

# Practical Interventions to Promote Circadian Adaptation to Permanent Night Shift Work: Study 4

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**Abstract** Scheduled bright light and darkness can phase shift the circadian clocks of night workers for complete adaptation to a night work, day sleep schedule, but few night workers would want this because it would leave them out of phase with the diurnal world on days off. This is the final study in a series designed to produce a compromise circadian phase position for permanent night shift work in which the sleepest circadian time is delayed out of the night work period and into the first half of the day sleep episode. The target compromise phase position was a dim light melatonin onset (DLMO) of 3:00, which puts the sleepest circadian time at ~10:00. This was predicted to improve night shift alertness and performance while permitting sufficient daytime sleep after work as well as late-night sleep on days off. In a between-subjects design, 19 healthy subjects underwent 3 simulated night shifts (23:00-7:00), 2 days off, 4 more night shifts, and 2 more days off. Subjects “worked” in the lab and slept at home. Experimental subjects received four 15-min bright light pulses during each night shift, wore dark sunglasses when outside, slept in dark bedrooms at scheduled times, and received outdoor afternoon light exposure (“light brake”) to keep their rhythms from delaying too far. Control subjects remained in normal room light during night shifts, wore lighter sunglasses, and had unrestricted sleep and outdoor light exposure. The final DLMO of the experimental group was 3:22 ± 2.0 h, close to the target of 3:00, and later than the control group at 23:24 ± 3.8 h. Experimental subjects slept for nearly all the permitted time in bed. Some control subjects who slept late on weekends also reached the compromise phase position and obtained more daytime sleep. Subjects who phase delayed (whether in the experimental or control group) close to the target phase performed better during night shifts. A compromise circadian phase position improved performance during night shifts, allowed sufficient sleep during the daytime after night shifts and during the late nighttime on days off, and can be produced by inexpensive and feasible interventions.

**Key words** human, shift work, circadian rhythms, bright light, melatonin, sleep, performance

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Night shift work is associated with numerous health risks (Koller, 1983; Costa, 1996). These include decreased sleep quantity with subsequent sleepiness and fatigue (Pilcher et al., 2000; Akerstedt, 2003), increased risk of cardiovascular dysfunction (Knutsson and Boggild, 2000), gastrointestinal disturbance (Scott, 2000; Knutsson, 2003), cancer (Hansen, 2006; Viswanathan et al., 2007), and reproductive dysfunction (Bisanti et al., 1996; Knutsson, 2003). Night shift work is also associated with decrements in psychological well-being (Bohle and Tilley, 1989; Scott et al., 1997) and disrupted social, family, and marital relationships (Staines and Pleck, 1984; Walker, 1985; White and Keith, 1990). Dropouts are common (Costa, 1996), resulting in rehiring and retraining costs.

The problems with sleep and wakefulness common to night shift work are due to misalignment between the circadian clock and the imposed sleep/wake schedule. These problems arise because the circadian clocks of most night shift workers do not shift to realign with a night work, day sleep schedule (Eastman et al., 1995). Because alertness and performance during night work can be seriously impaired (Akerstedt et al., 1994; Dinges, 1995), shift work is also associated with safety risks, pertaining not only to individual workers but also to society as a whole. Many night workers are attempting to remain awake and function around the sleepest circadian time.

Several approaches have been studied as possible ways to improve night shift alertness and performance, thereby attenuating the risks of preventable accidents or errors. Hypnotic medication can increase sleep duration in the daytime after night shifts but does not eliminate the nadir in alertness and performance that occurs during night work (Schweitzer et al., 1991; Walsh et al., 1995). Stimulants such as caffeine (Schweitzer et al., 2006) and modafinil (Walsh et al., 2004; Czeisler et al., 2005), bright-light exposure during night shifts used for its direct alerting effects (Campbell et al., 1995), and prophylactic naps (Schweitzer et al., 2006) can all improve alertness during night shifts but do not restore alertness and performance to daytime levels.

Scheduled exposure to bright light from light boxes or fixtures and scheduled dark/sleep episodes are established methods of shifting the circadian clock and have been used in laboratory and field studies to facilitate entrainment to a night work, day sleep schedule (e.g., Eastman, 1987; Czeisler et al., 1990; Campbell, 1995; Dawson et al., 1995; Boivin and James, 2002; Crowley et al., 2003). Shifting the circadian clock to phase delay and completely align

with a night work, day sleep schedule is the most effective way to normalize nighttime alertness and performance and to maximize daytime sleep quality and duration. However, this approach has limited utility for the majority of night shift workers because complete entrainment to a day sleep schedule would preclude shifting back to a nighttime sleep schedule on days off. Thus, the worker would have difficulty sleeping at night and would feel sleepy during the day on days off, which is a sacrifice that few shift workers would be willing to make.

Eastman and Martin (1999) proposed the idea of a compromise circadian phase position for permanent night shift work in which the circadian clock is delayed to partially entrain to a night work, day sleep schedule. The goal was to delay the temperature minimum ( $T_{min}$ , the sleepest circadian time) into the daytime sleep periods. Delaying the estimated  $T_{min}$  out of the night work period and into the first half of the daytime sleep period was shown to improve night shift alertness and performance (Crowley et al., 2004). When the  $T_{min}$  is delayed into the daytime sleep period, day sleep is hypothesized to be lengthened for those who would otherwise have trouble sleeping during the day because of circadian misalignment. Importantly, a compromise phase position is also hypothesized to facilitate late nighttime sleep and subsequent daytime alertness on days off.

