Received: 23 November 2021 | Revised: 30 March 2022 | Accepted: 11 April 2022

DOI: 10.1111/jpi.12801

ORIGINAL ARTICLE

Journal of Pineal Research Molecular, Biological, Physiological and Clinical Aspects of Melatonin | WILEY

High dose melatonin increases sleep duration during nighttime and daytime sleep episodes in older adults

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Funding information
National Institute on Aging; National Institutes of Health; National Institute of Research Resources; Brigham Research Institute

Abstract

Aging is associated with changes in sleep, and improving sleep may have important consequences for the health, cognition, and quality of life of older adults. Many prescription sleep aids increase the risk of nighttime falls, have adverse effects on next-day cognition, and are associated with increased mortality. Melatonin, a hormone secreted at night, increases sleep duration in young adults but only when administered during the day when endogenous levels are low. In a month-long cross-over study, we randomized 24 healthy older (age >55, mean 64.2 ± 6.3 years) participants to receive 2 weeks of placebo and 2 weeks of either a low (0.3 mg) or high (5.0 mg) dose of melatonin 30 min before lights out. Sleep was polysomnographically recorded and was scheduled during both the biological day and night using a forced desynchrony design. Although 0.3 mg melatonin had a trend towards increasing sleep efficiency (SE) overall, this was due to its effects on sleep during the biological day. In contrast, 5 mg melatonin significantly increased SE during both biological day and night, mainly by increasing the duration of Stage 2 non-rapid eye movement sleep and slightly shortening awakenings. Melatonin should be further explored as a sleep aid for older adults.

KEYWORDS
aging, biological clock, circadian rhythm, hypnotic effect, melatonin, sleep

1 | INTRODUCTION

Older people have a high prevalence of sleep deficiency, including fragmented sleep, insomnia, and early morning awakenings.[1–3] Even healthy older adults without chronic medical conditions or sleep disorders have shorter sleep with more awakenings than young adults.[4,5] Recently, both cross-sectional and prospective epidemiological studies[6,7] have revealed that older adults who sleep less than 5 h per night have more than double the risk of Alzheimer's disease and mortality over a 4–5 year follow-up interval, possibly due to the accumulation of amyloid-beta when sleep is disrupted and/or shortened.[8,9] Unfortunately, epidemiologic studies have also revealed that older adults who chronically take prescription hypnotics to help their sleep also have higher levels of incident dementia[7,10,11] as well as higher mortality,[7,12] although the direction of causality is not known. Prescription hypnotics have also been associated with greater nighttime fall risk[13] and greater risk of hip fracture[14] in older adults.

Exogenous supplementation of the pineal hormone melatonin, levels of which are often lower in older people,[15–17] has been hypothesized to improve sleep duration in older people. Melatonin, via MT1 receptors, acts to suppress the firing rate of neurons in the suprachiasmatic nucleus (SCN),[18–20] the central circadian pacemaker, thereby signaling the start of the biological night.[21,22] The human SCN, unlike most of the brain, has a high concentration of melatonin receptors.[20] Studies in young adults have indicated that melatonin acts as a chronohypnotic, improving sleep only when endogenous melatonin is not present and having little effect during the biological night when endogenous melatonin levels are high.[23]

There is evidence that the aged SCN is less sensitive to melatonin.[24] The number and density of MT1-expressing neurons in the SCN are decreased with normal aging and decreased to an even greater extent in individuals in the later stages of Alzheimer's disease than in age-matched controls.[25] That latter finding may explain the sleep and circadian disruptions associated with Alzheimer's disease.[26–30] There is also evidence of reduced day–night amplitude in melatonin receptor messenger RNA expression in the SCN and decreased receptor binding in the SCN with age.[31] Consolidation of the nocturnal sleep episode may require that the brain, and particularly the SCN, is exposed to sufficiently high levels of melatonin to activate a critical number of MT1 receptors necessary to quiet neuronal firing in the SCN.[32,33]

Given the evidence that both the number and the affinity of melatonin receptors may decline with age, and that the amount of nocturnal melatonin secretion may decline in some older people, particularly those individuals whose pineal glands become calcified with age,[34] we evaluated the sleep-promoting effects of a high dose as well as a low dose of exogenous melatonin in older adults.

In addition, the findings from young adults that exogenous melatonin only improves sleep when endogenous levels are low[23] led us to test the sleep-promoting effects of melatonin before sleep scheduled across all circadian phases. We, therefore, conducted a study on healthy older adults without sleep complaints to test whether melatonin can improve sleep when it is scheduled during the biological nighttime or during the biological daytime, and if so, whether the sleep-improving effects are dose-dependent.

2 | MATERIALS AND METHODS

2.1 | Participants

Participants were recruited for the study via newspaper advertisements and notices to community organizations. All were medically and psychologically healthy, as assessed during a screening process before study. The medical screening included routine clinical tests on blood and urine, an electrocardiogram, a chest radiograph, a physical examination, and a medical history to rule out acute or chronic illnesses and medication use. The psychological screening included the Minnesota Multiphasic Personality Inventory-2[35] and the Geriatric Depression Scale,[36] the Folstein Mini-Mental State Exam,[37] and a structured interview with a clinical psychologist to rule out current or past psychopathology. None were under the care of a physician for any chronic medical condition and none were regularly taking medications. They were instructed to abstain from caffeine, nicotine, alcohol, and all prescription and over-the-counter medications during the 3 weeks before study; compliance with this aspect of the study was verified upon admission to the laboratory by comprehensive toxicological analysis of their urine.

All participants were without major sleep complaints by history and were evaluated for sleep disorders by all-night polysomnography before admission. The average apnea–hypopnea index of the participants empaneled into the studies was 11.99 ± 7.3 (range: 0–29) and the average periodic limb movement index was 4.52 ± 9.1 (range: 0–35). All participants were instructed to maintain a regular ($\pm$30 min) sleep–wake schedule with 8 h in bed at their habitual times for the 3 weeks before study. During the week immediately before the study, compliance with this regular schedule was verified with a wrist activity monitor (Actiwatch-L; Philips Respironics).

