outcomes for PD patients.

## 2. Methods and materials

In preparing this review, we adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The study was conducted in line with the Cochrane Handbook for Systematic Reviews of Interventions [21] and was prospectively registered on PROSPERO (CRD42025641925).

### 2.1. Review question

What is the effect of melatonin on sleep quality and daytime sleepiness in patients with Parkinson's disease compared to a placebo?

### 2.2. Criteria for considering studies for this review

Studies satisfying the following criteria were included in this review:

- Population: Adults diagnosed with Parkinson's disease according to established diagnostic criteria (e.g., UK Parkinson's Disease Society Brain Bank criteria).
- Intervention: Melatonin, administered in any dose or formulation.
- Comparator: Placebo.
- Outcome measures: Studies reporting outcomes using validated scales, such as PSQI for sleep quality and ESS for daytime sleepiness.
- Study design: Randomized, placebo-controlled parallel-group trials (RCTs) assessing the effects of melatonin on sleep quality and/or daytime sleepiness in PD patients.

We excluded studies that were (1) non-randomized trials, observational studies, animal studies, studies not available in English, conference abstracts, or theses, (2) lacking a placebo-controlled group or using other drugs for comparison, (3) focused on patients diagnosed with neurodegenerative diseases other than Parkinson's disease (PD), (4) not reporting data on sleep quality or daytime sleepiness, (5) involving mixed populations where data specific to PD patients were not reported separately, and (6) including participants with significant neurological or psychiatric conditions other than PD that could interfere with sleep assessments.

### 2.3. Information sources and search strategy

A comprehensive search was conducted up to February 2025 across the following electronic databases: PubMed, Web of Science, Cochrane Library, Scopus, and ClinicalTrials.gov. Key search terms included "Parkinson's disease," "melatonin," and "sleep." The search strategy for PubMed was:

((melatonin) AND ("Parkinson's disease" OR Parkinson OR "PD") AND ("sleep" OR "sleep disorders" OR insomnia OR "sleep disturbance")). Full details of the search strategies for all databases are provided in the supplementary file 1.

### 2.4. Screening and study selection process

We utilized Rayyan for semi-automated screening of the literature search results [22]. The screening process was conducted in two phases: the first phase involved screening titles and abstracts to identify potential clinical studies, while in the second phase, full-text articles of the selected abstracts were retrieved for further eligibility assessment. Two independent reviewers (BD and WS) screened the titles and abstracts against the predefined criteria. Any discrepancies were resolved through discussion, and a third reviewer (AZ) was consulted when needed. The study selection process was tracked and documented using a PRISMA flowchart.

### 2.5. Data extraction

For all included studies, three reviewers (RA, ME, and AZ) independently extracted data using a standardized Excel sheet. The extracted data encompassed (1) study characteristics, (2) baseline characteristics of the study population, (3) risk of bias assessment, and (4) reliable data on the study outcomes for analysis.

### 2.6. Risk of bias assessment

The quality of the included studies was evaluated using version 2 of the Cochrane Risk of Bias (ROB) tool [23]. This tool assesses potential biases in five key domains: the randomization process, deviations from the intended interventions, missing outcome data, outcome measurement, and the selection of reported results. The evaluation process was conducted independently by two reviewers (RA and AZ), and any discrepancies were resolved through consensus with a third reviewer (ME) to ensure consistency and accuracy in the assessment.

### 2.7. Publication bias

In agreement with Egger et al., [24], we determined that examining potential publication bias using Egger's test for funnel plot asymmetry was not applicable in our review, as the number of included studies was fewer than ten.

### 2.8. Effect measures

The main outcomes measured in this review were the Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness Scale (ESS). The PSQI evaluates overall subjective sleep quality considering factors such as sleep duration, disturbances, and latency, with a global score where higher values indicate poorer sleep quality [25].

The ESS, on the other hand, measures subjective daytime sleepiness by assessing the likelihood of dozing off in various daily situations, with higher scores reflecting greater daytime sleepiness [26].

### 2.9. Data synthesis and analysis

The primary outcomes were the pooled mean differences in total PSQI and ESS scores from baseline to post-treatment between the Melatonin and Placebo groups. Heterogeneity was assessed using the Chi-square and $I^2$ statistics, with significant heterogeneity defined by a p-value less than 0.1 and an $I^2$ value greater than 50 %. When heterogeneity was encountered, a random-effect model was applied, and a sensitivity analysis (if applicable) was performed to further assess heterogeneity. Otherwise, a fixed-effect model was conducted.

None of the included RCTs reported the standard deviation of change scores (SD Change) within each group for the outcomes analyzed. However, Ahn et al. [27] provided 95 % confidence intervals (CIs) for the mean differences within each group, allowing us to calculate the SD Change for that study and the corresponding correlation coefficients (r). Furthermore, a sensitivity analysis exploring different correlation coefficients was performed to confirm the robustness of the imputed values for each outcome. Based on that, the coefficients that were considered optimal were used for computing the missing SD for the change scores in the remaining studies if needed. For studies reporting median and IQR for changes from baseline, we converted these values to mean and standard deviations based on Wan et al.'s formula [28] and used them in the analysis along with the imputed SDs. Supplementary Table 1 and Supplementary Table 4.

All formulas used for imputing the missing values were provided in the Cochrane Handbook for Systematic Reviews of Intervention (2nd edition, Section 6.5) [29]. All analyses were performed using RevMan version 5.4 for Windows.

### 2.10. Subgroup analyses

Subgroup analyses were performed to explore potential sources of variability such as treatment duration (4 weeks vs. 8–12 weeks), melatonin dose (≤4 mg vs. > 4 mg), and melatonin formulation (immediate-release vs. prolonged-release) on the total PSQI outcome.

