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Practical Circadian Interventions for Night Shift Work

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List of Abbreviations

Tmin	body temperature minimum (a marker for the phase of the circadian clock)
DLMO	dim light melatonin onset, the onset the melatonin secretion profile collected in dim light (a marker for the phase of the circadian clock)
PRC	phase response curve (graph describing the direction and magnitude of a phase shift depending on the time of the stimulus)
LD	light-dark
D/S	dark/sleep
BL	bright light
N SG	normal sunglasses
D SG	dark sunglasses
M	melatonin
PVT	psychomotor vigilance task
PRM	probed recall memory task
DSST	digit-symbol substitution test
SSS	Stanford Sleepiness Scale
KSS	Karolinska Sleepiness Scale
VAS	visual analog scale
POMS	Profile of Mood States
MANOVA	multivariate analysis of variance
ANOVA	analysis of variance

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Abstract

The circadian clock assures that diurnal animals, like humans, are alert during the day and asleep at night. Unfortunately, night shift workers are required to work during the "wrong" phase of their circadian cycle, when they are the most inefficient, sleepy, often fall asleep, and are most prone to accidents. Subsequently, they try to sleep during the day, again during the "wrong" phase of their circadian cycle, which results in disrupted and shortened sleep. The chronic sleep deprivation exacerbates the problem of having to work at night when the circadian clock makes people the sleepiest. Sleeping pills can help workers sleep during the day, but this does not eliminate the nighttime sleepiness and performance decrements caused by the circadian clock. Stimulants like coffee and pharmacological drugs can help workers remain alert during the night shift, but can interfere with subsequent daytime sleep. Furthermore, there is potential for side-effects, dependence and abuse with most drugs.

The best solution for night work is to phase-shift the circadian clock to align with the night work and day sleep schedule. This re-alignment (re-entrainment) will alleviate the physiological symptoms of night work because the period of sleepiness will now occur during the daytime sleep period and the period of alertness will occur during the night shift. We tested various combinations of interventions designed to phase delay circadian rhythms and thus produce re-alignment. Young subjects who were not real shift workers (median age = 22, n=67) participated in 5 consecutive simulated night shifts (23:00 to 07:00) in the lab. The various interventions included a fixed daytime dark period for sleep at home, bright light during the night shift, sunglasses for the commute home and melatonin at bedtime. The daytime dark period was from 8:30 to 15:30 after each night shift, which we think is a reasonable daytime sleep schedule for a real night shift worker. It started 1.5 hours after the end of the night shift, leaving ample time to commute home and get ready for bed. We covered the bedroom windows with thick black plastic to make the rooms very dark for sleeping during the day. Because the study was run in the summer (3 consecutive summers), we installed air conditioners for subjects that did not already have them. The fixed daytime dark period creates a shifted (phase delayed) light dark (LD) cycle that "tells" the circadian clock to phase shift, i.e., to entrain to the new LD cycle.

We have previously shown that bright light can either facilitate or inhibit the desired phase shift depending on its timing. Bright light before the body temperature minimum (Tmin) facilitates phase delays, whereas bright light after the Tmin facilitates advances. In this study, we exposed subjects to a gradually moving (delaying) pattern of intermittent bright light (~5000 lux, 20 min on, 40 min off, 4-5 light pulses/night) or kept them in ordinary room light (dim light, ~150 lux) during the night shifts. We tested intermittent bright light because in a real night work setting it may be difficult for workers to remain exposed to the light sources for an extended amount of time. We ended the series of bright light pulses at 5:00 during the first night shift because we estimated the average baseline Tmin would be at about 5:00, and thus the bright light would facilitate phase delays. We moved the pattern one hour later on each subsequent night shift in order to phase delay the rhythms as far as possible (to keep up with the gradually delaying Tmin). The bright light was produced by 3 light boxes set on the perimeter of a large, round table facing in toward the center of the table. Subjects sat in the openings in between the light boxes so that each subject faced a light box. The light boxes (Apollo Light Systems Inc., Orem, UT, 61.0 cm wide, 77.5 cm high, 12.1 cm deep) contained cool-white fluorescent lamps. Sunglasses with normal or very dark lenses (15 or 2 % light transmission) were used to attenuate sunlight during the commute home, which we expected to occur after the Tmin and thus inhibit the desired phase delay. Melatonin (1.8 mg, sustained release) or placebo was taken immediately before each daytime sleep (8:30am), a time expected to facilitate phase delays. A sustained release preparation was used to enhance the soporific effect throughout the daytime sleep period.

The study included 6 intervention groups (6 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. The 6 groups were: 1) dark daytime period for sleep + normal sunglasses, 2) dark daytime period for sleep + dark sunglasses, 3) dark daytime period for sleep + and dark sunglasses + melatonin, 4) dark daytime period for sleep + normal sunglasses + bright light, 5) dark daytime period for sleep + dark sunglasses + bright light, and 6) dark daytime period for sleep + dark sunglasses + bright light + melatonin. The subjects who did not get bright light during the night shift remained in room light. The subjects who did not take melatonin before bed took placebo (double-blind).

The dim light melatonin onset (DLMO) was our marker for the phase of the circadian clock, and was assessed before and after the night shifts (baseline and final). We estimated the Tmin as the DLMO + 7 hours. A reasonable goal for circadian adaptation to the night work and day sleep is to phase shift circadian rhythms so that the sleepiest part of the circadian cycle, the Tmin, falls within the daytime sleep episode. Therefore, subjects were categorized by their amount of re-entrainment (re-alignment) 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). Computerized neurobehavioral batteries were completed during each night shift. Sleep logs were verified by wrist activity monitors and photosensors worn around the neck like a medallion.

Subjects exhibited a wide range of baseline circadian phases, as would real night shift workers. We split the sample into earlier subjects (baseline Tmin $\leq$ 7:00, sunlight during the commute home fell after the Tmin and would thus inhibit the desired phase delay) and later subjects (baseline Tmin > 7:00). The later subjects were completely re-entrained regardless of intervention group, whereas the degree of re-entrainment for the earlier subjects was improved by some of the interventions. Most of the earlier subjects in group 1 did not entrain. When the earlier subjects were given bright light during the night shift (groups 4, 5 and 6) all but one achieved complete re-entrainment, and the phase delay shift for the rest 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 subjects phase delay more than normal sunglasses (group 2 compared to group 1). However, the darker sunglasses contain welders' lenses and are not designed for driving. Melatonin did not confer a benefit either for phase delaying or for increasing sleep duration.

Although subjects slept about 6.5 hours during the day, night shift sleepiness and performance did not improve unless there was circadian phase alignment (partial or complete re-entrainment). Subjects who re-entrained did significantly better than subjects who did not re-entrain on the Psychomotor Vigilance Task (PVT), the Digit Symbol Substitution Test (DSST), the Stanford Sleepiness Scale (SSS), the Karolinska Sleepiness Scale (KSS) and the Physical Exhaustion and Tiredness Visual Analog Scales (VAS). There was no difference in these neurobehavioral measures between those who were partially and completely re-entrained, perhaps because our subjects were so young and thus "phase tolerant."

This study showed that circadian adaptation to fixed night shifts is possible. Subjects with very late circadian rhythms need only maintain a fixed, dark, daytime period for sleep and wear normal sunglasses during the commute home. For subjects who start the night shift with earlier circadian rhythms, we 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 for complete circadian adaptation to night shift work.

Significant Findings

1. Most real night shift workers suffer from the misalignment of their circadian rhythms with their night work, day sleep schedules. All of the subjects in this study of fixed night shifts adhered to a regular, dark period for sleeping during the day after the night shift and wore sunglasses during the commute home. These measures alone were enough to phase delay the circadian clock so that the body temperature minimum (Tmin) occurred during daytime sleep, thus producing circadian adaptation, in many subjects.

2. Baseline circadian phase (the phase before starting night work) was the most important determinant of whether subjects phase delayed enough to achieve circadian adaptation. Specifically, subjects whose baseline body temperature minima (Tmin) occurred before the commute home were not as likely to phase delay and re-align their circadian rhythms with night work and day sleep. This can be explained by the fact that sun light during the commute home occurred after the Tmin and thus inhibited phase delays.

3. Very dark sunglasses worked better than normal sunglasses to help subjects with earlier baseline phases delay enough to achieve circadian adaptation to night work and day sleep.

4. The bright light pattern we used during the night shifts was very powerful. It helped phase delay all but one subject so much that their circadian rhythms were completely entrained to the daytime sleep schedule by the end of the block of night shifts, and probably for most of the daytime sleep periods.

5. Melatonin in the dose, preparation and timing we used (1.8 mg, sustained release, before daytime sleep at 8:30 am each day) did not confer a benefit.

6. Partial re-entrainment to night work and day sleep was as good as complete re-entrainment for improving night shift performance and alertness.

Usefulness of Findings

All the recommendations below are for producing circadian adaptation to night shift work by phase delaying circadian rhythms to align with night work and day sleep. They should only be used for fixed night shift systems in which there are several consecutive night shifts. They should not be used with rapidly rotating shift systems because the circadian clock can only be phase shifted by, at most, 2-3 hours per day, which is not fast enough to keep up with rapid rotations. Workers on rapid rotations have no choice but to suffer circadian misalignment. For occupations in which safety is critical (e.g. nuclear power plant operators, nurses in intensive care units) fixed shift systems are better because circadian adaptation is possible, as shown in the present study. The numbers below correspond to the items under "Significant Findings."

1. Night shift workers should go to bed as soon as possible after the night shift in a dark, quiet bedroom. They should spend a sufficient amount of time in the dark each day (e.g., 7-8 hours) regardless of whether they can sleep. The dark is a signal to "tell" their circadian clocks to phase shift. Commercial black-out shades are available and can be supplemented with thick curtains. A temporary solution, used in this study, was to use masking tape to attach thick (10 mil) black plastic (available in rolls from hardware stores) to the windows. Cracks of light were sealed with black photography (dark room) masking tape.

Workers should notify their family and friends of their daytime sleep schedule and ask not to be disturbed. They should adopt measures to ensure quiet, such as turning off or unplugging their phones, putting Do Not Disturb signs on their doorbells, and using masking noise if necessary. They should forgo errands, social activities, etc. during the time scheduled for dark because the light they would be exposed to will impede the adaptation of their circadian clocks. Employers should never ask night shift workers to stay late (e.g., to do overtime or double shifts) or attend daytime meetings. Meetings should be scheduled no later than the evening.

Night shift workers should wear sunglasses and avoid sunlight, as much as possible, on the way home from the night shift.

The above recommendations are technically simple, but difficult given the current social culture that tends to ignore the dangers and health consequences of sleep deprivation and working at night. Therefore, public education, similar to what is being done for the problems of smoking and obesity, is necessary to make it easier for workers and their employers to adopt these simple measure that can produce circadian adaptation.

2. Workers who start a block of night shifts with later circadian rhythms and maintain a fixed early dark period for sleep and wear normal sunglasses on the way home can achieve complete re-alignment of their circadian rhythms with night work and day sleep. Thus, "night owls" who naturally go to bed and wake later and workers who have partially phase delayed from previous night shifts will be more likely to adapt to night shift work.

3. Night shift workers who start a block of night shifts with earlier circadian phases should wear dark sunglasses on the commute home from the night shift. Sunglasses vary greatly in their light transmission (from about 10 to 90 %). The very dark lenses that helped the earlier subjects in this study transmitted 2% of visible light, and would not be suitable for workers who drive home. However, new lenses have recently been developed by Uvex Safety, Inc. that transmit only 12% of light and meet color traffic signal recognition requirements of ANSI Z80.3. These lenses, called Espresso, especially attenuate the shorter, blue wavelengths, to which the circadian clock is most sensitive. Therefore they should be especially useful for attenuating unwanted light that would advance the circadian clock during the commute home. These lenses come in stylish wrap-around frames called Bandits. These sunglasses are inexpensive and are available from Uvex Safety (http://www.uvex.com/eyewearindex.html). Workers who need to wear prescription eyewear during the commute need contact lenses in order to wear these sunglasses. Fit over glasses are not yet available with the Espresso lens.