The somewhat flexible timing of human sleep with respect to the phase of the circadian clock permits good-quality sleep in a compromise phase position. Under entrained conditions, the  $T_{min}$  falls in the latter half of a sleep episode, whereas when free running, a main sleep bout is typically initiated at about the  $T_{min}$  (Wever, 1979; Zulley et al., 1981). This shows that sleep is most likely for several hours before and after the  $T_{min}$ . Eastman and Martin (1999) estimated a phase tolerance interval for good sleep from 6 h before to 6 h after the  $T_{min}$ , which would vary depending on previous time awake and other factors such as age. In an analysis of forced desynchrony data, younger subjects were shown to have good sleep when the first 7 h of the sleep episode began or ended at about the  $T_{min}$  (Dijk et al., 1999). They also showed that the window of phase tolerance in older subjects was smaller and somewhat earlier. Our goal is to shift the circadian clock so that the  $T_{min}$ , the sleepest circadian time, is delayed to and stays in the compromise phase position, which is early in the time allotted for sleep after night shifts and late in the time for sleep on days off.

A previous simulated night shift study from our lab demonstrated that subjects whose circadian rhythms delayed the furthest during night shifts typically kept delaying (and delayed around the clock) when night shifts ended and a regular nocturnal sleep schedule was resumed (Martin and Eastman, 1998). To avoid this outcome, Eastman and Martin (1999) proposed what we now call a “light brake” of afternoon bright light designed to coincide with the phase advance portion of the light PRC to prevent the circadian clock from delaying past the desired phase position.

We conducted a series of studies to find a balance between phase-delaying light from light boxes during the night shifts plus the delay of the sleep/dark episode and phase-advancing light after sleep (the light brake) to achieve and maintain a target compromise phase position during alternations between blocks of night shifts and days off. Our goal was to achieve and maintain a target compromise phase position, defined as a dim-light melatonin onset (DLMO) of about 3:00 AM. At this circadian phase position, the Tmin, an estimate for the sleepest circadian time, which occurs about 7 h after the DLMO (Cagnacci et al., 1996; Goel, 2005, 2006), will fall at about 10:00 AM. In this series of studies, the sleep episodes for experimental groups started at 8:30 after night shifts and at 3:00 on days off. Thus, a Tmin of about 10:00 puts the sleepest circadian time early in the sleep period after night shifts and late in the sleep period on days off but always within the sleep episode and never during night work.

The results from the other studies in this series have been published (Revell et al., 2005; Lee et al., 2006; Smith et al., 2008; Smith and Eastman, 2008). Here we describe the final study in the series (called #4), which assessed circadian phase during baseline and again after a sequence of blocks of night shifts alternating with days off. The final circadian phase position for the experimental group was hypothesized to be later than for a control group of subjects and was predicted to be close to the target compromise phase position (DLMO ~3:00).

## METHODS AND DESIGN

A comprehensive description of the methods used in this series of studies can be found in study 1 (Lee et al., 2006).

## Subjects

Nineteen subjects completed the study ( $n = 9$  [4 male] in the experimental group;  $n = 10$  [4 male] in the control group). The mean age of the experimental group ( $25.0 \pm 6.4$ ) and control group ( $26.5 \pm 5.4$  years) was similar. The mean morningness-eveningness scores (Horne and Ostberg, 1976) for the experimental group ( $52.7 \pm 8.2$ ) and the control group ( $53.6 \pm 7.3$ ) were also similar and did not show strong morningness or eveningness. Subjects were nonsmokers, had a body mass index (BMI)  $<30$  kg/m<sup>2</sup>, habitually drank  $<300$  mg caffeine/day, and did not take prescription medications, except for 4 female subjects who used hormonal contraceptives. Subjects did not use recreational drugs, as confirmed by a urine toxicology screen when beginning the study. Subjects had not crossed more than 3 time zones or worked night shifts in the month preceding the study. The Rush University Medical Center Institutional Review Board approved this study. All subjects provided written informed consent.

## Sunglasses

Subjects wore sunglasses at all times when outside during daylight hours. Control subjects wore light sunglasses (36% average transmission, ranging from 0% transmission at 400 nm to about 55% at 650 nm). Experimental subjects wore darker sunglasses (15% average transmission, ranging from 0% at 400 nm to about 25% at 650 nm) that more strongly attenuated short-wavelength light. The spectral transmission of both lenses has been published (Lee et al., 2006).

## Baseline Sleep and Morning Light Schedule

During a 15-day baseline period, subjects maintained a structured sleep/wake schedule with at least 15 min of outdoor morning light exposure. Subjects were required to remain in bed in the dark from 23:00 to 7:00 on weeknights during baseline. Bedtime on weekends was between 23:00 and 00:00, with wake time between 7:00 and 8:00. Weekend naps were permitted from 13:30 to 16:30. A baseline phase assessment was conducted on days 15 to 16. After this phase assessment, subjects returned to the baseline schedule of sleep/wake and light exposure for an additional 6 days before coming to the lab for a series of night shifts and days off. An expanded diagram of the baseline portion of the study can be seen in Figure 1 in Lee et al. (2006).