## 3. Results

### 3.1. Study selection

Our search strategy in the databases initially retrieved 1350 results.

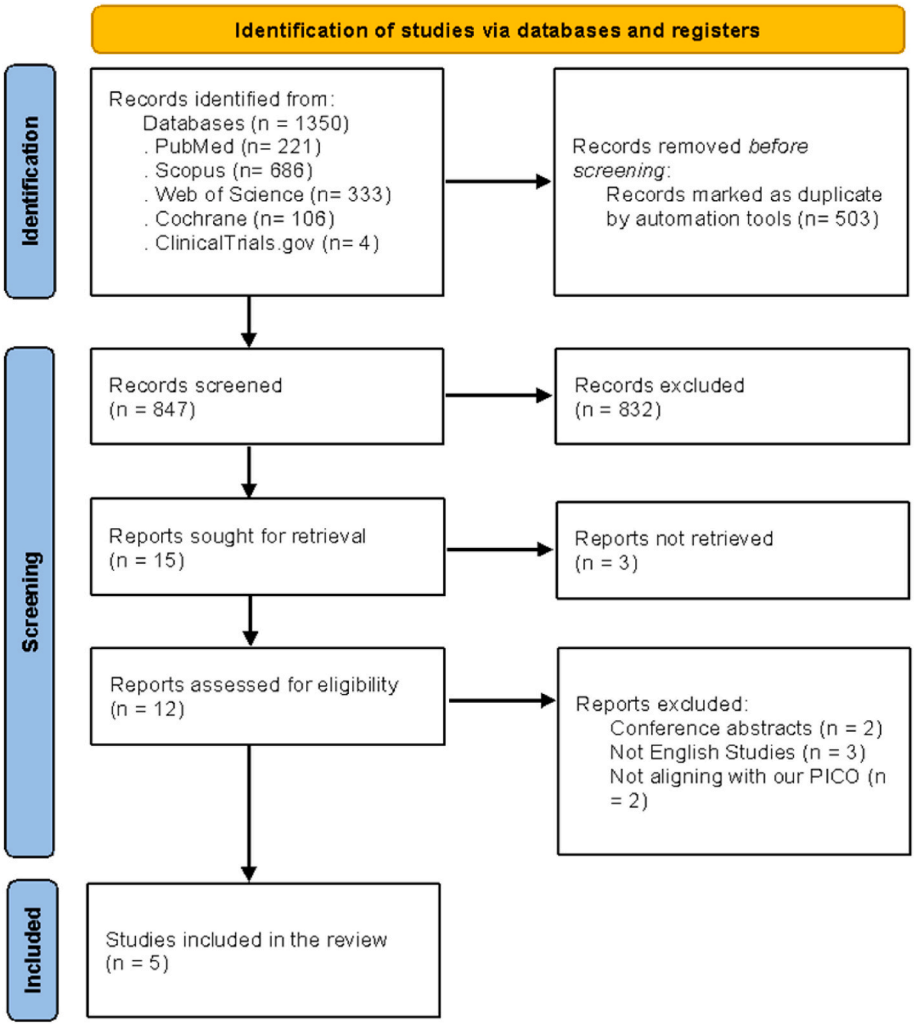


**Fig. 1.** PRISMA flowchart of the final included studies.

Automated tools removed 503 duplicates. Only five RCTs were included in our review after screening for eligibility based on our inclusion/exclusion criteria. The Selection process is outlined in [Fig. 1].

### 3.2. Studies characteristics

The total sample size of the included studies was 206, with 99 (48.06 %) in the melatonin group and 107 (51.94 %) in the placebo group. All studies had Parkinson's disease patients in similar age groups, except the study by Sugumaran et al. [30], which included younger patients in the melatonin and placebo groups (60.3 ± 6.3) (58.4 ± 8.8), respectively. The studies' characteristics are presented in [Table 1] [Table 2].

### 3.3. Quality assessment

Two studies [27,30] were assessed as having a high risk of bias, specifically in the domain of assessing deviations from intended interventions. As a result, they were deemed to have an overall high risk of bias. Additionally, the study by Medeiros et al. [31] had an overall judgment of some concerns due to incomplete information about the randomization and allocation process, as well as concerns regarding the measurement of outcomes. Similarly, the study by Gilat et al. [32] was also assessed with some concerns. While the authors mentioned applying intention-to-treat analysis for their primary data, they did not specify this for their secondary data, which is used in our meta-analysis, thus, it raised concerns in our opinion. In contrast, the study by Kakhaki et al. [33] was judged to have a low risk of bias across all domains. [Fig. 2].

### 3.4. Meta-analysis

#### 3.4.1. Quality of sleep - PSQI (Pittsburgh Sleep Quality Index)

Our primary outcome was the pooled mean difference in total PSQI scores (from baseline to post-treatment) between the Melatonin and Placebo groups. All five RCTs assessed the total PSQI scores, but none reported the standard deviation (SD) Change within each group. As detailed in the methods section, Ahn et al. [27] provided a correlation coefficient (r) value of (0.7) for both arms. The sensitivity analysis assuming varying correlations showed that the pooled mean difference varied slightly, ranging from −1.67 to −1.73, with no change in statistical significance. Thus, r = 0.7 was deemed appropriate to impute missing (SDs Change) when needed for both groups, as it was empirically justified by a comparable study and by the robust results of the sensitivity analysis. [Supplementary Table 1].

