Combinations of Bright Light, Scheduled Dark, Sunglasses, and Melatonin to Facilitate Circadian Entrainment to Night Shift Work

Stephanie J. Crowley, Clara Lee, Christine Y. Tseng, Louis F. Fogg, and Charmane I. Eastman[1]

Biological Rhythms Research Laboratory,
Rush University Medical Center, Chicago, IL 60612, USA

Abstract   Various combinations of interventions were used to phase-delay circadian rhythms to correct their misalignment with night work and day sleep. Young participants (median age = 22, *n* = 67) participated in 5 consecutive simulated night shifts (2300 to 0700) and then slept at home (0830 to 1530) in darkened bedrooms. Participants wore sunglasses with normal or dark lenses (transmission 15% or 2%) when outside during the day. Participants took placebo or melatonin (1.8 mg sustained release) before daytime sleep. During the night shifts, participants were exposed to a moving (delaying) pattern of intermittent bright light (~5000 lux, 20 min on, 40 min off, 4-5 light pulses/night) or remained in dim light (~150 lux). There were 6 intervention groups ranging from the least complex (normal sunglasses) to the most complex (dark sunglasses + bright light + melatonin). The dim light melatonin onset (DLMO) was assessed before and after the night shifts (baseline and final), and 7 h was added to estimate the temperature minimum (Tmin). Participants were categorized by their amount of re-entrainment based on their final Tmin: not re-entrained (Tmin before the daytime dark/sleep period), partially re-entrained (Tmin during the first half of dark/sleep), or completely re-entrained (Tmin during the second half of dark/sleep). The sample was split into earlier participants (baseline Tmin ≤ 0700, sunlight during the commute home fell after the Tmin) and later participants (baseline Tmin > 0700). The later participants were completely re-entrained regardless of intervention group, whereas the degree of re-entrainment for the earlier participants depended on the interventions. With bright light during the night shift, almost all of the earlier participants achieved complete re-entrainment, and the phase delay shift was so large that darker sunglasses and melatonin could not increase its magnitude. With only room light during the night shift, darker sunglasses helped earlier participants phase-delay more than normal sunglasses, but melatonin did not increase the phase delay. The authors recommend the combination of intermittent bright light during the night shift, sunglasses (as dark as possible) during the commute home, and a regular, early daytime dark/sleep period if the goal is complete circadian adaptation to night-shift work.

Key words   circadian rhythms, human, shift work, melatonin, bright light, sleep, phase shifts

Millions of night-shift workers maintain our 24-h society, but not without negative consequences. The most common complaint of shift workers is not getting enough sleep (e.g., Kecklund and Akerstedt, 1995). Other problems include fatigue, gastrointestinal disturbances, impaired performance, and diminished job and public safety (e.g., Folkard and Monk, 1985). These serious problems are caused by circadian misalignment. Night-shift workers are required to work during the "wrong" phase of their circadian cycle, when they are the most inefficient and sleepy, often fall asleep, and are most prone to accidents (e.g., Akerstedt, 1988; Mitler et al., 1988). Subsequently, they try to sleep during the day, again during the "wrong" phase of their circadian cycle, which results in disrupted and shortened sleep (e.g., Akerstedt, 1995). Phase-shifting circadian rhythms to align with night work and day sleep schedules (re-entrainment) can alleviate the physiological symptoms of night work because the period of sleepiness occurs during the new daytime dark period and the period of alertness occurs during the night shift.

The circadian clocks of real-shift workers do not usually phase shift (e.g., Akerstedt, 1995; Dumont et al., 2001) because they are exposed to the natural light-dark (LD) cycle and other possible 24-h zeitgebers (Eastman et al., 1995). Sunlight in the morning during the commute home after each night shift usually coincides with the phase-advance portion of the light phase response curve (PRC), which is after the temperature minimum (Tmin), and thus inhibits circadian rhythms from phase-delaying. Wearing dark goggles during the commute home can help attenuate advancing sunlight in the morning and facilitate re-entrainment to night work and day sleep (Eastman et al., 1994). Ensuring a dark environment for sleep as soon as possible after the night shift will further block out advancing light and will also form the basis of a delayed LD cycle that can delay the circadian clock.

Phase shifting circadian rhythms to completely re-entrain to the night work and day sleep schedule has been reliably produced in many field studies of simulated night work (see Eastman and Martin, 1999; Burgess et al., 2002 for reviews) and in a real night-shift work setting (Boivin and James, 2002) by using artificial bright light (BL) at night and constructing periods of darkness during the day. Our laboratory has frequently taken advantage of a gradually moving pattern of BL to phase-shift circadian rhythms (Eastman, 1992; Mitchell et al., 1997; Martin and Eastman, 1998; Burgess et al., 2003). Theoretically, the BL moves along

with the circadian clock and its PRC so that the BL always occurs at a more optimal time for the desired phase shift. A moving pattern of BL is also a way to facilitate a phase shift in participants with varying initial circadian phases. The BL acts like a broom, "sweeping" the participants with early and late circadian phases together and in the desired phase-shifting direction. For example, to facilitate a phase delay, BL timed to occur early in the night will be closer to the Tmin of the participants with earlier phases and phase delay these participants more than those with later phases. Then, as the BL moves later and later each night, it will fall closer to the Tmins of the participants with later phases and have more of a phase-shifting effect on those participants.

