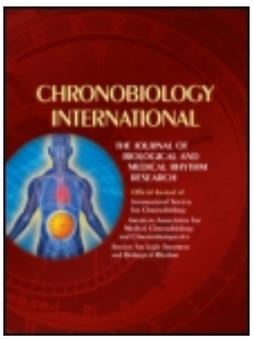

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MORNING MELATONIN HAS LIMITED BENEFIT AS A SOPORIFIC FOR DAYTIME SLEEP AFTER NIGHT WORK

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Exogenous melatonin administration in humans is known to exert both chronobiotic (phase shifting) and soporific effects. In a previous study in our lab, young, healthy, subjects worked five consecutive simulated night shifts (23:00 to 07:00 h) and slept during the day (08:30 to 15:30 h). Large phase delays of various magnitudes were produced by the study interventions, which included bright light exposure during the night shifts, as assessed by the dim light melatonin onset (DLMO) before (baseline) and after (final) the five night shifts. Subjects also ingested either 1.8 mg sustained-release melatonin or placebo before daytime sleep. Although melatonin at this time should delay the circadian clock, this previous study found that it did not increase the magnitude of phase delays. To determine whether melatonin had a soporific effect, we controlled the various magnitudes of phase delay produced by the other study interventions. Melatonin ($n = 18$) and placebo ($n = 18$) groups were formed by matching a melatonin participant with a placebo participant that had a similar baseline and final DLMO (± 1 h). Sleep log measurements of total sleep time (TST) and actigraphic measurements of sleep latency, TST, and three movement indices for the two groups were examined. Although melatonin was associated with small improvements in sleep quality and quantity, the differences were not statistically significant by analysis of variance. However, binomial analysis indicated that melatonin participants were more likely to sleep better than their placebo counterparts on some days with some measures. It was concluded that, the soporific effect of melatonin is small when administered prior to 7 h daytime sleep periods following night shift work.

Keywords Melatonin, Sleep, Night Shift Work, Sedative, Human, Circadian Rhythms

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INTRODUCTION

Exogenous melatonin has at least two disparate influences on human physiology and behavior. Melatonin acts as a chronobiotic agent, shifting the circadian clock according to a phase response curve (Zaidan et al., 1994; Lewy et al., 1998). In addition, under some conditions the hormone may induce a mild sedative effect during wakefulness and a soporific effect in an ensuing sleep period.

The authenticity of the putative soporific effect is still debated. Behavioral changes that have been reported following exogenous melatonin administration include deterioration of mood and performance, increases in fatigue, subjective and objective measurements of sleepiness, and alterations in subsequent sleep architecture. Not all studies, however, report that melatonin exerts a hypnotic effect. As others have noted (Dawson and Encel, 1993; Hughes and Badia, 1997), the bulk of the discrepancy in the literature on this matter can be attributed to the timing of melatonin administration. Sedative effects of exogenous melatonin administration are reliable during the late morning to early evening hours (Arendt et al., 1984; Lieberman et al., 1984; Dollins et al., 1993, 1994; Tzischinsky and Lavie, 1994; Nave et al., 1995; Reid et al., 1996; Hughes and Badia, 1997; Satomura et al., 2001), when circulating endogenous melatonin levels are low. In contrast, if oral melatonin is administered when the circulating level of the hormone above the basal daytime levels (e.g., in the late evening, when endogenous melatonin levels are rising), the sleep-promoting influence of the hormone on sleep architecture is attenuated or absent (James et al., 1987, 1990; Ferini-Strambi et al., 1993).

This report is on the soporific effect of melatonin administered in the morning immediately before each of five consecutive day sleep periods that followed simulated night shifts. In a study originally designed to produce circadian adaptation to shift work, melatonin administered in the morning did not significantly increase the magnitude of phase delays (Crowley et al., 2003). Here subjects given melatonin were matched with subjects given placebo by equating their circadian phase at the beginning and at the conclusion of the study. In doing this, two groups with the same magnitude of phase delay were formed. One of these groups received melatonin and the other placebo. The soporific effects of melatonin on daytime sleep were thus examined independent of its phase-shifting properties.

