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Effects of melatonin on sleep disturbances in multiple sclerosis: A randomized, controlled pilot study

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Abstract

Background: Sleep disturbances are commonly reported by people with multiple sclerosis (PwMS). However, optimal management of sleep disturbances is uncertain, and objective studies of sleep quality in PwMS are scarce.

Objectives: To determine the effect of exogenous melatonin on sleep quality and sleep disturbances in PwMS.

Methods: Thirty adult PwMS reporting sleep difficulties were recruited in a randomized, controlled, double-blind cross-over study. They took either melatonin or placebo for 2 weeks, and the opposite for the following 2 weeks. During weeks 2 and 4, an actigraph was used to capture mean total sleep time and sleep efficiency. Patient-reported outcomes (PROs) were collected at weeks 0, 2 and 4.

Results: Melatonin use significantly improved mean total sleep time ($p = 0.03$), with a trend towards higher sleep efficiency ($p = 0.06$). No PROs were significantly different; there was a trend for melatonin use to decrease mean Insomnia Severity Index score ($p = 0.07$), improve Pittsburgh Sleep Quality Index sleep quality component ($p = 0.07$), and improve NeuroQoL-Fatigue ($p = 0.06$). No other PROs showed differences between melatonin and placebo; nor did step count measured by actigraphy (all $p > 0.45$).

Conclusion: These results provide preliminary evidence that melatonin, a low-cost, over-the-counter supplement, could improve objective measures of sleep quality in PwMS.

Keywords: melatonin, multiple sclerosis, sleep disturbance, sleep quality, actigraph, patient-reported outcomes

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Introduction

Sleep disturbances are commonly seen in people with multiple sclerosis (PwMS), with a prevalence ranging from 25% to 54%.[1,2] These disturbances contribute to chronic symptoms and can exacerbate daytime somnolence and fatigue, which in turn affect patients' psychological well-being, physical activity, and social and professional capabilities.[3] To date, the optimal management of sleep disturbances is uncertain, and objective studies of sleep quality in PwMS are scarce.[4]

Melatonin (N-acetyl-5-methoxy-tryptamine) is a hormone that is synthesized primarily in the pineal gland. The circadian rhythm of melatonin secretion, with high levels at night and low levels during the day, parallels the circadian regulation of sleep.[5] Given its critical role in the regulation of the sleep/wake cycle, melatonin is frequently used to improve sleep disturbances, both in healthy individuals and in those with neurologic disease.[6] It has been reported that melatonin secretion is altered in PwMS, with endogenous melatonin levels significantly lower than in aged-matched controls,[4] a finding that is supported by independent observation of decreased sleep quality and prolonged sleep onset latency in PwMS.[7] Altered melatonin regulation and signaling has been

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implicated in PwMS, as indicated by observations including potential contribution of melatonin to seasonal risk of MS relapses,[8] and possible reduction of endogenous melatonin levels due to exogenous corticosteroid administration[9] and progressive pineal failure.[10] Increased serum proinflammatory cytokines and impaired immune cells circulating in MS[11] may disrupt melatonin production. Melatonin supplementation has been shown to have antioxidant effects and positive effects on quality of life (QoL) in PwMS. A study recruited 102 PwMS and 20 matched controls and administered melatonin at 5 mg/day for 90 days; at the end of the trial period, investigators observed a reduction of Multiple Sclerosis Impact Scale scores, a validated measure of QoL in PwMS, as well as a decrease in malondialdehyde levels, a compound related to inflammation.[12]

To the best of our knowledge, no studies have evaluated exogenous, dietary supplement melatonin as a low-cost, low-risk agent to reduce sleep disturbances in PwMS. In this randomized, double-blind, controlled pilot trial, we aimed to determine whether melatonin use is associated with better sleep quality and fewer sleep disturbances in PwMS, using both objective and subjective sleep measures. Specifically, we hypothesized that the use of melatonin would result in a longer total sleep time compared to the use of placebo, as measured by an actigraph device. Furthermore, the use of melatonin would improve sleep quality and sleep disturbances, as measured by Pittsburgh Sleep Quality Index score (PSQI)[13] and Insomnia Severity Index (ISI).[14]