In a real night-work setting, it may be difficult for workers to remain exposed to a light source for an extended amount of time. Intermittent exposure would be more likely to occur and more practical to implement. In one of our simulated night shift studies, 40-min light pulses (~5000 lux) alternating with 20 min of room light (< 500 lux) during the first 6 h of the night shift was used to help phase-delay circadian rhythms and produce re-entrainment to the daytime sleep schedule (Baehr et al., 1999). A subsequent laboratory study showed that 46 min of BL (~9500 lux) alternating with 44 min of dark over 5 h (timed with the majority of the light pulses after the Tmin to facilitate a phase advance) produced similar phase shifts as a 5 h, continuous light pulse (Rimmer et al., 2000). Similarly, a recent study in our lab showed that 3.5 h of intermittent BL (30 min of BL ≥ 3000 lux alternating with 30 min of room light < 60 lux) produced similar phase advances as 3.5 h of continuous light (≥ 3000 lux) (Burgess et al., 2003).

The pineal hormone melatonin (M) can also phase shift the circadian clock. The M PRC of Lewy et al. (1998) suggests that a small dose of M (0.5 mg) administered approximately 10 h after the dim light melatonin onset (DLMO) (in most cases, in the early morning hours) will produce the largest phase delay of circadian rhythms. See the simplified M PRC, Figure 1 in Burgess et al. (2002). We found that M helped phase-advance circadian rhythms to adapt to the night shift when sleep was taken in the afternoon/evening (an advance of sleep) (Sharkey and Eastman, 2002), but few studies have tested M to facilitate a phase delay and thus circadian adaptation to night work when sleep is taken in the morning/afternoon (a delay of sleep).
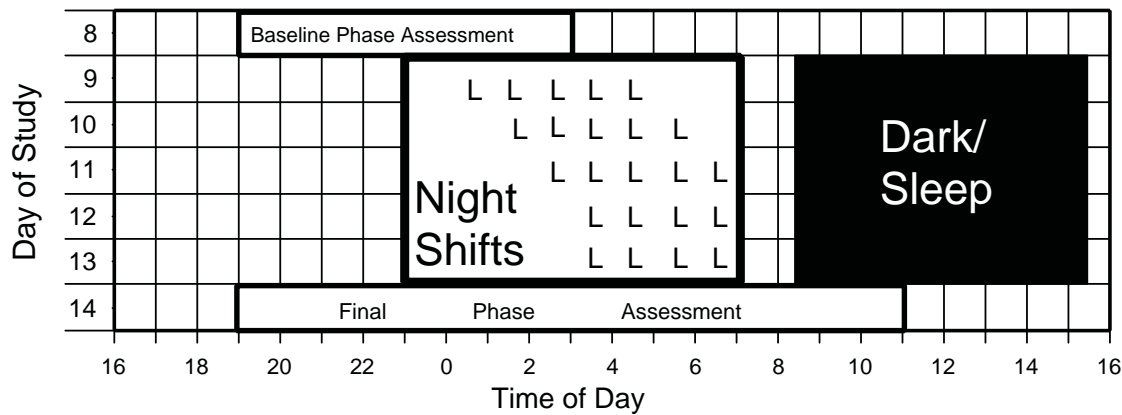
Figure 1. Second week of the protocol. The dim light melatonin onset was assessed on days 8 and 14. Simulated night shifts were from 2300 to 0700. L = bright light pulse (~5000 lux, for 20 min) for participants in the bright light groups. Normal room lighting (~150 lux) was used between bright light pulses and throughout the night for those in the remaining groups. Participants in 2 groups wore sunglasses with normal lenses while participants in the other groups wore sunglasses with very dark lenses during their commute home from the night shift and whenever they went outside during daylight. Participants in 2 groups took melatonin (1.8 mg, sustained release) and the remaining groups took placebo right before bedtime at 0830. All participants were required to be in bed, in the dark from 0830 to 1530 after each night shift.

The purpose of the current study was to test the relative contribution and the combined effectiveness of various interventions, namely, BL, sunglasses (SG), and M to phase-delay circadian rhythms and realign them with sleep in the morning after the night shift. Intermittent BL was used in a moving pattern during the night shift. From previous studies in our lab, we estimated that the Tmin, and thus the crossover point in the light PRC, would be, on average, around 0500 (Baehr et al., 2000). Therefore, we ended the BL during the first night shift at 0500 and moved it 1 h later on each subsequent night shift. We used 5 consecutive simulated night shifts from 2300 to 0700, as this is a common pattern in real shift-work settings. We required participants to remain in bed and in the dark from 0830 to 1530 after each night shift because we think that this is a reasonable daytime sleep schedule for a real night-shift worker. SG with normal or very dark lenses were used to attenuate sunlight during the commute home, which we expected to coincide with the phase-advance portion of the light PRC. M (1.8 mg, sustained release) was taken immediately before each daytime sleep (0830), a time expected to facilitate phase delays. The study included six intervention groups (six combinations of the interventions mentioned above), which differed in the type and number of interventions and therefore in the amount of effort that would be required if adopted by real night-shift workers and their employers.

MATERIALS AND METHOD

Participants

A total of 67 participants (35 females and 32 males) between the ages of 18 and 43 (mean age ± SD = 23.9 ± 6.2 years) completed the study. Participants did not have any obvious medical, psychiatric, or sleep disorders as assessed by interviews, the Minnesota Multiphasic Personality Inventory-2, a sleep questionnaire, and a health questionnaire. Participants were not taking prescription medications, except for oral contraceptives. To ensure the dose (mg/kg) of M was not too low, individuals who weighed more than 105 kg were excluded. Participants had not worked night shifts or traveled across more than 3 time zones within the month before starting the study. Most participants had never worked night shifts. The protocol was approved by the Rush-Presbyterian–St. Luke's Medical Center Institutional Review Board. All participants gave written informed consent and were paid for their participation.