Each gave written informed consent before study; the study was reviewed and approved by the Partners HealthCare Human Subjects Committee and was conducted in accordance with the principles outlined in the Declaration of Helsinki.

A total of 25 participants began the inpatient portion of the study. One withdrew consent on the fifth day of the study and was not included in any of the analyses reported here. One participant was withdrawn from the study by the investigators shortly before the end of Condition 2 (see below), but her data were included in the analyses. The 24 participants (13 women, 11 men) ranged in age from 55 to 78 years (mean $\pm$ SD: 64.2 ± 6.3 years), and their habitual bedtimes were, on average, $22{:}54 \pm 0{:}44$.

2.2 | Experimental protocol

Each study began with three baselines (BL) adaptation days, consisting of 16 h of wakefulness and an 8-h sleep episode scheduled according to each participant's

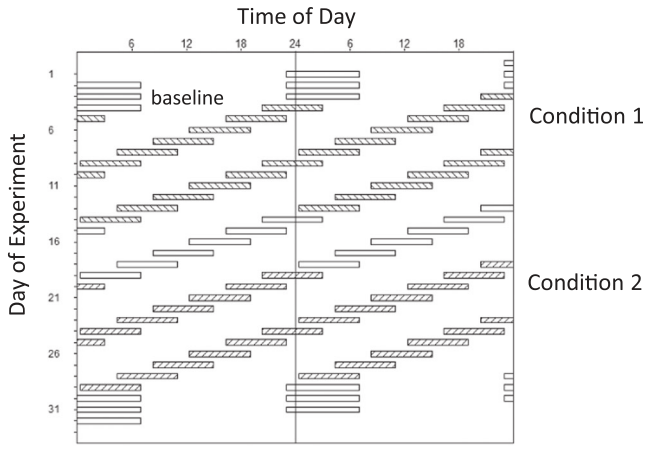

FIGURE 1 Double raster plot of the study protocol. Relative time of day is across the 48-h *x*-axis; days of the experiment are plotted both to the right of and beneath the previous day. Boxes represent scheduled sleep episodes. Open boxes on Nights 1–3 represent 8-h scheduled baseline sleep episodes during which all participants received a placebo on all three baseline nights. From Night 4 through Night 33, participants were scheduled to live on a 20-h "day," with bedtimes 4 h earlier each night than the previous night. Scheduled sleep episodes were at 6:40 and wake episodes were at 13:20. Hashed boxes represent melatonin/placebo nights, open boxes represent single-blind placebo nights. Participants were randomized to receive a placebo on each of the 12 nights during one of the two randomization blocks; following six nights of washout in which all participants received a placebo, they were then randomized to the opposite condition (melatonin/placebo) on each of the 12 nights in the second randomization block.

habitual bedtime and wake time. This was followed by a forced desynchrony protocol,[38–40] during which the participants were scheduled to a rest-activity cycle length of 20 h, with sleep episodes scheduled to begin 4 h earlier each day and continue for 1/3 of each cycle (6 h 40 min; see Figure 1). During the remainder of each 20-hour "day" (13 h 20 min), participants were awake and ambulatory within their study room. This was continued for 30 cycles (equivalent to 24 calendar days), followed by three 24-h readaptation days which were scheduled at the same times as the BL days.

2.3 | Experimental conditions

During the entire study, ambient light intensity during the scheduled waking episodes was dim (approximately 0.0087 W/m^2 [~3.3 lux] at 137 cm from the floor facing towards the walls with a maximum of 0.048 W/m^2 [15 lux] at 187 cm from the floor facing towards the ceiling), and during scheduled sleep episodes, all lights were turned off (complete darkness).

Throughout their study, each participant lived in a private study room that was free of external time cues. The study room had no windows, clocks, or other indication of the time of day, and the participants were not permitted to watch television or listen to the radio. Staff members were trained to avoid discussion of time-of-day information and did not wear watches. Participants were administered short tests of subjective mood and alertness approximately every 30 min, and approximately every 2 h were administered a performance test battery lasting approximately 20 min.[41] During their free time between tests, participants were allowed to pursue sedentary activities in their study room, which typically included reading, listening to music, watching videos, or pursuing hobbies.

2.4 | Drug condition and randomization

Identically-appearing melatonin and placebo capsules were manufactured by the Investigational Drug Service (IDS) of the Brigham and Women's Hospital (BWH) Pharmacy. Capsules were tested at manufacture, and then again annually to ensure that they contained the specified dosage (Chemir Polytech). Upon each participant's enrollment in the inpatient portion of the study, the IDS randomized the participant (see below) and packaged their 36 melatonin capsules individually, labeling them with participant number and order of administration.

During the BL nights (Sleep Episodes 1–3), the readaptation nights (Sleep Episodes 34–36), and Sleep Episodes 16–21, all participants were scheduled to receive a placebo capsule. The remaining nights of each study were divided into two conditions, for the first 12 (Condition 1, Sleep Episodes 4–15) and final 12 (Condition 2, Sleep Episodes 22–33) nights of the forced desynchrony portion of the study. Each participant was randomly assigned to receive a placebo in one of the conditions and melatonin in the other condition. Two doses of melatonin were tested, 0.3 (low dose) and 5 mg (high dose), with each participant receiving the same dose throughout the 12 nights of their melatonin condition. A total of four randomization groups thus resulted (placebo followed by 0.3 mg; placebo followed by 5.0 mg; 0.3 mg followed by placebo; 5.0 mg followed by placebo). Pills were administered 30 min before each bedtime by a Center for Clinical Investigation (CCI) nurse. Study staff involved in participant interactions, data collection, data processing, and preliminary data analysis remained blind to the condition of each participant until all had completed the study and all sleep data had been scored.