Methods

Participants

A total of 30 adults were recruited from the University of California San Francisco (UCSF) MS and Neuroinflammation Center between September 2019 and November 2020. Participants were either referred by their primary MS clinician or identified through review of their clinician's notes for mention of subjective sleep-related complaints. The inclusion criteria were: age between 20–70 years, diagnosis of MS by 2010 McDonald Criteria,[15] either PSQI ≥ 5[13] or ISI >14[14] over the past month, and able to read and write English. Individuals with nocturnal asthma, hypertension, impaired liver function, seizure disorder, use of melatonin or another sleep agent and/or over-the-counter sleep aids in the past 2 weeks, MS relapse, treatment with corticosteroids or infusible disease modifying therapies (DMTs) in the prior month and women attempting conception were excluded. Three of the participants had prior use of melatonin (3 mg). One stopped taking melatonin a few years prior, and the other two stopped taking melatonin 2 weeks before, study enrollment.

Study design

A randomized, placebo controlled, double-blind, crossover pilot study was performed. After providing informed consent and HIPAA authorization, participants were randomized by a study coordinator to receive either dietary supplement melatonin (white, peppermint-flavored pills) or placebo (white, peppermint-flavored mint, of similar size and taste to melatonin formulation) (see appendix for details) for the first 2 weeks of the study, and the opposite for the subsequent 2 weeks. There was no washout period given the short half-life of melatonin. Participants were instructed to take pills one hour before bedtime, to wear an actigraph device throughout weeks 2 and 4, and to complete their sleep diary online each day during the 1-month study period. Additional PROs (see below) measuring sleep, fatigue, walking ability, anxiety and depression were completed at baseline and at the end of week 2 (before switching to melatonin or placebo for the subsequent 2 weeks) and week 4 (study completion) (study flow in Figure 1).

Procedures

At baseline, participants were introduced to the sleep diary and PROs by a trained study coordinator who was blinded to the group randomization. Participants then took home one actigraph and two bottles of melatonin or placebo, according to their randomization assignment. For participants who were assigned to take melatonin for the first 2 weeks, each bottle contained 0.5 mg or 3 mg of white, peppermint-flavored melatonin pills. Participants were instructed to start with 0.5 mg melatonin (1 pill nightly), and if they observed no relief of sleep disturbances after 3 days, switch to the higher dosage of 3 mg from day 4 onwards. These dosages were selected since a range of melatonin doses between 0.5 mg to 5 mg appears to be safe and effective. However, although a high dose (i.e. 3 mg) melatonin helps sleep, it could cause daytime fatigue, headache, and increase of nocturnal motor activity. Therefore, we decided not to go higher than 3 mg for safety reasons. An identical set of two bottles were distributed to participants who were assigned to take placebo first to mimic active melatonin doses, though these bottles only contained the white, peppermint-flavored mint placebo. Participants were also instructed to change bottles if not effective at three days. Before the end of week 2, the research coordinator mailed a new package containing the actigraph device, along with 2 new bottles containing

