A Single Dose of Melatonin Prevents the Phase Delay Associated with a Delayed Weekend Sleep Pattern

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Study Objectives: This study was designed to test the hypotheses that a delayed weekend sleep pattern may lead to a phase delay of the endogenous circadian rhythm, and that melatonin administration can counteract the phase delay and prevent the sleep and functional impairments associated with this sleep pattern.

Design: A within-subject, counterbalanced design was used in which each subject participated in both placebo and melatonin conditions. Subjects' sleep-wake schedules were delayed by two hours on Friday and Saturday to simulate the delayed weekend sleep pattern. Six mg of melatonin or a placebo pill was administered double blind on Sunday late afternoon.

Setting: N/A

Participants: Ten healthy volunteers (mean age = 22.1 years old).

Measurements and Results: Salivary dim-light melatonin onset (DLMO) was measured on Friday and Monday nights. Subject's sleep was recorded with polysomnography on Sunday night and their levels of sleepiness, cognitive functioning and mood were assessed on Sunday night and Monday morning. Results show that the delayed weekend sleep pattern caused a 31.6 min delay of the endogenous melatonin rhythm. Melatonin administration counteracted the phase delay of endogenous melatonin onset. On Sunday, melatonin administration increased the sleepiness throughout the evening and reduced sleep onset latency at bedtime. On Monday morning, subjective sleepiness was decreased in the melatonin condition.

Conclusion: A delayed weekend sleep pattern did show a mild phase-delay effect on the endogenous circadian rhythm. A single dose of melatonin can acutely reverse the weekend drift.

Key words: Sleep; human; circadian rhythms; melatonin; delayed sleep; weekend sleep pattern

INTRODUCTION

IT IS A COMMON PRACTICE FOR YOUNG ADULTS TO GO TO BED LATE AND GET UP LATE DURING THE WEEKEND. Several survey studies have documented a delayed weekend sleep pattern in young adults and its association with sleep difficulty and poor school performance.[1-4] A survey study, for example, showed that first-year college students delayed their sleep-wake schedule by 1.5 hours over the weekend.[1] A subgroup suffered from a mild delayed sleep phase syndrome in which average sleep onset latency was 43 minutes during the weekdays and school performance was poorer compared to the rest of the sample. In high school students a negative relationship was also reported between the amount of delay of the weekend sleep schedule and academic performance.[2-4] Furthermore, the later the bedtime on the weekend the later the time of peak alertness on weekday mornings.[2,5] Similarly, a field experiment conducted in our laboratory demonstrated decreased subjective sleepiness and a trend of trouble falling asleep on Sunday night and significant functional impairments on Monday morning following one weekend of an imposed two-hour delayed sleep-wake schedule.[6]

This pattern of effects can be attributed to a drift in circadian phase.[1,7] The longer-than-24-hour endogenous period length of the sleep-wake cycle as well as the delay in exposure to time cues on the weekend mornings are mechanisms that may explain the pattern of changes produced by the delayed weekend sleep pattern.[6,8,9]

Coping strategies to help avoid the negative consequences of this sleep pattern are needed. The most direct way to prevent the adverse impact is to avoid staying up late and getting up late during the weekend. However, there are occasions when one simply cannot avoid this delayed weekend schedule due to social, academic, or work demands. Another strategy is to counteract the phase delay of circadian rhythms by inducing a phase advance in rhythms by the exposure to time cues. It is firmly established that exposure to a potent time cue, bright light, in the early morning effectively advances circadian rhythms.[9] However, this is not always practical since most people have difficulty getting up around the habitual arising time on the weekend when they have gone to sleep later than usual.

Another external stimulus that possesses phase-shifting properties is exogenous melatonin. Although there are still some debates about how generally effective melatonin is as a chronobiotic,[10] the phase response expected given the timing of melatonin delivery has been systematically demonstrated.[11,12] The most effective time to deliver melatonin to produce a phase advance is late subjective day.

In previous studies, near physiological doses (0.5 mg) to low pharmacological doses (2 to 5 mg) of melatonin in the late afternoon and early evening have been shown to induce phase advances as indicated by the endogenous melatonin, temperature and sleep-wake rhythms.[13-16] In a number of protocols, 5 mg of

Accepted for publication January 2001
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melatonin administered in the evening for two to six weeks has also been shown to decrease sleep onset latency and to advance the sleep-wake rhythm in patients with delayed sleep phase syndrome measured by subjective sleep logs, actigraphy, nocturnal polysomnography, and ambulatory polygraphic recording.[17-20] In addition, melatonin administration has also been used, with some success, to alleviate maladaptation to shift work[21,22] and jet lag.[23,24] These findings suggest that appropriately timed melatonin administration may be a potential strategy to address the circadian drift and adverse impact of the delayed weekend sleep pattern.

The aim of the present study is to demonstrate that there is a delay in the phase of the endogenous circadian rhythm following the delayed weekend sleep pattern, and to explore the use of a single dose of melatonin on Sunday night to counteract the phase delay and to prevent the adverse behavioral consequences. The delayed weekend sleep pattern was simulated on the weekends in the lab. A pill containing either 6 mg of melatonin or placebo was given to subjects late Sunday afternoon. The amount of phase shift in the endogenous circadian rhythm was measured by salivary dim-light melatonin onset (DLMO).[25-27] Subjective sleepiness, mood status, and cognitive functioning on Sunday night and Monday morning were also measured by subjective ratings and cognitive tests. Sleep on Sunday night was recorded with polysomnography.

In addition to its circadian rhythm shifting properties, melatonin administration has also been shown to possess acute sedating properties.[14,15,28-31] This acute sedative effect can be a potential adverse effect when melatonin is given in the late afternoon as a strategy to advance endogenous circadian phase. Thus, this study also measured the sedative effect of melatonin administration by periodically measuring subjective sleepiness and objective vigilance Sunday night.