2.5 | Data collection

Core body temperature (CBT) was collected continuously throughout each study using a rectal thermistor. Throughout most of the study, blood samples were collected hourly via an indwelling intravenous catheter connected to a 12-foot tubing so that samples could be collected from outside the room during scheduled sleep episodes. Blood samples were kept on ice for up to 1 h before being centrifuged. The resulting plasma was frozen until the samples were assayed for melatonin. Plasma samples were assayed at one of two assay laboratories. The initial 10 participants' samples were assayed by the Core Laboratory at the BWH CCI; because this facility was unable to accommodate the large volume of samples from this study, the remaining 14 participants' samples were assayed at Pharmasan Labs.

The electroencephalogram (EEG) was recorded during all sleep episodes using a standard montage (C3, C4, O1, O2), referenced to contralateral mastoids (A1, A2). In addition to the EEG, two electrooculograms (left outer canthus, right outer canthus), one submental electromyogram, and a 2-lead electrocardiogram were recorded. All signals were acquired using a digital ambulatory sleep recording system (Vitaport-2 or 3; Temec Instruments, Kerkrade, B.V.). The EEG signals were high-pass filtered at a time constant of one second and low-pass filtered at 70 Hz (Bessel fourth-order antialiasing; >80 dB). Finally, the signals were digitized with a resolution of 12 bit (range 500 μV; sampling rate 256 Hz, storage rate 128 Hz), stored on a Flash RAM card, and downloaded offline after wake time. All sleep episodes were scored visually according to standard criteria[42] by trained scorers who were blind to the study conditions.

We excluded Sleep Episode 1 from the analysis for all participants due to the "first-night" effect. We also excluded from our analysis any sleep episode that was missing more than 5% of the scheduled epochs due to equipment or sensor malfunction.[23] Sleep Episodes 2 and 3 were averaged for each participant to determine BL night information.

We defined sleep latency (SL) as the time from lights off until the occurrence of any stage of sleep. Awakenings were defined as the number of epochs or series of epochs within a sleep episode scored as wake; the average duration of all awakenings for each sleep episode was also calculated. For sleep-stage data, non-rapid eye movement (NREM) sleep (Stages 2-4), rapid eye movement (REM) sleep, slow-wave sleep (SWS; stages 3 and 4), and Stages 1–4 were calculated in minutes. Wakefulness during scheduled sleep and sleep efficiency (SE) were calculated as the percentage of total time in bed between lights off and lights on.

Each sleep episode was assigned a circadian phase of bedtime (see below). We then assigned each sleep episode during the FD segment (Sleep Episodes 4–33) to biological day (90°–240°) or biological night (240°–90°).

2.6 | Data analysis

The CBT data from each condition of the study was assessed for the intrinsic circadian period using non-orthogonal spectral analysis.[39,40] This analysis takes into account the 20-h periodicity in the data resulting from the imposed rest-activity schedule, and then simultaneously searches for a periodicity in the circadian range (search range = 15–30 h). Using the period and the projection of the CBT minimum on the first day of each condition (assigned circadian phase 0°), we then assigned a circadian phase from 0° to 359° to each minute of the FD segment of the study and used this to assign each sleep episode a circadian phase at bedtime.

Descriptive statistics are presented as percentages or mean (±standard deviation) unless otherwise noted. Linear mixed-effects models for repeated measures were used to study the effect of DRUG (melatonin, placebo) on SE, SL, and sleep time in various sleep stages. Generalized linear mixed-effects models with Poisson distribution were used to study the effect of DRUG (melatonin, placebo) on the number of awakenings. While DRUG was the main effect, SEX (female, male), ORDER (placebo-melatonin, melatonin-placebo), and TIME of drug (biological day, biological night) were also tested in the models. SUBJECT was treated as a random effect in the models to account for individual variability. Proportional hazards regression models were used to study the effect of DRUG (melatonin or placebo) on the duration of awakenings. Robust sandwich covariance estimates were used to account for intraindividual correlations. Residual plots and model assumptions were examined to assess model fit. For all statistical tests, the critical significance level is defined as $\alpha = .05$. All reported degrees of freedom and two-sided p-values are from the final statistical model for each measure. Final statistical models include DRUG as the primary variable of interest, all significant main effects, and all significant interactions, but exclude nonsignificant interactions. Note that because significant interactions vary between measures, degrees of freedom are not uniform. The analyses were performed with SAS 9.4.

Results in figures are presented as mean ± standard deviation, with all observations first averaged within, and then across participants.

3 | RESULTS

A total of 564 polysomnographically-recorded sleep episodes from the 24 participants were included in the analysis. Due to missing data from equipment or sensor malfunctions,[23] one BL sleep episode each from two participants was excluded, and nine nights from the forced desynchrony segment of the study (one night each from five participants, and two nights from two) were excluded. For one participant, posthoc analysis of the plasma melatonin data suggested that he inadvertently received melatonin on two of the nights he was supposed to have received a placebo; these two sleep episodes were excluded from the analysis.

There was no difference in age, sex distribution, habitual sleep–wake timing, or morningness–eveningness score between the participants in the low melatonin dose groups versus those in the high melatonin dose groups (see Table 1). On the BL nights, we did not find any difference in sleep onset latency between the low- and high-dose groups, there were no significant differences in the duration of any sleep stage, and there were no differences in the number or average duration of awakenings (see Table 1).

We did not find a significant sex difference in any outcome, and there was no significant order effect (placebo first, melatonin first) for either the low dose or the high dose for any sleep outcome examined. We, therefore, combined the placebo-first/melatonin-second and melatonin-first/placebo-second groups for the low dose and for the high dose for all subsequent analyses.