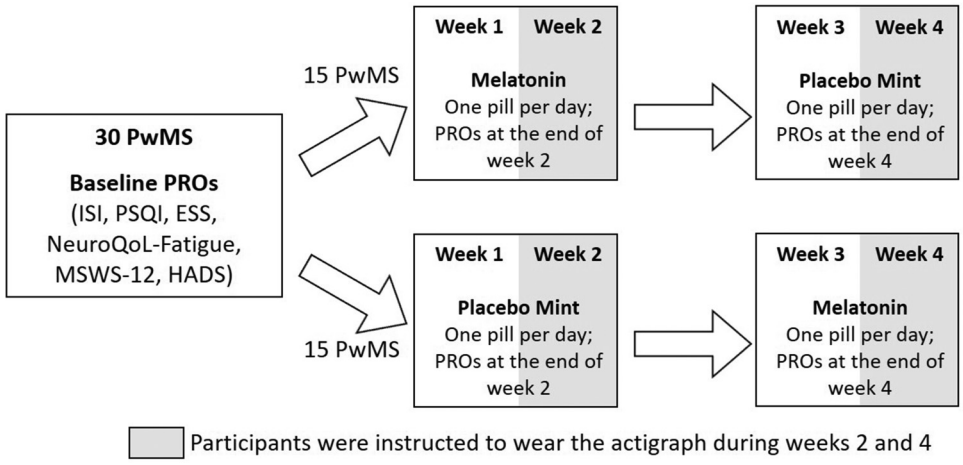

Figure 1. Study flow. PwMS, people with multiple sclerosis; PROs, Patient-reported outcomes; ISI, Insomnia Severity Index; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale; MSWS-12, Multiple Sclerosis Walking Scale −12; HADS, Hospital Anxiety and Depression Scale.

either melatonin or placebo, for the participant to use for the subsequent 2 weeks (weeks 3 and 4). At the end of week 2, before switching to melatonin or placebo for the subsequent 2 weeks, the participants completed the PROs online. The study structure and instructions of weeks 3 and 4 were identical to weeks 1 and 2: the only difference was the pills given to the participants (melatonin vs. placebo). At the end of the study, participants completed the PROs online and returned the actigraph devices and all bottles with any remaining pills via a prepaid Fedex envelope.

Outcome measures

Objective measures. An actigraph device (Model GT9X, ActiGraph Corp, Pensacola, Florida) was used to objectively characterize sleep-wake patterns. The device is watch-like, acceleration-sensitive and has been used to measures physical activity[16] and sleep/wake cycles[4] in PwMS. Participants were instructed to wear the actigraph device on their non-dominant wrist during weeks 2 and 4 for 7 consecutive days and only remove it when showering. ActiLife software (version 6.13.4) was used to perform wear time validation and to analyze the recorded data. Two trained researchers (K.E.P. and V.L.) reviewed each actigraph recording along with sleep diary to verify the actigraph data, using established protocols.[17] Participants had to have at least four valid days of wear time for each condition (melatonin vs. placebo) to be included in the analysis. Four participants were excluded based on these criteria. The measures of interest from the actigraph included mean total sleep time (during night-time while in bed), mean sleep efficiency (defined as total sleep time per time in bed) and total walking steps.

Patient-Reported outcomes (PROs). PROs assessing sleep disturbances, sleep quality, daytime sleepiness, fatigue, walking ability and anxiety and depression were administered at baseline and at the end of weeks 2 and 4.

Insomnia severity index (ISI). The ISI is a 7-item self-report questionnaire assessing the severity and impact of insomnia. A 5-point (0–4) Likert scale is used to rate each item yielding a total score ranging from 0 to 28. A higher score suggests more severe insomnia.[14]

Pittsburgh sleep quality index (PSQI). The PSQI is a self-rated instrument used to measure sleep quality and patterns. It consists of seven components (sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction) and a global score with a higher score indicating worse sleep quality.[13]

Epworth sleepiness scale (ESS). The ESS is a self-rated questionnaire assessing chances of dozing off or falling asleep while engaged in eight different situations. A higher score suggests a higher level of daytime sleepiness.[18]

NeuroQoL-Fatigue. NeuroQOL is a set of self-reported measures that assesses the health-related quality of life of adults with neurological disorders.[19] The fatigue item bank includes 19 items in which higher scores indicate more fatigue.

Multiple sclerosis walking scale −12 (MSWS-12). MSWS-12 is a self-reported measure of the impact of MS on walking.[20] All items are scored 1-5. A higher score indicates greater walking impairment.

Hospital anxiety and depression scale (HADS). The HADS contains 14 items and consists of two subscales: anxiety (HADS-A) and depression (HADS-D). Each item is rated on a 4-point (0–3) scale, yielding maximum scores of 21 for anxiety and depression.[21]

Outcomes

Our pre-specified primary outcome measures included mean total sleep time (time in bed spent sleeping after "lights off") as well as sleep quality (PSQI component 1, subjective sleep quality) and sleep disturbance (ISI). The secondary outcome measure was mean sleep efficiency (percentage of time asleep of total time in bed) as assessed by actigraph. Exploratory outcomes included daytime sleepiness (ESS), fatigue (NeuroQoL-fatigue), physical activity (MSWS-12 and step counts measured by actigraph) as well as mood (HADS).

