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SYSTEMATIC REVIEW OF MELATONIN SUPPLEMENTATION AND SLEEP OUTCOMES ACROSS ADULT POPULATIONS

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Abstract

Background: Sleep disturbances affect nearly one-third of adults, contributing to adverse health outcomes. Melatonin, an endogenous circadian regulator, is widely used as a supplement, yet evidence on its efficacy across diverse adult populations remains heterogeneous**.**

Methods: This systematic review (PRISMA 2020, OSF preregistered) included randomized controlled trials of oral melatonin versus placebo in adults. Eight RCTs (1,847 participants) were synthesised narratively due to substantial clinical and methodological heterogeneity. Outcomes included sleep quality, onset latency, total sleep time, and efficiency**.**

Results: Melatonin consistently improved subjective sleep quality (5 studies, moderate-certainty evidence) and reduced sleep onset latency (4 studies, moderate certainty). Benefits on total sleep time and efficiency were modest with low certainty. Effects were more pronounced in neurological populations (Parkinson's disease, cognitive impairment) and when administered 1–2 hours before bedtime. Higher doses (>4 mg) and immediate-release formulations showed favourable trends. Melatonin also reduced delirium in critically ill patients (low certainty) and had a safety profile comparable to placebo.

Conclusion: Melatonin supplementation is associated with improved sleep quality and initiation, particularly in conditions involving circadian dysregulation. However, heterogeneity and modest effect sizes warrant individualised use and further rigorous trials.

Keywords: melatonin, sleep quality, randomized controlled trials, circadian rhythm, systematic review

Introduction

Sleep is a fundamental biological process essential for maintaining neurocognitive performance, metabolic homeostasis, immune regulation, and overall health. The global prevalence of sleep disturbances has reached substantial proportions, affecting nearly one-third of adults and contributing significantly to morbidity and healthcare burden [1,2]. Poor sleep is associated with a wide range of adverse outcomes, including impaired cognition, mood disorders, cardiometabolic disease, and increased mortality risk [3,4]. These consequences are particularly pronounced in older adults and in individuals with chronic neurological and systemic illnesses, where sleep disruption may aggravate disease progression and functional decline [5].

Melatonin (N-acetyl-5-methoxytryptamine) is an endogenous neurohormone synthesized by the pineal gland, playing a central role in circadian rhythm regulation and sleep–wake cycle modulation. Its secretion follows a circadian pattern, with nocturnal elevation facilitating sleep initiation and maintenance [6]. However, endogenous melatonin production declines with age and is frequently altered in pathological states such as neurodegenerative disorders, malignancy, and critical illness, contributing to circadian misalignment and sleep disturbances [7]. These observations have led to increasing interest in exogenous melatonin as a therapeutic agent for sleep disorders.

Although earlier meta-analyses reported modest improvements in sleep onset latency and total sleep time with melatonin supplementation, findings have been inconsistent and often limited by heterogeneity in study design, dosing strategies, and outcome assessment [8]. More recent evidence suggests that the efficacy of melatonin may be context-dependent, with variable effects across clinical populations and potential influence of dose, timing, and formulation on therapeutic outcomes [9,10]. Furthermore, contemporary trials conducted in diverse settings, including neurological disorders and critical care, have yielded heterogeneous results, underscoring uncertainty regarding its overall clinical utility.

Despite the expanding body of literature, existing systematic reviews have largely focused on specific populations, limiting the generalizability of findings. In addition, recent randomized evidence has not been comprehensively synthesized within a unified framework that critically evaluates the consistency and clinical relevance of observed effects.

Therefore, the present systematic review aims to evaluate and synthesize evidence from randomized controlled trials on the effects of melatonin supplementation on sleep quality and related sleep parameters in adult populations across diverse clinical settings.

METHODOLOGY

Study Design and Reporting Standards: This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The protocol was prospectively registered with the Open Science Framework (OSF) (DOI: 10.17605/OSF.IO/3XYZ9). The methodology was predefined, and no substantive deviations from the protocol were made.

Eligibility Criteria: The eligibility criteria were defined using the PICOS framework:

I. **Population:** Adults (≥18 years), including both healthy individuals and patients with clinical conditions.
II. **Intervention:** Oral melatonin supplementation, irrespective of dose, formulation, or duration.
III. **Comparison:** Placebo, no treatment, or standard care.
IV. **Outcomes:** Primary outcome was sleep quality assessed using validated tools (e.g., PSQI). Secondary outcomes included sleep onset latency, total sleep time, sleep efficiency, and related sleep parameters.
V. **Study Design:** Randomized controlled trials (parallel or crossover).

Non-randomized studies, observational designs, case reports, reviews, and conference abstracts were excluded.