In the low-dose group, while there was no significant difference in SE in the melatonin condition compared with the placebo condition, there was a trend for greater SE and total sleep time (TST) overall (see Table 2 and Figure 2, lower panel) as well as during the biological daytime (see Table 3). Looking at all the sleep episodes, when the participants were in the low-dose melatonin condition, they had significantly more Stage 1 and Stage 2 sleep, significantly less SWS, and no difference in REM sleep than in the placebo condition. SL was not significantly different between the low-dose melatonin and placebo conditions, and while the number and average duration of awakenings were not different between the two conditions, there was a trend for less wakefulness in the low-dose melatonin condition (see Table 2).

In the high-dose group, overall there was significantly greater SE and TST in the melatonin condition compared with the placebo condition (see Figure 2, upper panel).

TABLE 1 Baseline characteristics of the low-dose (0.3 mg) melatonin and high-dose (5.0 mg) melatonin groups.

	Low dose $n = 12$ mean (std dev)	High dose $n = 12$ mean (std dev)	T or Z[a]	p
Age (years)	64.67 (6.15)	63.75 (6.68)	−0.35	.73
Sex	6 M, 6 F	5 M, 7 F	0.168	.682
Habitual bedtime	23.12 (0.54)	22.69 (0.86)	−0.146	.158
Habitual waketime	7.13 (0.52)	6.83 (0.78)	−0.347	.729
Morningness eveningness score	59.86 (6.15)	63.11 (9.83)	0.678	.498
Baseline sleep efficiency (%)	80.83 (5.38)	78.59 (8.24)	−0.791	.437
Stage 1 (min)	53.46 (31.64)	51.81 (23.77)	−0.144	.887
Stage 2 (min)	202.94 (27.59)	176.23 (41.70)	−1.850	.078
SWS (min)	42.83 (36.39)	59.79 (33.88)	1.181	.250
REM (min)	86.81 (26.02)	88.10 (19.33)	0.138	.892
TST (min)	386.04 (24.98)	375.94 (39.66)	−0.747	.463
Wake (min)	91.94 (25.59)	102.54 (39.68)	0.778	.445
SoL (min)	18.39 (17.37)	19.58 (19.54)	−0.123	.902
Awakenings (n)	28.42 (9.86)	28.79 (17.43)	−0.549	.583
Awakenings (average duration)	3.78 (2.31)	4.09 (1.91)	0.779	.436

Abbreviations: F, female; M, male; min, minutes; REM, rapid eye movement sleep; SoL, sleep onset latency; std dev, standard deviation; SWS, slow-wave sleep; TST, total sleep time.

[a]Wilcoxon rank-sum test.

TABLE 2 Overall sleep stage durations by dosage group.

	Overall					Overall				
	Placebo mean (standard deviation, std dev)	Low-dose mean (std dev)	Estimate (standard error, std err)	T ($df = 266$)	p	Placebo	High dose	Estimate (std err)	T ($df = 272$)	p
Sleep efficiency (%)	71.57 (7.15)	74.65 (6.31)	3.05 (1.81)	1.69	.0927	69.42 (9.04)	75.68 (5.68)	6.24 (1.81)	3.44	.0007
Stage 1 (minutes, min)	33.94 (16.52)	38.59 (23.76)	4.61 (1.59)	2.9	.0041	36.75 (21.31)	40.22 (19.41)	3.37 (1.49)	2.27	.0242
Stage 2 (min)	138.23 (18.22)	152.20 (21.17)	14.01 (4.68)	3	.003	119.81 (24.96)	146.25 (21.05)	26.50 (4.21)	6.29	<.0001
Stage SWS (min)	47.04 (23.75)	41.50 (26.85)	−5.56 (1.78)	−3.13	.002	54.28 (22.60)	44.59 (21.99)	−9.69 (1.98)	−4.9	<.0001
Stage NREM (min)	219.21 (23.48)	232.29 (27.39)	13.02 (5.36)	2.43	.0159	210.84 (25.56)	231.05 (16.82)	20.17 (5.14)	3.92	.0001
Stage REM (min)	66.37 (14.03)	65.76 (14.29)	−0.61 (2.83)	−0.22	.829	66.47 (14.93)	71.22 (11.59)	4.73 (2.93)	1.61	.1078
TST (min)	285.58 (28.41)	298.06 (25.10)	12.37 (7.22)	1.71	.0878	277.30 (36.10)	302.27 (22.77)	24.91 (7.25)	3.44	.0007
Stage wake (min)	113.50 (28.75)	100.58 (25.26)	−12.84 (7.16)	−1.79	.074	122.12 (36.10)	97.15 (22.76)	−24.91 (7.26)	−3.43	.0007
SoL (min)	20.53 (12.15)	17.37 (9.37)	−3.20 (3.93)	−0.81	.4172	17.84 (9.51)	16.03 (9.58)	−1.78 (2.31)	−0.77	.4419
Awakenings (n)	23.81 (9.04)	24.53 (10.49)	0.03 (0.02)	1.18	.2385	22.43 (9.67)	24.45 (13.30)	0.09 (0.02)	3.49	.0006
Awakenings (average duration)	6.03 (2.68)	5.19 (2.09)	0.17 (0.10)	2.76[a]	.0968	7.00 (3.38)	4.93 (2.97)	0.33 (0.10)	10.18[a]	.0014

Note: Mean (and std dev) for each sleep stage are presented in minutes, along with sleep efficiency and the number of awakenings; model-fit group difference estimates (and std err) are presented, as are T-values and p-values for the dosage group comparisons. Left: Placebo versus low dose (0.3 mg) melatonin; right: placebo versus high dose (5.0 mg) melatonin.

Abbreviations: df, degrees of freedom; NREM, non-REM sleep; REM, rapid eye movement sleep; SoL, sleep onset latency; SWS, slow-wave sleep; TST, total sleep time.

[a]Chi-square statistic, $df = 1$.