Protocol approval and consent

All study procedures were approved and in accordance with the ethical standards of the Committee for Human Research at the University of California at San Francisco (IRB No. 19-27108). Written informed consent was obtained from all participants.

Statistical analysis

To discern whether use of melatonin is associated with improvement in objectively measured sleep quality and sleep disturbances, differences in the mean total sleep time and mean sleep efficiency assessed by actigraphy between the melatonin and placebo conditions were evaluated by non-parametric Wilcoxon signed rank tests. The difference in total step counts, as measured by actigraphy, was also evaluated. To evaluate changes in PROs, differences between each condition (melatonin or placebo) and baseline (i.e. change scores) of each PRO (ISI, PSQI component 1 (subjective sleep quality), ESS, NeuroQoL-Fatigue, MSWS-12, HADS) were assessed by non-parametric Wilcoxon signed rank tests. All numerical data are presented as the mean ± the standard error of mean (SEM). The statistical threshold for significance was set as $p < 0.05$. All statistical analyses were conducted using SPSS 22.0 (IBM Corp, Armonk, New York).

Table 1. Baseline demographic and clinical characteristics of patients with multiple sclerosis enrolled in the trial.

Sex	26 women, 4 men
Age (yrs) (mean (SEM))	46.7 (1.8)
DD (yrs) (mean (SEM))	9.7 (1.0)
EDSS (median (IQR))	2 (2.5)
MS subtype	26 RRMS, 2 SPMS, 2 PPMS
Current DMT	8 oral, 1 first-line self-injectable, 16 infusion, 5 none
Height (cm) (mean (SEM))	169.4 (1.5)
Weight (kg) (mean (SEM))	82.6 (4.2)
BMI (kg/m^2) (mean (SEM))	28.8 (1.4)

yrs, years; SEM, standard error of mean; DD, disease duration; EDSS, Expanded Disability Status Scale; IQR, interquartile range; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; DMT, disease-modifying therapy.

Data availability

The trial protocol is available at https://clinicaltrials.gov/ct2/show/NCT04035889. De-identified data will be shared with any qualified investigator by request

Results

Participants

Thirty participants with a diagnosis of MS by 2010 McDonald Criteria[15] were recruited. Their baseline demographic and clinical characteristics are presented in Table 1; mean age was 46.7 ± 1.8 years (range: 31–66 years), mean disease duration 9.7 ± 1.0 years, and median Expanded Disability Status Scale (EDSS) was 2 (interquartile range ± 2.5, range: 0–6.5). All participants completed the study without side effects. Four participants had poor compliance with wearing actigraph device; 3 of them also did not complete subjective measures and were excluded from data analyses. Two other participants experienced technical issues during the recording period, and only provided PROs for analyses (CONSORT diagram in Figure 2).

Primary outcome measures

A small, but statistically significant, difference between the two conditions in mean total sleep time