In our study, sunglasses with normal lenses (15%) were sufficient to produce circadian adaptation in subjects who started the night shift with later circadian rhythms. Because workers may not know whether their circadian rhythms are early or late relative to their night shift hours, we recommend that they all wear sunglasses, the darker the better. However, it is possible for workers to estimate how important dark sunglasses are for facilitating their circadian adaptation. If their Tmin is before the end of the night shift, then dark sunglasses are more important because sunlight during the commute home will occur after the Tmin and inhibit the desired delay. In another study (Martin and Eastman, 2002), we showed that the Tmin can be estimated from sleep times in people who sleep freely, i.e., going to bed and waking up naturally with minimal schedule restraints. The midpoint of sleep averaged over the past 5 days was at about the Tmin (It was actually about ½ hour before the Tmin). Therefore, we propose this general rule: If the midpoint of natural sleep is before the end of the night shift, then dark sunglasses are very important. Workers need to be sleeping naturally and without sleep deprivation to derive this estimate of the Tmin from the midpoint of sleep. Therefore, they need to be on vacation, the

evening shift, or a late morning shift for about 5 days before the night shifts begin. Sleep times accompanying night shifts, early morning shifts, or even regular day shifts starting at 8 or 9 am, usually force sleep to occur at unnatural times relative to the circadian clock and should not be used to estimate the Tmin.

4. Intermittent bright light during the night shift was very effective in helping circadian rhythms to delay to align with night work and day sleep. The pattern we used was probably more powerful than necessary since it produced complete re-entrainment in all but one subject; for many purposes partial re-entrainment would be sufficient. The bright light could be cut back by using light of lower intensity and shorter durations. This should make it easier to install light sources in the workplace, and for workers to receive enough intermittent bright light. Furthermore, a stationery rather than moving pattern would probably be sufficient. The bright light should be available from the beginning of the night shifts and should end at about the time of the average Tmin of the workers. Because the circadian clock is most sensitive to short wavelengths of visible light (blue light), fluorescent lamps with the highest color temperature, e.g., "daylight" lamps should be used.

5. Melatonin is probably not effective for improving circadian adaptation to the night shift when a circadian rhythm phase delay is required, i.e., when workers go to sleep soon after the night shift. However, another study from our lab (Sharkey and Eastman, 2002) showed that melatonin can facilitate phase advances in a simulated night shift study in which subjects were required to take their sleep right before the night shift. In other words, the sleep/dark period was advanced rather than delayed. However, most night shift workers choose to go to sleep in the morning after the night shift (which is a delay of the sleep period).

6. Our computerized neurobehavioral assessment battery given during the night shifts did not detect any difference between subjects who achieved partial and those who achieved complete re-entrainment of their circadian rhythms to night work. Both groups had better performance and alertness than the subjects who did not re-entrain. Therefore, at least for very young night workers, only partial re-entrainment may be necessary for improving night shift performance. However, young people may be more flexible and more phase tolerant (able to sleep and work at inappropriate circadian phases) than older people.

Scientific Report

Introduction

Millions of night shift workers maintain our 24-h society. The night workers' schedule, however, causes many negative consequences. Their most common complaint is not getting enough sleep (Kecklund and Akerstedt, 1995). Other problems include fatigue, gastrointestinal disturbances, impaired performance, and diminished job and public safety (Johnson,LC et al., 1981; Minors and Waterhouse, 1981; Folkard and Monk, 1985; U.S. Congress and Office of Technology Assessment, 1991). 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, sleepy, often fall asleep, and are most prone to accidents (e.g., Akerstedt, 1988; Mitler et al., 1988; Torsvall et al., 1989; Smith et al., 1994; Dinges, 1995). 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., Tilley et al., 1982; Kogi, 1985; 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.,van Loon, 1963; Minors and Waterhouse, 1993; Roden et al., 1993; Akerstedt, 1995; Dumont et al., 2001) because they are exposed to the natural light-dark cycle and other possible 24-hr zeitgebers (Eastman et al., 1995a). Sunlight in the morning on 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 block out the advancing sunlight in the morning and facilitate re-entrainment to the night work and day sleep schedule (Eastman et al., 1994). Ensuring a dark environment for sleep as soon as possible after the night shift will further limit advancing light, and will also form the basis of a delayed light-dark (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 at night and constructing periods of darkness during the day. Our laboratory has frequently taken advantage of a gradually moving pattern of bright light to phase shift circadian rhythms (Eastman and Miescke, 1990; Eastman, 1992; Stewart et al., 1995; Stewart and Eastman, 1996; Mitchell et al., 1997; Martin and Eastman, 1998; Burgess et al., 2003). Theoretically, the bright light moves along with the circadian clock and its PRC so that the bright light always occurs at a more optimal time for the desired phase shift. A moving pattern of bright light is also a way to facilitate a phase shift in subjects with varying initial circadian phases. The bright light acts like a broom, "sweeping" the subjects with early and late circadian phases together and in the desired phase shifting direction. For example, to facilitate a phase delay, bright light timed to occur early in the night will be closer to the Tmin of the subjects with earlier phases and phase delay these subjects more than those with later phases. Then, as the bright light moves later and later each night, it will fall closer to the Tmins of the subjects with later phases and have more of a phase-shifting effect on those subjects.

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

would be 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 bright light (~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 bright light (30 min of bright light ≥ 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). Furthermore, a shorter duration of light pulses may be even more practical for some night shift workers. For example, one study showed that night nurses have time for 20-min light pulses (Costa et al., 1993).

The pineal hormone, melatonin, can also phase shift the circadian clock. The melatonin phase response curve (PRC) of Lewy et al. (1998) suggests that a small dose of melatonin (0.5 mg) administered approximately10 h after the DLMO (in most cases, in the early morning h) will produce the largest phase delay of circadian rhythms. See the simplified melatonin PRC, Fig 1 in Burgess et al. (2002). We found that melatonin 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 melatonin to facilitate a phase delay and thus circadian adaptation to night work when sleep is taken in the morning/afternoon (a delay of sleep). Melatonin also has a slight hypnotic effect (e.g.Matsumoto, 1999; Sharkey et al., 2001), which could benefit night shift workers when they sleep during the daytime.

The purpose of the current study was to test the relative contribution and the combined effectiveness of various interventions namely, bright light, sunglasses, and melatonin, to phase delay circadian rhythms and re-align them with sleep in the morning after the night shift. Intermittent bright light 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 5:00 (Baehr et al., 2000). Therefore, we ended the bright light during the first night shift at 5:00, and moved it 1 h later on each subsequent night shift. We used 5 consecutive simulated night shifts from 23:00 to 7:00, as this is a common pattern in real shift work settings. We required subjects to remain in bed and in the dark from 8:30 to 15:30 after each night shift because we think that this is a reasonable daytime sleep schedule for a real night shift worker. Sunglasses 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. Melatonin (1.8 mg, sustained release) was taken immediately before each daytime sleep (8:30am), a time expected to facilitate phase delays. A sustained release preparation was used to enhance the soporific effect throughout the daytime sleep period. The study included 6 intervention groups (6 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

Subjects

A total of 67 subjects (35 females and 32 males) between the ages of 18 and 43 (mean age ± SD = 23.9 ± 6.2 years) completed the study. Subjects 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. Subjects were not taking prescription medications, except for 7 females who were taking oral contraceptives. To insure

the dose (mg/kg) of melatonin was not too low, individuals who weighed more than 105 kg were excluded. Subjects had not worked night shifts or travelled across more than three time zones within the month before starting the study. Most subjects had never worked night shifts. The protocol was approved by the Rush-Presbyterian-St. Luke's Medical Center Institutional Review Board. All subjects gave written informed consent and were paid for their participation.

Design

This was a between-subjects design with 6 intervention groups (see Table 1). Subjects were randomly assigned to groups, although an effort was made to balance sex and morningness-eveningness among the groups. Two to three subjects were run simultaneously.

Night Shift and Dark/Sleep Schedule

The study took place during the summer months (July – September) of 3 consecutive summers. There were 7 days of baseline during which subjects could choose when they slept. The only restrictions were that they could not stay awake all night, and during summers 2 and 3 they were also told to go to bed before 2:00am. We did not require a standard sleep schedule because we wanted our subjects to have a range of circadian phases at baseline, like real shift workers.

Figure 1 displays the second week of the study protocol. We made subjects' bedrooms completely dark by covering their windows with thick, black plastic 3-4 days before the baseline phase assessment. Air conditioners were also installed if they did not already have one, as this provided a comfortable sleeping environment. Subjects were told to remain in bed for the entire 7 h dark/sleep (D/S) period (except for necessary bathroom trips), even if they could not sleep. Subjects recorded bedtime, estimated sleep onset, and estimated wake time (which could be earlier than out-of-bed time) on daily sleep logs every day during the study. A separate sleep log was filled out if the subject napped during the baseline week. Napping was not allowed during the second week. They also called the laboratory's voice mail system before bedtime and at wake time. Compliance to the daytime sleep schedule was monitored by actigraphy. Subjects wore an actiwatch (Actiwatch-64, MiniMitter Inc., Bend OR) on their non-dominant wrist. Subjects also wore an actiwatch with a photosensor (Actiwatch-L, MiniMitter Inc.) around their neck like a medallion to monitor their light exposure during the study. This captured light intensity at eye level better than when worn on the wrist. When subjects were in bed, they were told to place the photosensor face up on a night stand in their bedroom. Every 2-3 days, both actiwatches were downloaded to a computer and checked in the subject's presence (along with sleep logs and phone call records) to verify that they were following the dark/sleep restrictions.

Bright Light

Subjects in groups 4, 5 and 6 were exposed to a moving pattern of intermittent bright light (BL) (~5000 lux, 20-min pulses) during the night shifts (see Figure 1). The BL pulses were 1 h apart (i.e. 20 min BL alternating with 40 min room light). Three light boxes were set on the perimeter of a large, round table facing in toward the center of the table. Subjects sat in the openings in between the light boxes so that each subject faced a light box. The subjects'eyes were about 135 cm from the opposite light box. Subjects also received light from the other two light boxes, especially in their periphery. The light boxes (Apollo Light Systems Inc., Orem, UT) were 61.0 cm wide, 77.5 cm high, and 12.1 cm deep. They contained 4 U-shaped, cool-white fluorescent lamps (GE Wattmiser, 35 watts). Between bright light pulses, subjects remained in room light (~150 lux) produced by ceiling fixtures. Subjects in groups 1, 2 and 3 remained in constant room light (~150 lux) throughout the night. Light intensity was measured twice during

each bright light pulse and approximately every two h when in regular room light using an Ex Tech (model #401025) light meter (Waltham, MA), which has a flat round photosensor (4.5 cm diameter) attached to the light meter with a cord. The photosensor was placed over the subject's eye and in the direction of gaze. Subjects were required to move closer to the table if the readings were below 5000 lux. Reading was not allowed and interaction among subjects was encouraged for all groups.

Sunglasses

Subjects were required to wear sunglasses throughout the study whenever they were outside. During the baseline week (days 1-7), subjects wore sunglasses with normal lenses (N SG) (15% transmission, standard gray lens, Uvex Safety Inc, Smithfield RI). During the experimental week (days 8-14), two groups (1 and 4) continued to wear the normal sunglasses and the rest were given sunglasses with very dark lenses (D SG) (2% transmission, shade 5.0 welding lens, Uvex Safety Inc.). Both the normal and the dark sunglasses had the same black frames with top and side shields (Flashback frames, Uvex Safety Inc.). There were 1.5 h between the end of each night shift and bedtime. It was emphasized to the subjects that during this time it was especially important to wear their sunglasses. A staff member watched them put their sunglasses on before stepping outside after each night shift.