Design

There was a baseline week with no set sleep schedule. Figure 1 displays days 8-14 of the protocol. We made participants' bedrooms completely dark by cov-

ering their windows with thick, black plastic. Compliance to the daytime sleep schedule was monitored by actiwatches (Actiwatch-64, MiniMitter Inc., Bend, OR) worn on the wrist and photosensors (Actiwatch-L, MiniMitter Inc.) worn around the neck like a medallion. This was a between-subjects design with 6 combinations of interventions including the fixed daytime dark/sleep (D/S) schedule, normal sunglasses (N SG), dark sunglasses (D SG), bright light (BL) during the night shifts, and melatonin (M) before daytime sleep. The 6 groups were (1) D/S + N SG (*n* = 15), (2) D/S + D SG (*n* = 12), (3) D/S + D SG + M (*n* = 13), (4) D/ S + N SG + BL (*n* = 11), (5) D/S + D SG + BL (*n* = 9), and (6) D/S + D SG + M + BL (*n* = 7).

The intermittent BL (~5000 lux) was produced by 3 light boxes (61.0 cm wide, 77.5 cm high, 12.1 cm deep, cool white fluorescent lamps, Apollo Light Systems Inc., Orem, UT) set on the perimeter of a large, round table facing in toward the center of the table. Participants sat in the openings between the light boxes so that each participant faced a light box. Between BL pulses, participants remained in room light (~150 lux), whereas the other groups remained in constant room light (~150 lux) throughout the night.

Participants were required to wear SG whenever they were outside during the day. The study took place during 3 summers (July-September). During the baseline week, participants wore N SG (15% transmission, standard gray lens, Uvex Safety Inc, Smithfield, RI). During the 2nd week, groups 1 and 4 continued to wear N SG, and the rest were given D SG (2% transmission, shade 5.0 welding lens, Uvex Safety Inc.). Both SG had the same black frames with top and side shields (Flashback frames, Uvex Safety Inc.).

Participants in groups 3 and 6 took M (1.8 mg sustained release, Ecological Formulas, Concord, CA), whereas the remaining groups took a matching placebo just before bedtime at 0830. M was administered double-blind, the staff interacting with the participants and the participants themselves not knowing if they were taking M or placebo. Immediately upon waking at 1530, participants were required to provide a saliva sample using a Salivette (Starstedt, Newton, NC) to ensure ingestion of the pill.

Circadian Phase Assessments

Saliva samples were collected every 30 min using Salivettes. Participants remained seated in a semi-recumbent position in comfortable recliners in dim light (< 20 lux). Participants were not permitted to eat or drink in the 10 min before each sample. The samples were centrifuged immediately following collection and placed in a freezer. Radioimmunoassay analyses were later performed by Pharmasan Labs (Osceola, WI). All samples from a single participant were run in the same assay. The intra-assay and inter-assay variability were 12.1% and 13.2%, respectively. The lower limit of detection of the assay was 0.7 pg/mL.

Other Procedures

Participants documented their daily intake of caffeine, medications, and alcohol. Caffeine was not restricted during the baseline period but was not allowed 6 h before or during the phase assessments, during the night shifts, or after the night shifts in the 1.5 h before daytime sleep. Nonsteroidal anti-inflammatory drugs were prohibited 72 h before the baseline phase assessment until the end of the study, as these suppress melatonin (Murphy et al., 1996). Alcohol was prohibited 48 h before the baseline phase assessment until the end of the study. Participants were breathalyzed before each phase assessment and night shift to ensure compliance with this rule.

Participants completed daily sleep logs and did performance tests during the night shifts. These data will be reported elsewhere.

Data Analysis

To determine the DLMO, a threshold was calculated by taking 35% of the average of the 3 highest points. An absolute threshold of 3 pg/mL was used for 2 participants (1 in group 2 and 1 in group 6) because the threshold calculated using our standard procedure was too high for 1 of the M profiles in each pair of profiles. The DLMO was calculated by linearly interpolating between the times of the samples before and after M levels crossed and stayed above the threshold. The phase shift was the difference between baseline DLMO and final DLMO.

We categorized the amount of re-entrainment that each participant attained based on the final DLMO. A reasonable goal for circadian adaptation to the night-work and day-sleep schedule is to phase-shift circadian rhythms so that the sleepiest part of the circadian cycle, the Tmin, falls within the daytime sleep episode. To estimate the Tmin, a constant of 7 h was added to the DLMO because the Tmin falls approximately 7 h after the DLMO (Cagnacci et al., 1996; Brown et al., 1997; Eastman et al., 2000; Sharkey and

Eastman, 2002). Therefore, the participants whose final DLMOs were before 0130 were defined as not re-entrained because their estimated Tmins occurred before 0830, that is, before daytime sleep. The participants whose final DLMOs occurred between 0130 and 0500 were defined as partially re-entrained because their estimated Tmins occurred during the first half of daytime sleep. Last, the participants whose final DLMOs occurred after 0500 were defined as completely re-entrained because their estimated Tmins occurred during the 2nd half of sleep.

Circadian phase variables were analyzed using a one-way multivariate analysis of variance and Tukey HSD post hoc tests. Dependent variables were baseline DLMO, final DLMO, and phase shift. Chi-square analyses were performed using the 3 re-entrainment categories.

Summary statistics are presented as means and standard deviations unless otherwise indicated.