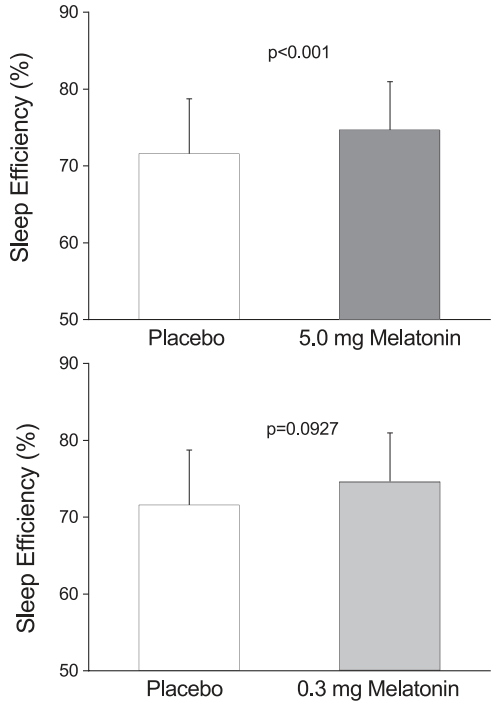

FIGURE 2 Overall sleep efficiency by condition and dosage group. Mean (±standard deviation) sleep efficiency averaged across all 12 nights in the placebo condition (white bar, left) and melatonin condition (gray bar, right). Upper panel: Placebo versus high dose (5.0 mg) melatonin; lower panel: placebo versus low-dose (0.3 mg) melatonin.

When the participants were in the high-dose melatonin condition they had significantly more Stage 1 and Stage 2 sleep, significantly less SWS, and no difference in REM sleep than in the placebo condition. SL was not significantly different between the high-dose melatonin and placebo conditions. There were significantly more, but shorter awakenings in the high-dose melatonin condition than in the placebo condition, and overall the participants had significantly less wakefulness in the high-dose melatonin condition compared with the placebo condition (see Table 2).

In the low-dose group, there was no significant difference in SE or TST in either the biological day or the biological night between the low-dose melatonin or placebo conditions, although there was a trend towards greater SE and TST in the low-dose melatonin condition during the biological day (see Figure 3, lower panel). Although there were trends for differences in sleep stages, the only significant differences were a significant increase in Stage 1 sleep and an increase in the number of awakenings during the biological night in the low-dose melatonin condition compared with the placebo condition (see Table 3). During the biological day, there was significantly more Stage 2 sleep and significantly

TABLE 3 Sleep stage durations by dosage group and biological time of scheduled sleep opportunity.

	Biological night				Biological day			
	Placebo mean (standard deviation, std dev)	Low-dose mean (std dev)	Estimate (standard error, std err)	T ($df = 144$) p	Placebo mean (std dev)	Low-dose mean (std dev)	Estimate (std err)	T ($df = 109$) p
Sleep efficiency (%)	78.54 (6)	80.37 (5.54)	1.44 (1.88)	0.77 .4449	62.3 (10.03)	66.69 (11.12)	4.55 (2.58)	1.76 .0804
Stage 1 (minutes, min)	35.4 (17.62)	39.48 (23.0)	4.36 (2.06)	2.12 .036	32.85 (16.24)	37.54 (25.37)	4.60 (2.51)	1.83 .0703
Stage 2 (min)	149.29 (21.03)	160.2 (21.03)	10.89 (5.67)	1.92 .0569	122.84 (26.57)	140.04 (29.81)	16.62 (6.88)	2.42 .0174
Stage SWS (min)	47.72 (26.64)	43.82 (27.8)	−3.89 (2.40)	−1.62 .1075	45.58 (21.65)	38.91 (25.94)	−6.68 (2.43)	−2.75 .007
Stage NREM (min)	232.41 (18.82)	243.5 (19.85)	10.44 (6.04)	1.73 .086	201.28 (34.49)	216.48 (43.63)	14.95 (8.44)	1.77 .0794
Stage REM (min)	81.07 (15.32)	77.47 (16.52)	−3.83 (2.98)	−1.29 .1997	47.16 (11.72)	49.69 (14.18)	3.30 (3.04)	1.09 .2803
TST (min)	313.48 (23.89)	320.97 (22.16)	5.89 (7.48)	0.79 .4323	248.44 (39.78)	266.17 (44.17)	18.37 (10.27)	1.79 .0765
Stage Wake (min)	85.68 (24.01)	78.46 (21.9)	−5.65 (7.49)	−0.76 .4515	150.51 (40.25)	131.62 (44.70)	−19.64 (10.16)	−1.93 0.0558
Latency (min)	19.32 (19.02)	12.69 (5.4)	−7.52 (6.37)	−1.18 .2397	20.94 (12.17)	23.33 (15.57)	2.29 (3.62)	0.63 .5283

(Continues)

TABLE 3 (Continued)