MATERIALS AND METHODS

A detailed description of the methods employed in the data collection for this study can be found in (Crowley et al., 2003). Here we describe a compendium of those procedures that are necessary to understand the

overall study design, as well as the details that are unique to the current data analysis.

Participants were free of medical and psychiatric disorders, as assessed by in-person interviews, the Minnesota Multiphasic Personality Inventory-2, and a health questionnaire. Two sleep questionnaires were used to identify and exclude subjects with disturbed nighttime sleep, excessive daytime sleepiness, or irregular sleep habits. In addition, people taking prescription medications other than oral contraceptives were excluded. Participants provided written consent and were paid for their participation. The Rush University Medical Center Institutional Review Board approved all study procedures, which also adhered to the ethical standards of the journal (Touitou et al., 2004).

There was a baseline week during which sleep times were unrestricted. Figure 1 depicts the study protocol from days 8 to 14. Baseline circadian phase was assessed on day 8 using 30 min saliva samples to determine the dim light melatonin onset (DLMO). Then there were 5 consecutive simulated night shifts, from 23:00 to 07:00 h. Time in bed was fixed after each simulated night shift, from 08:30 to 15:30 h, and occurred at

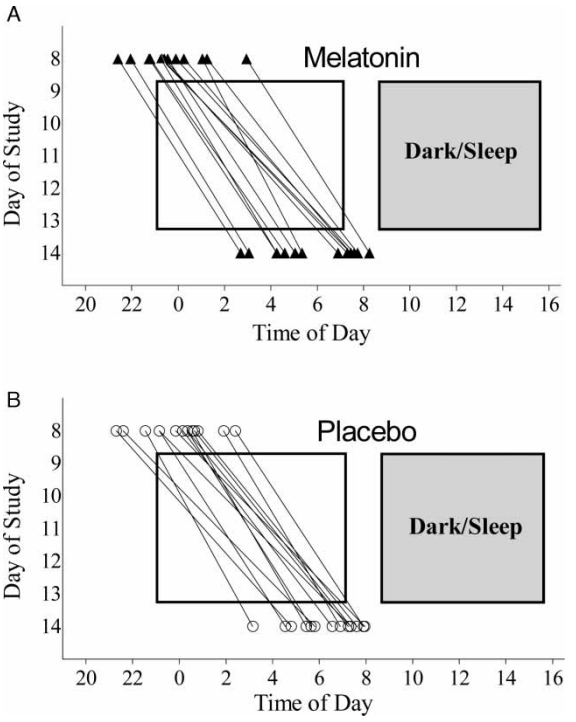

FIGURE 1 Subjects who took melatonin or placebo before daytime sleep were matched for circadian phase. Lines connect the baseline and final dim light melatonin onsets (DLMOs) for each individual. The open rectangles indicate the time of the five consecutive night shifts (23:00 to 07:00 h). The shaded rectangles indicate the five daytime sleep episodes (08:30 to 15:30 h).

home in bedrooms that we made completely dark by covering all windows with opaque black plastic. A final phase assessment followed the five simulated night shifts and day sleep episodes.

The effectiveness of several different combinations of treatments in producing the phase delays necessary for adaptation to these simulated night shifts were assessed in the previous analysis (Crowley et al., 2003). The four treatments included: 1) the enforced daytime dark/sleep period after each night shift, 2) intermittent bright light exposure during the night shifts, 3) wearing sunglasses with normal or very dark lenses when outside during daylight hours, and 4) oral melatonin or placebo before daytime sleep. Six groups were formed, with each group undergoing a specific combination of these four treatments. Two of the six groups (combined n = 20) were given 1.8 mg sustained-release melatonin (Ecological Formulas, Concord, California), while the other four groups (combined n = 47) were given an identical placebo. The pharmacokinetics of this melatonin preparation was assessed in our lab (Sharkey, 2000) in four normally entrained subjects who slept at night. They took the sustained release dose at 10:00 h, and then gave saliva samples every 30 min for 8 h while remaining awake. Melatonin levels were well above nighttime endogenous levels for about 5 h after ingestion, and gradually decreased over the next 3 h. In the current study, oral self-administration of the pill was double-blind, and occurred just prior to each daytime sleep period at 08:30 h. Immediately after waking from each day sleep period, at 15:30 h, participants gave a saliva sample using a salivette (Sarstedt, Newton, North Carolina). These samples were later analyzed along with the samples from phase assessments. The purpose of this single saliva sample was to ensure that the pill was ingested as instructed, and to also determine the salivary melatonin level after the sleep period. Participants had already given numerous saliva samples during the baseline phase assessment and were familiar with this procedure.