METHODS

Subjects

Subjects were recruited from college settings by flyers and public announcements. Prior to the experiment, potential subjects were interviewed for sleep and medical history and were asked to complete the Morningness-Eveningness (M/E) Questionnaire.[32] Inclusion criteria for participation were: 1) 18 to 30 years of age; 2) non-shift worker, no travel across time zones during the month prior to the study, and on a regular sleep-wake schedule; 3) nonsmoker and not using psychoactive drugs; and 4) no history of or current report of a sleep, medical, neurological, or psychiatric disorder. In addition, only Evening Type and Neither Type potential subjects, as measured by the M/E Questionnaire, were included. This criterion was instituted because Evening Types have been shown to be associated with a delayed circadian phase,[33-35] and therefore may be prone to developing the weekend sleep phase delay. Also, female potential subjects with premenstrual dysphoric disorder[36] were excluded because the endogenous melatonin rhythm has been shown to vary at different stages of the menstrual cycle in these individuals.[37] Two female subjects (#4 and #16) reported chronic use of oral contraceptives before and during the study. The consumption of oral contraceptives has been shown to abolish the melatonin rhythm in one study.[38] However, these two subjects showed clearly defined salivary DLMOs and their patterns of shifts in salivary DLMOs were not different from the average of the rest of the subjects. Therefore, all of their data were included in the analysis.

A total of 19 potential subjects started the study. Nine subjects either withdrew because of difficulty following the designated sleep-wake schedule, or were dropped because of failing to call into voice mail to report their bedtime and wake time.

Ten subjects (2 males and 8 females), between the ages of 19 and 29 (mean=22.1 years), completed the study. The means of the subjects' reported weekday and weekend sleep-wake schedule were 11:55 P.M. to 7:55 A.M. and 1:23 A.M. to 9:56 A.M., respectively. Their average habitual total time in bed (TBT) on weekdays was 8.0±0.9 hours and on the weekend TBT was 8.6 ± 1.4 hours. All of the subjects completing the study were Neither Type (mean M/E score=47.7, SD=3.7).

The experimental protocol was approved by the Institutional Review Board of the City College of New York. Informed consent was obtained from each subject, and written documentation was obtained. Subjects received $200 upon the completion of the study as compensation.

Procedures

The experiment was a within-subject design, with one pre-experimental week followed by two experimental weeks: one melatonin condition and one placebo condition. The sequence of the two conditions was counterbalanced across subjects. Each week started on a Tuesday night and ended the next Tuesday morning. Throughout the study, subjects were required to keep a daily sleep log and to refrain from taking naps. Alcohol consumption was prohibited during the study; however there was no testing conducted to monitor compliance. Caffeine consumption was limited to one cup of coffee or one can of caffeinated drink per day before noon when subjects were at home and was totally restricted when subjects were in the lab.

Pre-Experimental Week

A sleep-wake schedule for the study was designated for each subject according to his or her reported habitual bedtime and wake-up time. During the pre-experimental week, subjects slept at home and followed the designated sleep-wake schedule for the entire week to stabilize their sleep-wake rhythm. They were required to call an automatic time-stamped voice mail system everyday immediately upon awakening in the morning and prior to going to bed to report their sleep-wake schedule.

Experimental Weeks

Subjects followed the same procedures for the two experimental conditions except for the pills given on Sunday evening. Their sleep-wake schedule on Friday and Saturday nights were delayed by two hours to simulate the delayed weekend sleep pattern, and bedtime was delayed for one hour on Monday night in order to continue to collect the last saliva sample. They followed their habitual schedule for the rest of the week. Subjects slept at home from Tuesday to Thursday. On Friday, Saturday, Sunday and Monday nights, subjects came to the City College of New York sleep lab in the early evening and stayed overnight. Illumination level was maintained below 50 lux when subjects