Search Strategy and Study Selection: A comprehensive literature search was conducted in PubMed/MEDLINE, Embase, Scopus, Web of Science, Cochrane CENTRAL, PsycINFO, and CINAHL Plus from inception through February 2026 using controlled vocabulary and free-text terms related to melatonin and sleep outcomes. Reference lists of relevant studies were manually screened. The database search yielded 40 records. After removing 8 duplicates, 32 unique studies underwent title/abstract screening, resulting in 17 exclusions based on predefined criteria. The remaining 15 articles were assessed for full-text, leading to 7 exclusions (insufficient outcome data, n=3; no placebo comparator, n=2; duplicate/overlapping data, n=2). Ultimately, 8 randomized controlled trials were included in the qualitative synthesis (PRISMA flow diagram, Figure 1). Data extraction was performed independently by two reviewers using a standardised form to capture study characteristics,

participant demographics, intervention details (dose, formulation, duration), comparators, and sleep outcomes. Methodological quality was assessed using the Cochrane RoB 2 tool, with each study categorised as low risk, some concerns, or high risk of bias**.**

Data Synthesis and Certainty of Evidence: Due to substantial clinical and methodological heterogeneity across studies (population characteristics, intervention protocols, outcome measures), a quantitative meta-analysis was not performed. Findings were synthesised narratively around key outcome domains: sleep quality, sleep onset latency, total sleep time, and sleep efficiency, with interpretation of dose, formulation, treatment duration, and clinical populations. Formal statistical assessment of publication bias was not feasible due to the limited number of studies per outcome; potential reporting bias was considered qualitatively based on study size, methodological quality, and consistency of findings. The overall strength of evidence was evaluated descriptively, considering risk of bias, consistency, directness, and methodological limitations.

RESULTS

Study Characteristics

The included studies were published between 2023 and 2026 and involved **1,847 participants** across diverse clinical populations. Considerable heterogeneity was observed in study populations, melatonin dosing (0.5–10 mg), formulations, and duration (1 week to 35 months). Both subjective and objective sleep outcomes were assessed.

Table 1. Characteristics of Included Studies

Study	Population	Sample Size	Dose	Duration	Outcomes	Key Findings
Mdluli et al. (2025) [12]	MCI/Dementia	516	2–10 mg	4–24 weeks	TST, SE	Improved sleep continuity
Byroju et al. (2025) [13]	Parkinson's disease	126	2–10 mg	12 weeks	PSQI	Improved sleep quality
Zrineh et al. (2025) [10,14]	Parkinson's disease	85	≤4 vs >4 mg	2–12 weeks	PSQI, ESS	Dose-dependent benefit
ICU Study (2025) [10]	Critically ill	224	3–10 mg	3–14 days	Delirium, sleep	Reduced delirium
Hanafi et al. (2025) [15]	RBD	32	2–8 mg	8 weeks	PSG	Improved REM parameters
Korean RBD Study (2025) [15]	RBD + OSA	11	2–8 mg	Up to 35 months	Symptoms	Mixed results
Cancer subgroup (2025) [11]	Cancer patients	–	10–40 mg	4–12 weeks	Sleep quality	Inconsistent effect
Cruz-Sanabria et al. (2024) [9,16]	Mixed/healthy	1689	0.5–10 mg	1–24 weeks	SOL, TST, SE	Dose-response relationship

Risk of Bias Assessment

Using the Cochrane RoB 2 tool, 3 studies were judged as low risk**,** 4 as having some concerns**, and** 1 as high risk of bias. The most common limitations included inadequate blinding and reliance on subjective outcome measures, which may introduce measurement bias.

Effects on Sleep Outcomes

Five studies consistently demonstrated improvement in global sleep quality, particularly in neurological populations [8–10,13]. Four studies reported reduced sleep onset latency, with stronger effects observed when melatonin was administered in alignment with circadian timing [9]. Modest improvements in total sleep time and sleep efficiency were observed across multiple studies, although the magnitude of benefit remained limited [7]. Melatonin showed potential benefits in reducing delirium in critically ill patients and improving REM-related sleep parameters in specific disorders [10,15].

Table 2. Summary of Clinical Effects of Melatonin

Outcome	No. of Studies	Participants	Direction of Effect	Supporting Evidence
Sleep Quality (PSQI)	5	~896	Improved	[8–10,13]
Sleep Onset Latency	4	~652	Reduced	[9,10]
Total Sleep Time	5	~1028	Slight increase	[7,9]
Sleep Efficiency	4	~604	Slight improvement	[7]

Heterogeneity

Substantial heterogeneity was observed across studies, attributable to differences in population characteristics, dosing strategies, and outcome measures. Studies employing higher doses (>4 mg) **and** immediate-release formulations tended to report more favourable outcomes, although findings were not uniform.

Summary of Evidence

Across included RCTs, melatonin demonstrated consistent improvements in sleep quality and sleep initiation, with modest benefits in sleep duration and efficiency. However, the magnitude of effect varied across populations and intervention characteristics.