Melatonin

Subjects in groups 3 and 6 took melatonin (M) (1.8 mg sustained release, Ecological Formulas, Concord CA), while the remaining groups took a matching placebo just before bedtime at 8:30 each day during the second week. The melatonin was administered double-blind; the staff interacting with the subjects and the subjects themselves did not know if they were taking melatonin or placebo. Immediately upon waking at 15:30, subjects were required to provide a saliva sample using a Salivette (Starstedt, Newton, NC) to insure ingestion of the pill. Subjects in groups 2 and 3 were run simultaneously as were subjects in groups 5 and 6.

Circadian Phase Assessments

On days 8 and 14, subjects arrived at the laboratory at 18:30 for circadian phase assessments. Starting at 19:00 saliva samples were collected every 30 minutes using Salivettes. Subjects remained seated in a semi-recumbent position in comfortable recliners in dim light (< 20 lux). Chocolate, bananas, and lipstick were not allowed 6 h before or during each phase assessment, as these products interfere with the melatonin assay. Toothpaste and mouthwash were also not allowed during the phase assessments. Subjects were allowed to eat and drink (no alcohol, caffeine, chocolate, or bananas), except in the 10 minutes before a saliva sample. If subjects ate or drank anything, they were required to brush their teeth and rinse with water 10 minutes before the sample while they remained seated. The saliva 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 subject were run in the same assay. The intra-assay and inter-assay variablilty were 12.1% and 13.2% respectively. The lower limit of detection of the assay was 0.7 pg/mL.

Performance, Sleepiness, and Mood Assessments

Subjects completed the Neurobehavioral Assessment Battery (NAB), developed by Dr. David F. Dinges and John W. Powell at the University of Pennsylvania. This computerized battery, which takes about 20-25 minutes, was started at 4:05, 5:05, and 6:05 during each night shift. We chose these times because they are typically when real night workers are most sleepy

and show the most decrement in performance. Scores from these 3 test bouts were later averaged for each night shift. To familiarize the subjects with the various tests, practice batteries were completed at 23:05, 0:05, 1:05, and 2:05 during the first night shift and at 23:05 on subsequent nights. The following tests were examined: the Psychomotor Vigilance Task (PVT; Dinges and Powell, 1985), a probed recall memory task (PRM; Dinges et al., 1993), the digit-symbol substitution test (DSST; Wechsler, 1958), the Stanford Sleepiness Scale (SSS; Hoddes et al., 1973), the Karolinska Sleepiness Scale (KSS; Akerstedt and Gillberg, 1990), 3 visual analog mood scales (VAS), and the Profile of Mood States (POMS; McNair et al., 1971).

The PVT was designed to test sustained attention. Subjects used a hand-held device with two buttons, one for the right and one for the left hand. Visual reaction time was measured by the subject pressing the button controlled by their dominant hand when they saw a series of numbers count up in milliseconds. The counting stopped when the subject pressed the button. This gave a reaction time in milliseconds. Two variables were extracted from this test: mean response time (RT) and number of lapses during each night shift. The number of lapses was calculated by first determining the number of RTs $\geq$ 500 milliseconds and then transforming that number with the formula, square root (x) + square root (x + 1). This square root transformation converted a score of 0 lapses to 1 lapse and reduced larger scores.

For the PRM task, a list of 6 word pairs was displayed before the PVT for 30 seconds. After the PVT, subjects were presented with one word from each pair in a different order and asked to recall the other word in the pair by typing it on the keyboard. Subjects had 5 minutes to recall the matching word. The variable for the PRM task was the number of words recalled.

For the DSST, 9 symbols were presented in a row with associated numbers (1-9) beneath each symbol. There were 24 different symbols in the DSST and the computer program randomly selected 9 for each test bout. The symbols and numbers remained displayed throughout the test bout. Then, one symbol was shown on the screen and subjects had to type the number associated with the symbol. Immediately after a number was entered, the next symbol was shown. The same symbol was never presented in succession. Following a 15 second practice period, scoring began and continued for 90 seconds. The variable extracted for the DSST was the percentage of correctly paired symbols and numbers.

In each battery of tests, there were two presentations of the SSS and VAS, once before and once after the performance/alertness tasks (PVT, PRM, and DSST). The second presentation of both scales is more sensitive than the first, especially at an unfavorable circadian time (Babkoff et al., 1991). Therefore, we used the second bouts in the analysis. The SSS included 7 statements describing feelings of sleepiness ranging from "feeling active and vital; alert; wide awake" (1) to "almost in reverie; sleep onset soon; lost struggle to remain awake" (7). The 3 visual analog mood scales asked the subject "How do you feel right now?" with the scale anchor points: 1) physically exhausted to energetic, 2) sharp to mentally exhausted, and 3) fresh as a daisy to tired to death. The KSS was presented after the performance/alertness tasks. Subjects were asked to rate their sleepiness on a 9 point scale, ranging from "very alert" (1) to "very sleepy, great effort to keep awake, fighting sleep" (9). The POMS was presented at the end of the test bout. Subjects were presented with 65 adjectives and asked to respond to each on a scale ranging from "not at all" (1) to "extremely" (5). The Total Mood Disturbance scores were analyzed.

Other Procedures

Subjects 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. Non-steroidal-anti-inflammatory drugs (NSAIDs) 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. Subjects were breathalyzed before each phase assessment and night shift to insure compliance with this rule.

Data Analysis

To determine the DLMO, a threshold was calculated by taking 35% of the average of the three highest points. An absolute threshold of 3 pg/mL was used for 2 subjects (one in group 2 and one in group 6) because the threshold calculated using our standard procedure was too high for one of the melatonin profiles in each pair of profiles. The DLMO was calculated by linearly interpolating between the times of the samples before and after melatonin 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 subject 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, those subjects' whose final DLMO was before 1:30 were defined as not re-entrained because their estimated Tmins occurred before 8:30, i.e. before daytime sleep. Those subjects' whose final DLMO occurred between 1:30 and 5:00 were defined as partially re-entrained because their estimated Tmins occurred during the first half of daytime sleep. Lastly, those subjects' whose final DLMO occurred after 5:00 were defined as completely re-entrained because their estimated Tmins occurred during the second half of sleep. Obviously, subjects whose circadian rhythms delayed enough to be classified as partially or completely re-entrained based on their phase during the final phase assessment, may not have had their Tmins occur during all the daytime sleep periods. However, we can safely assume that subjects categorized as completely re-entrained had more days in which their Tmins occurred during daytime sleep than those categorized as partially re-entrained. The subjects were also divided into these three re-entrainment categories for the analysis of sleep log data and the performance, sleepiness, and mood measures.

Total daytime sleep duration after each night shift was calculated from sleep logs (final wake time minus sleep onset minus awakenings within sleep > 5 minutes). The mean daytime sleep duration for all 5 days was calculated for each subject and then averaged for each of the three re-entrainment categories.

Light levels were taken from the Actiwatch-L photosensor worn around the neck. Two correction factors were applied to these readings, one for the error of measurement in the Actiwatch -L and one for wearing sunglasses. If the Actwatch-L measured more than 10% above or below what was measured by a light meter (Ex-Tech Instruments, Waltham MA), then a conversion factor was calculated and applied to the values measured by that Actiwatch-L. To determine the conversion factor, the Actiwatch-L and light meter were placed side by side and exposed to various light intensities. The light levels measured by the Actiwatch-L were plotted against the light levels recorded by the light meter and a linear regression line was generated. The slope of the line was used as the conversion factor. Then, the light levels were corrected again for the type of sunglasses that the subject wore (N SG transmit 15% and D SG transmit 2% of light to the eye). Subjects could have been outside during daylight between 7:00 and 8:30 and

from 15:30 until sunset. The correction for sunglasses was applied during these 2 time intervals when light levels were $\geq$ 500 lux, because if the levels were $\geq$ 500 lux then the subject was probably outside. Once these corrections were made, light levels were averaged into 20-min bins for each subject and then subsequently averaged for each of the 6 intervention groups.

Circadian phase variables were analyzed using a one-way multivariate analysis of variance (MANOVA) with a between-groups factor of intervention group. When significant, univariate analyses were examined and Tukey HSD post-hoc tests were performed to identify the significant group differences. Dependent variables were baseline DLMO, final DLMO, and phase shift.

Performance, sleepiness, and mood measures were analyzed using a 3 x 5 repeated measures ANOVA with the two independent factors being re-entrainment category (not re-entrained, partially re-entrained, and completely re-entrained) and night shift (1, 2, 3, 4 and 5). A parallel analysis was conducted for the daytime sleep duration with the two independent factors being re-entrainment category and day sleep (1, 2, 3, 4 and 5). Greenhouse-Geiser corrections were used to correct for violations of sphericity for the within-subjects effects. When a significant interaction was found, simple main effects analyses were conducted to determine the source of the interaction.

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

Results

Light/Dark Exposure

Figure 2 shows how the pattern of light exposure differed among the groups. Groups 1, 2 and 3 were exposed to typical room light levels during the night shifts (23:00 to 7:00), whereas the BL groups (4, 5 and 6) were exposed to BL pulses that can clearly be seen. Although the BL pulses in the figure reach about 2500 lux, as measured by the neck medallion, the light readings taken by research assistants using a light meter photosensor held over the eye and in the direction of gaze measured > 5000 lux. The figure shows an increase in light intensity when subjects wearing normal sunglasses (group 1 and 4) left the lab at 7:00. For the other groups, the dark sunglasses kept light levels during the commute home similar to the light levels recorded during the normal room light of the night shifts. For group 1, the highest light intensities were during the commute home time and in the afternoon after the dark/sleep period, whereas for the rest of the groups, the levels during the night shift were as high or higher than the levels at any other time of day. For all groups, the dark/sleep period (8:30 to 15:30) was delayed by many h compared to the average dark/sleep period during baseline, as shown by the bar at the top of the figure.

Circadian Phase

Figure 3 shows examples of melatonin profiles. The phase delay shift was 6.4 h for the subject in the top panel and 5.0 h for the subject in the bottom panel. The subject in the bottom panel showed high levels of melatonin at the beginning of the final phase assessment, which started at 19:00, due to the exogenous melatonin taken before going to sleep that morning at 8:30. Many (16 out of 20) subjects in the melatonin groups showed these higher residual levels at the beginning of the final phase assessment. The average melatonin concentration from the samples taken at home after waking from daytime sleep at 15:30 was 130.1 $\pm$ 84.2 pg/mL for the

subjects that took melatonin before sleep and 5.0 ± 4.4 pg/mL for the subjects that took placebo.

Figure 4 displays the baseline and final DLMO and the estimated baseline and final Tmin for each subject. In group 1 (top row), there were various magnitudes of phase shifting ranging from very small shifts to very large delay shifts, and thus subjects fell into all 3 re-entrainment categories: not re-entrained, partially re-entrained, and completely re-entrained (i.e. the estimated final Tmin occurred before dark/sleep, within the first half of dark/sleep, or within the second half of dark/sleep). Similar results were found in group 2 (second row); subjects fell into all 3 re-entrainment categories. All of the subjects in group 3 were partially or completely re-entrained. All of the subjects in groups 4, 5, and 6 (except for 1 subject in group 4) were completely re-entrained. Table 2 shows the percentage of subjects in each intervention group that fell into the 3 re-entrainment categories.

Table 3 shows that the final DLMO was later and the phase shifts were larger as the interventions became more complex (i.e. as the intervention group number increased from 1 to 6). A multivariate one-way ANOVA found significant effects when baseline DLMO, final DLMO, and phase shift were examined as dependent variables [$F(10,116) = 3.16$, $p = 0.001$, F estimate based on Wilks' Lambda]. This significant multivariate effect justified examining the associated univariate analyses. Significant main effects of intervention group were found for the final DLMO [$F(5,59) = 5.00$, $p = 0.001$] and for phase delay shift [$F(5,59) = 4.42$, $p = 0.002$]. The final DLMO was significantly later in group 4, 5, and 6 (the groups exposed to BL during the night shifts) when compared to group 1 (p values = 0.025, 0.003, and 0.006, respectively). The phase delay shift was also greater in groups 4, 5 and 6 when compared to group 1 (p values = 0.012, 0.013, and 0.007, respectively). There was also an unexpected significant main effect of intervention group for baseline DLMO [$F(5,59) = 2.96$, $p = 0.019$]. Pair-wise comparisons showed that the baseline DLMO for group 5 was later than group 2 ($p = 0.035$).