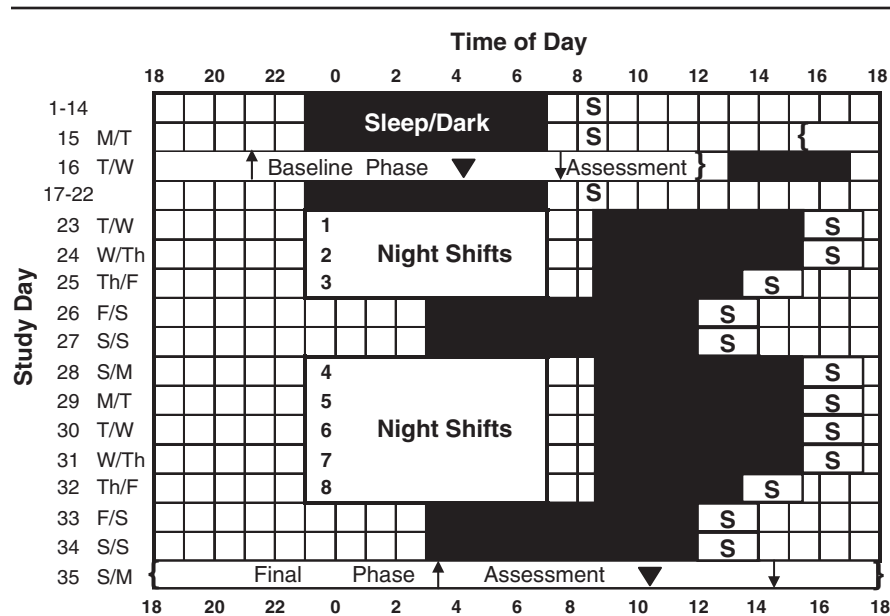


Figure 1. Diagram illustrating the study protocol. Experimental subjects received four 15-min bright light pulses during each of the 8 night shifts (numbered 1-8 within the night shift boxes), timed to delay circadian rhythms, while control subjects remained in room light. The "S" (for sunlight) on days 23 to 34 depicts the light brake for experimental subjects, designed to keep circadian rhythms from delaying too far. The sleep schedule (black areas) shown on days 23 to 34 is for the experimental group only. Control subjects followed the same baseline sleep schedule and sequence of night shifts and days off but chose when to sleep on days 23 to 34. The "S" on days 1 to 22 (baseline) indicates that all subjects were required to go outside for at least 15 min of sunlight between 8:00 and 9:00. The average dim light melatonin onset (DLMO, upward arrows) and offset (DLMOOff, downward arrows) and the estimated sleepest circadian time (DLMO + 7 h, triangles) for the experimental group are shown during the baseline phase assessment (day 16) and the final phase assessment (day 35). In the text, study day numbers correspond to the rows shown in the figure, the 24 h from 18:00 to 18:00.

Here we show the entire sequence of night shifts and days off with the baseline section of the studies condensed (Fig. 1). Study 0 in this series (Revell et al., 2005) demonstrated that when subjects follow this prescribed baseline sleep/wake and outdoor light exposure schedule, circadian phase determined in phase assessments 1 week apart was similar (day 16 and day 23 in Fig. 1). Consequently, circadian phase when beginning the first night shift (day 23) was estimated by the phase at the time of the baseline phase assessment 1 week earlier.

### Night Shift Light

Subjects came to the lab for 8 night shifts from 23:00 to 07:00 (Fig. 1). On each night shift, the experimental subjects were exposed to four 15-min intermittent bright-light pulses from light boxes containing fluorescent lamps (5095K, Sun Ray, Sun Box Company, Gaithersburg, MD). The first pulse

began at 00:45, and the last pulse ended at 4:00. Note that in the earlier studies of this series (Lee et al., 2006; Smith et al., 2008; Smith and Eastman, 2008), there was a fifth light pulse that ended at 5:00. In the present study, we omitted this fifth light pulse because during the final phase assessment in study 3, experimental subjects had delayed slightly more than desired (mean final DLMO 4:34). Measured at a typical distance and angle of gaze, the illuminance of the bright-light pulses was ~4100 lux, the irradiance was ~1200  $\mu\text{W}/\text{cm}^2$ , and the photon density was  $\sim 3.1 \times 10^{15}$  photons/ $\text{cm}^2/\text{sec}$ . Light pulses were separated by 45 min of normal overhead fluorescent room light (<50 lux, 4100K). Subjects in the control group remained in this normal room light throughout the night shifts.

### Daytime Sleep and Afternoon Light Schedule

Experimental subjects were required to remain in bed during scheduled times after night shifts and on weekends off (black shaded areas in Fig. 1). We ensured that the bedrooms of experimental subjects were completely dark by putting black plastic over their windows. Scheduled sleep was from 8:30 to 15:30 (7 h) on days 23-24 and 28-31, from 8:30 to 13:30 (5 h) after the last night shift before a weekend off (days 25 and 32), and from 3:00 to 12:00 (9 h) on weekends off (days 26-27 and 33-34; Fig. 1). Sleep after the last night shift in each block before a weekend off was curtailed to build a small amount of homeostatic sleep pressure for the subsequent earlier bedtime the following night as well as to permit an earlier light brake. Experimental subjects were required to go outside for at least 15 min of light exposure within the first 2 h after awakening on days 23 to 34. The purpose of this "light brake" was to keep their circadian clocks from delaying past the target compromise phase position. Sleep and light exposure for control subjects were unrestricted.