RESULTS

Figure 2 displays the baseline and final DLMO and the estimated baseline and final Tmin for each participant. In groups 1 and 2 (top 2 rows), there were various magnitudes of phase shifting ranging from no phase shift to very large delay shifts, and thus participants fell into all 3 re-entrainment categories. The participants in group 3 were all either partially or completely re-entrained. The participants in groups 4, 5, and 6 were completely re-entrained, except for 1 participant in group 4.

We expected baseline phase position to have a large influence on subsequent phase shift. The baseline Tmins ranged from 0312 to 0942. Participants with later circadian phases needed less of a phase delay for re-entrainment. Furthermore, baseline phase-influenced when sunlight during the commute home time from the night shifts occurred relative to the light PRC. We expected that most participants would have crossover points (estimated by the baseline Tmin) before the travel home time (before 0700), so that sunlight during the commute would coincide with the phase-advance portion of the light PRC and inhibit the phase delay. However, many participants had baseline Tmins later than we expected (after 0700), which means that light during the commute home would facilitate rather than inhibit the phase delay. Thus, we divided each intervention group into 2 groups: earlier participants (baseline Tmin ≤ 0700) and later participants (baseline

Tmin > 0700). Also, because the outcome in the three BL groups was so similar, we combined them in the following analysis.

A summary of phase measures from the earlier participants is displayed in Table 1. The final DLMOs, and therefore the estimated final Tmins, became later as the interventions became more complex (i.e., as the group number increased), and the phase delay shifts became larger. A multivariate one-way ANOVA found significant effects when baseline DLMO, final DLMO, and phase delay shift were analyzed as dependent variables, $F(6, 74) = 4.43$, $p = 0.001$, F estimate based on Wilks' Lambda, which justified examining the associated univariate analyses. As expected, there was no significant main effect of intervention group for baseline DLMO. A significant main effect was found for final DLMO (and therefore for final Tmin), $F(3, 38) = 8.082$, $p < 0.001$, and for phase delay shift, $F(3, 38) = 9.02$, $p < 0.001$. Pairwise comparisons showed that the final DLMO (and final Tmin) was later in the BL groups ($p < 0.001$) and in group 3 ($p = 0.014$) when compared to group 1. There was a trend ($p = 0.059$) for the final DLMO (and final Tmin) to be later in group 2 compared to group 1. The phase delay shift was significantly larger in group 2 ($p = 0.018$), group 3 ($p = 0.003$), and the BL groups ($p < 0.001$) when compared to group 1. The phase measures from the later participants are not shown in a table, because they were similar for all intervention groups and the Ns were too small for statistical analyses. The baseline DLMOs were around 0100, the final DLMOs were between 0600 and 0700, the final Tmins were between about 1300 and 1400, and the phase delay shifts were about 5-6 h.

Table 2 shows that all the later participants achieved complete re-entrainment, regardless of intervention group. However, for the earlier participants, the intervention group had a large influence on subsequent re-entrainment. Chi-square tests for goodness of fit were run on the proportions for the earlier participants. Because the n was too small in some of the cells, we combined 2 of the re-entrainment categories. First, we combined the participants in the partial and complete re-entrainment categories and compared them to the participants who were not re-entrained. There was a significant difference between the intervention groups, $\chi^2 (3, n = 42) = 16.55$, $p = 0.001$. Specifically, the proportion of participants who did not re-entrain was significantly greater in group 1 than in the other intervention groups. Second, we combined the participants who were not re-entrained
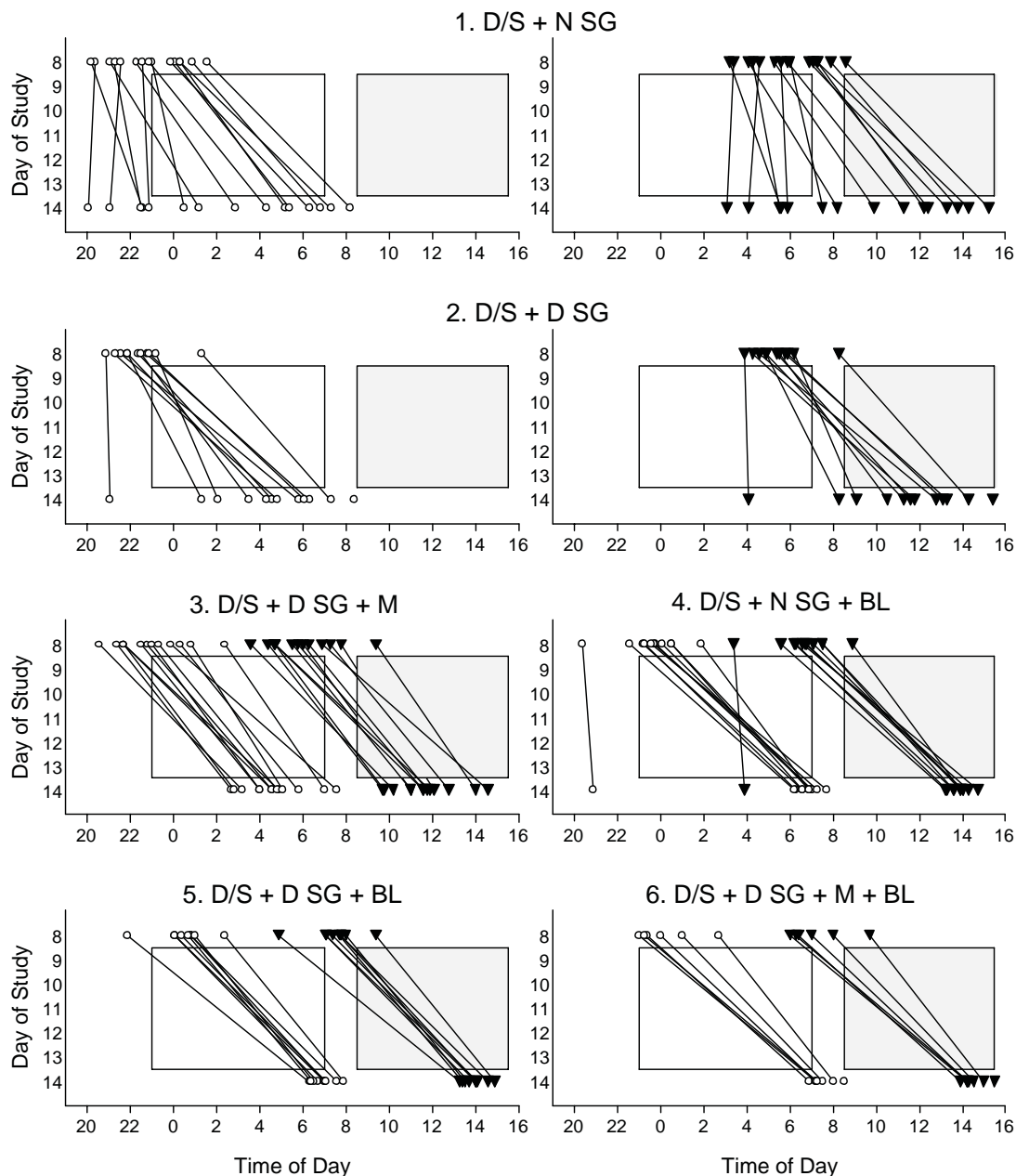
Figure 2. Baseline and final phase markers for each individual participant in each intervention group. Open circles indicate dim light melatonin onsets (DLMOs), and filled triangles indicate estimated Tmins (DLMO + 7 h). The white rectangles show the 5 consecutive night shifts (2300 to 0700). The shaded rectangles show the 5 daytime dark/sleep episodes (0830 to 1530) after each night shift. Lines connect the baseline and final phase markers for each participant. For 2 participants (1 in group 2 and 1 in group 6), only the final DLMO was available. Note that for groups 1 and 2, the DLMOs and Tmins are plotted separately, whereas for the remaining groups, the DLMOs and Tmins are plotted on the same graph.