We expected baseline phase position to have a large influence on subsequent phase shift. Subjects 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 subjects would have crossover points (estimated by the baseline Tmin) before the travel home time (before 7:00), so that sunlight during the commute would coincide with the phase advance portion of the light PRC and inhibit the phase delay. Then, if the rhythms delayed from the baseline to the final phase assessment, the Tmin would eventually occur after the travel home time, so that sunlight would facilitate the delay. However, many subjects had baseline Tmins later than we expected (after 7:00), which means that light during the commute home could have facilitated rather than inhibited the phase delay, even after the first night shift. Given these facts about baseline phase and the somewhat unequal distribution of baseline phases among the intervention groups, we divided each intervention group into two groups: earlier subjects (baseline Tmin $\leq$ 7:00) and later subjects (baseline Tmin > 7:00). Also, because the outcome in all of the bright light groups was so similar, these three groups (4, 5, and 6) were combined in the following analysis.

A summary of phase measures from the earlier subjects is displayed in Table 4. The baseline DLMOs were similar (about 22:00 to 23:00). The final DLMOs, and therefore the estimated final Tmins, became later as the interventions became more complex (i.e. as the intervention group number increased). The mean final Tmin fell before the time corresponding to daytime sleep (before 8:30) for group 1, in the first half of the time corresponding to daytime sleep for groups 2 and 3, and in the second half of the time corresponding to daytime sleep for the bright light groups. 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 [F(3,38) = 2.45, p = 0.079]. 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]. Pair-wise 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 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 subjects 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 1:00, the final DLMOs were between 6:00 and 7:00, the final Tmins were between about 13:00 and 14:00, and the phase delay shifts were about 5-6 h.

Table 5 shows that all the later subjects achieved complete re-entrainment, regardless of intervention group. However, for the earlier subjects, 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 subjects. Because the N was too small in some of the cells, we combined two of the re-entrainment categories. First, we combined the partial and complete re-entrainment categories and compared them to the subjects who were not re-entrained. There was a significant difference between the intervention groups, χ^2 (3, n = 42) = 16.55, p = 0.001. Specifically, the proportion of subjects who did not re-entrain was significantly greater in group 1 than in the other intervention groups. Secondly, we combined the proportion of subjects who were not re-entrained and partially re-entrained and compared them to the subjects 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 subjects who were completely re-entrained was significantly greater in the bright light groups than the other intervention groups. These findings are based on an examination of the cell standardized residuals derived from the associated contingency table.

In summary, if the baseline circadian phase was late enough, then complete re-entrainment occurred in all intervention groups. Even the subjects in group 1, who only had normal sunglasses and no melatonin and no bright light during the night shifts, achieved complete re-entrainment. However, if the baseline phase was earlier (Tmin before the start of the commute home time) then the subjects in intervention group 1 fared worse than the subjects in all of the other intervention groups. They were less likely to entrain to the daytime dark/sleep schedule. Thus, adding darker sunglasses conferred a significant benefit. There were no statistically significant differences between groups 2 and 3 by any of the analyses. Therefore, adding melatonin to the dark sunglasses did not change the phase shift. The subjects in the bright light groups were more likely to achieve complete re-entrainment than subjects in the other three intervention groups. Furthermore, the outcome in the three bright light groups was very similar in that all except one subject achieved complete re-entrainment (see Figure 4). Thus, in general, the darker sunglasses and melatonin did not enhance the phase shift if subjects received bright light during the night shift.

Daytime Sleep

All but 3 subjects reported sleeping between 6 and 7 h (averaged over the 5 days) after the night shifts. There was a significant but weak correlation between final phase and sleep duration (r = 0.28, p=0.023, 2-tailed). However, there was no difference between those who were not re-entrained (6.5 $\pm$ 0.6 h), partially re-entrained (6.6 $\pm$ 0.3 h), or completely re-entrained (6.7 $\pm$ 0.2 h). As expected, all subjects slept less during the night shift week than during the

baseline week (7.5 ± 0.7, 8.0 ± 0.6, and 8.1 ± 0.7 h, respectively). Sleep duration was not different between groups 2 and 3 (6.6 ± 0.4 h and 6.7 ± 0.2 h) or between groups 5 and 6 (6.8 ± 0.3 h and 6.7 ± 0.2 h), which were the groups that differed only in that one group took melatonin before daytime sleep and the other took placebo.

Night Shift Performance, Sleepiness, and Mood Assessments

Figure 5 displays some of the measures from the computerized batteries during the night shifts. First, the graphs will be described, and then the statistics will be presented. Response time on the PVT (upper-left panel) became longer over the 5 night shifts for the subjects who did not re-entrain. Response time for subjects who attained re-entrainment (either partial or complete) was shorter than for those who did not re-entrain, and stayed the same as the night shifts progressed. The number of words recalled in the PRM test (upper-right panel) showed a similar trend. Those who did not re-entrain recalled fewer words as the night shifts progressed. Those who attained re-entrainment (partial or complete) recalled more words throughout the 5 night shifts than those who did not re-entrain.

Self-reported sleepiness on the SSS (middle-left panel) showed that the subjects who did not re-entrain became sleepier as the night shifts progressed while subjects who attained re-entrainment (partial or complete) became less sleepy as the night shifts progressed. POMS Total Mood Disturbance (middle-right panel) was higher for the subjects who did not re-entrain than for those that attained complete re-entrainment. There was a slight decrease in total mood disturbance over the 5 night shifts for those subjects who were partially re-entrained. Physical Exhaustion VAS (lower-left panel) was higher for those who were not re-entrained. The subjects who attained partial or complete re-entrainment became less physically exhausted as the night shifts progressed. Mental Exhaustion VAS (lower-right panel) showed a similar trend.

The repeated measures ANOVAs showed that the main effect of re-entrainment category was significant or close to significance for all of the variables analyzed: mean response time on the PVT [$F(2,64) = 10.97$, $p < 0.001$], lapses on the PVT [$F(2,64) = 9.42$, $p < 0.001$], the percent correct in the DSST [$F(2, 64) = 4.90$, $p = 0.010$], PRM [$F(2,64) = 2.53$, $p = 0.088$], SSS [$F(2,64) = 4.61$, $p = 0.014$], KSS [$F(2,64) = 4.40$, $p = 0.016$], Physical Exhaustion VAS [$F(2,64) = 4.70$, $p = 0.012$], Tiredness VAS [$F(2,64) = 4.14$, $p = 0.020$], Mental Exhaustion VAS [$F(2,64) = 2.62$, $p = 0.080$], and POMS Total Mood Disturbance [$F(2,64) = 2.53$, $p = 0.088$]. There were two measures that showed a significant main effect of night shift: mean response time on the PVT [$F(2,149) = 5.63$, $p = 0.003$] and Physical Exhaustion VAS [$F(3,221) = 2.77$, $p = 0.035$]. There were also two measures that showed a significant interaction: mean response time on the PVT [$F(5, 149) = 4.36$, $p = 0.001$] and SSS [$F(7,222) = 2.56$, $p = 0.015$]. Simple main effects analyses revealed that the source of the interactions were significant differences (all $p < 0.001$) between the 3 re-entrainment categories during the last 3 night shifts.

Discussion

This study showed that bright light during the night shift was the strongest factor for producing circadian adaptation to the night shift, i.e. for helping circadian rhythms delay to align with the daytime sleep schedule. Very dark sunglasses (darker than normal sunglasses) used during the commute home after the night shift also helped delay circadian rhythms. However, we could not demonstrate a benefit from the administration of sustained release melatonin before daytime sleep.

We converted the DLMOs obtained in this study to estimated Tmins (by adding the

constant of 7h) for two 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. Akerstedt and Gillberg, 1982; Johnson,MP et al., 1992). We have 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 (Minors et al., 1991; Jewett et al., 1994; Van Cauter et al., 1994).

During the baseline week subjects were free to sleep at times they chose, whereas in all of our previous simulated night shift studies subjects were required to follow fixed baseline sleep schedules (Eastman, 1992; Eastman et al., 1994, 1995b; Mitchell et al., 1997; Martin and Eastman, 1998; Baehr et al., 1999; Sharkey and Eastman, 2002). We designed the study with free baseline sleep because we wanted our subjects to start the night shift with a wide range of circadian phases, to simulate what we would expect in real night shift workers. The resulting baseline Tmins ranged from 3:12 to 9:42. The subjects who had Tmins before the start of the commute time home at 7:00 (the earlier subjects) benefitted the most from our interventions, whereas the later subjects achieved complete re-entrainment regardless of intervention group.

Sunglasses for the commute time home

For the earlier subjects, sunlight during the commute home probably coincided with the phase advance portion of their light PRC, which can explain why they phase delayed more with the darker sunglasses (group 2 vs group 1). The combination of the dark/sleep period and the dark sunglasses produced re-entrainment in most subjects. However, the darker lenses were designed for welders and are not approved for driving. Therefore, the mode of transportation is an essential detail to consider when recommending such sunglasses. The normal lenses transmit 15% of light and are approved for driving (i.e. meets color traffic signal recognition requirements). Recently, Uvex Safety Inc. has developed "espresso" lenses which transmit 12% of light and are approved for driving. It is possible that if our earlier subjects in group 1 had worn these 12% lenses, then more of them would have re-entrained to the daytime sleep schedule. Our subjects 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 subjects to re-entrain with just normal sunglasses. The discovery that the circadian system is most sensitive to blue wavelengths (420-480 nm) (Brainard et al., 2001; Thapan et al., 2001) should lead to the development of lenses that selectively block these wavelengths.

In conclusion, we recommend wearing sunglasses 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 circadian adaptation in workers who start the night shift with earlier circadian phases.

All of the later subjects achieved complete re-entrainment regardless of the interventions that were implemented (Table 5). For these subjects, light during the commute home (which was primarily at the beginning of the 7:00 - 8:30 window) probably coincided with the delay portion of the light PRC, helping these subjects delay further. Thus, they probably did not need to wear sunglasses during their commute home. So how could real shift workers know whether they were early or late and thus whether they should wear very dark sunglasses? We have shown that the DLMO, and thus the Tmin, can be accurately predicted using sleep logs from the last 5

nocturnal sleep periods in free sleepers (Martin and Eastman, 2002). In that study, the estimated Tmin was 2.9 h before wake. In the current study, the estimated baseline Tmin was 3.1 h before wake. Thus, we can recommend the general rule that if a worker's average wake-up time in the 5 days preceding the night shifts is 3 or more h after the start of their commute home time, then they don't need to wear sunglasses (except of course for UV protection). However, the worker must have a few days of free sleep with relatively unrestricted wake times (i.e., days off or evening shift) from which to estimate wake-up time.

Bright light during the night shift

When our subjects were given bright light during the night shift, all but one early subject achieved complete re-entrainment. Darker sunglasses did not confer an additional advantage, not even for the earlier subjects. This makes sense given the light exposure patterns shown in Fig 2. For the bright light groups, the bright light pulses were the most intense light in the 24-h day, even for subjects who wore the normal sunglasses (group 4). Thus, there was a phase delayed, large amplitude LD cycle for all 3 bright light groups, which phase delayed their circadian rhythms. The circadian system responds to the relative intensities of light throughout the 24 h day, rather than absolute intensities, to distinguish day from night (Lynch et al., 1981; Meyer and Millam, 1991). Thus, the LD cycle for groups 2 and 3 was also clearly shifted, although the amplitude was much lower, which can explain why the phase shifts were smaller (c.f., Wever, 1965). Laboratory studies on humans have also shown that appropriately timed room light can help phase shift circadian rhythms towards re-entrainment to a shifted dark/sleep period when presented over a background of dimmer light (Boivin et al., 1996). For the subjects in group 1, light during the commute home was relatively intense compared to the rest of the 24 h, and as mentioned earlier coincided with the phase advance portion of the PRC for earlier subjects. This can explain why re-entrainment was less likely for these subjects. Thus, we predict that as long as the light during the night shift is more intense and of sufficient duration, compared to light during the commute home, and there is a clear shift in the dark period, then re-entrainment is very likely to occur (as for our groups 2 and 3).