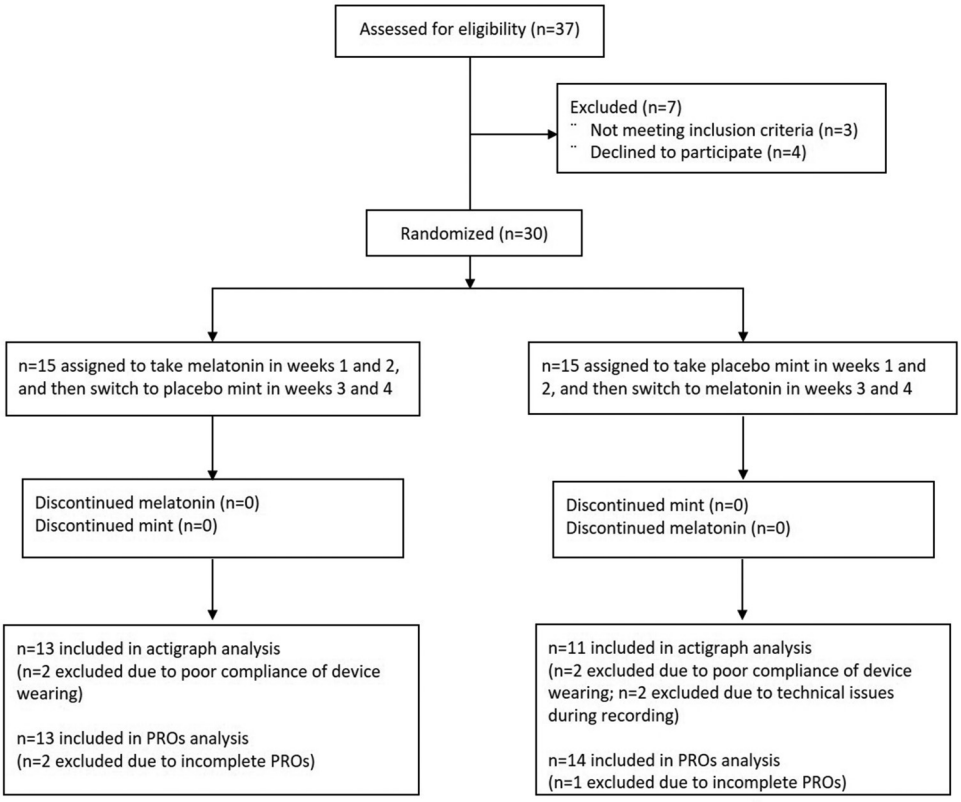

Figure 2. CONSORT diagram. PROs, Patient-reported outcomes.

was found (melatonin vs. placebo: 7.0 ± 0.2 h vs. 6.7 ± 0.3 h, $p = 0.03$). The difference between the two conditions was about 18 min, which is close to the clinically significant threshold (i.e. 20 min).[22] With respect to the subjective primary outcome measures, the mean ISI score (sleep disturbance) reduced by 3.5 points during the melatonin condition, vs. 2.4 points in the placebo condition ($p = 0.07$), and the mean PSQI component 1 (sleep quality) by -0.3 ± 0.1 for melatonin vs. 0.0 ± 0.1 for placebo ($p = 0.07$). Table 2 listed results of outcome measures in melatonin and placebo conditions and the threshold of clinically meaningful improvement for each measure if established.[22–26]

Given that the circulating melatonin levels decrease with physiologic aging and the increment in serum melatonin levels induced by oral administration of melatonin is greater in older people,[27] Spearman's correlation analyses were conducted to explore the relationship between age and mean total sleep time and change scores of ISI and PSQI component 1 in melatonin condition. A negative correlation was observed between age and mean total sleep time ($r = -0.43$, $p = 0.02$). No significant correlation was found between age and change scores of ISI ($r = 0.31$, $p = 0.11$) and PSQI component 1 ($r = 0.31$, $p = 0.11$).

Secondary outcome measure

Sleep efficiency was nominally higher during melatonin condition, though this was not statistically significant (melatonin vs. placebo: $84.7 \pm 1.2\%$ vs. $83.2 \pm 1.4\%$, $p = 0.06$) (Table 2).

Exploratory outcome measures

The NeuroQoL-Fatigue score also showed a trend towards greater fatigue reductions in the melatonin condition (-4.7 ± 1.9) vs. placebo condition (-2.4 ± 2.2, $p = 0.06$). None of the other exploratory outcomes including ESS, MSWS-12, HADS or total step count measured by actigraphy, were different between the two conditions (all $p > 0.45$) (Table 2).

Discussion

In this study, we evaluated the effects of melatonin on sleep quality and sleep disturbance in PwMS, using both objective (actigraphy) and subjective sleep measures. Melatonin use was associated with greater total sleep time; furthermore, sleep efficiency and self-reported sleep measures, including sleep quality, sleep

Table 2. Results of objective outcome measures and PROs in patients with multiple sclerosis in melatonin and placebo conditions.