and partially re-entrained and compared them to the participants who were completely re-entrained. Again there was a significant difference between the intervention groups, χ^2 (3, n = 42) = 21.58, $p < 0.001$. Specifically, the proportion of participants who were completely re-entrained was significantly greater in the BL groups than the other intervention groups.

In summary, if the baseline circadian phase was late enough, then complete re-entrainment occurred in all intervention groups. However, if the baseline phase was earlier (Tmin before the start of the commute home time), then the participants in intervention group 1 were less likely to entrain to the night work and day sleep schedule. Thus, adding darker SG con-

Table 1. Circadian phase measures from earlier participants,[a] means (in clock time) and standard deviations (in hours)

Intervention Group	N	Baseline DLMO Mean	Baseline DLMO SD	Final DLMO Mean	Final DLMO SD	Final Tmin[b] Mean	Phase Delay Shift Mean	Phase Delay Shift SD
1. D/S + N SG	10	21:54	1.2	00:24	3.2	7:24	2.5	2.5
2. D/S + D SG	10	22:12	0.7	3:36	2.8[†]	10:36[†]	5.4	2.6*
3. D/S + D SG + M	10	22:18	1.0	4:18	1.4*	11:18*	6.0	1.0**
4, 5, and 6 Bright Light Groups	12	23:00	1.0	6:06	2.9***	13:06***	7.1	2.1***

NOTE: DLMO = dim light melatonin onset.
a. Participants with baseline DLMOs before 0000 h, and thus estimated baseline Tmins before 0700 h (before the start of the commute home time).
b. Estimated from final DLMO. DLMO + 7 h = Tmin.
*$p < 0.05$. **$p < 0.01$. ***$p < 0.001$. †$p < 0.10$ (all two-tailed) when compared to group 1.

Table 2. Percentage of participants within each re-entrainment category for earlier participants and for later participants

Intervention Group	N	Earlier Participants[a] Not[c]	Earlier Participants[a] Partial[d]	Earlier Participants[a] Complete[e]	N	Later Participants[b] Not[c]	Later Participants[b] Partial[d]	Later Participants[b] Complete[e]
1. D/S + N SG	10	70%[f]	20%	10%	5	0%	0%	100%
2. D/S + D SG	10	20%	50%	30%	1	0%	0%	100%
3. D/S + D SG + M	10	0%	90%	10%	3	0%	0%	100%
4, 5, and 6 Bright Light Groups	12	8%	0%	92%[g]	14	0%	0%	100%

NOTE: DLMO = dim light melatonin onset.
a. Baseline DLMO ≤ 0000, and thus estimated baseline Tmin ≤ 0700 (before the start of the commute home time from the night shifts).
b. Baseline DLMO > 0000, and thus estimated baseline Tmin > 0700 (after the start of the commute home time from the night shifts).
c. Final DLMO earlier than 0130, and therefore estimated final Tmin before the time corresponding to daytime dark/sleep.
d. Final DLMO between 0130 and 0500, and therefore estimated final Tmin during the time corresponding to the first half of daytime dark/sleep.
e. Final DLMO later than 0500, and therefore estimated final Tmin during the time corresponding to the second half of daytime dark/sleep.
f. Significantly different from the other intervention groups by a chi-square analysis when the partial and complete re-entrainment categories were combined.
g. Significantly different from the other intervention groups by a chi-square analysis when the not re-entrained and partial re-entrainment categories were combined.

ferred a significant benefit. There were no statistically significant differences between groups 2 and 3 by any of the analyses. Therefore, adding M to the D SG did not change the phase shift. The participants in the BL groups were more likely to achieve complete re-entrainment than participants in the other 3 intervention groups. Furthermore, the outcome in the 3 BL groups was very similar in that all except 1 participant achieved complete re-entrainment. Thus, in general, D SG and M did not enhance the phase shift if participants received BL during the night shift.