We used a moving pattern of bright light pulses in order to phase delay the rhythms as far as possible. In fact, the final Tmins were so late that we can assume that circadian adaptation was achieved during most of the 5 night shifts (Fig 4). 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. Thus, the bright light pattern we used was too powerful. The ideal bright light pattern should delay the rhythms to re-align 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 bright light, durations shorter than 20 min, fewer pulses of bright light per night, and fewer nights with bright light.

The circadian rhythms of our subjects were probably prevented from delaying further by light exposure coinciding with the phase advance portion of the light PRC upon waking at 15:30. We have incorporated light "brakes" for "halting the delay" into other schedules for night workers (Stewart et al., 1995; Stewart and Eastman, 1996; Eastman and Martin, 1999; Burgess et al., 2002). In the current study, there were no special light requirements placed upon the subjects upon waking at 15:30. Furthermore, they were required to wear their sunglasses whenever they went outside, to simplify instructions. In retrospect, we should have asked them to go out soon after waking and given them very light sunglasses for this time, to help keep the rhythms from delaying too far.

There are circumstances in which partial rather than complete re-entrainment would 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. In our young subjects, partial re-entrainment was sufficient to improve performance decrements, sleepiness, and mood during the night shift. Therefore, we have proposed 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 bright light pattern designed to produce 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 second block of night shifts. Future studies are planned to test such compromise schedules. However, older workers may be less phase tolerant and may need complete re-entrainment to achieve substantial benefits (Campbell, 1995; Dijk et al., 1999). Obviously, the ideal degree of re-entrainment depends on many factors, including the hazard potential of the job.

A recent study (Boivin and James, 2002) tested bright light 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 (dark/sleep, normal sunglasses (15% transmission, Uvex) and bright light). They were exposed to about 3000 lux of intermittent bright light 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 dark/sleep, clear glasses, and their usual lighting during the night shift (~100 lux). Both groups were permitted to sleep freely on days off. All the subjects in the treatment group achieved partial or complete re-entrainment, whereas the subjects 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 dark/sleep 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 (23:00 to 7:00). During the night shifts, subjects were exposed to either room light (~150 lux) for the entire night shift or bright light (~2500 lux, continuous) for the first 6 h of each night shift. After each night shift, they either slept from 8:00 to 16:00 (fixed sleep) or they 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 subjects achieved re-entrainment by our definition. Almost none of the subjects in the other groups phase delayed enough for re-entrainment. The results from the Bright Free group show that despite bright light during the night shift, when subjects 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 dark/sleep period after night work.

Melatonin Administration

When we compared groups 2 vs. 3 and groups 5 vs. 6 (placebo vs. melatonin), there were no statistically significant differences by any of our analyses. Therefore, there was no benefit in taking this particular dose of melatonin (1.8 mg sustained release) at this particular time (8:30 am or about 9 h after the baseline DLMO). All of the subjects in bright light groups 5 and 6 achieved complete re-entrainment. Melatonin could not increase the phase delay because they were already phase shifted as far as possible, creating a ceiling effect (Fig 4). However, when

groups 2 and 3 are considered, there was room for many subjects to phase delay later.

Perhaps a non-optimal timing or dose of melatonin was the reason that larger delays were not produced in group 3. Figure 6 shows a schematic melatonin PRC. The time that the 0.5 mg dose produced the largest phase delay was about 10 h after the DLMO. The average baseline DLMO for group 3 was at about 23:00. Thus, the melatonin administered at 8:30 was 9.5 h after the DLMO (top arrow under the PRC), which was at about the best time to produce a phase delay with a 0.5 mg dose. However, the 1.8 mg sustained release preparation we used probably remained in the circulation longer than the immediate release 0.5 mg dose used to generate this PRC. We estimate that the sustained release dose lasted about 11.5 h, but it varied widely among individuals. Thus, for a person with a DLMO at 23:00 it is possible that the tail end of the sustained release dose impinged upon the phase advance portion of the PRC. However, most of the melatonin was released over the same interval of time as the immediate release dose which produced the maximum delay. Thus, the first dose of melatonin was probably at a good time to produce phase delays. As the circadian rhythms of our subjects shifted later, the melatonin administration at 8:30 occurred at earlier and earlier times relative to the melatonin PRC, as shown by the rest of the horizontal arrows. If the DLMO delayed as far as 6:00, then the melatonin administered at 8:30 began on the tail end of the phase advance portion of the PRC (bottom arrow). But again, because of the sustained release dose, the tail end of the dose probably coincided with the phase delay portion of the PRC. Thus, the net effect was probably little or no phase shift. Thus, as the rhythms delayed, the timing of the dose probably became less effective. The only way to optimize the dose would have been to administer it later and later as the rhythms delayed (as we did for bright light), but that would have interfered with sleep. We estimate that melatonin had the greatest phase delaying effect when the DLMO was between about 21:00 and 2:00, but clearly, more melatonin PRCs using different doses of melatonin are needed. If our estimate is correct, then the melatonin did not contribute to delaying the DLMO much past about 2:00. The final DLMOs for group 3 were all later than 2:00, which means that other factors besides melatonin were probably responsible for these delays. A glance at the group 2 final DLMOs shows that just dark/sleep and dark sunglasses produced final DLMOs this late.

Melatonin was always paired with the darker sunglasses. Since the darker sunglasses helped the earlier subjects delay, the darker sunglasses may have masked the delaying effects of melatonin. Unfortunately, we did not test a group with normal sunglasses and melatonin, which may have revealed the hormone's possible phase delaying abilities.

Many studies have shown melatonin's phase advancing effects (e.g. Attenburrow et al., 1995; Krauchi et al., 1997; Sharkey and Eastman, 2002). However, the current study was one of the few in which melatonin 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 melatonin administered at 8:00 (2 mg), 11:00 (1 mg) and 14:00 (1 mg) vs placebo. There was no difference between the phase delay shifts attained by those that took melatonin or those that took placebo (4.7 h vs. 4.2 h) probably because the times of melatonin administration coincided with both the phase delay and phase advance portions of the melatonin 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 (21:30 to 7:30) and 7 consecutive days off. Melatonin (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 melatonin was taken during one two-week block and placebo was taken during the other. The DLMO was assessed weekly. Only 7 out of the 24 subjects responded to melatonin during the night shift week, meaning that their final DLMO was shifted at least 3 h later with melatonin in comparison to placebo. Some delayed and some advanced equally as far with placebo or melatonin, and others did not shift with either treatment. These variable results could be due to

different light exposure patterns created by the subjects' sleep schedules and whether or not they wore sunglasses. The timing of melatonin administration varied because the workers chose when they went to sleep and took the melatonin before going to sleep.

In conclusion, neither these studies nor our current study provide much evidence that melatonin can help phase delay circadian rhythms in a night shift work situation. Further study should be done after more basic research on the phase delaying properties of melatonin.

Daytime Sleep

There was a significant correlation showing that more daytime sleep was associated with greater re-alignment of circadian rhythms with dark/sleep, but it was very weak. There was no difference in daytime sleep duration among the 3 re-entrainment categories. Subjects slept almost all of the allotted 7 h, probably because they were relatively young and phase tolerant (able to sleep at the wrong circadian phase, c.f. Dawson and Campbell, 1991). In our previous simulated night shift studies we found moderate significant correlations between daytime sleep duration and phase shift, showing that circadian re-alignment improved sleep (Eastman et al., 1994, 1995b; Martin and Eastman, 1998). Other simulated night shift studies have also found that phase delay shifts resulted in better sleep quality or duration (Czeisler et al., 1990; Dawson and Campbell, 1991; Dawson et al., 1995). One possible reason for not finding a strong relationship in the current study is that we limited the time in bed to 7 h, whereas in the other studies the daytime dark period was 8 h. Sleep is most difficult during the day (after the night shift) in the last half of the sleep period (e.g. Sharkey et al., 2001). It is possible that the effect of circadian re-alignment would have shown up more if we required a longer daytime sleep period. However, we think that most real night shift workers would not make the time to spend more than about 7 h in bed during the daytime.

In this study, sleep duration was not greater in the groups that took melatonin compared to the matching groups that received placebo. In one of our previous simulated night shift studies (Sharkey et al., 2001) circadian rhythms were purposely not shifted, and the same preparation of melatonin (1.8 mg) taken before bed lengthened daytime sleep. In that study subjects were required to stay in bed in the dark for 8 h, and the improvement was only seen in the second half of sleep. Thus, the 7 h time in bed in the current study could have kept us from detecting an effect of melatonin. In that previous study, melatonin was only effective for daytime sleep after the first night shift. It did not improve sleep after the second night shift, suggesting a tolerance effect. In the current study, melatonin did not even improve sleep after the first night shift. Again, we only made subjects stay in bed for 7 h, so perhaps melatonin would have helped if they had a longer sleep opportunity.

In the simulated night shift study of Dawson et al (1995), 4 mg of melatonin spread out over the 8 h daytime sleep period did not produce circadian re-entrainment, but it did improve sleep quality. Perhaps the larger dose of melatonin or the longer time in bed was responsible for showing improved sleep with melatonin. Studies of real night shift workers have shown varying results. Melatonin (1 mg, 6 mg, and 10 mg) did not improve sleep during the day after the night shift in emergency room physicians and emergency medical services personnel (James et al., 1998; Jorgensen and Witting, 1998; Jockovich et al., 2000). In contrast, melatonin (5 mg and 6 mg) improved daytime sleep after the nights shifts in police officers and night nurses (Folkard et al., 1993; Yoon and Song, 2002). These conflicting results might be due to different light exposure and sleep schedules in these field studies. Obviously, more work needs to be done to determine under which conditions melatonin can help the daytime sleep of night shift workers, and whether tolerance develops.

Night Shift Performance, Sleepiness and Mood

Although our subjects obtained a decent amount of sleep during the daytime, circadian re-alignment was necessary to improve neurobehavioral measures during the night shift. The subjects who were not re-entrained were sleepier, performed worse, and felt worse than those that achieved re-entrainment (partial or complete). These results are similar to our other simulated night shift studies in which large phase shift subjects (corresponding to re-entrained subjects) had less POMS fatigue and mood disturbance than small phase shift subjects (corresponding to not entrained subjects). In these previous studies we also found correlations between the magnitude of the phase shift and POMS scales showing that the more re-alignment of circadian rhythms with sleep, the better our subjects felt (Eastman et al., 1994, 1995b; Martin and Eastman, 1998). Other simulated night shift studies used bright light and produced partial re-entrainment (Dawson and Campbell, 1991) or complete re-entrainment (Czeisler et al., 1990; Dawson et al., 1995), and also found higher levels of cognitive performance and alertness in the groups that re-entrained compared to control groups that did not.

Interestingly, in the current study there were no differences on the night shift measures between the subjects that were partially re-entrained and those who were completely re-entrained. These data suggest that for young and healthy adults, partial re-entrainment is sufficient to improve the neurobehavioral problems associated with night shift work. We do not know of any other studies which compared partial to complete re-entrainment. However, similar simulated night shift studies on young subjects (Dawson and Campbell, 1991) and middle aged subjects (Campbell, 1995) suggest that while partial re-entrainment is sufficient for young subjects, complete re-entrainment may be necessary to reap similar benefits in older subjects.

This study has many practical applications for night shift workers and their employers. We showed that circadian re-entrainment helps alleviate the neurobehavioral problems associated with a night worker's schedule. Even partial re-entrainment can help alleviate these problems, at least in a younger population of night shift workers. Simple habits like wearing sunglasses 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 promote some circadian adjustment. Bright light exposure during the night shifts can help adjust circadian rhythms even more. Exposure to bright light during the night shift may be more difficult to implement individually. However, knowing that circadian adjustment would add to the productivity and quality of work, employers of 24-h companies may take the initiative and install bright light banks or ceiling fixtures in the work place. Employers could also take the initiative of educating their employees about the different options available to them to help them feel and perform better as a night shift worker.