In subgroup analyses, a random-effect model was used to account for the heterogeneities between studies. There was no significant difference between Melatonin and placebo in improving total PSQI score when using doses ≤4 mg [27,30–32] (mean difference [95 % CI] = −1.26 [−2.72, 0.20], $I^2$ = 58 %, overall effect P = 0.09). However, applying a leave-one-out sensitivity analysis excluding the Gilat study [32] eliminated the heterogeneity and shifted the pooled effect to statistical significance (mean difference [95 % CI] = −1.74 [−2.63, −0.85], $I^2$ = 0 %, overall effect P = 0.0001). [Supplementary Table 2].

The (>4 mg dose) subgroup included only one study [33], thus, the pooled estimate (mean difference [95 % CI] = −2.90 [−4.02, −1.78], $I^2$ = NA, overall effect P < 0.00001) reflected the effect reported by that individual study.

Taking Melatonin for 4 weeks significantly improved the total PSQI scores [27,31] (mean difference [95 % CI] = −2.43 [−3.98, −0.88], $I^2$ = 0 %, overall effect; P = 0.002). However, taking melatonin for (8–12) weeks did not demonstrate a statistically significant effect on total PSQI compared to placebo [30,32,33] (mean difference [95 % CI] = −1.24 [−3.15, 0.67], $I^2$ = 83 %, overall effect; P = 0.2). A leave-one-out sensitivity analysis excluding the Gilat et al. [32] study resulted in a significant pooled effect favoring melatonin, albeit with persistent heterogeneity (mean difference [95 % CI] = −2.14 [−3.61, −0.67], I2 = 72 %, overall effect; P = 0.004). [Supplementary Table 3].

Furthermore, based on melatonin formulation, the immediate-release melatonin showed a significant improvement in total PSQI scores (mean difference [95 % CI] = −2.20 [−3.32, −1.08], $I^2$ = 45 %, overall effect P = 0.0001) [30,31,33]. Conversely, the prolonged-release formulation [27,32] showed an insignificant pooled effect estimate (mean difference [95 % CI] = −0.61 [−4.15, 2.93], $I^2$ = 83 %, overall effect P = 0.74). Sensitivity analysis was not applicable as the subgroup included only two studies. [Fig. 3].

#### 3.4.2. Daytime Sleepiness-ESS (Epworth Sleepiness Scale)

Four studies assessed daytime sleepiness using total ESS scores [27,30–32] but none of them reported the (*SD Change*) within each group. However, Ahn et al. [27] provided the needed values to derive the correlation coefficients, which were found to be (r = 0.9) in the melatonin group and (r = 0.5) in the placebo group. Sensitivity analysis assuming different coefficient combinations showed a variation in the pooled estimation ranging from −0.81 to −1.02 with a loss of significance in some scenarios. This indicated that the pooled estimates were sensitive to the correlation assumptions. [Supplementary Table 4]. The presented Forest plot below used the (r = 0.9, r = 0.5) derived from the Ahn et al. study [27] to impute missing SD of change within groups. Melatonin showed a significant reduction in the total ESS score compared to placebo (mean difference [95 % CI] = −0.97 [−1.81, −0.14, I2 = 12 %, overall effect; P = 0.02). [Fig. 4].

## 4. Discussion

We conducted this systematic review and meta-analysis to evaluate the effects of melatonin on sleep quality and daytime sleepiness in patients with Parkinson's disease. Our findings indicate that melatonin may improve sleep quality measured by PSQI and provide a slight benefit for daytime sleepiness measured by ESS in this population, particularly with short-term use of immediate-release formulations.

Regarding excessive daytime sleepiness, four studies were included in our analysis and showed that melatonin may modestly reduce daytime sleepiness measured by the ESS (MD = −0.97, P = 0.02). This effect was largely driven by Sugumaran et al. [30] trial that contributed 69 % of the weight to the ESS meta-analysis. This trial included a younger cohort than other studies and reported heightened self-monitoring of sleep habits among participants, suggesting age or behavioral influence on this outcome. Notably, this finding contradicts previous trials by

**Table 1**
Studies' characteristics 1.

| Study/Year | Country | Design | Sample size (N) | Study Duration(weeks) | Gender(M/F) | | Disease Duration/years (Mean/SD) | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Melatonin | Placebo | Melatonin | Placebo |
| **Sugumaran/2024** | India | Parallel RCT | 73 | 8 weeks | 22/13 | 23/15 | 3.0 ± 1.8 | 3.6 ± 3.6 |
| **Kakhaki/2020** | Iran | Parallel RCT | 51 | 12 weeks | 16/9 | 16/10 | 5.7 ± 1.9 | 5.5 ± 2.1 |
| **Ahn/2020** | Republic of Korea | Parallel RCT | 34 | 4 weeks | 8/8 | 9/9 | 5.0 ± 5.9 | 4.2 ± 4.4 |
| **Gilat/2019** | Australia | Parallel RCT | 30 | 12 weeks | 12/3 | 13/2 | 5.07 ± 3.9 | 6.13 ± 4.4 |
| **Medeiros/2007** | Brazil | Parallel RCT | 18 | 4 weeks | 7/1 | 7/3 | 6.40 ± 2.59 | 7.70 ± 6.52 |

N: Number; SD: Standard deviation; M/F: Male/Female.