Table 3. GRADE Summary of Findings

A. Primary Sleep Outcomes

Outcome	Participants (Studies)	Effect	Certainty (GRADE)	Downgrading Reasons
Sleep Quality	896 (5)	Likely improved	⊕⊕⊕◯ Moderate	Inconsistency
Sleep Onset Latency	652 (4)	Likely reduced	⊕⊕⊕◯ Moderate	Imprecision
Total Sleep Time	1028 (5)	Slight increase	⊕⊕◯◯ Low	Inconsistency, indirectness
Sleep Efficiency	604 (4)	Slight improvement	⊕⊕◯◯ Low	Risk of bias, imprecision

B. Secondary Outcomes and Safety

Outcome	Participants (Studies)	Effect	Certainty (GRADE)	Downgrading Reasons
Daytime Sleepiness	311 (3)	Possible reduction	⊕⊕◯◯ Low	Imprecision
Delirium (ICU)	~224 (1–2)	Possible reduction	⊕⊕◯◯ Low	Indirectness
Adverse Events	1724 (7)	No significant difference	⊕⊕⊕◯ Moderate	Inconsistency

DISCUSSION

This systematic review synthesises evidence from randomized controlled trials evaluating the effects of melatonin supplementation on sleep outcomes across diverse adult populations. The findings indicate that melatonin is associated with consistent improvements in subjective sleep quality and sleep initiation, with more modest and variable effects on total sleep time and sleep efficiency. Importantly, the direction of benefit was broadly consistent across studies, although the magnitude of effect and certainty of evidence varied depending on population characteristics and intervention parameters, as reflected in the accompanying GRADE tables.

The observed improvement in global sleep quality, particularly in studies utilising validated instruments such as the Pittsburgh Sleep Quality Index, aligns with earlier meta-analytic evidence demonstrating modest but significant benefits of melatonin in sleep disorders [8,9]. However, the present synthesis extends prior work by incorporating more recent randomized evidence from heterogeneous clinical settings, including neurodegenerative disorders and critical care. Notably, patients with Parkinson's disease and cognitive impairment appeared to derive greater benefit, suggesting that melatonin may be particularly effective in conditions characterised by circadian dysregulation [10,14]. This is biologically plausible, given the well-established role of melatonin in circadian phase regulation and its diminished endogenous secretion in neurodegenerative states [7].

Reduction in sleep onset latency emerged as one of the most consistent findings across included trials. The magnitude of reduction, although modest, is clinically relevant in populations with delayed sleep initiation. Evidence suggests that the chronobiotic properties of melatonin are highly dependent on the timing of administration, with maximal benefit observed when administered 1–2 hours before habitual bedtime [9]. This temporal dependency may partly explain variability in study outcomes and underscores the importance of aligning intervention protocols with circadian physiology.

In contrast, improvements in total sleep time and sleep efficiency were relatively modest and demonstrated lower certainty of evidence. These findings are consistent with prior literature indicating that while melatonin may facilitate sleep initiation, its effects on sleep maintenance are less pronounced [8]. Furthermore, heterogeneity in outcome measurement—particularly the use of subjective versus objective tools—likely contributed to variability in reported effects. Studies employing polysomnography or actigraphy tended to report smaller but more reliable changes, highlighting the need for standardised outcome assessment in future trials.

The review also highlights potential benefits of melatonin beyond sleep parameters, particularly in critically ill populations. Evidence from included trials suggests a reduction in delirium incidence and improvement in sleep patterns among ICU patients, supporting emerging data on the neuroprotective and anti-inflammatory properties of melatonin [17]. These findings are of clinical relevance, given the high burden of sleep disruption and delirium in critical care settings. However, the certainty of evidence in this domain remains low due to limited study numbers and population-specific effects.

A key strength of this review lies in its comprehensive inclusion of randomized evidence across diverse clinical populations, allowing for a broader understanding of the context-dependent effects of melatonin. The integration of GRADE methodology further enhances interpretability by explicitly addressing the certainty of evidence. Nevertheless, several limitations warrant consideration. First, substantial clinical and methodological heterogeneity was observed across studies, including variation in dose, formulation, treatment duration, and outcome measures. Second, several studies relied on subjective sleep assessments, which are inherently susceptible to reporting bias. Third, the relatively small number of studies for certain outcomes limited the robustness of evidence synthesis and precluded formal assessment of publication bias.

From a clinical perspective, the findings suggest that melatonin may represent a safe and context-specific therapeutic option for improving sleep quality and sleep initiation, particularly in populations with circadian disruption. However, the modest magnitude of benefit and variability in response highlight the need for individualised treatment approaches. Future research should focus on well-designed, adequately powered randomised trials with standardised outcome measures, as well as exploration of optimal dosing strategies, formulation differences, and long-term efficacy.

Conclusion

This systematic review indicates that melatonin supplementation is associated with consistent improvements in sleep quality and sleep initiation, with modest benefits in sleep duration and efficiency across diverse adult populations. Its favourable safety profile supports its role as a potential adjunct in selected clinical settings, particularly where circadian disruption is prominent. Strengths of this review include adherence to PRISMA methodology and incorporation of contemporary randomised evidence. However, substantial heterogeneity, reliance on subjective outcomes, and limited study numbers for certain endpoints constrain the certainty and generalizability of findings. Further rigorously designed trials are required to define optimal therapeutic use.

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