## Circadian Phase Assessments

The baseline phase assessment lasted from 15:30 on day 15 until 12:00 on day 16. A final 24-h phase assessment began at 18:00 on day 35. During phase assessments, saliva was sampled every 30 min under dim light (<5 lux) using a salivette (Sarstedt, Newton, NC). Samples were frozen and shipped on dry ice to Pharmasan Labs (Osceola, WI), where they were radioimmunoassayed for melatonin. The sensitivity of the assay was 0.7 pg/mL. The intra-assay variability was 12.1%, and the interassay variability was 13.2%.

## Performance Testing

Performance was assessed during both day shifts and night shifts. During 3 day shifts on study days 17, 18, and 21, the Automated Neurophysiological Assessment Metrics (ANAM) test battery (Cernich et al., 2007) was completed on desktop computers beginning at 10:05, 12:05, 14:05, and 16:05. During night shifts, the ANAM battery was administered beginning at 00:05, 2:05, 4:05, and 6:05 (see Smith et al., 2008, Figure 2). The ANAM included simple reaction time (SRT), procedural reaction time, code substitution, mathematical processing, and delayed matching-to-sample tasks.

## Additional Procedures

An Actiwatch-L (AWL, Mini Mitter, Bend, OR) was worn around subjects' dominant wrist to verify compliance with the sleep/wake schedule. Bedtime, sleep onset, wake time, and nighttime awakenings >5 min were recorded on daily sleep logs. To measure light exposure, a second AWL device was worn on a cord around the neck (a light medallion). Subjects recorded the time that they were outside during daylight hours on daily light logs. Compliance with requirements for outdoor light exposure was verified using light recordings from the neck-worn AWL.

Subjects completed daily event logs to record alcohol, caffeine, and over-the-counter medication intake. During the baseline portion of the study,  $\leq 2$  alcoholic drinks per day were allowed. Alcohol was prohibited the day before a night shift and in the 24 h prior to and during each phase assessment. Caffeine ( $\leq 300$  mg) was permitted before 17:00 on baseline days 1-15 and 18-22 but was prohibited during night shifts and in the 6 h before and during both phase assessments. For the experimental group, caffeine was also prohibited during the travel home period in

between the night shifts and daytime sleep, as well as in the 6 h preceding sleep on weekend days off.

## DATA ANALYSIS

### Circadian Phase

A locally weighted least squares (LOWESS) curve was fit to each melatonin profile (GraphPad Prism). The DLMO and DLMOff for each melatonin profile were determined using the same method as in the other studies in this series. A threshold was calculated by taking the average of the 5 lowest, consecutive raw data points plus 15% of the average of the 5 highest, consecutive raw data points. The DLMO was the time the fitted curve exceeded and remained above the threshold, while the DLMOff was the time the fitted curve dropped and remained below the threshold.

These 2 circadian phase markers were analyzed with a repeated-measures multivariate analysis of variance (MANOVA). Dependent variables were the DLMO and DLMOff. The between-subjects factor of group had 2 levels: experimental and control. The within-subjects factor of time had 2 levels: baseline and final. A significant MANOVA was followed by a repeated-measures ANOVA on each phase marker. A significant interaction was elucidated with simple main effects (Winer, 1971).

### Ambient Light Exposure

Light (lux) recorded from the AWL around the neck was analyzed using the Actiware Version 5.0 software. For the experimental group, light exposure was determined for the travel home period after night shifts (7:00-8:30) as well as for the first 2 h after awakening from daytime sleep on days 23 to 34 when subjects were required to receive at least 15 min of outdoor light (the light brake). For control subjects, light exposure was summarized for the time between 7:00 and 12:00 for study days 23 to 34 as an estimate of phase-advancing light exposure.

Measurements of 2 light levels were calculated from the neck-worn AWL: the number of minutes of light >10 lux and >1000 lux. Light levels were corrected for the transmission of sunglasses when subjects were outside during daylight hours. For experimental subjects, when light exposure recorded by the medallion was 1000 lux, they received ~150 lux at the cornea because their sunglasses had ~15% transmission.

For control subjects, when light exposure recorded by the medallion was 1000 lux, they received ~360 lux at the cornea because their sunglasses had ~36% transmission. These 150- and 360-lux thresholds were used to calculate the number of minutes that subjects were in bright light and are probably indicative of outside light exposure because exposure to 1000 lux or greater rarely occurs indoors.

Light exposure for the control group was correlated with the final DLMO, with the hypothesis that more morning light exposure during the day after night shifts and on weekends off would be associated with an earlier final DLMO. For the experimental group, afternoon light exposure (the light brake) was correlated with final DLMO with the hypothesis that greater afternoon light exposure would be associated with an earlier final DLMO. However, because baseline and final circadian phase were significantly correlated for the experimental group (see Results), partial correlations between light exposure and final DLMO, controlling for baseline DLMO, are also presented for both groups.

## Sleep

Total sleep time (TST) was measured with sleep logs and verified with actigraphy. TST was calculated by taking the difference between the sleep onset and waking time, excluding awakenings >5 min.