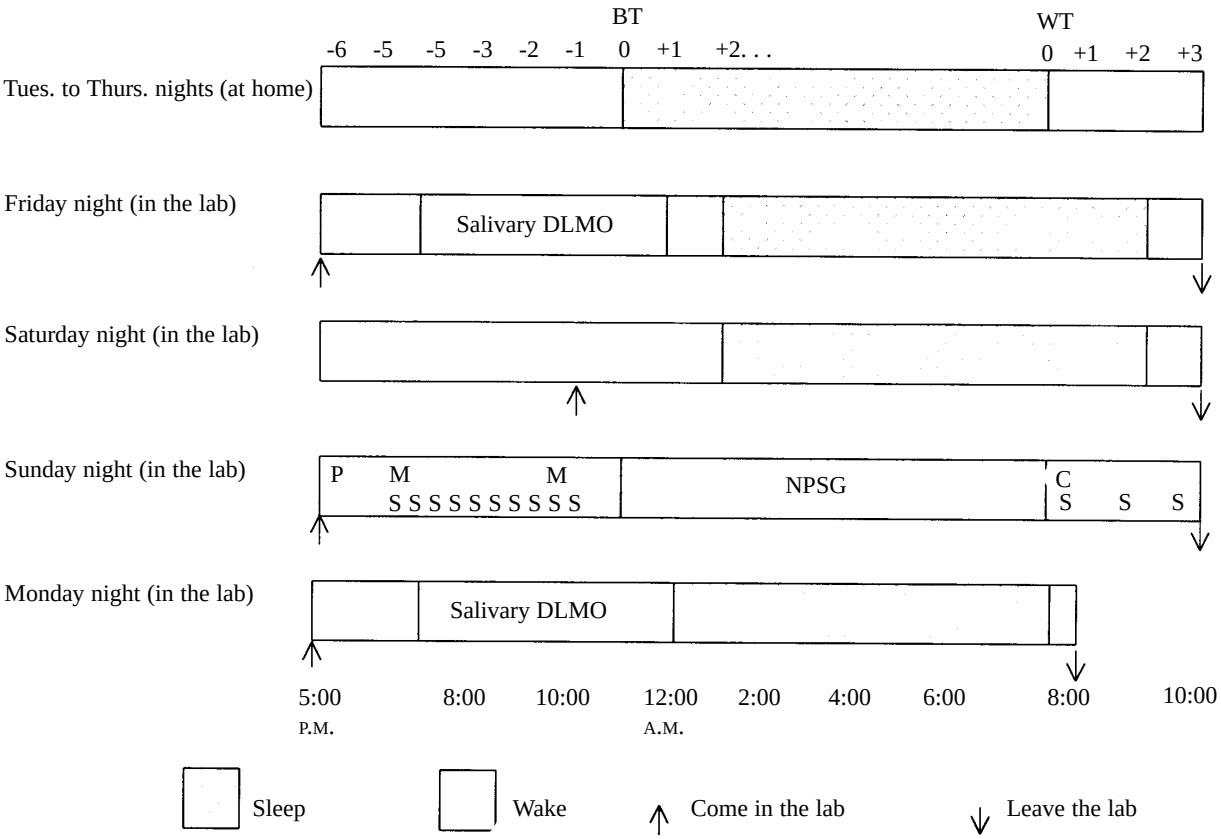

Figure 1—Experimental procedures for Melatonin condition and Placebo condition. The procedures for the two conditions were the same except for the pill given. The time for different experimental activities were decided based on subjects' designated habitual bedtime (BT) and designated habitual wake-up time (WT). The clock time at the bottom of the figure illustrates the time of experimental activities for a subject whose designated sleep schedule is 11:00 p.m. to 7:00 a.m.

were awake in the lab and was near total darkness after subjects went to bed in order to attenuate the suppressing effect of light exposure on endogenous melatonin.[38,39]

On Sunday nights, a pill containing either 6 mg of melatonin (melatonin condition) or mannitol (placebo condition) was administered 5.5 hours before subject's habitual bedtime in a double blind manner. The average time of melatonin administration was 6:04 P.M. This time was chosen because the phase response curve of melatonin indicates that to induce a phase advance, timing of melatonin administration is best between ten hours before bedtime and two hours after bedtime.[11-12] Since subjects' endogenous circadian rhythm was expected to be mildly delayed on Sunday night, a relatively late time within the window to produce a phase advance was chosen.

Figure 1 illustrates the experimental procedures and sleep-wake schedule for the two experimental weeks.

Measurements

Salivary dim-light melatonin onset (DLMO) Test. The salivary DLMO test was conducted on Friday and Monday nights in both melatonin and placebo conditions to determine the phase position of the circadian rhythm of endogenous melatonin secretion. The post-test of salivary DLMOs was administered on Monday night instead of Sunday night in order to prevent the saliva samples from being contaminated by the exogenous melatonin given on Sunday early evening. The elimination half-life of 100 mg of melatoninn administered orally, as assessed by salivary melatonin, has been shown to be 38 minutess.[40] Therefore, in normal individuals exogenously delivered melatonin of 6 mg should be completely eliminated by 25.5 hours after administration when the first saliva sample was taken on Monday night. Saliva samples were collected every 30 minutes from four hours before the designated habitual bedtime to one hour past the designated habitual bedtime.

For each sample, subjects were asked to sit down for at least 10 minutes before the collection of the sample in order to avoid the effect of changing posture on melatonin level.[41,42] At least 3 ml of saliva was collected for each sample. Saliva samples were then centrifuged and stored at -20°C. The amount of melatonin contained in each sample was measured by a double-antibody radioimmunoassay conducted at the Biochemical Lab of the New York Hospital-Cornell Medical Center (White Plains, New York), following the procedures provided by American Laboratory Products Co. (Windham, NH). Samples were analyzed in duplicate with two separate batches of assay. Samples from the same subject were analyzed by the same batch. The intra-assay and inter-assay coefficients of variation were 4.1 and 8.9%, respectively. The onset time of nighttime salivary melatonin was calculated as the first interpolated point above 4.0 pg/ml of melatonin

Table 1—Mean and SD for Stanford Sleepiness Scale ratings on Sunday evening and Monday morning (N=10)

Time	Melatonin Mean	Melatonin SD	Placebo Mean	Placebo SD
Sunday Evening				
Bedtime - 4.5hrs	2.2	1.0	1.9	1.0
Bedtime - 4hrs	2.7	.8	2.4	1.5
Bedtime - 3.5hrs**	4.3	1.3	2.5	1.5
Bedtime - 3hrs**	3.6	1.0	2.4	1.2
Bedtime - 2.5hrs	3.6	1.1	2.7	1.2
Bedtime - 2hrs**	4.7	1.3	3.4	1.3
Bedtime - 1.5hrs**	4.5	1.0	3.3	0.8
Bedtime - 1hr**	5.1	0.9	3.8	1.1
Bedtime - 0.5hr*	5.6	0.5	4.4	1.0
Bedtime	5.8	1.0	4.9	1.4
Monday Morning				
Wake-up + 1hr	2.4	0.8	2.9	0.7
Wake-up + 2hrs	1.4	0.5	1.6	0.8
Wake-up + 3hrs	1.9	1.2	1.8	1.3

Significant on Tukey Test: *p<.05; **p<.01
Higher values indicate increased subjective sleepiness.

that continued above this threshold level in later samples. This threshold criterion has been validated in previous studies.[19,41,43]

Sleep recording. Nocturnal polysomnographic (NPSG) recordings were conducted Sunday night. Electrodes for NPSG recording were also applied on Saturday night to habituate subjects to the procedure, although no sleep recording was conducted. The NPSG montage included electroencephalogram (EEG) with C3 or C4 and O1 or O2 referenced to linked mastoids (A1+A2), electro-oculogram (EOG), chin electromyogram (EMG) and electrocardiogram (EKG). The records were scored according to standard procedures,[43,45] manually in 30-second epochs by trained scorers who were blind to the experimental conditions.