DISCUSSION

We found that the circadian phase of participants before starting night work was the most important factor for determining whether their circadian rhythms would delay enough to align with the daytime sleep schedule and thus produce circadian adaptation to night work. During the baseline week, participants were free to sleep almost anytime because we wanted them to start the night shift with a wide range of circadian phases, to simulate what we would expect in real night-shift workers. The participants who had Tmins before the start of the commute time home at 0700 (the earlier participants) benefited the most from our interventions, whereas the later participants achieved complete re-entrainment regardless of intervention group. For the earlier participants, 1) intermittent BL during the night shift consistently produced large phase delays; 2) very dark SG used to attenuate sunlight during the commute home after the night shift helped delay circadian rhythms more than normal SG; 3) however, we could not demonstrate a benefit from the administration of M before daytime sleep.

We converted the DLMOs obtained in this study to estimated Tmins (by adding the constant of 7 h) for 2 reasons of convenience. First, the Tmin is an estimate for the sleepiest part of the circadian cycle and the time of greatest performance decrements, although for some measures and protocols the "circadian dip" is actually slightly later (e.g., Johnson et al., 1992). We

previously defined circadian adaptation as phase shifting the Tmin out of the night shift and into the daytime sleep period (Eastman and Martin, 1999; Burgess et al., 2002), and here further subdivided it into either partial or complete re-entrainment. A second reason for referring to the Tmin instead of the DLMO is that the Tmin is an estimate for the light PRC crossover point from delays to advances (Czeisler et al., 1989; Eastman and Martin, 1999), although in some studies it appears to be slightly later (e.g., Minors et al., 1991).

Sunglasses for the Commute Time Home

For the earlier participants, sunlight during the commute home probably coincided with the phase advance portion of their light PRC. This can explain why so many participants did not re-entrain when they wore normal SG and why significantly more participants were re-entrained when they wore darker SG (group 2 vs. group 1). However, the darker welders lenses were not designed for driving, whereas the normal lenses do meet color traffic signal recognition requirements. Therefore, the mode of transportation is an essential detail to consider when recommending welders glasses. Our participants were tested in the summer and were exposed to relatively intense light during the commute. Light intensity would be lower in winter, especially at more extreme latitudes, or during earlier commute times. In those circumstances, we would expect more participants to re-entrain with just normal SG. In conclusion, we recommend wearing SG during the commute home (as dark as possible), combined with an early, regular dark period for sleep after the night shift as a simple, inexpensive, and effective way to produce at least some degree of circadian adaptation in workers who start the night shift with earlier circadian phases.

Bright Light during the Night Shift

When our participants were exposed to intermittent BL during the night shift, 96% of them (26/27) achieved complete re-entrainment. Given BL, darker SG and M conferred no additional benefit. BL and normal SG (and of course the D/S period) produced complete re-entrainment, even in participants with earlier baseline phases.

We used a moving pattern of BL pulses to phase-delay the rhythms as far as possible. However, most of the Tmins clustered near the end of dark/sleep. It

would have been better to have the Tmins delay no further than about 2-3 h before wake, for a more normal phase relative to sleep (cf. Baehr et al., 2000). Thus, the BL pattern we used was too powerful. The ideal BL pattern should delay the rhythms to realign with sleep as fast as possible, but then not delay them much further in subsequent days. Modifications that could be tested include a stationary pattern of light pulses, lower intensities of BL, durations shorter than 20 min, fewer pulses of BL per night, and fewer nights with BL.

There are circumstances in which partial rather than complete re-entrainment might be preferable, such as for night shift workers who would not be able to cope with the symptoms caused by misalignment of their circadian rhythms on their days off. Therefore, we have designed compromise schedules (Eastman and Martin, 1999; Burgess et al., 2002) in which circadian phase is delayed so that the worker is partially entrained to a night work and day sleep schedule and partially entrained to sleeping at night and enjoying leisure time during their days off. The worker is instructed to adopt as late a sleep schedule as possible during days off, and we would use a BL pattern that produces partial re-entrainment. These schedules are intended for permanent night work systems, and the goal is to achieve partial re-entrainment during all night shifts, starting with the 2nd block of night shifts. Future studies are planned to test such compromise schedules. However, older workers are less phase tolerant and may need complete re-entrainment to achieve substantial benefits (Campbell, 1995; Dijk et al., 1999). Obviously, the ideal degree of entrainment to day sleep and night work depends on many factors, including the hazard potential of the job. Another solution to complete adaptation to the night shift, such as after extended periods of night work on offshore oil rigs or during space shuttle missions, is to use light boxes to help workers adjust back to day life (Stewart et al., 1995; Bjorvatn et al., 1999).