Correlation analyses were performed using the sleep duration of the control group. To assess whether sleep times on the weekend days off (days 26-27 and 33-34) were associated with circadian phase during the final phase assessment, we correlated average weekend bed and wake times with final DLMO. When a control subject had multiple sleep episodes on a single study day, the bed and wake times of the longest sleep episode were used. To test the hypothesis that those control subjects with later DLMOs during the final phase assessment would have greater TST after night shifts, we correlated TST during day sleep episodes after night shifts with final DLMO. Pearson's product moment correlations were used where assumptions of normality were met, and Spearman's rank correlations were used where the data were not normally distributed.

## Performance

For brevity, here we report only data from the SRT task, although the different tasks in the ANAM test

battery yielded similar results. Difference-from-baseline scores were calculated for median reaction time (RT) and the number of minor and major lapses (RT >500 and >1500 msec, respectively) on the SRT task. Performance on the second and third day shifts (days 18 and 21) were averaged to form a baseline value. This baseline value was subtracted from scores on each night shift test bout to obtain the difference-from-baseline scores. Higher difference-from-baseline scores thus indicate a longer RT or more lapses, relative to the daytime baseline values.

Performance for the dependent variables on the SRT task was correlated with final DLMO with the hypothesis that subjects with later final DLMOs would perform better than subjects with earlier final DLMOs. We expected that an association between final DLMO and performance would be strongest late in the night shifts, when performance for real night shift workers is most impaired. We also expected that improvements in performance would be most evident in the latter half of the second week of night shifts, when the circadian clocks of experimental subjects were close to a compromise phase position. Thus, the average performance for the 4:30 and 6:30 test bouts from night shifts 6 to 8 was correlated with final DLMO. Pearson product moment correlations were used for these analyses when the distributions were normal. Because several of the performance variables were not normally distributed or were strongly affected by outliers, we also report Spearman rank correlations.

Summary statistics for all data are means and standard deviations unless otherwise indicated. A 2-tailed significance level of .05 was used.

## RESULTS

### Circadian Phase

Table 1 indicates the average position of the phase markers during the baseline and final phase assessments. Individual DLMOs are depicted in Figure 2. The average phase markers for the experimental group are also shown in the protocol diagram (Fig. 1). The average final DLMO of the experimental group (3:22) was very close to the target compromise phase position of 3:00. The average final DLMO of the control group was 23:24, but there were large individual differences in final phase position, with several subjects' final DLMO as late as the experimental group and other subjects showing a small phase advance (Fig. 2).

**Table 1.** Circadian Phase Markers Determined from Analysis of Salivary Melatonin

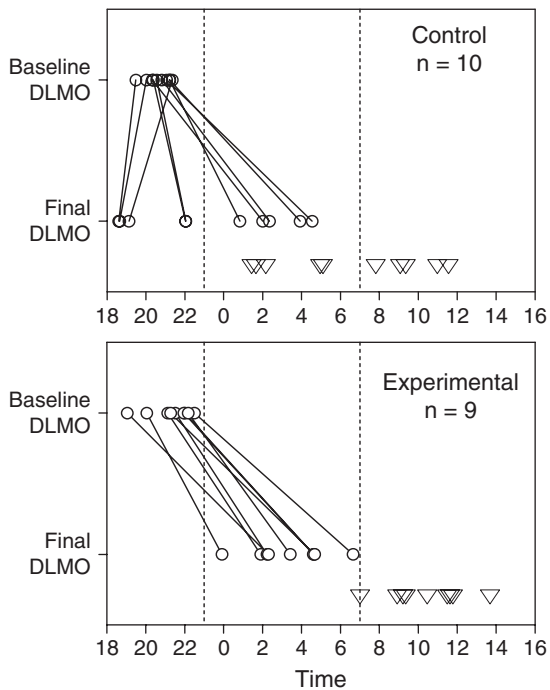
	Experimental		Control	
	Baseline	Final	Baseline	Final
DLMO	21:18 (1.1)	03:22 (2.0)*	20:39 (0.6)	23:24 (3.8)
Midpoint <sup>a</sup>	2:23	8:55	1:58	5:07
DLMO + 7h <sup>b</sup>	4:18	10:22	3:39	6:24
DLMOff	7:28 (1.4)	14:28 (2.2)*	7:18 (1.0)	10:49 (3.2)

Values are mean clock time (SD in hours).

a. Calculated as halfway between the DLMO and DLMOff.

b. Estimated sleepest circadian time and estimated temperature minimum.

\*Significantly later than the final phase of the control group,  $p < 0.001$ .



**Figure 2.** Position of the dim light melatonin onset (DLMO) for individual subjects during the baseline and final phase assessments. Lines are included to connect the DLMOs of each subject and may not reflect the time course of the phase shift, which may not have been linear. The start and end time of the night shifts is shown by the dotted vertical lines. The sleepest circadian time (DLMO + 7 h) for each subject during the final phase assessment is depicted by the triangles.

There was a significant group-by-time interaction for both the DLMO,  $F(1, 17) = 6.75, p = 0.02$ , and the DLMOff,  $F(1, 17) = 8.54, p = 0.01$ . The DLMO and DLMOff of the 2 groups did not differ during the baseline phase assessment ( $p > 0.05$ ), but the experimental group had a significantly later final DLMO and DLMOff than did the control group ( $p < 0.001$ ).