**Table 2**
Studies' characteristics 2.

| Study/Year | Levodopa equivalent dose (mg/day) (Mean/SD) | | Intervention (Melatonin) | | Comparator | Outcome | |
|---|---|---|---|---|---|---|---|
| | Melatonin | Placebo | Dose (mg) | F Formulation | | Sleep Quality | Daytime Sleepiness |
| Sugumaran/2024 | 506.0 ± 155.8 | 478.6 ± 135.0 | 3 mg | Immediate-release capsule | Placebo | PSQI | ESS |
| Kakhaki/2020 | 578 ± 249 | 532 ± 160 | 10 mg | Immediate-release capsule | Placebo | PSQI | NA |
| Ahn/2020 | NA | NA | 2 mg | Prolonged-release capsule | Placebo | PSQI | ESS |
| Gilat/2019 | 640.1 ± 310 | 621.6 ± 376 | 4 mg | Prolonged-release capsule | Placebo | PSQI | ESS |
| Medeiros/2007 | 600 ± 226.69 1 | 650 ± 248.611 | 3 mg | Immediate-release capsule | Placebo | PSQI | ESS |

Levodopa equivalent dosages were taken directly from studies where available. [1] last study reported the levodopa dose, which may not be directly comparable. SD: Standard Deviation; PSQI: Pittsburgh Sleep Quality Index; ESS: Epworth Sleepiness Scale.

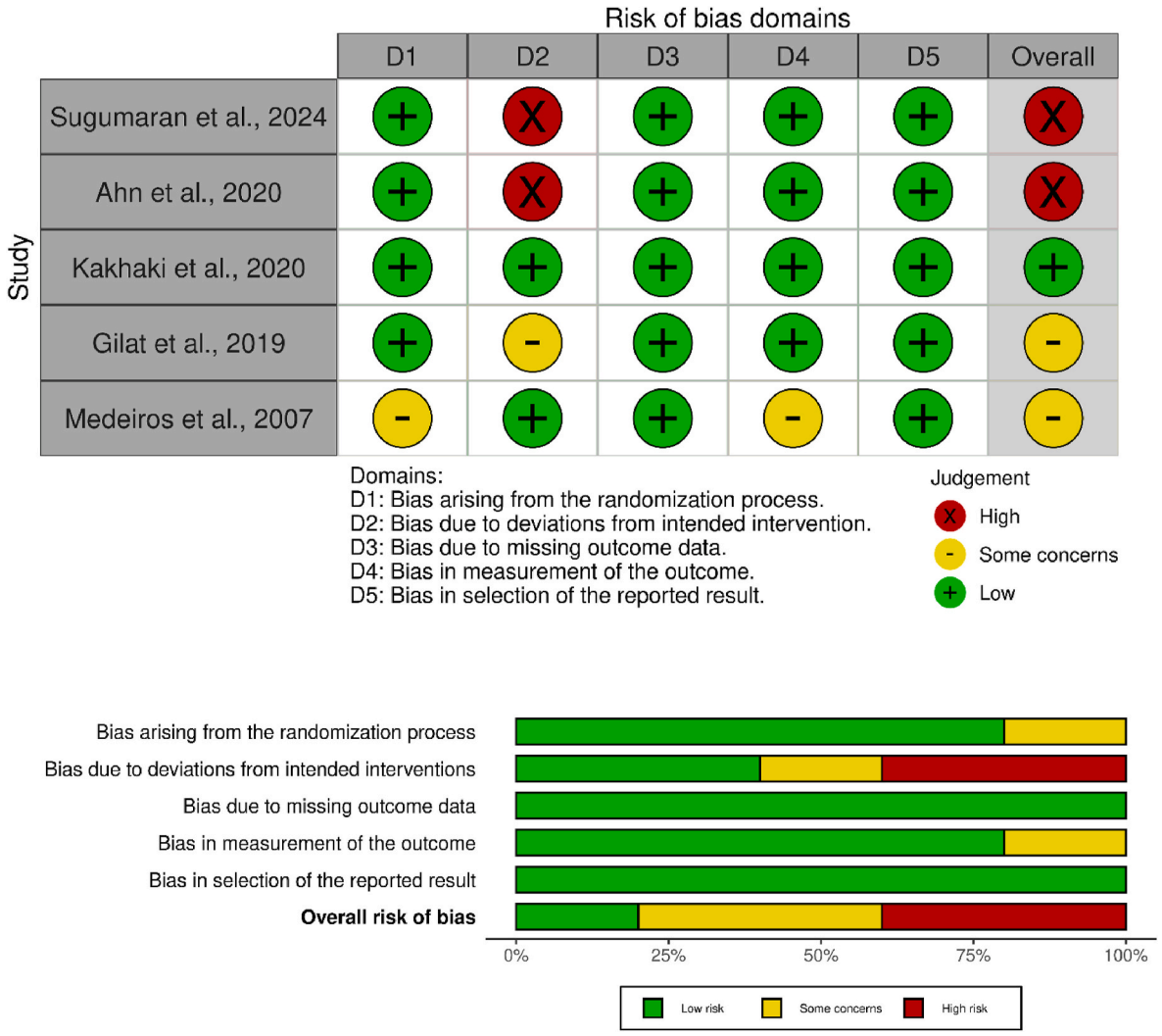


**Fig. 2.** Quality assessment of included RCTs using ROB 2.0.

Litvinenko et al. [34], who reported worsened ESS scores after 6 weeks of melatonin administration [4.1 ± 1.4 to 4.7 ± 1.4; p = 0.06], and Delgado Lara et al. [35], who found no significant improvements in ESS scores, highlighting inconsistency across the literature.

Our subgroup analyses revealed several important patterns. Immediate-release formulations demonstrated greater efficacy than prolonged-release formulations. A potential explanation could be that immediate-release formulations achieve higher peak plasma concentrations more rapidly, potentially facilitating faster sleep onset. However, this finding is based on only 64 patients receiving prolonged-release melatonin across two studies [27,32], which limits our confidence in this observation.

In terms of treatment duration, shorter treatment (4 weeks) exhibited better efficacy than longer treatment (8–12 weeks). This finding should be interpreted cautiously, as this subgroup analysis was based on only 52 PD patients in the 4-week treatment category, with all studies having exactly 4-week durations rather than a range of shorter periods. The observed reduction in efficacy with longer treatment may relate to progressive neurodegeneration affecting sleep-regulating brain structures, though it could also result from the small number of included trials and their heterogeneous populations.