The current report is on a subgroup of the total sample (Table 1). At this point, we attempted to match each participant that received melatonin to a participant that received placebo using the position of the baseline and the final DLMO as the matching criteria. Matches were defined as a melatonin participant having both a baseline and final DLMO within 1 h of those of the placebo participant.

Of the 20 participants that received melatonin, 18 could be matched with a placebo participant using the aforementioned criteria, yielding a total sample size of 36. For the baseline DLMO, the average difference between the melatonin participant and the matching placebo participant was 31 min; for the final DLMO, the average difference was 23 min. The melatonin and placebo groups were similar in age, gender, circadian phase at baseline and final phase assessment, morningness-eveningness

tendency (Horne and Ostberg, 1976), and number of participants per group receiving bright light as part of the treatment protocol (Table 1).

Participants kept detailed sleep logs throughout the entire study, and estimates of total sleep time (TST) were calculated. Awakenings greater than 5 min in duration were subtracted from total sleep time calculations. To confirm compliance with the study protocol of being in bed from 08:30 to 15:30 h and to assess sleep quality and quantity during the sleep periods, participants wore actiwatches (Actiwatch-64, MiniMitter, Inc., Bend, Oregon). Wearing actiwatches also helped participants learn to keep accurate sleep logs because we compared activity data with subjective sleep logs in the presence of the subject every 1 to 3 days during the study. This comparison made their record keeping errors more apparent, and encouraged attention to detail in the logs.

Actigraphic measurements of sleep parameters were determined by Actiware-Sleep (version 3.4) software. Using the Sleep Analysis menu with a High sensitivity setting, the software calculated sleep parameters based on a time window beginning 1 h before scheduled bedtime, and ending 1 h after scheduled rise time. Sleep latency (SL) and TST were obtained for the daytime sleep periods, where SL is defined as the time from lights out to the first epoch identified as sleep. In addition, three other measurements of sleep quality were analyzed: the number of movement minutes (MM), the mean activity score (MAS), and the sleep fragmentation index (SF). SF is the ratio of the number of 1 min epochs with movement compared to the number of 1 min epochs with no activity counts. MM is a measure of the total amount of time within the sleep period during which movement occurred, where 1 min of movement is defined as having 4 or greater activity counts, and is said to be "mobile." MAS is a measure of the activity per 1 min epoch during the sleep period. Both MM and MAS include movements during wakefulness and transient movements that occur while sleep is maintained. However, MM and MAS are not redundant measures because the former is based only on epochs that exceed the

TABLE 1 Demographic, Circadian Phase, and Study Condition Information of Participants by Group

	Melatonin (n = 18)	Placebo (n = 18)
Male : Female	7 : 11	9 : 9
Age (yrs)	24.9 ± 7.1	23.8 ± 5.8
Baseline DLMO (SD in h)	23 : 30 ± 1.5	23 : 30 ± 1.5
Final DLMO (SD in h)	5 : 42 ± 1.7	5 : 48 ± 1.5
Phase delay (h)	6.2 ± 1.2	6.3 ± 1.2
Morningness-eveningness	47.9 ± 8	45.7 ± 7
Participants receiving bright light	6	8
Participants wearing dark sunglasses	18	10

Values are mean ± SD.

baseline activity threshold of 4 or more activity counts and were thus scored as "mobile," while MAS incorporates all activity counts during the sleep period, regardless of whether scored as "mobile" or "immobile."