	Biological night					Biological day				
	Placebo mean (standard deviation, std dev)	Low-dose mean (std dev)	Estimate (standard error, std err)	T ($df = 144$)	p	Placebo mean (std dev)	Low-dose mean (std dev)	Estimate (std err)	T ($df = 109$)	p
Awakenings (n)	23.59 (8.27)	25.38 (10.69)	0.07 (0.03)	2.13	.0349	23.93 (10.53)	23.28 (10.48)	−0.03 (0.04)	−0.68	.497
Awakenings (average duration) (min)	4.46 (2.15)	3.65 (1.68)	0.23 (0.14)	2.66[a]	.1026	8.34 (4.75)	7.38 (3.99)	0.13 (0.16)	0.65[a]	.4185
	Placebo mean (std dev)	High dose mean (std dev)	Estimate (std err)	T ($df = 148$)	p	Placebo mean (std dev)	High dose mean (std dev)	Estimate (std err)	T ($df = 111$)	p
Sleep efficiency (%)	76.68 (7.62)	80.67 (4.52)	3.89 (1.85)	2.1	.0374	60.47 (12.06)	69.7 (9.02)	8.87 (2.84)	3.12	.0023
Stage 1 (min)	38.68 (23.50)	42.22 (20.07)	2.89 (2.05)	1.41	.1604	34.33 (20.21)	37.54 (19.52)	3.85 (2.02)	1.91	.0591
Stage 2 (min)	130.68 (27.30)	151.51 (21.39)	20.74 (4.84)	4.28	<.0001	105.93 (28.53)	141.69 (27.28)	34.01 (6.82)	4.98	<.0001
Stage SWS (min)	58.18 (26.46)	46.72 (22.77)	−11.14 (2.57)	−4.33	<.0001	50.25 (19.94)	41.64 (22.18)	−8.03 (2.93)	−2.74	.0071
Stage NREM (min)	227.54 (19.61)	240.45 (15.95)	12.53 (5.42)	2.31	.0224	190.51 (36.57)	220.86 (26.80)	29.78 (8.46)	3.52	.0006
Stage REM (min)	78.78 (17.27)	81.78 (13.30)	2.95 (3.32)	0.89	.3754	51.03 (15.12)	57.5 (11.12)	5.57 (3.84)	1.45	.1502
TST (min)	306.32 (30.37)	322.24 (18.09)	15.56 (7.40)	2.1	.0372	241.54 (48.24)	278.37 (36.09)	35.38 (11.35)	3.12	.0023
Stage wake (min)	93.09 (30.22)	77.11 (17.72)	−15.64 (7.43)	−2.1	.037	157.89 (48.36)	121.13 (36.17)	−35,28 (11.36)	−3.11	.0024
Latency (min)	15.78 (10.53)	11.52 (8.70)	−4.11 (2.16)	−1.9	.0598	19.95 (11.11)	23.25 (19.84)	2.41 (4.25)	0.57	.5714
Awakenings (n)	24.24 (10.78)	24.02 (11.33)	−0.01 (0.03)	−0.17	.8633	19.9 (9.27)	25.22 (16.28)	0.22 (0.04)	5.72	<.0001
Awakenings (average duration) (min)	4.52 (3.01)	3.37 (1.33)	0.33 (0.19)	3.09[a]	.0789	10.26 (5.08)	6.63 (5.04)	0.37 (0.20)	3.40[a]	.0653

Note: Mean (and std dev) for each sleep stage are presented in min, along with sleep efficiency and the number of awakenings; model-fit group difference estimates (and std err) are presented, as are T-values and p-values for the dosage group comparisons. Biological night: Sleep opportunities beginning between 240° and 90°; biological day: sleep opportunities beginning between 90° and 240°. Top panel: Placebo versus low-dose (0.3 mg) melatonin; bottom panel: placebo versus high dose (5.0 mg) melatonin.

Abbreviations: *df*, degrees of freedom; NREM, non-REM sleep; REM, rapid eye movement sleep; SoL, sleep onset latency; SWS, slow-wave sleep; TST, total sleep time.

[a]Chi-square statistic, $df = 1$.