Outcome Measures	Melatonin ($N = 30$)	Placebo ($N = 30$)	p-value
Primary outcome measures (mean (SEM))			
Mean total sleep time (hours)[a]	7.0 (0.2)	6.7 (0.3)	**0.03***
ISI change score[b]	−3.5 (0.8)	−2.4 (0.8)	0.07
PSQI, component 1 change score	−0.3 (0.1)	0.0 (0.1)	0.07
Secondary outcome measures (mean (SEM))			
Mean sleep efficiency (%)[c]	84.7 (1.2)	83.2 (1.4)	0.06
Exploratory outcomes measures (mean (SEM))			
ESS change score[d]	−1.2 (0.7)	−1.1 (0.7)	0.92
NeuroQoL-Fatigue change score	−4.7 (1.9)	−2.4 (2.2)	0.06
MSWS-12 (%) change score[e]	−3 (2)	2 (2)	0.45
HADS-Anxiety change score	0.4 (0.6)	0.5 (0.5)	0.92
HADS-Depression change score	0.03 (0.42)	−0.03 (0.50)	0.81
HADS-Total change score[f]	0.44 (0.85)	0.44 (0.80)	0.94
Step Count	66,802 (4675.7)	67,573 (5423.6)	0.84

PROs, Patient-reported outcomes; SEM, standard error of the mean; ISI, Insomnia Severity Index; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale; MSWS-12, Multiple Sclerosis Walking Scale −12; HADS, Hospital Anxiety and Depression Scale. *$p < 0.05$.
[a]the clinically significant threshold of mean total sleep time is 20 min.[22.]
[b]a 6-point reduction on the ISI is recommended for a clinically meaningful improvement.[26.]
[c]the clinical significance difference of sleep efficiency is 5%.[22.]
[d]clinically meaningful improvement of the ESS lies between −2 and −3.[24.]
[e]an 8-point improvement on the MSWS-12 is recommended for a clinically meaningful improvement in walking ability.[23.]
[f]the clinically meaningful improvement of the HADS is around −1.5.[25]

disturbances and fatigue, were also nominally improved (though these results were neither statistically nor clinically significant). Overall, these results support the hypotheses that melatonin is associated with improvement in sleep quality and sleep disturbances in PwMS.

Studies have shown that PwMS with sleep disturbances have a higher risk of developing co-morbid conditions like heart disease, obesity and diabetes.[28] It is of great importance to improve sleep and possibly reduce long-term health consequences caused by poor sleep in PwMS; however, sleep disorders are under-recognized and under-treated in this population. Melatonin has been found beneficial in certain disorders thought to have low melatonin secretion such as autism[29] and when melatonin timing is suboptimal, such as delayed sleep-wake phase disorder.[30] Here, we found that exogenous melatonin, a low-cost, low-risk agent, might mitigate sleep disturbances in PwMS given beneficial effects on total sleep time and higher sleep efficiency, as measured by the actigraph. Of note, a negative correlation between age and mean total sleep time was found – participants with lower age showed a longer mean total sleep time, indicating that younger participants may have a better response to the use of melatonin to improve sleep. However, well-designed studies are warranted to investigate age effects.

Actigraph objectively quantifies sleep parameters including sleep quality and sleep disturbances, with advantages including low-cost and non-invasiveness. Validation studies in healthy participants have indicated a 90% concordance between actigraphy and polysomnography.[31] PwMS have demonstrated enthusiasm for using digital technologies to pursue routine and rehabilitation care and monitor their MS[32] (e.g. through smartphone or activity trackers). Here, we extended these observations by incorporating a digital device into a sleep study in PwMS. The device can provide information including sleep activities and daytime activity level, which may help to track long-term responses to interventions targeting sleep disturbances in PwMS.