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1. Crowley, S.J., Lee, C., Tseng, C.Y., Fogg, L.F., and Eastman, C.I. Combinations of bright light, scheduled dark, sunglasses and melatonin to facilitate circadian entrainment to night shift work. J. Biol. Rhythms, in press, 2003.

2. Burgess, H.J., Sharkey, K.M., and Eastman, C.I. Bright light, dark and melatonin can promote circadian adaptation in night shift workers. Sleep Medicine Reviews, 6: 407-420, 2002.

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Table 1. Intervention groups

Group	Interventions	Codes	N[a]
1	Dark / Sleep + Normal Sunglasses	D/S + N SG	15
2	Dark / Sleep + Dark Sunglasses	D/S + D SG	11 (12)
3	Dark / Sleep + Dark Sunglasses + Melatonin	D/S + D SG + M	13
4	Dark / Sleep + Normal Sunglasses + Bright Light	D/S + N SG + BL	11
5	Dark / Sleep + Dark Sunglasses + Bright Light	D/S + D SG + BL	9
6	Dark / Sleep + Dark Sunlglasses + Melatonin + Bright Light	D/S + D SG + M + BL	6 (7)
Total			65 (67)

[a] Numbers in parentheses are Ns including the subjects whose baseline DLMO could not be determined and thus only the final DLMO is available.

Table 2. Percentage of subjects within each intervention group categorized by degree of re-entrainment to the daytime sleep schedule.

	Re-entrainment Category		
	Not[a]	Partial[b]	Complete[c]
Intervention Group	(n = 10)	(n = 16)	(n = 41)
1. D/S + N SG	47%	13%	40%
2. D/S + D SG	17%	42%	42%
3. D/S + D SG + M	0%	69%	31%
4. D/S + N SG + BL	9%	0%	91%
5. D/S + D SG + BL	0%	0%	100%
6. D/S + D SG + M + BL	0%	0%	100%

[a] Final DLMO earlier than 1:30, and therefore estimated final Tmin before the time corresponding to daytime dark/sleep

[b] Final DLMO between 1:30 and 5:00, and therefore estimated final Tmin during the time corresponding to the first half of daytime dark/sleep.

[c] Final DLMO later than 5:00, and therefore estimated final Tmin during the time corresponding to the second half of daytime dark/sleep.

Table 3. Circadian phase measures, means (in clock time) and standard deviations (in hours).

Intervention Group	N	Baseline DLMO Mean (SD)	Final DLMO Mean (SD)	Phase Delay Shift Mean (SD)
1. D/S + N SG	15	22:48 (1.7)	2:30 (4.0)	3.6 (2.6)
2. D/S + D SG	11	22:24 (1.2)	4:18 (3.0)	5.5 (2.4)
3. D/S + D SG + M	13	22:54 (1.6)	4:42 (1.5)	5.8 (1.0)
4. D/S + N SG + BL	11	23:36 (1.4)	5:54 (3.0)*	6.3 (2.1)*
5. D/S + D SG + BL	9	00:30 (1.2)†	6:54 (0.5)**	6.5 (0.9)*
6. D/S + D SG + M + BL	6	00:12 (1.4)	7:30 (0.6)**	7.1 (1.1)**

*$p<0.05$ and **$p<0.01$ (two-tailed) when compared to group 1.

†$p<0.05$ (two-tailed) when compared to group 2.

Table 4. Circadian phase measures from earlier subjects[a], means (in clock time) and standard deviations (in hours)

Intervention Group	N	Baseline DLMO Mean (SD)	Final DLMO Mean (SD)	Final Tmin[b] Mean	Phase Delay Shift Mean (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)***

[a]Subjects with baseline DLMOs before 0:00, and thus estimated baseline Tmins before 7:00 (before the start of the commute home time).

[b]Estimated from final DLMO. DLMO + 7h = Tmin.

*$p<0.05$, **$p<0.01$, and ***$p<0.001$ (all two-tailed) when compared to group 1.

[§]$p<0.10$ (two-tailed) when compared to group 1.

Table 5. Percentage of subjects within each re-entrainment category for earlier subjects and for later subjects.

		Earlier Subjects[a]				Later Subjects[b]		
		Re-entrainment Category				Re-entrainment Category		
Intervention Group	N	Not[c]	Partial[d]	Complete[e]	N	Not[c]	Partial[d]	Complete[e]
1. D/S + N SG	10	70%*	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%‡	14	0%	0%	100%

[a]Baseline DLMO $\leq$ 0:00, and thus estimated baseline Tmin $\leq$ 7:00 (before start of the commute home time from the night shifts).

[b]Baseline DLMO > 0:00, and thus estimated baseline Tmin > 7:00 (after the start of the commute home time from the night shifts).

[c]Final DLMO earlier than 1:30, and therefore estimated final Tmin before the time corresponding to daytime dark/sleep

[d]Final DLMO between 1:30 and 5:00, and therefore estimated final Tmin during the time corresponding to the first half of daytime dark/sleep.

[e]Final DLMO later than 5:00, and therefore estimated final Tmin during the time corresponding to the second half of daytime dark/sleep.

* Significantly different from the other intervention groups by a chi-square analysis when the partial and complete re-entrainment categories were combined.

‡Significantly different from the other intervention groups by a chi-sqaure analysis when the not re-entrained and partial re-entrainment categories were combined.

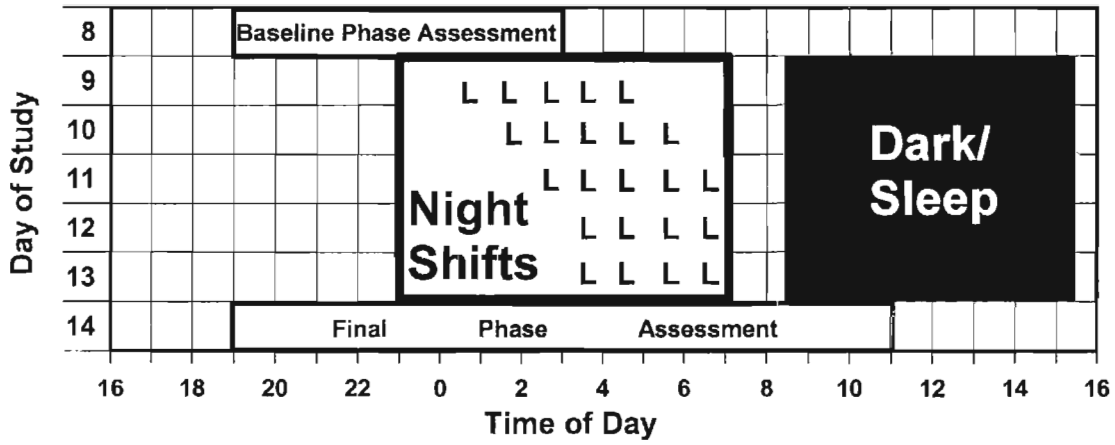


Figure 1. Experimental week of the study protocol. Circadian phase was assessed on days 8 and 14 to determine the salivary DLMO. Simulated night shifts (23:00 to 7:00) took place on days 9-13. L = bright light pulse (~5000 lux, for 20 min) for subjects in the bright light groups (4, 5, and 6). Each bright light pulse started 20 min before the hour and ended on the hour (e.g. 6:40 to 7:00). Normal room lighting (~150 lux) was used between bright light pulses and throughout the night for those in the remaining groups (1, 2 and 3). Subjects wore sunglasses with normal lenses (groups 1 and 4) or very dark lenses (groups 2, 3, 5, and 6) during their commute home from the night shift and whenever they went outside during daylight. Subjects in groups 3 and 6 took melatonin (1.8 mg, sustained release) and the remaining groups took placebo right before bedtime at 8:30. All subjects were required to be in bed, in the dark from 8:30 to 15:30 on days 9-13.

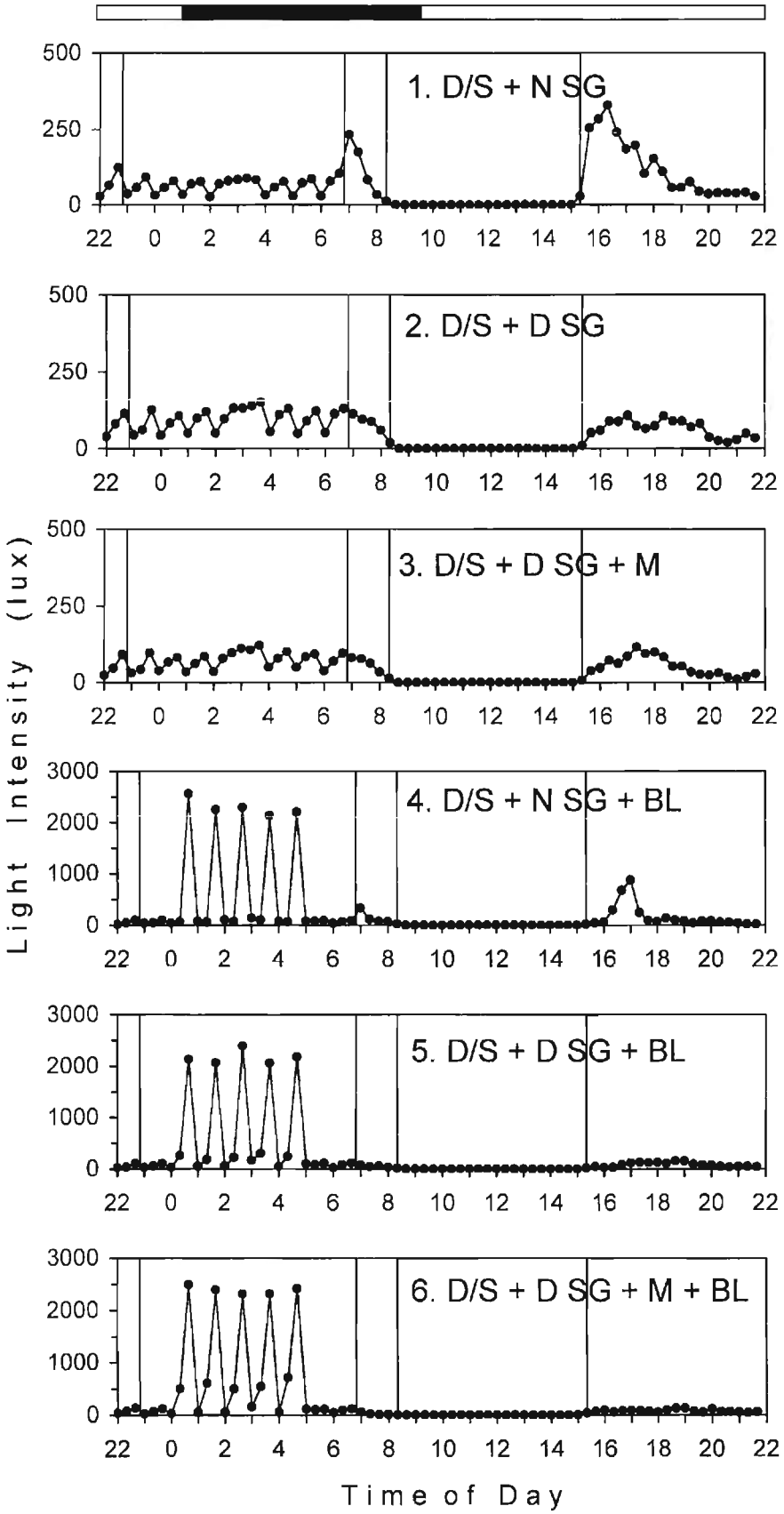


Figure 2. Light intensity for the 24 h period which included the first night shift and the first dark/sleep episode for each intervention group. Light levels were corrected for actiwatch error and the wearing of sunglasses and then averaged into 20-min bins. Vertical lines enclose the points that occurred during the night shift (23:00 to 7:00) and during the dark/sleep period (8:30 to 15:30). The black bar on the top represents the average dark/sleep time during baseline (0:53 to 9:25). Note the different scales on the y-axis for groups 1, 2, and 3 compared to groups 4, 5 and 6.