For the experimental group, circadian phase before beginning night shifts was associated circadian phase at the end of the series of night shifts, such that later baseline DLMOs were associated with later final DLMOs ( $r = .70, p = 0.04$ ). This association for the control group did not reach statistical significance ( $r = .54, p = 0.11$ ).

### Ambient Light Exposure

For the experimental group, exposure to bright light (>1000 lux at light medallion, >150 lux at cornea) during the travel home window averaged  $18.0 \pm 12$  min. Experimental subjects were compliant in getting  $\geq 15$  min afternoon outdoor light exposure within 2 h after awakening from sleep on days 23 to 34 (the light brake). The average exposure to bright light during those 2 h was  $27.4 \pm 16$  min. There was a negative relationship between this afternoon light exposure and the position of the final DLMO. The Pearson correlation between the total minutes of light exposure >10 lux during the light brake on study days 23 to 34 and the position of the final DLMO was  $r = -.46, p = 0.21$ . When controlling for baseline DLMO, the partial correlation was  $-.72, p = 0.04$ , indicating that those subjects with more afternoon light exposure had earlier final DLMOs. When this association was tested using minutes of light exposure >1000, the correlations were small and not significant (Pearson correlation  $r = .05, p = 0.91$ ; partial correlation =  $.15, p = 0.72$ ).

For the control group, more bright light exposure between 7:00 and 12:00 during the night shift section of the study (days 23-34) was associated with an earlier final DLMO. The total number minutes of light >10 lux was negatively correlated with final DLMO ( $r = -.79, p < 0.01$ ). When controlling for baseline DLMO, the partial correlation was  $-.69, p = 0.04$ . The number of minutes >1000 lux at the light medallion was also negatively correlated with final DLMO ( $r = -.83, p < 0.01$ ). When controlling for baseline DLMO, the partial correlation was  $-.75, p = 0.02$ .

### Sleep

Light exposure data indicated that experimental subjects were compliant with the schedule sleep episodes in darkness. Subjects in the experimental group slept for nearly all of the allotted time in bed (TIB), and there was little variability in sleep duration between subjects. When TIB for the experimental

group was 7 h, experimental subjects slept  $6.7 \pm 0.3$  h while control subjects slept  $6.6 \pm 1.6$  h. When TIB for the experimental group was 5 h, experimental subjects slept  $4.8 \pm 0.3$  h, while control subjects slept  $5.7 \pm 1.4$  h. On days off when TIB for the experimental group was 9 h, experimental subjects averaged  $8.6 \pm 0.4$  h, while control subjects slept  $9.0 \pm 2.1$  h.

The timing and the duration of sleep for the control group showed considerable variability (Fig. 3). Some control subjects had long consolidated sleep bouts after night shifts, slept late on weekends (days off), and had later final DLMOs (e.g., Fig. 3H-J). Other subjects had very short and fragmented daytime sleep after night shifts, woke up early in the morning on days off, and had earlier final DLMOs (Fig. 3A-C). Average weekend wake time and bedtime were significantly correlated with final DLMO, such that later weekend sleep was associated with a later final DLMO (wake time  $r = .91$ ,  $p < 0.001$ ; bedtime  $r = .81$ ,  $p < 0.01$ ). The average duration of TST on the days after night shifts was also positively correlated with final DLMO ( $\rho = .81$ ,  $p < 0.01$ ). Control subjects with a final DLMO close to the target compromise phase position (later than 1:30) averaged  $7.1 \pm 0.1$  h of daytime sleep after night shifts, while subjects with final DLMOs earlier than 1:30 averaged  $6.0 \pm 1.0$  h of daytime sleep after night shifts.

### Performance

On the first night shift, subjects in both the experimental and control groups had a longer RT and an increase in the number of lapses (data not shown). Performance improved as the night shifts progressed, but there were no differences between the experimental and control groups. This can be explained by the fact that several control subjects had final DLMOs as late as the experimental group. Consequently, the data for both groups were combined for correlation analyses to assess the relationship between final circadian phase and performance.

During the middle of the second block of night shifts, an association between final DLMO and performance became evident. Subjects with later final DLMOs responded faster and had fewer attentional lapses than subjects with earlier final DLMOs (Fig. 4). In those subjects whose final DLMO was close to or later than the compromise phase position (e.g., after ~1:30, at least late enough to move the estimated sleepest circadian time out of the time for night work and into the time for daytime sleep for experimental subjects), median RT in some