Regarding dosage, while the single study using 10 mg (Kakhaki et al. n = 51 patients) [33] showed a stronger effect than the pooled analysis of studies using ≤4 mg, drawing conclusions regarding dose-effect

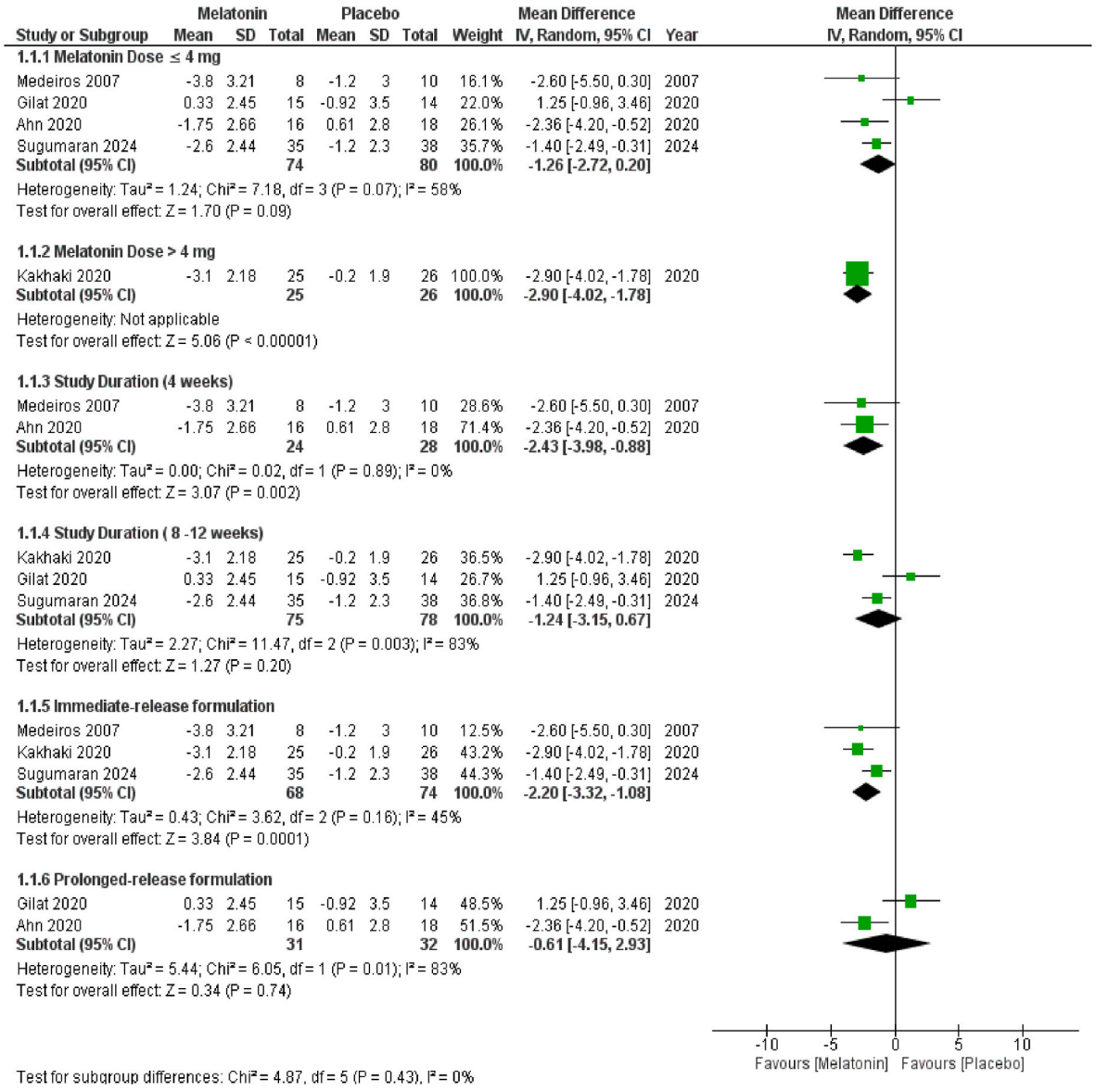


**Fig. 3.** Forest Plot of Melatonin Effect vs Placebo on Total PSQI Score (With Subgroup Analyses).

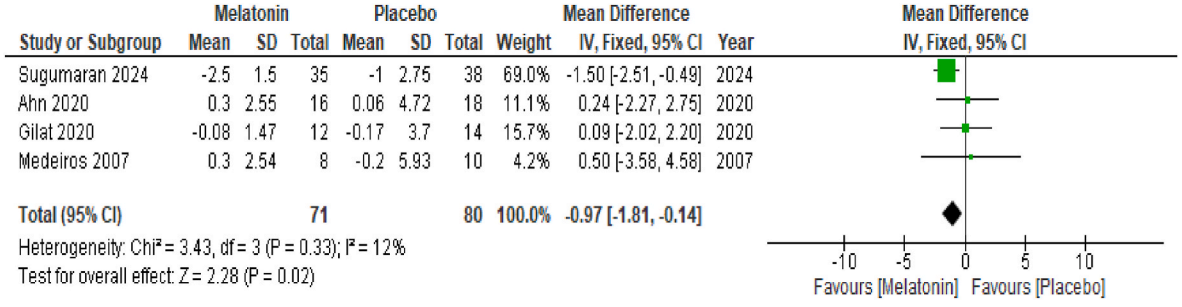


**Fig. 4.** Forest Plot of melatonin effect vs placebo on the Total *ESS Score*.

relationships from this single study is inappropriate. Larger studies systematically comparing different melatonin dosages are needed to establish optimal therapeutic ranges.