Subjective ratings. Subjects' level of sleepiness was assessed on the Stanford Sleepiness Scale (SSS)[44,46] every 30 minutes on Sunday evening and hourly on Monday morning. A modified procedure, which required subjects to sit quietly in a dark room with their eyes closed for one minute before each SSS rating, was instituted in an attempt to eliminate the masking effects of behavioral arousal on subjective sleepiness. Subjects' mood status was also evaluated right before going to bed and immediately after waking up on Sunday nights with visual analog mood scales (VAMS). The VAMS required subjects to rate 12 separate mood-related descriptions (e.g. "active," "tense," "sad," "happy") by marking a vertical stick on a 100-mm horizontal line with two poles labeled "very little" on the left and "very much" on the right.

Performance tests. Performance tests administered included the Multiple Vigilance Test (MVT), a nine-choice simple reaction time test, a word-list memory test (WMT), and the Controlled Oral Word Association (COWA). The tests were selected to measure cognitive domains which have been shown to be sensitive to sleep loss and are associated with learning and performance at work or school.[45,47-49,51] A practice trial of the performance tests was administered as an orientation on Saturday nights. MVT was administered twice on Sunday night (4.5 hours and one hour before bedtime) and once on Monday morning immediately after getting up. All the other tests were given once on Monday morning right after waking up.

The MVT is a computerized visual continuous performance test used to assess lapses in attention or vigilance and impulsivity, in which subjects were asked to respond to a target stimulus (a letter H) among non-target figures (a side-way letter H). The nine-choice simple reaction time test displayed a 3x3 array of nine squares on a computer screen with one target square filled with red color for subjects to press the key on the keypad that corresponded to the red square. The WMT required subjects to recall a list of 24 words presented one at a time on a computer screen right after the presentation. The COWA consisted of three word-naming trials in which subjects were given one minute to generate as many words as they could think of that began with a given letter of the alphabet. Alternate forms of the WMT and the COWA were used for each day.

Data Analysis

ANOVAs were used to compare different measures between the conditions and between different days. Sequences of the two conditions (melatonin first placebo second vs. placebo first melatonin second) was also compared to evaluate potential order effects. No sequence main effects were found in any of the comparisons.

One subject's (#2) first two salivary samples on Friday night in the placebo condition contained very high levels of melatonin (82.3 and 51.5 pg/ml) and declined rapidly on later samples and yielded a continuous rise later near bedtime. The first two samples were considered to be contaminated and were omitted in the figure and analysis. Another subject's (#1) fifth sample on Friday night in the melatonin condition also was inconsistently high (49.5 pg/ml) compared to other samples for this subject. This data point was also omitted. Also, two subjects in the melatonin condition on Monday night showed sustained melatonin levels above 4 pg/ml at the beginning of sampling. The times of the first saliva sampling (four hours prior to their habitual bedtime) were

Table 2—NPSG parameters on Sunday night: comparison between melatonin and placebo condition (N=10)

	Melatonin		Placebo			
Variable	**Mean**	**SD**	**Mean**	**SD**	**F**	p
TST	461.4	25.7	461.3	26.7	0.14	.91
SE	95.6	1.5	95.3	1.5	0.50	.50
TWT%	4.6	1.6	4.8	1.4	0.13	.73
WASO%	3.5	1.6	2.8	1.4	3.04	.12
Stage 1%	6.9	3.3	7.5	4.1	0.49	.50
Stage 2%	57.9	6.6	56.9	5.6	0.31	.59
Stage 3%	9.7	3.9	10.9	2.2	1.38	.27
Stage 4%	3.0	3.9	2.8	2.9	0.03	.86
SWS%	12.7	6.3	13.6	4.3	0.46	.52
NREM%	77.5	4.5	78.1	4.2	0.35	.57
REM%	22.5	4.5	22.0	4.2	0.35	.57
SOL	4.9	2.7	7.9	4.8	5.98*	.04
S2L	6.8	2.1	12.3	6.6	6.83*	.03
SWSL	18.0	4.8	17.6	7.1	0.02	.89
REML	72.6	48.6	71.1	39.4	0.05	.84
# of Arousals	47.6	19.0	50.8	21.0	0.75	.41

TST = total sleep time (min); SE = sleep efficiency (%); TWT% = percentage of total wake time after light-out; WASO% = percentage of wake time after sleep onset; Stage 1% = percentage of stage 1 sleep; Stage 2 = percentage of stage 2 sleep; Stage 3 = percentage of stage 3 sleep; Stage 4 = percentage of stage 4 sleep; SWS = percentage of slow wave sleep; SOL = sleep onset latency; S2L = stage 2 sleep onset latency; SWSL = SWS onset latency; REML = REM sleep onset latency
*p<.05