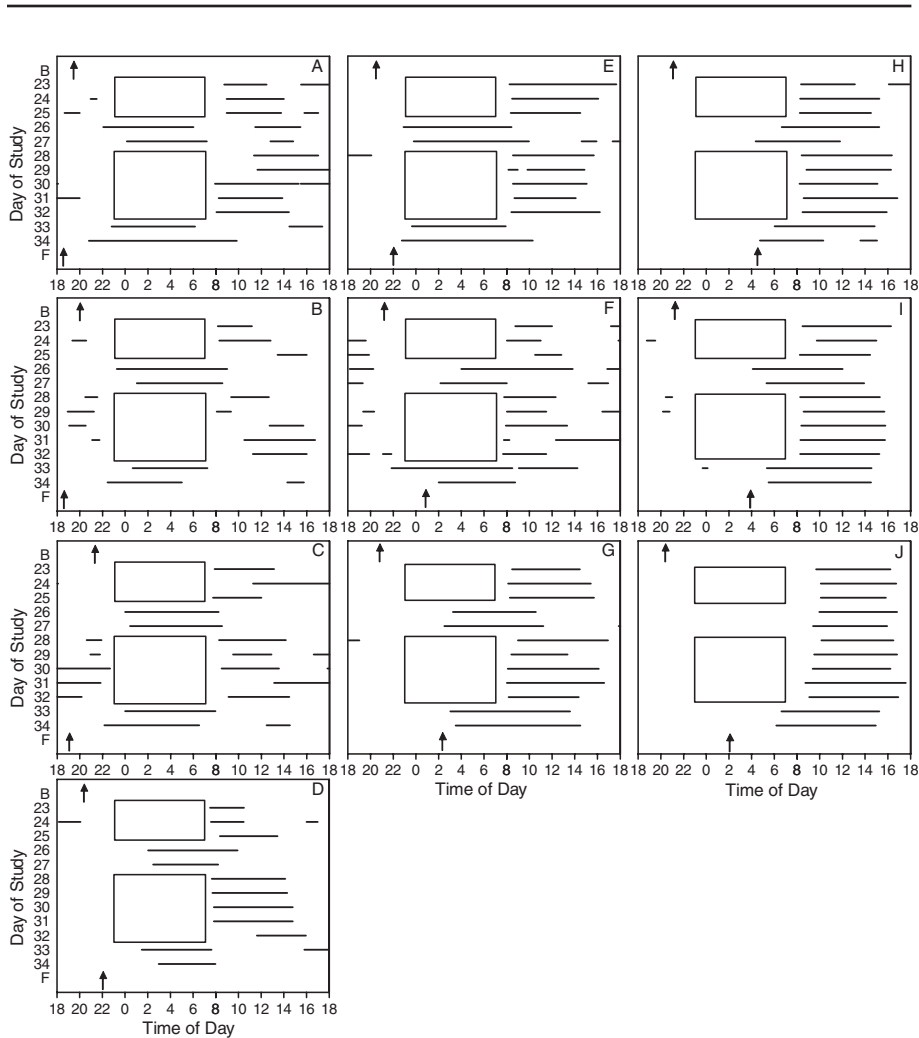
subjects remained up to about 100 msec longer than at baseline, and some subjects had up to about 20 more minor lapses per test than at baseline. Nonetheless, subjects with final DLMOs later than 1:30 had no more major lapses than during their baseline performance, while most subjects with earlier final DLMOs had an increased number of major lapses (bottom panel of Fig. 4).

## DISCUSSION

This is the final study in a series assessing circadian phase during a shift work schedule consisting of blocks of night shifts alternating with weekends off. This study showed that after the entire sequence, the average final DLMO for the experimental group was very close to our target compromise phase position of 3:00 and significantly later than that of the control group. The estimated sleepest circadian time was delayed out of the time for night work and into the time for daytime sleep (after 8:30) for 8 of the 9 experimental subjects. In contrast, only 4 of the 10 control subjects had their sleepest circadian time delayed this far. This study has shown that practical and feasible interventions, including a total of only 1 h bright light per night shift, can produce a circadian phase position that is compatible with both night shifts and days off.

Employers may be willing to install light boxes or fixtures if they can be shown that it will increase productivity and reduce absenteeism and dropouts. Very bright light may not be necessary as it has been shown in another simulated night shift study that medium-intensity light (~1200 lux) produced phase shifts of similar magnitude to bright light (~5700 lux) (Martin and Eastman, 1998). The rigid pattern of intermittent bright light used in the present study may also be unnecessary. The pattern could depend on the particular work environment. However, judging by this series of studies, we would not recommend bright-light pulses after 4:00, as they could phase shift the circadian clock slightly past the compromise phase position, as was the case in study 3 (Smith and Eastman, 2008).

The prescribed sleep schedule would likely be acceptable to many real night shift workers if they experienced the benefits of improved sleep and reduced fatigue. Wearing sunglasses on the commute home would also likely be acceptable since many people wear them and because sunglasses are recommended for protection against ultraviolet light. To simplify the



**Figure 3.** Sleep times (dark horizontal lines) for control subjects arranged according to average weekend (days off) wakeup time (study days 26-27 and 33-34). Earliest average weekend wake time shown in top left panel (A), with progressively later wake times plotted down the left column (B-D), and then from the top down the middle column (E-G), and top down the right column (H-J). Boxes indicate times of night shifts. Upward arrows indicate the time of the dim light melatonin onset (DLMO) during the baseline and final phase assessments (B and F on *y*-axis, respectively). Note that the final DLMO tends to be later in the subjects with later weekend wake times.

rules in our study, we required the subjects to wear sunglasses anytime they were outside during daylight. Real night shift workers may only need to wear sunglasses during the commute home after night work when morning light exposure coincides with the advance portion of the PRC and would thus inhibit the desired phase delay. However, this hypothesis remains to be tested because selective use of sunglasses only in the morning may increase the phase advance in response to the afternoon light brake (due to greater outside light reaching the retina) and decrease overall sensitivity to the phase-delaying light pulses at night (cf. Hebert et al., 2002).