Melatonin was generally well tolerated, with no major adverse effects reported in any of the included studies. The most common side effect was drowsiness, occurring in 88.6 % of participants in the melatonin group versus 60.5 % in the placebo group (Sugumaran et al.) [30]. Kakhaki et al. [33] reported headache and daytime sleepiness in two participants each from the melatonin group. The Gilat study [32] reported mild headaches, fatigue, and morning sleepiness in similar proportions between treatment groups. Interestingly, both Ahn et al. [27] and Medeiros et al. [31] reported no adverse effects at all. Overall,

these results suggest that melatonin is generally safe and well-tolerated by PD patients, with drowsiness being the most frequently reported side effect.

A recent RCT by Hadi et al. [36] gave important comparative data on melatonin versus other commonly used sleep medications in PD patients. This three-arm, double-blind RCT compared melatonin (3 mg/day), clonazepam (1 mg/day), and trazodone (50 mg/day) in 93 PD patients with subjective sleep complaints over a 4-week treatment period. All three medications significantly improved PSQI scores without statistical differences between groups. However, melatonin was superior in reducing REM Sleep Behavior Disorder symptoms, a finding particularly relevant given the high prevalence of RBD in PD patients. This aligns with the growing clinical preference for melatonin as a first-line RBD treatment due to its favorable safety profile [37]. Regarding daytime sleepiness, trazodone showed greater ESS improvement than clonazepam, with melatonin showing intermediate efficacy.

These findings further validate earlier clinical recommendations from Loddo et al. [38], who suggested melatonin as a potential treatment of choice for PD patients with contraindications to clonazepam (such as OSAS, cognitive impairment, or high fall risk) due to its superior safety profile, particularly in patients receiving polytherapy.

A prospective observational pilot study by Liguori et al. [39] demonstrated that 2 mg prolonged-release melatonin significantly decreased sleep latency assessed by polysomnography (PSG) in 12 PD patients after a treatment duration of 3 months, though other PSG parameters remained unchanged. A significant reduction in daytime sleepiness measured by ESS was reported, while PSQI scores showed a trend of improvement, complementing the findings on melatonin's efficacy. This study provided additional objective evidence supporting melatonin's effects on sleep parameters and daytime functioning in PD patients.

The inconsistent results observed across studies examining melatonin's effects can largely be attributed to methodological differences, including varying inclusion criteria, assessment protocols, and statistical approaches. Additionally, the complex pathophysiology of sleep disturbances in PD, involving neurodegenerative changes, abnormal beta oscillations in the basal ganglia, glymphatic system dysfunction, and altered neurotransmitter pathways [40,41], may also contribute to the observed inconsistencies and the clinical diversity of sleep issues in PD.

It's worth mentioning that the trials included in our review varied in their target population, with Ahn et al. [27] study examining PD patients with poor sleep quality, Gilat et al. [32] study focusing specifically on RBD symptoms, Kakhaki et al. [33] study investigating metabolic profiles alongside sleep parameters, and Medeiros et al. [31] study including patients with relatively young disease onset. These different phenotypes may represent distinct pathophysiological mechanisms that may respond differently to melatonin therapy, suggesting that treatment strategies should be tailored to specific sleep disturbance phenotypes rather than applying a one-size-fits-all approach.

Based on the comprehensive review by Duan et al. (2025) [42], several other therapeutic approaches exist for managing sleep disturbances in PD. Non-pharmacological options include cognitive behavioral therapy for insomnia (CBT-I), which has shown significant efficacy in reducing insomnia severity in PD patients; various exercise modalities such as aerobic training, resistance training, Qigong, yoga, Brazilian Samba, and Tai Chi, which had shown positive effects on sleep quality among PD patients; bright-light therapy which can improve sleep quality and circadian rhythm regulation; and deep brain stimulation, which primarily treats motor symptoms but secondarily improves sleep by reducing nocturnal motor disturbances. Emerging therapeutic approaches include biofeedback therapy, which showed significant improvements in both objective and subjective sleep quality after 3 weeks of treatment; photobiomodulation therapy using He-Ne lasers, which enhanced sleep duration, reduced sleep latency, and improved sleep efficiency without adverse events through a mechanism believed to involve increased melatonin secretion that helps regulate circadian rhythms; low-intensity pulsed ultrasound treatment (LIPUS); and music therapy.

Pharmacological options encompass benzodiazepine receptor agonists, orexin receptor antagonists like suvorexant, and dopaminergic medications strategically timed for nocturnal symptoms (controlled-release levodopa, non-ergot dopamine agonists like pramipexole, ropinirole, and rotigotine). For mood-related sleep disturbances, antidepressants (including SSRIs like sertraline, SNRIs like venlafaxine, and sedating drugs like trazodone and mirtazapine) can be effective. Nevertheless, treatment selection should be individualized based on the specific sleep complaint, comorbidities, and the patient's overall clinical profile.

### 4.1. Strengths and limitations

Our review has several strength points. We followed the PRISMA guidelines and only included randomized, parallel-group, placebo-controlled trials. Additionally, we performed subgroup analyses by melatonin dosage, formulation, and treatment duration to examine the effects of these variations in PD patients. Furthermore, we incorporated sensitivity analysis to mitigate heterogeneity whenever possible and followed the Cochrane Handbook Guidelines for imputation of missing SD values of the change within groups using empirically justified correlation coefficients, aiming to make our results more robust.