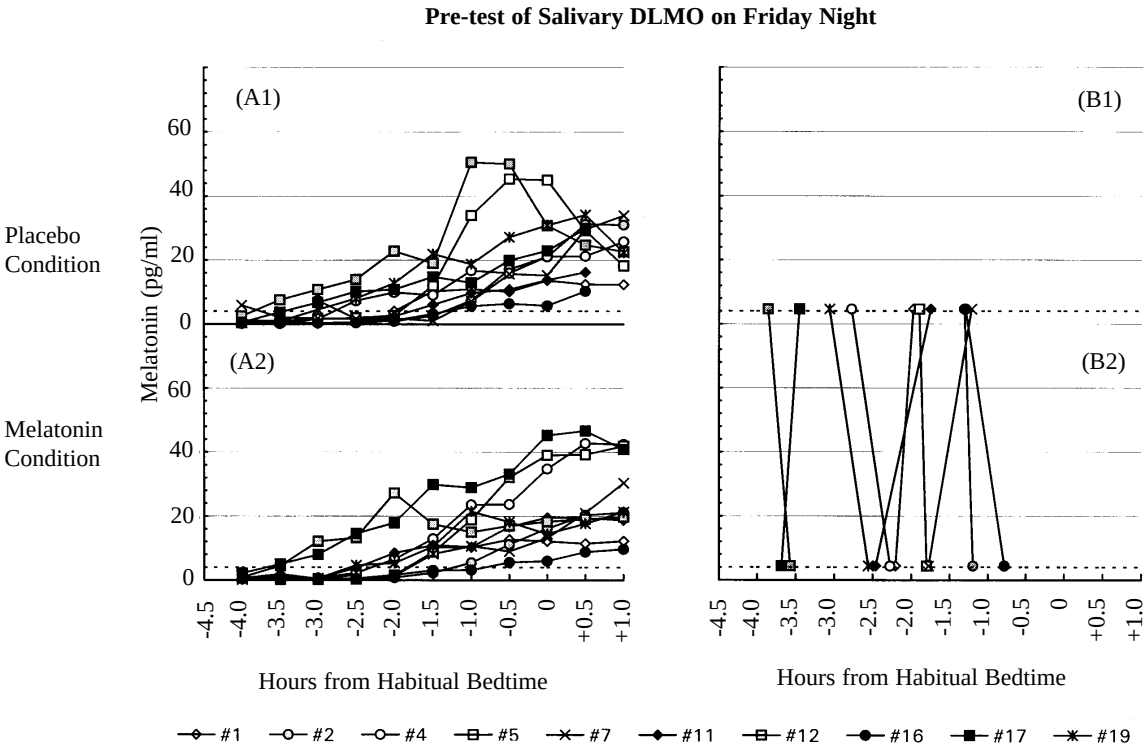

Figure 2—Pre-test of salivary Dim-light Melatonin Onset (DLMO) on Friday Night: (A1) Individual salivary melatonin levels at half hour intervals on the Friday night preceding placebo administration on Sunday night. The doted line represents the melatonin onset criterion at 4 pg/ml. (A2) Individual salivary melatonin levels at half hour intervals on the Friday night preceding melatonin administration on Sunday night. (B1) Individual subjects' melatonin onset time on the Friday night preceding placebo administration on Sunday night. The onset of melatonin secretion was determined by the first interpolated point between salivary melatonin levels below and above 4 pg/ml in which all later samples were above threshold. (B2) Individual melatonin onset time on the Friday night preceding melatonin administration on Sunday night.

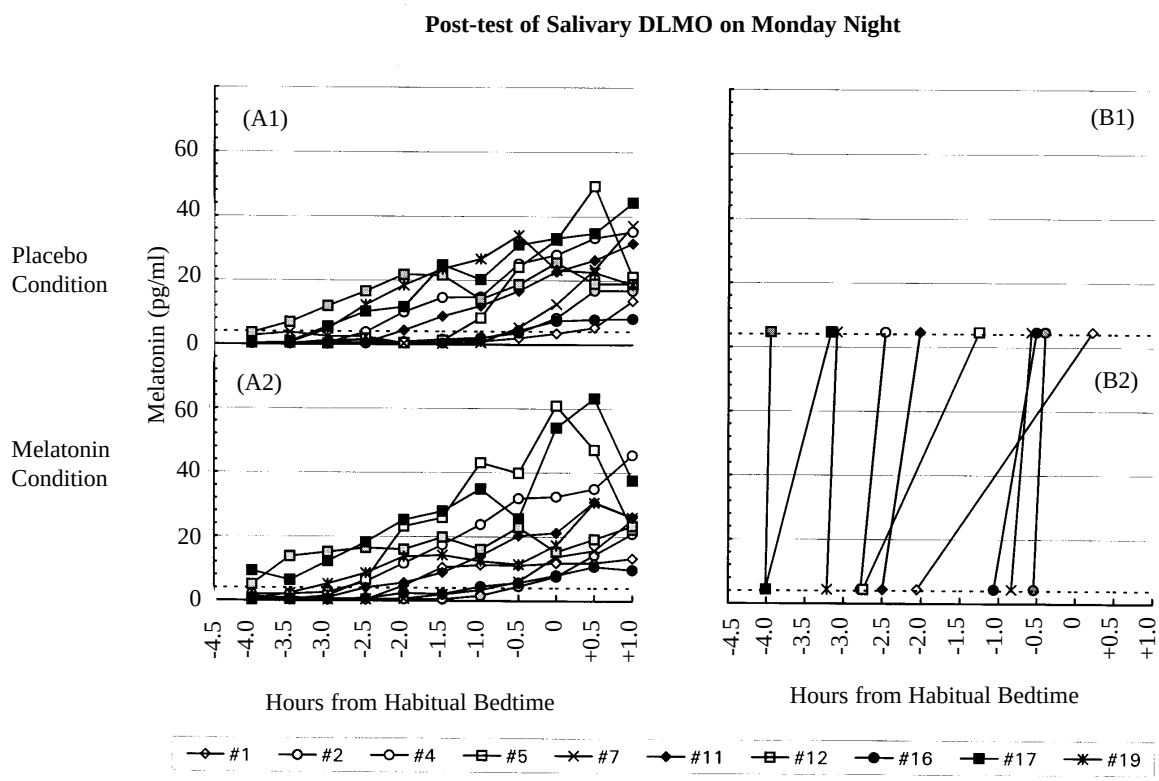

Figure 3—Post-test of salivary Dim-light Melatonin Onset (DLMO) on Monday Night: (A1) Individual salivary melatonin level at half hour intervals on the Monday night after placebo administration on Sunday night. The doted line represents the melatonin onset criterion at 4 pg/ml. (A2) Individual salivary melatonin levels at half hour intervals on Monday night after melatonin administration on Sunday night. (B1) Individual melatonin onset time one day after placebo administration on Sunday night. The onset of melatonin secretion was determined as described in Figure 2. (B2) Individual melatonin onset time one day after melatonin administration on Sunday night.

assigned as their salivary DLMO time.