Some of the control subjects adopted daytime sleep schedules that were more extreme than what

we required for the experimental subjects. These subjects reached the compromise phase position even without bright-light pulses during night shifts or wearing darker sunglasses. These subjects slept during the day at roughly the same times on days off as after night shifts (e.g., Fig. 3H-J). We did not require our experimental subjects to sleep in the afternoon on days off because we believe most night shift workers would not find this acceptable. Our schedule is a compromise in that it requires that shift workers sleep until noon on their days off. We speculate that night shift workers who are most severely affected by the shift schedule would be willing to sacrifice weekend morning activities if they experienced the benefits of reduced circadian misalignment. A compromise schedule may prevent shift workers who are most troubled by night work from dropping out.

Although all experimental subjects were able to sleep for all of the allotted time in bed, not all control subjects were able to obtain adequate sleep after night shifts. Control subjects with later final DLMOs consistently had longer sleep

episodes during the day after night shifts. Control subjects with earlier final DLMOs had less and more variable duration daytime sleep. One reason that some control subjects with early final DLMOs were nonetheless able to sleep for a reasonable length of time during the day (e.g., Fig. 3E) could be the relatively young age of our control subjects, who may have been phase tolerant (Dawson and Campbell, 1991).

Final circadian phase for control subjects was earlier and more variable than for experimental subjects. Two related factors that appeared to contribute to final DLMO for control subjects were morning light exposure throughout the 12 days of the night shift schedule and wake time on weekends

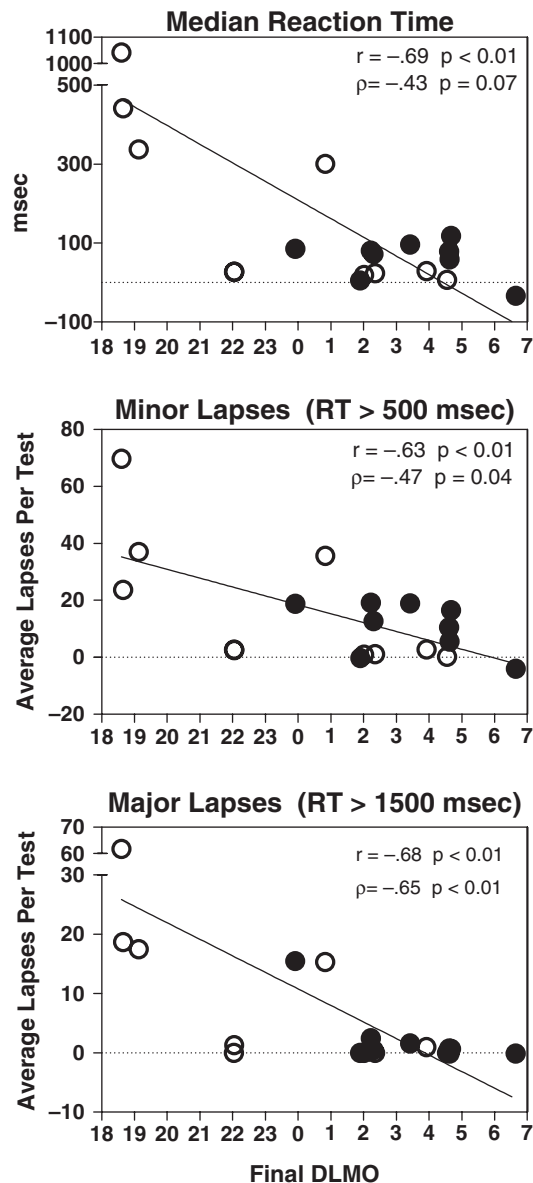


Figure 4. Performance on the simple reaction time task for experimental subjects (filled circles) and control subjects (open circles) versus final dim light melatonin onset (DLMO). The average performance for the 4:30 and 6:30 test bouts on the last 3 night shifts (6-8) is shown. All data are differences from each subject's individual baseline score. Higher scores indicate poorer performance.

(days off). Control subjects with less light exposure during the mornings and those who slept later on their days off had later final DLMOs. Both of these factors resulted in less light exposure on the advance portion of the light PRC, facilitating phase delays.

Like real night shift workers, the performance of all the subjects was impaired during the first several

night shifts, with an increase in RT and number of lapses. By the last 3 night shifts, about the time we estimate that a compromise phase position was achieved for most of the experimental subjects, there was a consistent relationship between performance and circadian phase, in that subjects with later final DLMOs had faster RTs and fewer lapses than subjects with earlier final DLMOs. Despite this improvement, performance was not back to baseline levels for some subjects. However, it is noteworthy that major lapses had completely returned to baseline levels (which for most subjects was zero major lapses) in subjects with a final DLMO later than ~1:30, while the majority of subjects with earlier final DLMOs had a substantial increase in the frequency of major lapses.

This study has several limitations. The well-being of experimental subjects on days off was not assessed. Although achieving a compromise phase position was associated with improvements in night shift performance (current study), as well as subjective alertness and well-being during the night shifts (Smith and Eastman, manuscript in preparation), we do not know how subjects felt on their days off. This is an important facet of a compromise phase position because real shift workers would likely need to feel good during the afternoon on their days off to comply with this schedule. A second limitation of this study was that our subjects were relatively young and possibly phase tolerant because they volunteered to participate in a night shift study. These subjects may have had an easier time sleeping in a compromise phase position than real night shift workers. Future studies should test compromise schedules such as this in real shift workers.

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