However, several important limitations should be considered when interpreting our findings. First, the small number of included studies and total sample size ($n = 206$) limits statistical power, particularly for subgroup analyses, and restricts the ability to conduct more powerful exploratory analyses, such as meta-regression, to explore potential dose-response relationships. Second, the heterogeneous patient populations with varying inclusion criteria and characteristics may limit generalizability. Third, the varying quality of included studies affects confidence in our pooled estimates. Fourth, our reliance on subjective outcome measures (PSQI and ESS) may not fully capture changes in sleep architecture that would be detectable with polysomnography (PSG) or other objective measures.

Despite these limitations, our findings offer valuable insights into the potential therapeutic role of melatonin in enhancing sleep quality and reducing daytime sleepiness in patients with Parkinson's disease, laying the groundwork for future practice guidelines. We recommend that future research should include: (1) larger well-designed RCTs with diverse PD populations; (2) systematic evaluation of different melatonin doses, formulations, and treatment durations; (3) head-to-head comparisons with other sleep medications; and (4) investigation of which PD subgroups derive the greatest benefit from melatonin. Studies with longer follow-up periods would also help determine whether the apparent reduction in efficacy over time represents a true effect or an artifact of the limited available data.

## 5. Conclusions

In conclusion, this systematic review and meta-analysis suggest that melatonin may improve sleep quality and modestly reduce daytime sleepiness in patients with Parkinson's disease, with some evidence favoring immediate-release formulations and shorter treatment durations. However, given the inherent limitation of our meta-analysis, these findings should be interpreted cautiously, with larger well-designed RCTs needed to confirm our findings. In terms of safety, melatonin appears to be well-tolerated with minimal adverse effects, making it a potentially valuable option within a comprehensive approach to addressing sleep disturbances in PD.

## CRediT authorship contribution statement

**Azzam Zrineh:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Rami**

**Akwan:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Muhammad M. Elsharkawy:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation. **Bashar Douden:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **Wadi Sleibi:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **Mohamed Eldesouki:** Writing – review & editing, Supervision.

## Ethics approval and consent to participation:

N/A.

## Consent for publication:

N/A.

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## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2025.106540.