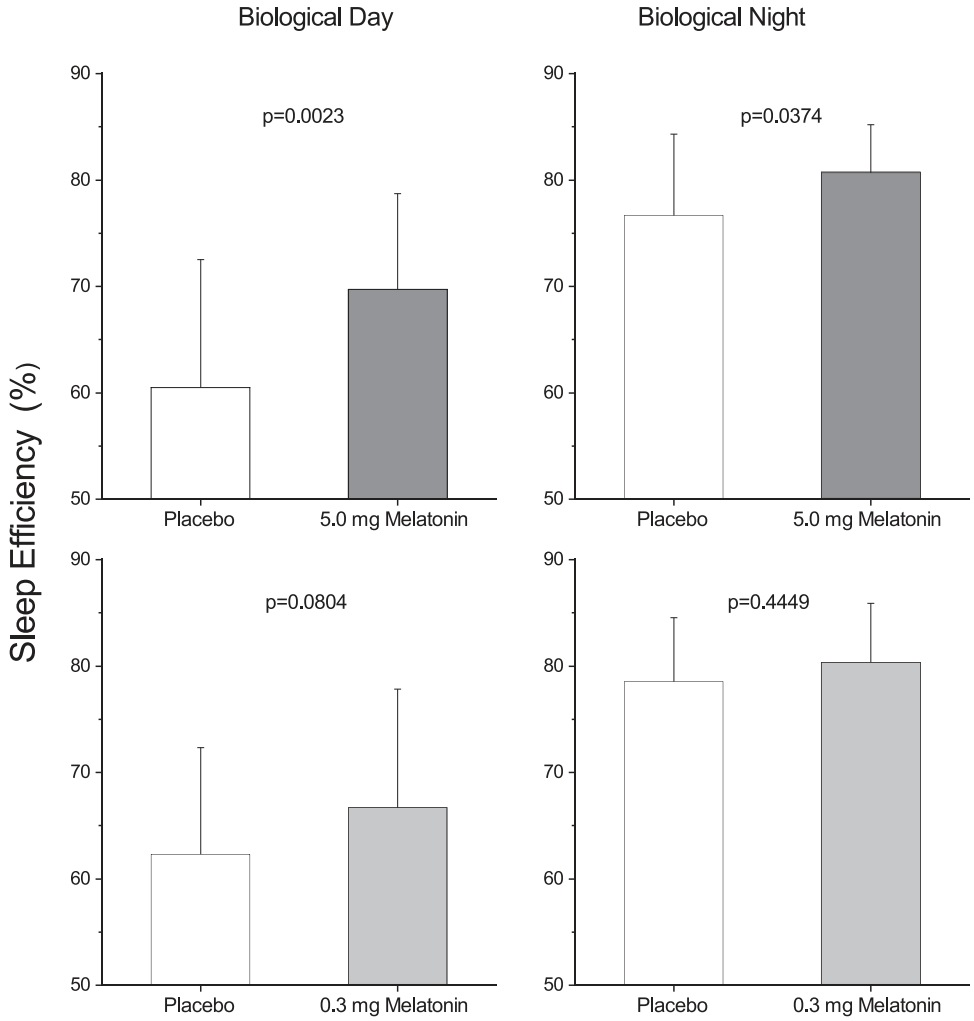

FIGURE 3 Sleep efficiency during the biological day and biological night by condition and dosage group. Biological day: Sleep opportunities beginning between 90° and 240°; biological night: sleep opportunities beginning between 240° and 90°. Upper panel: Mean (±standard deviation) sleep efficiency averaged across all biological day (left) or biological night (right) sleep episodes in the placebo condition (white bars) and high-dose (5.0 mg) melatonin condition (gray bars). Lower panel: Mean (±standard deviation) sleep efficiency averaged across all biological day (left) or biological night (right) sleep episodes in the placebo condition (white bars) and low-dose (0.3 mg) melatonin condition.

less SWS in the low-dose melatonin condition than in the placebo condition (see Table 3).

The high-dose melatonin group showed significantly greater SE and TST when sleep was scheduled during either the biological day or the biological night compared with the placebo condition (see Figure 3, upper panel). The high-dose melatonin group showed significantly more Stage 2 sleep and NREM sleep, and significantly less SWS and wakefulness when sleep was scheduled during either the biological day or the biological night compared with the placebo condition (see Table 3). During both the biological day and biological night, there was a trend for the duration of awakenings to be shorter in the high-dose melatonin condition compared with the placebo condition, and while the number of awakenings was not different between the high-dose melatonin condition and placebo condition during the biological night, there were significantly more awakenings in the high-dose melatonin condition compared with placebo when sleep occurred during the biological day (see Table 3).

4 | DISCUSSION

In a randomized, placebo-controlled trial of 24 healthy older adults scheduled to sleep at all different circadian phases, we found that presleep administration of a 5 mg dose of melatonin increased TST by 25 min compared with placebo. When only considering sleep scheduled

during the biological daytime when endogenous melatonin was absent, presleep administration of 5 mg melatonin as compared to placebo increased sleep duration by more than half an hour. When 5 mg melatonin was administered before sleep scheduled to occur during the biological nighttime when endogenous melatonin was present, it was still able to increase sleep duration significantly, by more than 15 min. In contrast, while presleep administration of low-dose (0.3 mg) melatonin increased Stage 1, Stage 2, and NREM sleep duration, neither the 12-min change in TST overall nor the 18-min increase in TST during biological day sleep was statistically significant. These data reveal that a higher dose of melatonin may be required to reliably increase TST in healthy older adults, consistent with evidence from animal studies that MT1 receptor affinity decreases with aging.

These findings in healthy older adults contrast with findings from a similar study we carried out on young adults.[23] In that study, we used a between-participant design to compare the impact of a low dose (0.3 mg), high dose (5.0 mg), or placebo on sleep scheduled on a 3-week, 20-h forced-desynchrony protocol. We found no significant change in SE during nighttime sleep for either the low dose or high-dose melatonin groups compared with the placebo group, likely because average nocturnal SE was already quite high in those young participants, at 88%. When we examined sleep scheduled to occur during the biological daytime when endogenous melatonin was not present, both low dose and high dose melatonin significantly improved SE, with no difference between the doses in those young adults.

Our current results also contrast with those from several prior studies in which melatonin was tested in older adults. In general, those studies did not find any effect of melatonin on the duration of sleep in older adults, whether they had sleep complaints or not (see Sateia et al.[43] for a summary). However, those prior studies used lower doses of melatonin (typically 2 mg) than the 5 mg dose we found to be effective. Additional studies are needed to determine whether doses between 2 and 5 mg are effective for sleep promotion in older adults.

In summary, we demonstrated that in healthy older adults without major sleep complaints, a 5 mg dose of melatonin can improve sleep in both the biological daytime and the biological nighttime. While these findings remain to be replicated in larger trials, they suggest that melatonin holds the potential for improving sleep in older adults. A recent report found that over the past 2 decades, there has been a threefold increase in the number of US adults age 65 and older who report using melatonin in the past month,[44] despite the lack of existing evidence for its efficacy and despite recommendations from the American Academy of Sleep Medicine that physicians should not recommend its use to older patients.[43] Future studies should be carried out to investigate whether higher (between 2 and 5 mg) doses of melatonin improve sleep in older adults with insomnia or other sleep complaints, and to investigate the mechanism(s) underlying the age-related difference in response to melatonin that we have observed. With that information, a personalized, age-related dosing regimen for melatonin to improve sleep can be developed.

AUTHOR CONTRIBUTIONS

Drs. Charles A. Czeisler and Jeanne F. Duffy designed the experiments. Dr. Jeanne F. Duffy carried out the experiments, and collected, and processed the data. Mr. Joseph M. Ronda designed and supported hardware and software for the study execution, data collection, and data processing; Dr. Wei Wang carried out the statistical analyses. All authors contributed to writing the paper and reviewed the final version of the paper.

ACKNOWLEDGMENTS

The studies were supported by NIH Grant P01 AG09975 and were conducted in the Brigham and Women's Hospital General Clinical Research Center supported by M01 RR02635; additional support for data analysis was provided by NIH Grants AG06072 and AG044416; Jeanne F. Duffy received support from the Brigham and Women's Hospital (BWH), Brigham Research Institute fund to sustain research excellence. The authors would like to thank the study participants; D. McCarthy and C. O'Brien for participant recruitment; H. Lam of the BWH Investigational Drug Service for melatonin capsule production and participant randomization; K. B. McKay, M. J. Duverne, R. Webb, V. Hobbes, V. Sparkes, and R. F. Dimanche of the Division of Sleep and Circadian Disorders (DSCD) Chronobiology Core for assisting with the data collection and processing; the BWH Center for Clinical Investigation staff; B. J. Lockyer, E. Riel, and G. Renchkovsky of the DSCD Sleep Core for scoring the sleep recordings; and J. K. Wyatt, R. J Hughes, and D. J. Dijk for thoughtful discussions regarding a similar study conducted in young adults.