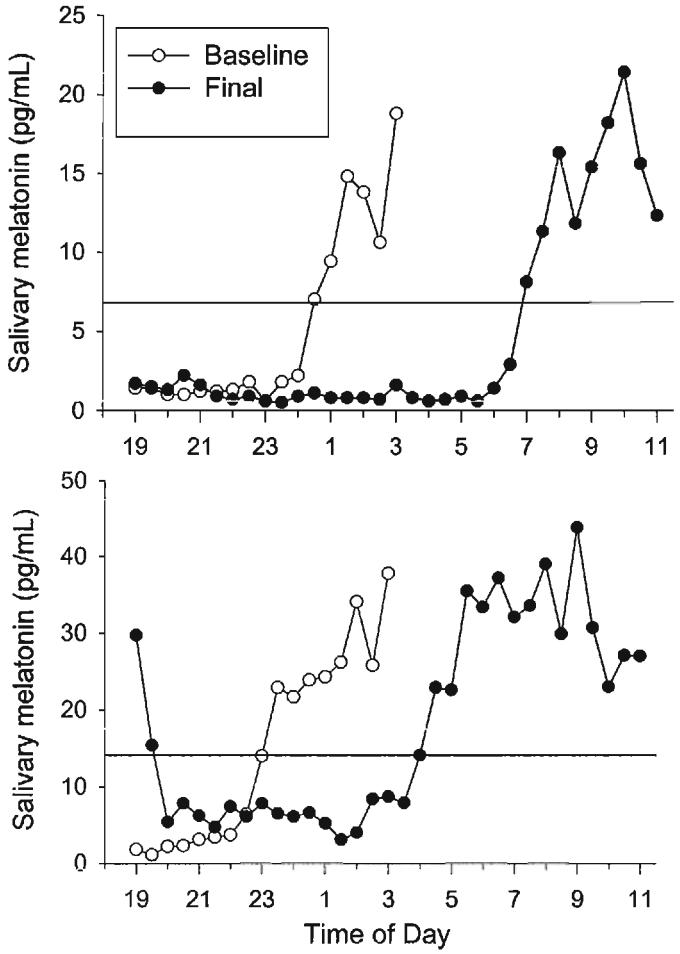
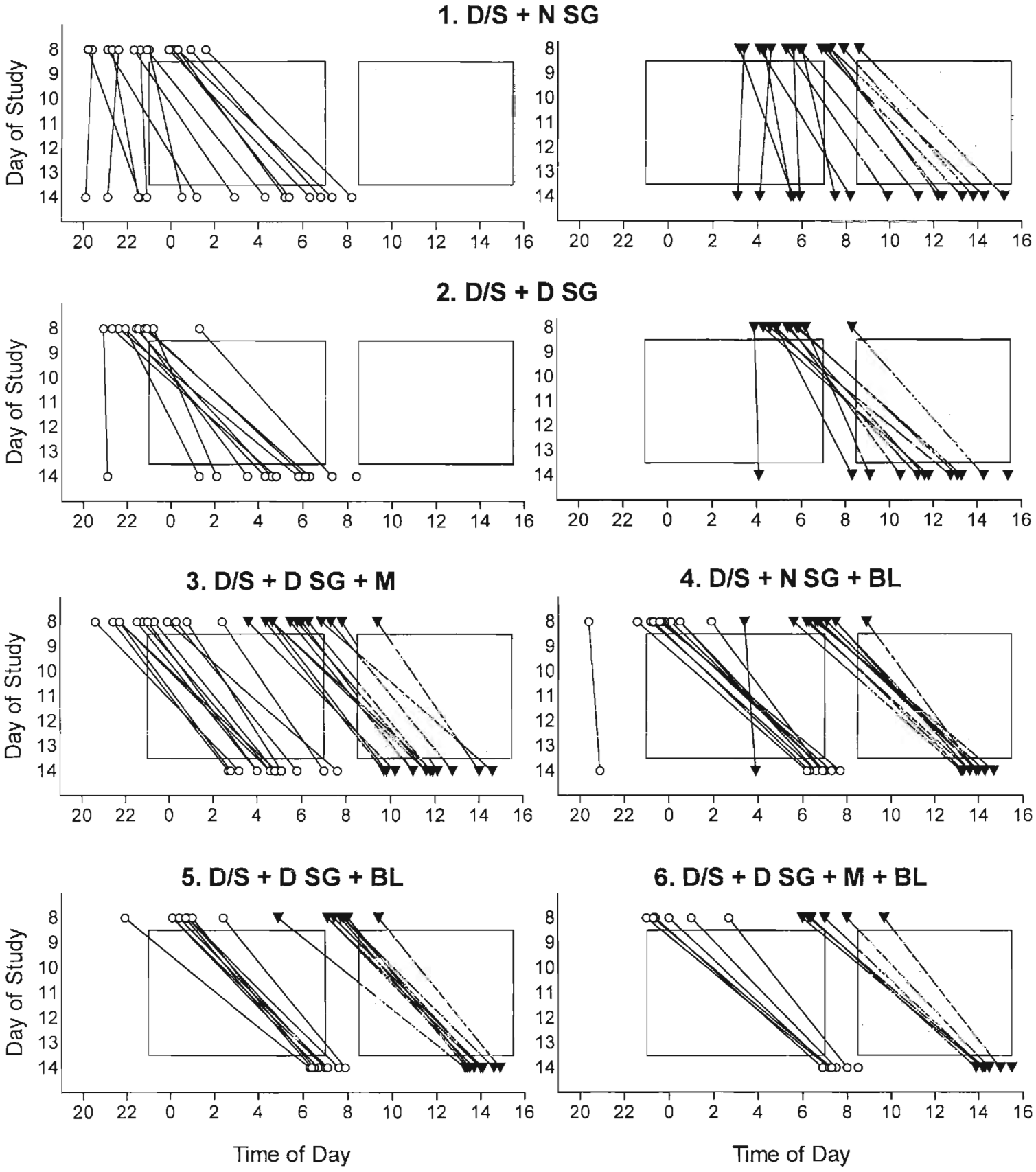


Figure 3. Melatonin profiles from two subjects. Open circles are melatonin levels during the baseline phase assessment and filled circles are melatonin levels during the final phase assessment. The horizontal line is the individually tailored threshold for each subject. The top panel shows the profiles for a subject in one of the groups that took placebo and the bottom panel shows the profiles for a subject in one of the groups that took melatonin.

Figure 4. Baseline and final phase markers for each individual subject in each intervention group. Open circles indicate DLMOs and filled triangles indicate estimated Tmins (DLMO + 7h). The white rectangles show the 5 consecutive night shifts (23:00 to 7:00). The shaded rectangles show the 5 daytime dark/sleep episodes (8:30 to 15:30) after each night shift. Lines connect the baseline and final phase markers for each subject. For two subjects (one in group 2 and one 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.

Figure 4.


1. D/S + N SG
2. D/S + D SG
3. D/S + D SG + M
4. D/S + N SG + BL
5. D/S + D SG + BL
6. D/S + D SG + M + BL
Day of Study
8
9
10
11
12
13
14
20 22 0 2 4 6 8 10 12 14 16
Time of Day

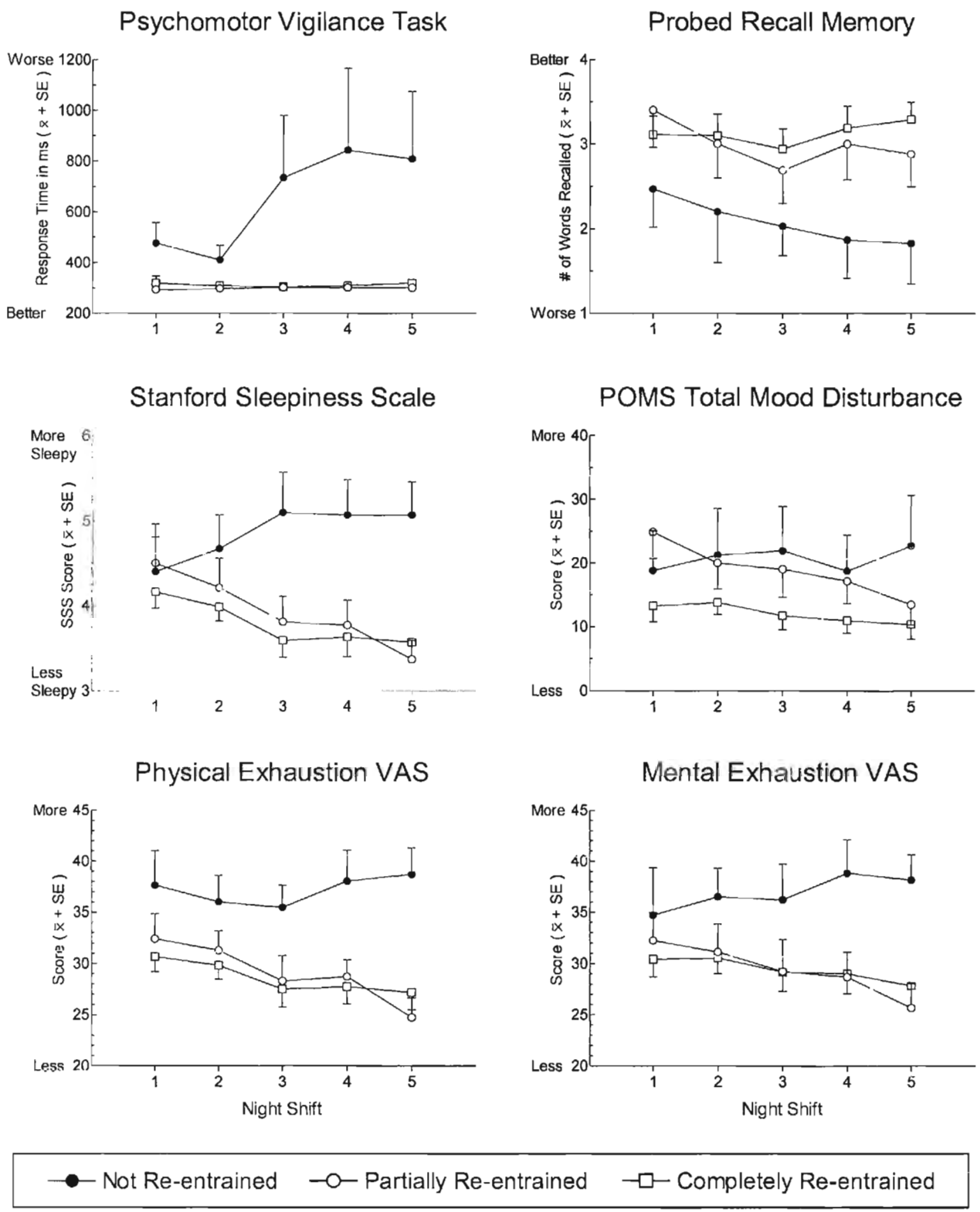


Figure 5. Performance, sleepiness, and mood measures obtained during the night shifts for the subjects who were not re-entrained (filled circles; n = 10), partially re-entrained (open circles; n = 16), and completely re-entrained (open squares; n = 41).