In addition to the objective measures, improvements in PROs that characterize sleep disturbance, sleep quality and fatigue were observed in the melatonin condition

compared to the placebo condition. Sleep disturbances have been reported to be a significant contributor to fatigue in PwMS[7]: sleep disturbances at night contribute to daytime fatigue.[33] A previous study has shown that treatment of sleep disorders can improve fatigue.[34] Fatigue is defined as the lack of physical or mental energy, perceived by the individual to interfere with usual or desired activities.[35] Since fatigue is a primary determinant of poor QoL and may worsen cognitive domains such as information processing, memory and attention,[36] relief of fatigue could help PwMS to reduce the profound impacts of fatigue on their social and professional capabilities as well as their QoL. The production of melatonin can be affected by several factors, including aging, night shift work, disrupted light–dark cycles and nutritional factors. Light has a suppressive effect on melatonin levels.[37] Several vitamins and minerals play essential roles in the production of melatonin. Diets rich in vegetables, fruits, vitamins and minerals could modify melatonin production.[38] Modifying lifestyle (e.g. keep the lights soft in the evening) to avoid factors that may suppress the melatonin synthesis may help sleep.

Of note, in this study, null results were discovered for changes in daytime sleepiness (ESS), mood (HADS) and walking ability (MSWS-12), as well as ambulatory activity (actigraph-detected step count). Although individuals with insomnia frequently report fatigue, these individuals do not always feel sleepiness during the daytime. Studies have suggested that subjective fatigue and excessive daytime sleepiness represent two different dimensions.[39] Subjective fatigue without sleepiness is frequently reported by individuals complaining of poor sleep, whereas feeling sleepiness without fatigue is rare.[40] In accordance with this, it is possible that melatonin mitigates symptoms of fatigue, with limited effects on daytime sleepiness.

A bidirectional relationship between sleep disturbance and affective disorders (e.g. depression and anxiety) has been reported in PwMS. Poor sleep is associated with depression, and vice versa.[41] A previous study demonstrated that sleep quality is associated with physical fatigability measured by the six-minute walk test in PwMS.[42] It is possible that the relatively small sample size in this pilot study limited the study power to demonstrate changes in HADS, MSWS-12 or actigraph step counts. Further, these domains may show more of a therapeutic lag (i.e. require a longer timeframe before showing a response). A longer follow-up with sustained improvement in sleep is needed to reveal improvement in these domains. Another possible explanation relates to the timeframe of the study: it was conducted between September 2019 and November 2020, with more than half of the participants (i.e. sixteen) participating amid the COVID-19 pandemic and shelter-in-place requirements. The pandemic and the shelter-in-place order could have substantially influenced the mood[43] and mobility[44] of PwMS, including our study participants. Future studies should continue using both objective and subjective measures to investigate whether the improvement in sleep disturbances would result in positive effects on mood and physical activity in PwMS. In addition to the small number and short study duration, a third limitation is that we did not screen patients based on specific sleep parameters for inclusion (e.g. only patients with difficulty in sleep initiation or sleep maintenance); nor did we formally evaluate them for obstructive sleep apnea or other symptoms suggestive of a sleep disorder (e.g. snoring, restless legs, parasomnias). As noted, a longer study timeframe may be needed to uncover effects on additional domains. Another factor that may have affected the observed results is the heterogeneity of the enrolled participants. For example, not all participants were on DMTs, and among the twenty-five participants who were on treatment, different DMTs were used. The effects of different DMTs on sleep is unclear and may have interfered with the results of our study. The participant population had overall mild disease burden, with a median EDSS of 2 and mean disease duration of 10 years. Therefore, the results should be interpreted with caution when applied to a broader MS population with more advanced or severe disease.

In summary, the current pilot study suggests that melatonin, a low-cost, low-risk, over-the-counter supplement, can potentially alleviate sleep disturbances and fatigue and improve sleep quality in PwMS. Given the high prevalence of sleep disturbances in PwMS and the long-term health consequences and disease impacts caused by poor sleep, larger studies are needed to unravel the complex relationship between MS and sleep disturbances, as well as develop successful interventions. Awareness of potential contributors of poor sleep in MS may be important for early interventions. Sleep disturbance should be routinely evaluated in standard MS care.

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Disclosures

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Data availability statement

The data of this research will be made available by the authors, without undue reservation.

Declaration of conflicting interests

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Supplemental material

Supplemental material for this article is available online.

Trial Registration

ClinicalTrials.gov NCT04035889.

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