One subject's sleep log of Friday night was not completed due to an experimenter's error; therefore he is excluded from analysis on this portion of data. However, his sleep log on Sunday night and Monday morning and other measures were complete and were included for statistical analysis.

RESULTS

Subjective Sleep on Friday and Saturday Nights

Total sleep time (TST) and sleep efficiency (SE) on Friday and Saturday nights were compared between the two conditions in order to make sure the sleep prior to melatonin administration were equivalent between the conditions. The mean (±SD) TST was 458.4±37.5 minutes for the melatonin condition and 455.7±30.3 minutes for the Placebo condition, and the mean (±SD) SE was 95.1±6.0 % for the Melatonin condition and 94.1±6.5 % for the placebo condition. ANOVAs showed no significant differences for TST and SE between the Conditions.

Salivary DLMO

Individual melatonin curves and the salivary DLMO time on Friday and Monday nights for both conditions are presented in Figures 2 and 3. The individual salivary DLMO phase shift between Friday and Monday for both conditions are also presented in Figure 4. ANOVA results for salivary DLMO showed a significant interaction between condition and day ($F[1,8]=8.7$, $p<.05$), but no significant condition ($F[1,8]=4.4$, n.s.) or day ($F[1,8]=1.4$, n.s.) main effects. Post-hoc comparisons with the Tukey method showed that baseline salivary DLMOs on Friday night were not significantly different between the two conditions (Tukey $q=0.3$, n.s.). However, there was a significant delay of salivary DLMO of 31.6 min in the placebo condition (Friday night mean=21:18 h vs. Monday night mean=21:49 h; $q=4.66$, $p<.05$), but not in the Melatonin condition (Friday night mean=21:19 h; Monday night mean=21:11 h; $q=1.2$, n.s.).

Although the two mean baseline salivary DLMOs on Friday night in the two conditions were nearly identical, individual subjects showed variations of their baseline salivary DLMOs that ranged from 0.1 to 49.7 minutes (Figure 2). A Pearson correlation was performed to examine the consistency of the baseline salivary DLMO measurement between placebo and melatonin conditions and a correlation coefficient of 0.89 was obtained ($p=.001$). Also, as indicated in Figure 4, individual data showed that the salivary DLMO was delayed over the weekend in seven out of the ten subjects in the placebo condition, ranging from 17.1 to 128.8 min. The other three subjects showed minimal to mild advances of 1.9, 5.3, and 16.0 min.. In the melatonin condition, seven subjects demonstrated minimal to moderate advances in salivary DLMO, ranging from 2.2 to 55.6 min. Although the other 3 subjects showed delays, two (#1 and #2) showed smaller

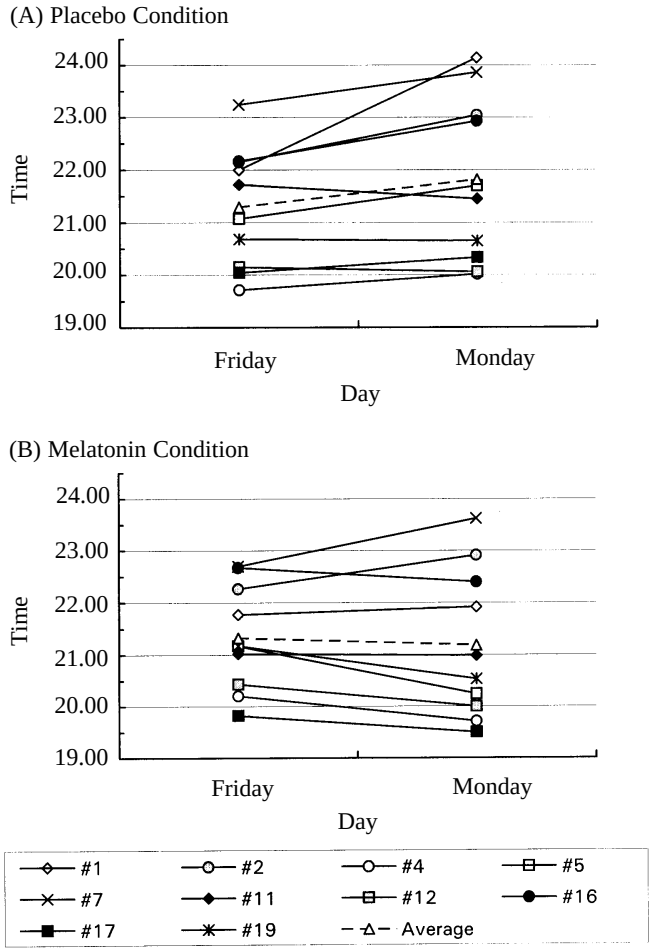

Figure 4—Shifts of Individual salivary Dim-light Melatonin Onset (DLMO) Time from Friday to Monday Nights: (A) Shifts of individual melatonin onset time from the Friday before placebo administration on Sunday night to the Monday after placebo administration. The doted line represents the average salivary DLMO shift. (B2) Shifts of individual melatonin onset time from the Friday before melatonin administration on Sunday night to the Monday after melatonin administration. The doted line represents the average salivary DLMOshift.

delays compared to their Placebo condition. Only one subject (#7) showed a greater delay of salivary DLMO in the Melatonin condition than in the Placebo condition.