## References

[1] Kouli A, Torsney KM, Kuan W-L. Parkinson's disease: etiology, neuropathology, and pathogenesis. 2018.
[2] Santos García D, et al. Non-motor symptoms burden, mood, and gait problems are the most significant factors contributing to a poor quality of life in non-demented Parkinson's disease patients: results from the COPPADIS Study Cohort. Parkinsonism Relat Disord Sep. 2019;66:151–7. https://doi.org/10.1016/j.parkreldis.2019.07.031.
[3] Kurihara K, et al. Impact of motor and nonmotor symptoms in Parkinson disease for the quality of life: the Japanese Quality-of-Life Survey of Parkinson Disease (JAQPAD) study. J Neurol Sci Dec. 2020;419:117172. https://doi.org/10.1016/j.jns.2020.117172.
[4] Li X, et al. Trends and hotspots in non-motor symptoms of Parkinson's disease: a 10-year bibliometric analysis. Front Aging Neurosci 2024;16(Jan). https://doi.org/10.3389/fnagi.2024.1335550.
[5] Minakawa EN. Bidirectional relationship between sleep disturbances and Parkinson's disease. Front Neurol Jul. 2022;13. https://doi.org/10.3389/fneur.2022.927994.
[6] Zhu J, et al. Nonmotor symptoms affect sleep quality in early-stage Parkinson's disease patients with or without cognitive dysfunction. Front Neurol 2020;11(Apr). https://doi.org/10.3389/fneur.2020.00292.
[7] Hermann W, et al. Sleep disturbances and sleep disordered breathing impair cognitive performance in Parkinson's disease. Front Neurosci 2020;14(Aug). https://doi.org/10.3389/fnins.2020.00689.
[8] Yi Q, et al. Worse sleep quality aggravates the motor and non-motor symptoms in Parkinson's disease. Front Aging Neurosci 2022;14(Jun). https://doi.org/10.3389/fnagi.2022.887094.
[9] Salawu F, Olokoba A. Excessive daytime sleepiness and unintended sleep episodes associated with Parkinson's disease. Oman Med J Jan. 2015;30(1):3–10. https://doi.org/10.5001/omj.2015.02.
[10] Samizadeh M-A, et al. Parkinson's disease: a narrative review on potential molecular mechanisms of sleep disturbances, REM behavior disorder, and melatonin. Brain Sci Jun. 2023;13(6):914. https://doi.org/10.3390/brainsci13060914.
[11] Zuzuárregui JRP, During EH. Sleep issues in Parkinson's disease and their management. Neurotherapeutics Oct. 2020;17(4):1480–94. https://doi.org/10.1007/s13311-020-00938-y.
[12] Stefani A, Högl B. Sleep in Parkinson's disease. Neuropsychopharmacology Jan. 2020;45(1):121–8. https://doi.org/10.1038/s41386-019-0448-y.
[13] Savage RA, Zafar N, Yohannan S, Miller J-MM. Melatonin. 2025.
[14] Kvetnoy I, et al. Melatonin as the cornerstone of neuroimmunoendocrinology. Int J Mol Sci Feb. 2022;23(3). https://doi.org/10.3390/ijms23031835.
[15] Afzal A. Melatonin as a multifunctional modulator: emerging insights into its role in health, reproductive efficiency, and productive performance in livestock. Front Physiol Dec. 2024;15. https://doi.org/10.3389/fphys.2024.1501334.
[16] Alghamdi BS. The neuroprotective role of melatonin in neurological disorders. J Neurosci Res Jul. 2018;96(7):1136–49. https://doi.org/10.1002/jnr.24220.
[17] Guo R, Ye J, Liao B, Luo X, Rao P. The relationship between anesthesia and melatonin: a review. Front Pharmacol 2023;14:1255752. https://doi.org/10.3389/fphar.2023.1255752.
[18] Luo F, et al. Melatonin and autophagy in aging-related neurodegenerative diseases. Int J Mol Sci Sep. 2020;21(19):7174. https://doi.org/10.3390/ijms21197174.
[19] Srinivasan V, Pandi-Perumal S, Cardinali D, Poeggeler B, Hardeland R. Melatonin in Alzheimer's disease and other neurodegenerative disorders. Behav Brain Funct Dec. 2006;2(1):15. https://doi.org/10.1186/1744-9081-2-15.
[20] Auld F, Maschauer EL, Morrison I, Skene DJ, Riha RL. Evidence for the efficacy of melatonin in the treatment of primary adult sleep disorders. Sleep Med Rev Aug. 2017;34:10–22. https://doi.org/10.1016/j.smrv.2016.06.005.
[21] Cumpston M, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database Syst Rev Oct. 2019. https://doi.org/10.1002/14651858.ED000142.
[22] Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. Syst Rev Dec. 2016;5(1):210. https://doi.org/10.1186/s13643-016-0384-4.
[23] Sterne JAC, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ Aug. 2019:l4898. https://doi.org/10.1136/bmj.l4898.
[24] Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ Sep. 1997;315(7109):629–34. https://doi.org/10.1136/bmj.315.7109.629.
[25] Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatry Res May 1989;28(2):193–213. https://doi.org/10.1016/0165-1781(89)90047-4.
[26] Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep Nov. 1991;14(6):540–5. https://doi.org/10.1093/sleep/14.6.540.
[27] Ahn JH, et al. Prolonged-release melatonin in Parkinson's disease patients with a poor sleep quality: a randomized trial. Parkinsonism Relat Disord Jun. 2020;75:50–4. https://doi.org/10.1016/j.parkreldis.2020.03.029.
[28] Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol Dec. 2014;14(1):135. https://doi.org/10.1186/1471-2288-14-135.
[29] Higgins JPT, et al., editors. Cochrane Handbook for systematic reviews of interventions. Wiley; 2019. https://doi.org/10.1002/9781119536604.
[30] Sugumaran R, Sai Krishna KS, Saibaba J, Narayan SK, Sandhiya S, Rajeswari M. Melatonin on sleep in Parkinson's disease: a randomized double blind placebo controlled trial. Sleep Med Dec. 2024;124:502–9. https://doi.org/10.1016/j.sleep.2024.10.020.
[31] Medeiros CAM, Carvalhedo de Bruin PF, Lopes LA, Magalhães MC, de Lourdes Seabra M, Sales de Bruin VM. Effect of exogenous melatonin on sleep and motor dysfunction in Parkinson's disease. J Neurol Apr. 2007;254(4):459–64. https://doi.org/10.1007/s00415-006-0390-x.
[32] Gilat M, et al. Melatonin for rapid eye movement sleep behavior disorder in Parkinson's disease: a randomised controlled trial. Mov Disord Feb. 2020;35(2):344–9. https://doi.org/10.1002/mds.27886.
[33] Daneshvar Kakhaki R, et al. Melatonin supplementation and the effects on clinical and metabolic status in Parkinson's disease: a randomized, double-blind, placebo-controlled trial. Clin Neurol Neurosurg Aug. 2020;195:105878. https://doi.org/10.1016/j.clineuro.2020.105878.
[34] V Litvinenko I, V Krasakov I, V Tikhomirova O. [Sleep disorders in Parkinson's disease without dementia: a comparative randomized controlled study of melatonin and clonazepam]. Zh Nevrol Psikhiatr Im S S Korsakova 2012;112(12):26–30.
[35] Delgado-Lara DL, et al. Effect of melatonin administration on the PER1 and BMAL1 clock genes in patients with Parkinson's disease. Biomed Pharmacother Sep. 2020;129:110485. https://doi.org/10.1016/j.biopha.2020.110485.
[36] Hadi F, et al. Safety and efficacy of melatonin, clonazepam, and trazodone in patients with Parkinson's disease and sleep disorders: a randomized, double-blind trial. Neurol Sci Oct. 2022;43(10):6141–8. https://doi.org/10.1007/s10072-022-06188-4.
[37] Matar E, McCarter SJ, St Louis EK, Lewis SJG. Current concepts and controversies in the management of REM sleep behavior disorder. Neurotherapeutics Jan. 2021;18(1):107–23. https://doi.org/10.1007/s13311-020-00983-7.
[38] Loddo G, et al. The treatment of sleep disorders in Parkinson's disease: from research to clinical practice. Front Neurol 2017;8(Feb). https://doi.org/10.3389/fneur.2017.00042.
[39] Liguori C, et al. Effects of melatonin prolonged-release on both sleep and motor symptoms in Parkinson's disease: a preliminary evidence. Neurol Sci Sep. 2022;43(9):5355–62. https://doi.org/10.1007/s10072-022-06111-x.
[40] Samizadeh M-A, et al. Parkinson's disease: a narrative review on potential molecular mechanisms of sleep disturbances, REM behavior disorder, and

melatonin. Brain Sci Jun. 2023;13(6):914. https://doi.org/10.3390/brainsci13060914.
[41] Duan X, et al. Insomnia in Parkinson's disease: causes, consequences, and therapeutic approaches. Mol Neurobiol Feb. 2025;62(2):2292–313. https://doi.org/10.1007/s12035-024-04400-4.

[42] Duan X, et al. Insomnia in Parkinson's disease: causes, consequences, and therapeutic approaches. Mol Neurobiol Feb. 2025;62(2):2292–313. https://doi.org/10.1007/s12035-024-04400-4.