DATA ANALYSIS

TST from sleep logs was analyzed using a repeated measures analysis of variance (ANOVA). The between-subjects factor of group had two levels: melatonin and placebo. The within-subjects factor of time had five levels, corresponding to the five days of sleep. The remaining data, derived from actigraphy, consisted of TST, SL, MM, MAS, and SF, for each of the day sleep periods. Analysis of these five dependent variables was done using a repeated measures multivariate analysis of variance (MANOVA). As in the ANOVA, the between-subjects factor of group for the MANOVA consisted of two levels, melatonin and placebo, while the within-subjects factor of time consisted of the five day sleep periods.

In another set of analyses, the 7 h day sleep periods were subdivided into three segments: the first 3 h, from 08:30 to 11:30 h, the middle 2 h, from 11:30 to 13:30 h, and the final 2 h, from 13:30 to 15:30 h. A separate repeated measures MANOVA was performed on the TST, MM, MAS, and SF for each of these three sleep segments.

An analysis of covariance (ANCOVA) (for the sleep log TST) and multivariate analysis of covariance (MANCOVAs) (for all actigraphic measurements) were also performed incorporating the final circadian phase position (i.e., final DLMO) as a covariate. This was done to determine if those participants who had only partially re-established the normal phase relationship between the sleep period and the circadian clock benefited more from the melatonin than those who had fully re-entrained. The ANOVA and MANOVAs were considered to be significant at the $p < 0.05$ level, two-tailed.

RESULTS

As expected, the afternoon salivary melatonin levels upon awakening from daytime sleep were much higher in the group that took melatonin at bedtime (Table 2). Thus, the sustained-release dose provided elevated levels of melatonin throughout the 7 h daytime sleep episode. The afternoon melatonin levels of the placebo group appeared to increase gradually over the five days.

All of the participants slept quite well. Sleep efficiencies for the five day sleep episodes, calculated from sleep logs, averaged 96% and 94% for the melatonin and placebo groups, respectively. When derived from actigraphy, the sleep efficiencies were 83% and 81% for the melatonin and placebo groups, respectively. The lower values with actigraphy are likely

TABLE 2 Salivary Melatonin Concentrations (pg/ml) upon Awakening from Daytime Sleep at 15:30 h in Subjects Who Took Melatonin or Placebo Before Bed at 08:30 h. Values are mean ± SD

Day sleep period	Melatonin group	Placebo group
1	132.2 ± 121.1	2.0 ± 1.3
2	121.7 ± 97.9	3.6 ± 4.7
3	140.9 ± 105.0	4.1 ± 3.4
4	153.8 ± 109.2	4.7 ± 4.3
5	149.6 ± 98	8.3 ± 7.0

due to the fact that sleep was scored with a high sensitivity setting, which tends to score any movements as wake.

Sleep log TST was slightly longer for the melatonin group than placebo group for day sleep episodes 1, 3, and 5 (Figure 2, panel a), but this difference did not reach statistical significance by ANOVA. The main effect of group and the day by group interaction were not significant. Incorporating the time of the final DLMO as a covariate to account for degree of re-entrainment did not change this result.

The actigraphy data indicated that although the melatonin group had better sleep on almost all measures, at least on some days, this difference was not statistically significant (Figure 2, panels b-f). A MANOVA including measurements of TST, SL, MM, MAS, and SF revealed both a non-significant main effect of group and a non-significant day by group interaction. Incorporating the final DLMO as a covariate to account for degree of re-entrainment did not change this result.

Breaking the sleep period down into the first, middle, and last segments did not yield statistically significant group differences on any of the dependent variables for any portion of the sleep period. MANOVAs done on each of the three segments showed that the main effect of group and group-by-day interactions were not significant.

Although the ANOVA and MANOVAs did not yield statistically significant comparisons, we observed slightly, but consistently, better measurements of sleep in those participants who received melatonin (Figure 2). Consequently, we calculated the binomial probabilities for the measures of sleep for each matched pair of subjects. For each day, the value of a given sleep parameter (e.g., TST) was compared for each pair to determine whether the melatonin or the placebo member of the pair had a better outcome measured with that parameter (e.g., more TST). The number of melatonin members sleeping better was then compared to the number of placebo members sleeping better, and the binomial probability of these two numbers (e.g., 11 vs. 7) was determined, assuming that if there was no effect of melatonin, the probability that either member would sleep better by chance was $p = 0.50$.