CONFLICTS OF INTEREST

Dr. Wei Wang reports that she is a consultant to the National Sleep Foundation. Dr. Charles A. Czeisler reports grants/contracts to BWH from Dayzz Live Well Ltd., Delta Airlines, FAA, Jazz Pharmaceuticals, NHLBI, NIA, NIOSH, NASA, Puget Sound Pilots, Regeneron Pharmaceuticals/Sanofi, and DOD; grants/gifts to Monash University from CDC Foundation, with funding from BNY Mellon and WHOOP; is/was a paid

consultant or received lecture fees from Emory University, Inselspital Bern, UCLA, Institute of Digital Media and Child Development, Klarman Family Foundation, National Council for Mental Wellbeing, National Sleep Foundation, Physician's Seal, SRS Foundation, Tencent Holdings, Teva Pharma Australia, With Deep, and Vanda Pharmaceuticals Inc., in which Dr. Czeisler holds an equity interest; received travel support from Aspen Brain Institute, Bloomage International Investment Group, UK Biotechnology and Biological Sciences Research Council, Bouley Botanicals, Dr. Stanley Ho Medical Development Foundation, EBRS, German National Academy of Sciences (Leopoldina), National Safety Council, National Sleep Foundation, Stanford Medical School, Tencent Holdings, and Vanda Pharmaceuticals; receives research/education support through BWH from Arbor Pharmaceuticals, Avadel Pharmaceuticals, Beijing Zhaode Healthcare Management Consulting Co., Bryte, Alexandra Drane, Eisai, Harmony Biosciences, Jazz Pharmaceuticals, Johnson & Johnson, Mary Ann & Stanley Snider via Combined Jewish Philanthropies, NeuroCare Inc., Optum, Philips Respironics, Regeneron Pharmaceuticals, Regional Home Care, ResMed, San Francisco Bar Pilots, Sanofi, Schneider, Simmons, Sleep Cycle, Sleep Number, Sysco, Teva Pharmaceuticals Industries, and Vanda Pharmaceuticals; is/was an expert witness in legal cases, including those involving Advanced Power Technologies, Aegis Chemical Solutions LLC, Amtrak; Casper Sleep Inc., C&J Energy Services, Catapult Energy Services Group, Covenant Testing Technologies, Dallas Police Association, Enterprise Rent-A-Car, Espinal Trucking/Eagle Transport Group/Steel Warehouse Inc., FedEx, Greyhound Lines Inc./Motor Coach Industries/FirstGroup America, PAR Electrical Contractors Inc., Product & Logistics Services LLC/Schlumberger Technology Corp/Gelco Fleet Trust, Puckett Emergency Medical Services LLC, Puget Sound Pilots, Union Pacific Railroad, United Parcel Service, and Vanda Pharmaceuticals; serves as the incumbent of an endowed professorship provided to Harvard University by Cephalon Inc.; and receives royalties from McGraw Hill, and Philips Respironics for the Actiwatch-2 and Actiwatch Spectrum devices. Dr. Czeisler's interests were reviewed and are managed by the BWH and MGB in accordance with their conflict of interest policies. Drs. Jeanne F. Duffy and Mr. Joseph M. Ronda declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. Shared datasets will not contain identifying information per the regulations outlined in HIPPA. Per Mass General Brigham (MGB, formerly Partners HealthCare System) policies, any investigator or entity requesting the data must request the data in writing in an agreement outlining how the data will be used, protected, and maintained, for example, through a formal Data Use Agreement (DUA) negotiated by an MGB office or a template letter agreement signed by the sharing and receiving PIs. All such requests must include: List of HIPAA identifiers (if any) requested; Institutional Review Board (IRB) protocol number and/or written IRB exemption determination from the requestor's institution; outside party entity name, PI name, and administrative contact information; the purpose of data exchange; and relevant background information. The MGB policy includes a requirement that for outgoing data with information on human subjects or PHI, IRB approval must be received before DUA execution. Review and negotiation of an outgoing DUA from/to a non-profit institution, government agency, or other public entity is handled by MGB Research Management. In 2015, MGB established the Partners Data & Tissue Sharing Committee (PDTSC) to evaluate requests to disclose or provide access to MGB clinical and research data and tissue to external parties. The PDTSC is charged with ensuring that clinical data and tissue sharing with external parties (both non-profit and for-profit organizations) is consistent with the charitable mission of MGB and its affiliated hospitals. To that end, the PDTSC acts as a data and tissue steward and facilitates consistent and responsible sharing of MGB clinical and research data and tissue assets to promote research and improve patient care. Not all data-sharing situations are subject to PDTSC review. When PDTSC review is required, the committee alone is empowered to determine whether the data and/or tissue sharing arrangement may move forward. PDTSC review is typically required in the following situations: Data sharing request intends to leverage data solely as part of product development or commercial validation; scope of use includes secondary use to leverage data or derived data as part of product development, validation, study, or other commercial activities; the request is to share deidentified data fields beyond disease status or basic demographic information; the costs to collect and transmit data have not been factored into payment or financial considerations; insights or results from the study are not being shared back with MGB or affiliated hospital/institution. The data request is outside the original scope of work, or the request is for a significant amount of data.

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How to cite this article: Duffy JF, Wang W, Ronda JM, Czeisler CA. High dose melatonin increases sleep duration during nighttime and daytime sleep episodes in older adults. *J Pineal Res*. 2022;e12801. doi:10.1111/jpi.12801