A recent study (Boivin and James, 2002) tested BL on night nurses by setting up light boxes in the nursing station. Circadian rhythms were measured before and after an average of 12 8-h night shifts, with some days off in between. The treatment group was given a combination of interventions similar to our group 4 (D/S, N SG (15% transmission, Uvex) + BL). They were exposed to about 3000 lux of intermittent BL during the first 6 h of every night shift and were instructed to go to bed for 8 h starting 2 h after the end of the night shift. The control group had D/S, clear glasses, and

their usual lighting during the night shift (~100 lux). Both groups were permitted to sleep freely on days off. All the participants in the treatment group achieved partial or complete re-entrainment, whereas the participants in the control group showed a wide range of final circadian phases, from none to complete re-entrainment. This study demonstrates that interventions similar to our group 4 can be implemented in a real shift work setting and are effective in producing circadian adaptation, despite intervening days off.

As in all of our previous simulated night shift studies, we used a fixed daytime D/S period to create a strong, shifted LD cycle. The utility of this technique was corroborated by a recent study (Horowitz et al., 2001). Circadian phase was measured before and after 3 consecutive simulated night shifts (2300 to 0700 h). During the night shifts, participants were exposed to either room light (~150 lux) for the entire night shift or BL (~2500 lux, continuous) for the first 6 h of each night shift. After each night shift, they either slept from 0800 to 1600 h (fixed sleep) or chose when they slept, which was often later (free sleep). There were 4 groups: Room Free, Bright Free, Room Fixed, and Bright Fixed. The Bright Fixed group phase-delayed the most, and about half of these participants achieved re-entrainment by our definition. Almost none of the participants in the other groups phase delayed enough for re-entrainment. The results from the Bright Free group show that despite BL during the night shift, when participants were free to choose their own daytime sleep schedules, circadian adaptation was unlikely to occur. These results confirm our recommendation that night shift workers adopt an early fixed D/S period after night work.

Melatonin Administration

When we compared groups 2 versus 3 and groups 5 versus 6 (placebo vs. M), there were no statistically significant differences by any of our analyses. Therefore, there was no benefit in taking this particular dose of M (1.8 mg sustained release) at this particular time (0830 h or about 9 h after the baseline DLMO). All of the participants in BL groups 5 and 6 achieved complete re-entrainment. M could not increase the phase delay because they were already phase-shifted as far as possible, creating a ceiling effect (Fig. 2). However, when groups 2 and 3 are considered, there was room for many participants to phase-delay later. Perhaps a nonoptimal timing or dose of M was the reason that

the circadian rhythms of some of the participants in group 3 did not delay further.

Many studies have shown M's phase-advancing effects (e.g., Krauchi et al., 1997; Sharkey and Eastman, 2002). However, the current study was one of the few in which M was tested to delay circadian rhythms in humans and in which circadian phase was measured. One simulated night shift study (Dawson et al., 1995) tested M administered at 0800 (2 mg), 1100 (1 mg), and 1400 h (1 mg) versus placebo. There was no difference between the phase-delay shifts attained by those who took M or those who took placebo (4.7 h vs. 4.2 h) probably because the times of M administration coincided with both the phase-delay and phase-advance portions of the M PRC. In another study (summarized in Sack and Lewy, 1997), 24 night shift workers (nurses and hospital clerical staff) alternated between 7 consecutive 10-h night shifts (2130 to 0730 h) and 7 consecutive days off. M (0.5 mg immediate release) or placebo was administered at bedtime after the night shifts and at bedtime during their week off. This was a double-blind crossover design, and M was taken during one 2-week block and placebo was taken during the other. The DLMO was assessed weekly. Only 7 out of the 24 participants responded to M during the night shift week, meaning that their final DLMO was shifted at least 3 h later with M in comparison to placebo. Some delayed and some advanced equally as far with placebo or M, and others did not shift with either treatment. These variable results could be due to different light exposure patterns created by the participants' sleep schedules and whether or not they wore SG. The timing of M administration varied because the workers chose when they went to sleep and took the M before going to sleep. In conclusion, neither these studies nor our current study provides much evidence that M can help phase-delay circadian rhythms in a night shift work situation.

CONCLUSIONS

This study has many practical applications for night shift workers and their employers. Simple habits like wearing SG during the commute home (the darker the lenses the better), creating a dark bedroom, and adhering to a regular daytime sleep schedule starting soon after the night shift can reduce circadian misalignment. Adding appropriately timed intermittent BL during night shifts is a good way to produce complete re-entrainment of circadian rhythms to day

sleep and night work. Future studies should focus on determining the ideal degree of re-entrainment for various circumstances (e.g., age of worker, hazard potential of job) and the optimal light pattern to produce the desired amount of realignment.

ACKNOWLEDGMENTS

REFERENCES

Akerstedt T (1988) Sleepiness as a consequence of shift work. Sleep 11:17-34.

Akerstedt T (1995) Work hours, sleepiness and the underlying mechanisms. J Sleep Res 4(Suppl. 2):15-22.

Baehr EK, Fogg LF, and Eastman CI (1999) Intermittent bright light and exercise to entrain human circadian rhythms to night work. Am J Physiol 277:R1598-R1604.

Baehr EK, Revelle W, and Eastman CI (2000) Individual differences in the phase and amplitude of the human circadian temperature rhythm: with an emphasis on morningness-eveningness. J Sleep Res 9:117-127.

Bjorvatn B, Kecklund G, and Akerstedt T (1999) Bright light treatment used for adaptation to night work and re-adaptation back to day life. A field study at an oil platform in the North Sea. J Sleep Res 8:105-112.

Boivin DB and James FO (2002) Circadian adaptation to night-shift work by judicious light and darkness exposure. J Biol Rhythms 17:556-567.