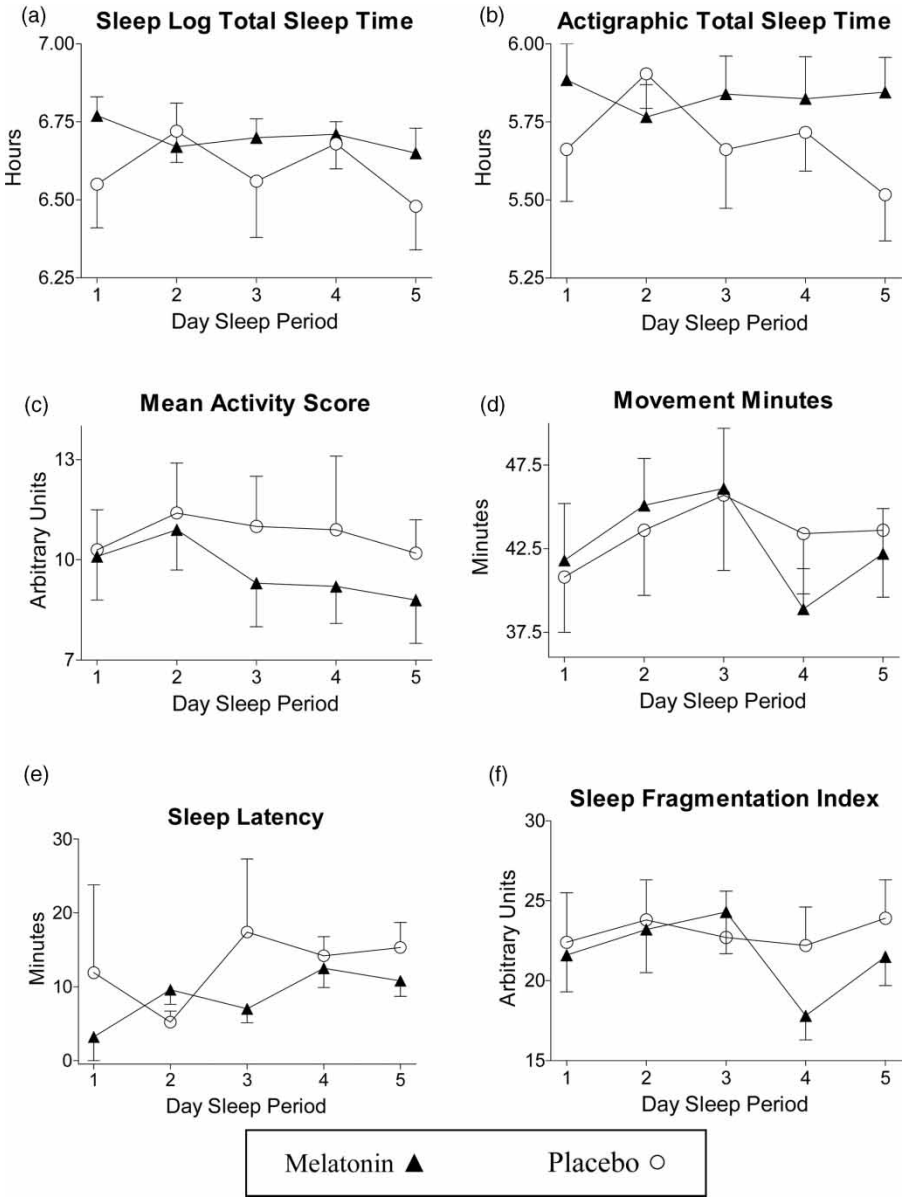

FIGURE 2 Sleep parameters of the melatonin and placebo groups during the five day sleep episodes. Total sleep time was determined by sleep logs (a) and actigraphy (b). Mean activity score (c), movement minutes (d), sleep latency (e), and sleep fragmentation index (f) are derived from actigraphy. Symbols show mean values and error bars show SEM.