Sleepiness, Mood ratings, and Vigilance Test on Sunday Night

The results for the SSS ratings on Sunday evening is presented in Table 1. ANOVA showed a significant interaction between Condition and Time of the ratings ($F[9,63]=2.1$, $p<.05$). Subjects rated themselves sleepier 3.5 hours before bedtime (two hours after melatonin ingestion). This increased subjective sleepiness was sustained until one half-hour before bedtime, except for the rating at 2.5 hours before bedtime. ANOVA on MVT showed no significant difference between conditions on all the variables.

VAMS ratings at Sunday bedtime showed subjects were "wearier" (melatonin condition mean [±SD]=72.7±8.6 vs. placebo condition mean=47.9±22.7) and marginally more "irritable" (Melatonin condition mean=43.6±33.7 vs. placebo condition mean=20.4±22.8) on the melatonin condition than on the placebo condition ($F[1,8]=6.32$, $p<.05$ and $F[1,8]=4.85$, $p=.06$, respectively). No other VAMS variables on Sunday night was significantly different between conditions.

Sleep on Sunday night

As indicated in Table 2, NPSG recording on Sunday night showed shorter SOL and shorter latency to stage 2 sleep in the melatonin condition than in the Placebo condition. There were no differences on any of the other NPSG variables between the two conditions. In terms of the sleep log, there were no differences between the two conditions on any of the variables, except for a near significant trend to be less difficult to wake up in the morning in the melatonin condition (3.0±1.2) compared to the placebo condition (4.3±1.9; $F[1,8]=3.98$, $p=0.08$).

Sleepiness, Mood Ratings, and Cognitive Performance on Monday Morning

On Monday morning, subjects rated themselves less "sleepy" (melatonin condition mean [±SD]=46.2±33.1 vs. placebo condition mean=67.5±18.7) and "overall feeling better" (melatonin condition mean=51.2±14.3 vs. placebo condition mean=38.0±10.3) on the VAMS following the melatonin night compared to the morning after placebo ($F[1,8]=6.06$ and 9.78, respectively, $p<.05$). In addition, ratings of "alert" (Melatonin condition mean=35.6±21.3 vs. placebo condition mean=22.9±13.3) and "effort to do anything" (Melatonin condition mean=57.7±21.6 vs. placebo condition mean=49.5±20.9) were improved and approached significance ($F[1,8]=4.65$, $p=.06$ and $F[1,8]=4.28$, $p=.07$, respectively). The SSS ratings on Monday morning, on the other hand, were not different between melatonin and placebo conditions (see Table 1). The absence of differences between the melatonin and placebo conditions was also the case for the MVT. Similarly, none of the performance tests on Monday morning showed difference between the conditions.

DISCUSSION

This study has shown that a delayed weekend sleep pattern produces a phase delay in the onset time of melatonin secretion, a marker of endogenous circadian phase. Previous studies had shown that naturally occurring as well as a simulation of the delayed weekend sleep pattern led to prolonged sleep onset latency and impaired cognitive and academic performance.[1-3,6] Although the reported sleep and performance problems suggested a phase delay as the presumed mechanism, no direct evidence had been presented. In the current study, we have shown that there is an average delay of 31.6 minutes in the rhythm of the nocturnal onset of melatonin secretion after two nights of a prescribed delay in the timing of the sleep-wake schedule. This delay may be due to the delay of sleep-wake schedule as well as the delay in exposure to morning light associated with the delayed schedule.

The other major finding of the current study is that melatonin administration at the time predicted from the phase response curve[11,12] can counteract the phase delay associated with the delayed weekend sleep pattern, reduce sleep latency on Sunday night and improve sleepiness and general mood ratings on

Monday morning. Although the difference in salivary DLMO between the melatonin and placebo conditions suggests that a phase advance mechanism is responsible for the shift in endogenous circadian phase after melatonin administration, a number of issues should be noted.

Questions have been raised as to the generalizability of the endogenous melatonin rhythm as a measure of circadian phase when evaluating the effect of exogenous melatonin administration.[10] While exogenous melatonin has been shown to consistently and systematically shift the endogenous melatonin rhythm, it's effect on other indices of circadian rhythmicity have not been consistent. Melatonin administration has been shown to shift body temperature and cortisol rhythms in some studies[14,16,50,52] but not in others.[11,19] To explain the inconsistent results, it has been suggested that the administration of exogenous melatonin can alter the dynamics of endogenous melatonin due to an endocrine feedback effect.[19] Models have suggested that repeated exposure to exogenous melatonin changes the sensitivities of neuronal receptors involved in melatonin synthesis. Alternatively, melatonin administration may alter the levels of the enzymes involved in melatonin synthesis. Either of these proposed mechanisms may be responsible for changes in endogenous melatonin level.[19] However, these are not likely explanations for the current findings because melatonin was administered only one time and the salivary DLMO post-test was conducted one day after the melatonin administration. While the high reliability of salivary DLMO in the current study suggests it is a stable marker of circadian phase, using additional measures to help characterize the endogenous circadian rhythm, such as core body temperature and cortisol rhythms, may be required to clarify the effect of exogenous melatonin administration on circadian phase.

Instead of a phase advance effect, shortening the endogenous period length by exogenous melatonin may be an alternative explanation for the current results.[10] Since melatonin phase was inferred by measuring the onset time, shortening of tau and phase advance of the endogenous rhythm are both consistent with an earlier salivary DLMO time. Employing a continuous measure of circadian rhythmicity for a longer period of time is needed to clarify the role of these two mechanisms.