Brown EN, Choe Y, Shanahan TL, and Czeisler CA (1997) A mathematical model of diurnal variations in human plasma melatonin levels. Am J Physiol 272:E506-E516.

Burgess HJ, Crowley SJ, Gazda CJ, Fogg LF, and Eastman CI (2003) Preflight adjustment to eastward travel: 3 days of advancing sleep with and without morning bright light. J Biol Rhythms 18:318-328.

Burgess HJ, Sharkey KM, and Eastman CI (2002) Bright light, dark and melatonin can promote circadian adaptation in night shift workers. Sleep Med Rev 6:407-420.

Cagnacci A, Soldani R, Laughlin GA, and Yen SSC (1996) Modification of circadian body temperature rhythm during the luteal menstrual phase: role of melatonin. J Appl Physiol 80:25-29.

Campbell SS (1995) Effects of times bright-light exposure on shift-work adaptation in middle-aged subjects. Sleep 18:408-416.

Czeisler CA, Kronauer RE, Allan JS, Duffy JF, Jewett ME, Brown EN, and Ronda JM (1989) Bright light induction of strong (type 0) resetting of the human circadian pacemaker. Science 244:1328-1333.

Dawson D, Encel N, and Lushington K (1995) Improving adaptation to simulated night shift: timed exposure to bright light versus daytime melatonin administration. Sleep 18:11-21.

Dijk DJ, Duffy JF, Riel E, Shanahan TL, and Czeisler CA (1999) Ageing and the circadian and homeostatic regulation of human sleep during forced desynchrony of rest, melatonin and temperature rhythms. J Physiol 516.2:611-627.

Dumont M, Benhaberou-Brun D, and Paquet J (2001) Profile of 24-h light exposure and circadian phase of melatonin secretion in night workers. J Biol Rhythms 16:502-511.

Eastman CI (1992) High intensity light for circadian adaptation to a 12-h shift of the sleep schedule. Am J Physiol 263:R428-R436.

Eastman CI, Boulos Z, Terman M, Campbell SS, Dijk D-J, and Lewy AJ (1995) Light treatment for sleep disorders: consensus report: VI. Shift work. J Biol Rhythms 10:157-164.

Eastman CI and Martin SK (1999) How to use light and dark to produce circadian adaptation to night shift work. Ann Med 31:87-98.

Eastman CI, Martin SK, and Hebert M (2000) Failure of extraocular light to facilitate circadian rhythm reentrainment in humans. Chronobiol Int 17:807-826.

Eastman CI, Stewart KT, Mahoney MP, Liu L, and Fogg LF (1994) Dark goggles and bright light improve circadian rhythm adaptation to night-shift work. Sleep 17:535-543.

Folkard S and Monk TH (1985) *Hours of Work: Temporal Factors in Work-Scheduling*, John Wiley & Sons, Ltd., New York.

Horowitz TS, Cade BE, Wolfe JM, and Czeisler CA (2001) Efficacy of bright light and sleep/darkness scheduling in alleviating circadian maladaptation to night work. Am J Physiol Endocrinol Metab 281:E384-E391.

Johnson MP, Duffy JF, Dijk DJ, Ronda JM, Dyal CM, and Czeisler CA (1992) Short-term memory, alertness and performance: a reappraisal of their relationship to body temperature. J Sleep Res 1:24-29.

Kecklund G and Akerstedt T (1995) Effects of timing of shifts on sleepiness and sleep duration. J Sleep Res 4(Suppl. 2):47-50.

Krauchi K, Cajochen C, Mori D, Graw P, and Wirz-Justice A (1997) Early evening melatonin and S-20098 advance circadian phase and nocturnal regulation of core body temperature. Am J Physiol 272:R1178-R1188.

Lewy AJ, Bauer VK, Ahmed S, Thomas KH, Cutler NL, Singer CM, Moffit MT, and Sack RL (1998) The human phase response curve (PRC) to melatonin is about 12 hours out of phase with the PRC to light. Chronobiol Int 15:71-83.

Martin SK and Eastman CI (1998) Medium-intensity light produces circadian rhythm adaptation to simulated night-shift work. Sleep 21:154-165.

Minors DS, Waterhouse JM, and Wirz-Justice A (1991) A human phase-response curve to light. Neurosci Lett 133:36-40.

Mitchell PJ, Hoese EK, Liu L, Fogg LF, and Eastman CI (1997) Conflicting bright light exposure during night shifts impedes circadian adaptation. J Biol Rhythms 12:5-15.

Mitler MM, Carskadon MA, Czeisler CA, Dement WC, Dinges DF, and Graeber RC (1988) Catastrophes, sleep, and public policy: consensus report. Sleep 11:100-109.

Murphy PJ, Myers BL, and Badia P (1996) Nonsteroidal anti-inflammatory drugs alter body temperature and suppress melatonin in humans. Physiol Behav 59:133-139.

Rimmer DW, Boivin DB, Shanahan TL, Kronauer RE, Duffy JF, and Czeisler CA (2000) Dynamic resetting of the human circadian pacemaker by intermittent bright light. Am J Physiol 279:R1574-R1579.

Sack RL and Lewy AJ (1997) Melatonin as a chronobiotic: treatment of circadian desynchrony in night workers and the blind. J Biol Rhythms 12:595-603.

Sharkey KM and Eastman CI (2002) Melatonin phase shifts human circadian rhythms in a placebo-controlled simulated night-work study. Am J Physiol Regul Integr Comp Physiol 282:R454-R463.

Stewart KT, Hayes BC, and Eastman CI (1995) Light treatment for NASA shiftworkers. Chronobiol Int 12:141-151.