From 6 different dependent measures (sleep log TST, actigraphic TST, SL, MM, MAS, and SFI) examined on each of the 5-day sleep periods, 30 binomial analyses were performed. In 5 of these 30 analyses, the melatonin participants had better sleep than the placebo participants

(each $p < 0.05$). Two other analyses indicated a trend towards melatonin participants displaying better sleep ($p < 0.10$). In one of the comparisons, the placebo participants slept significantly better than the melatonin participants ($p < 0.05$). No statistically significant differences were found for the other 22 comparisons. The significant comparisons favoring melatonin were observed for actigraphic TST on day sleep 1, SL on days 1 and 5, and MAS on days 1 and 5. While these binomial probabilities did not adjust for experiment-wise α, the number of probabilities that might be expected to be significant at $p < 0.05$ by chance given 30 comparisons is 1.5. We obtained more than three times this number of significant probabilities for our melatonin participants sleeping better, while there was only a single probability to suggest that placebo participants slept significantly better, which argues against these probabilities being spurious.

DISCUSSION

Most of the subjective and objective sleep parameters analyzed indicated improved sleep with melatonin compared to placebo, but the differences were small and only statistically significant on a few days using binomial estimation. As discussed earlier, many investigators have speculated that exogenous melatonin may have a greater effect if administered while endogenous melatonin levels are low, which is usually in the daytime. In this study, melatonin taken at 08:30 h coincided with all phases of the melatonin profiles, including the rise, the peak, and the fall. A further complication is that we do not know the levels of endogenous melatonin in our subjects when they took the pill because we do not know how much melatonin was suppressed by light during the night shifts and the travel home period. The soporific effect of melatonin may depend on the circadian phase of ingestion, possibly due to variation in melatonin receptor density, which is in part determined by recent levels of circulating melatonin. In rats, melatonin receptors in the suprachiasmatic nucleus and pars tuberalis of the anterior pituitary are down-regulated in response to elevated nocturnal endogenous levels of melatonin, or in pinealectomized animals, by injections of melatonin (Gauer et al., 1993a, 1993b, 1994). Similar findings have been reported in heterologously expressed human melatonin receptors (Gerdin et al., 2004). It is possible that the minimal response we observed to exogenous melatonin in the morning may be attributable to administration that was frequently at an insensitive circadian phase, due to a reduced number of melatonin receptors available following prolonged exposure to elevated endogenous melatonin levels.

Previous laboratory-controlled and field studies have found a mild but statistically significant sedative effect of melatonin on daytime sleep (Folkard et al., 1993; Dawson et al., 1995; Yoon and Song, 2002). These

effects include increased TST and improvements in sleep quality with melatonin relative to placebo. Two of these studies (Folkard et al., 1993; Yoon and Song, 2002) could not distinguish whether the observed changes in sleep measurements were due to the phase-shifting or the sleep-inducing property of exogenous melatonin because circadian phase assessments were not performed. In the third (Dawson et al., 1995), there was better sleep quality in a group ($n = 8$) receiving three doses of melatonin, two of which were taken during the sleep period. These melatonin subjects had phase delays equivalent to a placebo group ($n = 8$), suggesting that the improvements in sleep were due to the hormone's soporific effect. This study also reported a sustained decrease in core body temperature in those receiving melatonin, which is consistent with the hypothesis that melatonin exerts a soporific effect via its hypothermic properties (Sack et al., 1997; Cajochen et al., 2003).

The only study using polysomnography to examine the effect of melatonin on daytime sleep after night shifts was performed by our group (Sharkey et al., 2001). The same sustained-release preparation was used (1.8 mg melatonin) and was given prior to a slightly longer daytime sleep episode than in the current study (8 h *vs.* 7 h). There was a modest improvement in sleep with melatonin compared to placebo: an increase in TST and sleep efficiency, and a corresponding decrease in wake after sleep onset. However, this effect was only observed on the first of two day sleep periods and only during the last 4 h of the sleep period. Melatonin appeared to have a greater impact on those individuals with poorer sleep quality during the day. Furthermore, this effect was likely due to a soporific rather than a chronobiotic effect of melatonin because the potential phase delaying effects of melatonin were purposefully counteracted by bright light during the simulated "drive home" period. The melatonin-placebo difference being present on the first but absent on the second day sleep period in this study is similar to our present findings, in which melatonin produced slightly more TST on the first but not the second day sleep (Figure 2, panels a and b).