The current study's lack of a control condition in which the habitual sleep-wake schedule could be compared to the placebo condition of the delayed schedule limits the assessment of sleep onset latency and behavioral consequences produced by the delayed schedule. However, our recent field study employing many of the same measures as in the current work and other studies have shown that following the weekend delayed sleep pattern, the sleep on Sunday night is disturbed.[6] Nevertheless, in the current study a clinically significant insomnia was not produced. The mean sleep onset latency on Sunday night in the placebo condition was 11.3 min on the sleep log and 7.9 min on the NPSG recording, values that are well within normative levels.

A possible reason why the delayed schedule did not generate greater sleep onset difficulties may be mild chronic sleep deprivation that has been reported in individuals of this age.[51,53] Consistent with this interpretation is the high NPSG sleep efficiency of 95.3% on Sunday night, suggesting that subjects were able to sleep well because they had a sleep debt. While we monitored bedtimes through a voice mail system from the nights spent at home and we set the sleep schedule Friday and Saturday night, we assessed sleep objectively on only Sunday night. Therefore, sleep may have been curtailed prior to Sunday night which would explain the absence of long sleep latencies on the placebo condition of the delayed schedule.

Another explanation of the failure to produce a sleep onset problem on Sunday night is that the subjects studied were not from the subgroup of individuals who are prone to be affected by a phase delay. We did not study evening type individuals who have been shown to have a delayed circadian rhythm and may be susceptible to sleep initiation problems.[33-35] The potential subjects who were evening types were either excluded because of the strict inclusion criteria or could not follow the prescribed sleep-wake schedule and were dropped from the study.

Melatonin significantly decreased NPSG sleep onset latencies compared to placebo. Although the mean difference was only three minutes this finding suggests that the phase advance produced by melatonin may be able to improve Sunday night sleep onset difficulties following a weekend sleep pattern.

An alternative explanation for the shortened sleep onset latencies found is the sedative effect of melatonin. In spite of the short half-life of melatonin,[52,54] previous studies have shown that the sedative effect of melatonin persists for five hours after administration.[28,30] Our results showed that the increase in subjective sleepiness started two hours after melatonin administration and lasted up to five hours after administration. While sleepiness near and at bedtime were not elevated this may be due to the acute arousing effects of getting ready for bed. Therefore, some residual sedating effect at bedtime may have contributed to the decreased sleep onset latencies. Similarly, the protracted sleepiness during the evening following melatonin administration may have led subjects to expect to be able to fall asleep easily. This readiness for sleep may have facilitated sleep onset.

Melatonin also produced positive effects on Monday morning, including reduced sleepiness, increased alertness and less difficulty waking. These effects do not appear to be due to improved sleep which, except for the noted sleep onset latency differences, were remarkably similar in the placebo and melatonin conditions. The absence of any differences on the cognitive measures on Monday morning may reflect insensitivity of the tests or the relatively minor phase delay produced by the sleep-wake schedule change. It is also possible that sleep inertia may have impaired subjects' cognitive performance in both conditions, and therefore masked the effects of a mild phase delay. Studies that induce greater than a half-hour phase delay are needed to evaluate the potential benefits of Melatonin on morning performance.

However, it should also be noted that three of our ten subjects (#11, #12, #19) did not show a phase delay in the placebo condition. Examination of age, gender, M/E score, and sleep-wake pattern revealed no differences from the rest of the subjects in these parameters. Also, three subjects (#1, #2, and #7) remained phase delayed in the melatonin condition and one of them showed a larger delay in comparison to the placebo condition. These results suggest individual differences in people's reaction to a sleep schedule phase delay and to the phase shifting effects produced by melatonin. Evening melatonin administration may benefit certain groups of individuals and not others. Future studies will be needed to focus on this issue.

Individuals who have a history of delayed sleep phase syndrome may also benefit from episodic melatonin treatment. After successful treatment of this circadian rhythm problem, there is a

substantial vulnerability for relapse if they fail to maintain a regular sleep-wake schedule. The relapse rate of delayed sleep phase syndrome within one year after successful treatment has been reported to be as high as 91.5%.[17] Late afternoon ingestion of melatonin following the occasions when bedtimes have been delayed may be a practical and effective way to prevent a full fledged relapse to the syndrome.

Another group that might benefit from evening melatonin are adolescents who prefer a delayed sleep phase, suggesting a possible delay in their endogenous circadian rhythm.[53,55-55,57] It is very difficult for individuals in this age group to avoid staying up late occasionally during the weekend for social or academic reasons. The need to arise early on Monday morning because of the typical high school schedule exacerbates the problems associated with the weekend delayed sleep pattern. One approach to this problem has been the suggestion to start school later in the morning.[4143] The intermittent administration of melatonin in the late afternoon on Sunday in adolescents may be an alternative approach to facilitate sleep onset at night and improve alertness and ease of arising Monday morning. However, precaution should be taken when considering this approach, since continuous melatonin administration has been reported to inhibit sexual maturation in non-human animals.[56,58,57,59] The safety of melatonin treatment in adolescents requires further studies.

Although a single dose of melatonin may have yielded potential benefits, precaution should be taken because of its sedative effect. Consistent with previous findings,[14,15] the current study has shown that melatonin increased sleepiness throughout the evening. General precautions regarding the dangers of operating machinery or driving after melatonin ingestion are advised. Also, the sedative as well as the phase shifting effects of melatonin have been shown to be dose dependent.[14] Thus, the optimal dosage of melatonin which can generate sufficient phase advance while keeping the sedative effect to a minimum requires further investigation.

AKNOWLEDGMENTS

We would like to thank Drs. Margaret Moline, Lauren Broch, and Michael Terman for their assistance. Financial support: This research was partially supported by PSC-CUNY Research Award No. 669578 to Professor Spielman

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