Several studies have examined the effectiveness of melatonin in improving the daytime sleep of emergency medicine personnel (James et al., 1998; Jorgensen and Witting, 1998; Jockovich et al., 2000). Each of these studies was a placebo-controlled crossover design, and two of them (James, et al., 1998; Jorgensen and Witting, 1998) administered relatively high doses of melatonin (6 mg and 10 mg, respectively). Small increases in sleep quality and quantity in association with melatonin were observed on a number of different measures in these studies, but few of these differences reached statistical significance. These largely negative findings could have been due to the fact that the subjects were chronically sleep deprived because of sleep restriction, and thus started out with high

sleep efficiencies. For example, (Jorgensen and Witting's 1998) sample of resident physicians worked up to 5 consecutive 12 h night shifts and slept an estimated 6 h per day. In addition, the time spent in bed for the daytime sleep periods in these three studies, (between 6.25 h and 7.3 h), was left up to the subjects. Given the relatively short time that subjects devoted to sleeping and the sleep debt they may have carried, it is not surprising that both melatonin and placebo groups slept well in the daytime (sleep efficiencies between 90 and 95%). It is unclear if melatonin could have improved sleep quality or increased TST if more time was devoted to day sleep, or if the short sleep periods were a result of the inability to sleep due to circadian misalignment combined with melatonin not improving sleep. The observed high sleep efficiencies of all the subjects would seem to support the former hypothesis.

A ceiling effect, composed of several components may have attenuated potential differences between the melatonin and placebo groups in our study. First, the slightly short length of allotted time for daytime sleep (7 h) may have precluded significant group differences. The primary problem when initiating sleep in the morning is difficulty maintaining sleep later in the day (Akerstedt, 1995), which is consistent with the finding that most improvement in daytime sleep after ingesting melatonin occurred in the last 4 h of an 8 h period in bed (Sharkey et al., 2001). Consequently, we used a sustained rather than an immediate-release formulation of melatonin to try to promote sleep later in the day. However, the 7 h time in bed may not have allowed sufficient time for the soporific effect of melatonin to be manifest. This problem of a short time allotment for sleep may also have been present in other studies examining the sedative effect of melatonin given after night shift work (e.g., Jorgensen and Witting, 1998).

A second contributing factor to a ceiling effect may be phase tolerant subjects. Our subjects were young, healthy, and therefore likely phase tolerant, suggesting they could sleep well at an adverse circadian phase (see, e.g., Dawson and Campbell, 1991). Even our placebo subjects had high sleep efficiencies ($>$90% according to sleep logs), leaving little room for improvement in sleep quality. In addition to being phase tolerant, the enforced dark environment that was conducive for sleep may also have contributed to the relatively good sleep of our placebo group, and in turn, to a lack of significant group differences. It is also difficult to ascertain the relative impact of a placebo effect on the sleep of these subjects. All subjects knew that they could be taking melatonin, a highly publicized putative sleep aid, and we did not employ a no-pill condition. Consequently, the relative contribution of merely ingesting a pill may be an additional reason that the participants receiving the placebo pill slept quite well (for discussion of placebo effects, see Jones, 1977; Shapiro and Morris, 1978; Eastman, 1990).

One of the most consistent effects of exogenous melatonin administration in the daytime hours is a shortened SL (Dollins et al., 1994; Nave et al., 1995; Zhdanova et al., 1995; Reid et al., 1996; Hughes and Badia, 1997). We found some evidence for a shortened SL with melatonin; binomial probabilities indicated that significantly more melatonin subjects fell asleep sooner than placebo subjects on 2 of the 5 days (and see Figure 2e). However, other studies of morning melatonin after night work have not observed this shortened SL (James et al., 1998; Jorgensen and Witting, 1998; Sharkey et al., 2001). One possible explanation for the discrepancy is the large difference in the homeostatic sleep drive among the subjects of the various studies. Some studies that reported shorter sleep latencies gave melatonin during the daytime following a full night of sleep when the homeostatic sleep drive would be relatively low. In contrast, following night work, the homeostatic sleep drive is higher and the hypnotic impact of melatonin on SL may be masked because all participants may fall asleep quickly. Thus, melatonin cannot shorten SL when it is already very short.

It is possible that exogenous melatonin could improve sleep quality more in an older population. Melatonin production decreases with age in some individuals, and this decrease is associated with complaints of sleep disturbance (Nair et al., 1986; Sharma et al., 1989; Haimov et al., 1994). Melatonin deficient elderly subjects have shown improvement in nighttime sleep quality when taking daily doses of exogenous melatonin (Garfinkel et al., 1995, 1997; Haimov et al., 1995). Consequently, the impact of exogenous melatonin on daytime sleep might be more evident in an older population.

Sample size does not appear to explain the discrepancy between those studies suggesting that melatonin improves daytime sleep quality and quantity and those that have found no support for this hypothesis. Several studies reporting that melatonin was beneficial when taken prior to day sleep were comprised of small sample sizes (e.g., $n = 23$, Folkard et al., 1993; $n = 16$, Dawson et al., 1995; $n = 12$, within subjects, Yoon and Song, 2002). Conversely, several studies with slightly larger samples sizes have not achieved statistically significant effects (e.g., $n = 18$, within subjects, Jorgensen and Witting, 1998; $n = 22$, within subjects, James et al., 1998; $n = 19$, within subjects, Jockovich et al., 2000). Post-hoc power analysis for our sample indicated that even when using the largest mean difference in sleep log TST (day sleep period 1, melatonin group sleeping 13 mins more than placebo group), a 0.05 one-tailed significance level and power of 0.80 would require a total sample size of 112 to achieve statistical significance.

Tools and methodology that are sensitive to subtle changes in electrophysiology will be most useful in eliciting a precise description of the

impact of melatonin on sleep. Ferini et al. (1993) administered 100 mg of melatonin at 22:30 h and monitored nighttime sleep using polysomnography. While no changes in sleep architecture were evident by conventional sleep staging methods (Rechtschaffen and Kales, 1968), alterations in the EEG microstructure were observed in association with melatonin, indicating improved sleep quality. A smaller dose (5 mg) given prior to a daytime nap did not alter sleep latency or architecture, but was associated with enhanced EEG power in the sleep spindle frequency band (Dijk et al., 1995). Thus, measurements using actigraphy or polysomnography, while in many cases capable of providing precise quantitative information about sleep length and architecture, may not consistently detect the subtle physiological changes that melatonin induces.

Although many investigators have used both immediate and sustained release melatonin formulations, few studies have compared the soporific or phase-shifting effects of these two types of preparations. The temporal precision of an immediate-release preparation might be most effective for phase shifting or sleep initiation, while the longer temporal duration of a sustained-release preparation might be more appropriate for sleep maintenance. Such speculation is consistent with a study of melatonin replacement in elderly insomniac patients in which administration of 2 mg immediate-release melatonin was associated with decreased sleep latency, whereas 2 mg of sustained-release melatonin was associated with increased sleep maintenance, relative to placebo (Haimov et al., 1995).

In summary, the 1.8 mg sustained-released melatonin did not confer substantial benefit, relative to placebo, on the daytime sleep quality or quantity of our participants undergoing simulated night shift work. One reason for this may be that on most days, for most subjects, melatonin was administered when circulating levels of endogenous melatonin were elevated. Another reason may be a ceiling effect in sleep quantity. If the opportunity for sleep was greater than 7 h, then subjects may have had more trouble maintaining sleep, and melatonin may have had a chance to improve sleep. However, it is unlikely that real night shift workers will allot more than 7 h in bed during the day for sleep, thus limiting its potential impact. To date, the clearest benefit of melatonin for night shift workers stems from its ability to phase advance circadian rhythms (Sharkey and Eastman, 2002), and thus is limited to situations in which workers want to sleep before rather than after a night shift.

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