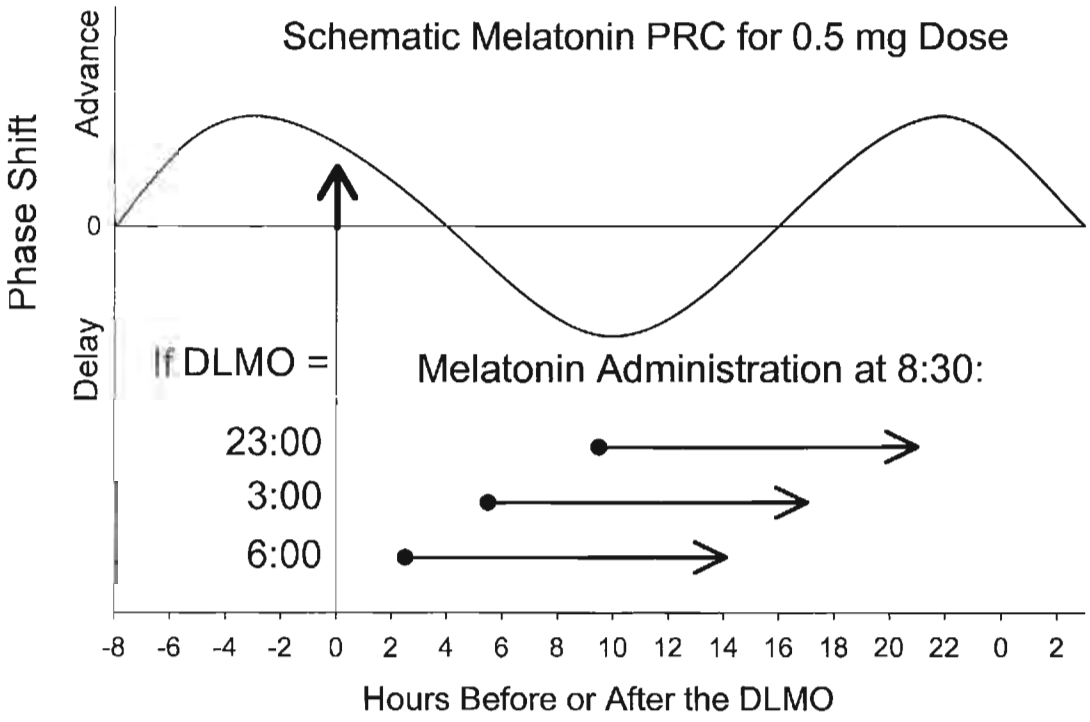


Figure 6. Schematic melatonin PRC adapted from Burgess et al. (2002) based on the data of Lewy et al. (1998) showing the phase shift produced by 0.5 mg of melatonin administered at various times relative to the DLMO (upward arrow). Below the PRC are examples of DLMO times and horizontal arrows showing when the melatonin administration at 8:30 occurred relative to the melatonin PRC. The horizontal arrows extend for 11.5 h after administration (marked by the circle) to show about how long the sustained release 1.8 mg dose of melatonin remained in the subjects' body.

Memorandum

Scanned 12/16/14

Date: November 4, 2003

From: Adele M. Childress, Ph.D., Program Official AMC
Office of Extramural Programs, NIOSH, E-74

Subject: Final Report Submitted for Entry into NTIS for Grant 5 R01 OH003954-02.

To: William D. Bennett
Data Systems Team, Information Resources Branch, EID, NIOSH, P03/C18

The attached final report has been received from the principal investigator on the subject NIOSH grant. If this document is forwarded to the National Technical Information Service, please let us know when a document number is known so that we can inform anyone who inquires about this final report.

Any publications that are included with this report are highlighted on the list below.

Attachment
cc: Sherri Diana, EID, P03/C13

List of Publications

Burgess HJ, and Eastman CI, How Well do Fixed and Free Sleep Schedules Predict the Dim Light Melatonin Onset in Young Healthy Subjects? Sleep, 26:A95, 2003.

Lee C, Tseng CY, Crowley SJ, Fogg LF, and Eastman CI, Alignment of Circadian Rythms to Daytime Slepp Improves Performance and Alertness in Night Shift Workers. Sleep, 26: A97, 2003

Crowley SL, Lee C, Tseng CY, Fogg LF, and Eastman CI, Combinations of Bright Light, Scheduled Dark, Sunglass and Melatonin to Facilitate Circadian Entrainment to Night Shift Work, J. Biol Rythms, in 2003

Lee C, Tseng CY, Crowley SL, Fogg LF, and Eastman CI, Alignment of Circadian Rhythims to Daytime Sleep Improves Performance and Alertness in Night Shift Workers. Sleep, 26: A97,

Crowley SL, Lee C, Tseng CY, Fogg LF, and Eastman CI, Circadian Adaptation to Night Shift Work: Daytime Dark is Good, Adding Light During the Night Shift is Better. Sleep, 25: A155-6, 2002

Burgess HJ, Sharkey KM, and Eastment CI, Bright Light, Dark and Melatonin can Promote Circadian Adaptation in Night Shift Workers. Sleep Medicine Reviews, 6:407-420, 2002.

Crowley SJ, and Eastman CI, Black Plastic and Sunglasses can Help Night Workers. 15th Internation Symposium on Night Shiftwork, 18:65 Japan, September, 2001

Title:	Practical Circadian Interventions for Night Shift Work
Investigator:	Charmane I. Eastman, Ph.D.
Affiliation:	Rush-Presbyterian-St. Luke's Medical Center
City & State:	IL
Telephone:	(312) 942-4472
Award Number:	5 R01 OH003954-02
Start & End Date:	9/30/1999–9/29/2003
Total Project Cost:	$846,000
Program Area:	Organization of Work
Key Words:	work organization, intervention

Final Report Abstract:

Abstract

The circadian clock assures that diurnal animals, like humans, are alert during the day and asleep at night. Unfortunately, night shift workers are required to work during the "wrong" phase of their circadian cycle, when they are the most inefficient, sleepy, often fall asleep, and are most prone to accidents. Subsequently, they try to sleep during the day, again during the "wrong"

phase of their circadian cycle, which results in disrupted and shortened sleep. The chronic sleep deprivation exacerbates the problem of having to work at night when the circadian clock makes people the sleepiest. Sleeping pills can help workers sleep during the day, but this does not

eliminate the nighttime sleepiness and performance decrements caused by the circadian clock.

Stimulants like coffee and pharmacological drugs can help workers remain alert during the night shift, but can interfere with subsequent daytime sleep. Furthermore, there is potential for side- effects, dependence and abuse with most drugs.

The best solution for night work is to phase-shift the circadian clock to align with the night work and day sleep schedule. This re--alignment (re-entrainment) will alleviate the physiological symptoms of night work because the period of sleepiness will now occur during the daytime sleep period and the period of alertness will occur during the night shift. We tested various combinations of interventions designed to phase delay circadian rhythms and thus produce re-alignment. Young subjects who were not real shift workers (median age = 22, n=67) participated in 5 consecutive simulated night shifts (23:00 to 07:00) in the lab. The various

interventions included a fixed daytime dark period for sleep at home, bright light during the night shift, sunglasses for the commute home and melatonin at bedtime. The daytime dark period was from 8:30 to 15:30 after each night shift, which we think is a reasonable daytime sleep schedule for a real night shift worker. It started 1.5 hours after the end of the night shift, leaving ample time to commute home and get ready for bed. We covered the bedroom windows with thick black plastic to make the rooms very dark for sleeping during the day. Because the study was run in the summer (3 consecutive summers), we installed air conditioners for subjects that did not already have them. The fixed daytime dark period creates a shifted (phase delayed) light dark (LD) cycle that "tells" the circadian clock to phase shift, i.e., to entrain to the new LD cycle.

We have previously shown that bright light can either facilitate or inhibit the desired phase shift depending on its timing. Bright light before the body temperature minimum (Tmin) facilitates phase delays, whereas bright light after the Tmin facilitates advances. In this study, we exposed subjects to a gradually moving (delaying) pattern of intermittent bright light (~5000 lux, 20 min on, 40 min off, 4-5 light pulses/night) or kept them in ordinary room light (dim light, ~ 150 lux) during the night shifts. We tested intermittent bright light because in areal night work setting it may be difficult for workers to remain exposed 1:0 the light sources for an extended amount of time. We ended the series of bright light pulses at 5:00 during the first night shift
because we estimated the average baseline Tmin would be at about 5:00, and thus the bright light would facilitate phase delays. We moved the pattern one hour later on each subsequent night shift in order to phase delay the rhythms as far as possible (to keep up with the gradually delaying Tmin). The bright light was produced by 3 light boxes set on the perimeter of a large, round
table facing in toward the center of the table. Subjects sat in the openings in between the light boxes so that each subject faced a light box. The light boxes (Apollo Light Systems Inc., Orem, UT, 61.0 cm wide, 77.5 cm high, 12.1 cm deep) contained cool-white fluorescent lamps. Sunglasses with normal or very dark lenses (15 or 2% li~~ht transmission) were used to attenuate sunlight during the commute home, which we expected to occur after the Tmin and thus inhibit the desired phase delay. Melatonin (1.8 mg, sustained release) or placebo was taken immediately before each daytime sleep (8:30am), a time expected to facilitate phase delays. A sustained release preparation was used to enhance the soporific effect throughout the daytime sleep period.

The study included 6 intervention groups (6 combinations of the interventions mentioned above), which differed in the type and number of interven1:ions and therefore in the amount of effort that would be required if adopted by real night shift workers and their employers. The 6 groups were: 1) dark daytime period for sleep + normal sunglasses, 2) dark daytime period for
sleep + dark sunglasses, 3) dark daytime period for sleep ,- and dark sunglasses + melatonin, 4)
dark daytime period for sleep + normal sunglasses + bright light, 5) dark daytime period for sleep + dark sunglasses + bright light, and 6) dark daytime period for sleep + dark sunglasses + bright light + melatonin. The subjects who did not get bright light during the night shift remained in room light. The subjects who did not take melatonin before bed took placebo (double-blind).
The dim light melatonin onset (DLMO) was our marker for the phase of the circadian clock, and was assessed before and after the night shifts (baseline and final). We estimated the Tmin as the DLMO + 7 hours. A reasonable goal for circadian adaptation to the night work and day sleep is to phase shift circadian rhythms so that the sleepiest part of the circadian cycle, the Tmin, falls within the daytime sleep episode. Therefore, subjects were categorized by their amount of re-entrainment (re-alignment) based on their final Tmin: not re-entrained (Tmin before the daytime dark/sleep period), partially re-entrained (Tmim during the first half of dark/sleep), or completely re-entrained (Tmin during the second half of dark/sleep). Computerized neurobehavioral batteries were completed during each night shift. Sleep logs were verified by wrist activity monitors and photo sensors worn around the neck like a medallion.
Subjects exhibited a wide range of baseline circadian phases, as would real night shift workers. We split the sample into earlier subjects (baseline Tmin> 7:00, sunlight during the commute home fell after the Tmin and would thus inhibit the desired phase delay) and later subjects (baseline Tmin > 7:00). The later subjects were completely re-entrained regardless of
intervention group, whereas the degree of re-entrainment for the earlier subjects was improved by some of the interventions. Most of the earlier subjects in group 1 did not entrain. When the earlier subjects were given bright light during the night shift (groups 4,5 and 6) all but one achieved complete re-entrainment, and the phase delay shift for the rest 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 subjects phase delay more than normal sunglasses (group 2 compared to group 1). However, the darker sunglasses contain welders' lenses and are not designed for driving. Melatonin did not confer a benefit either for phase delaying or for increasing sleep duration.
Although subjects slept about 6.5 hours during th(: day, night shift sleepiness and performance did not improve unless there was circadian phase alignment (partial or complete re- entrainment). Subjects who re-entrained did significantly. better than subjects who did not re- entrain on the Psychomotor Vigilance Task (PVT), the Digit Symbol Substitution Test (DSST), the Stanford Sleepiness Scale (SSS), the Karolinska Sleepiness Scale (KSS) and the Physical Exhaustion and Tiredness Visual Analog Scales (V AS). There was no difference in these neurobehavioral measures between those who were partially and completely re-entrained, perhaps because our subjects were so young and thus "phase tolerant."

This study showed that circadian adaptation to fixed night shifts is possible. Subjects with very late circadian rhythms need only maintain a fixed, dark, daytime period for sleep and wear normal sunglasses during the commute home. For subjects who start the night shift with earlier circadian rhythms, we 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 for complete circadian adaptation to night shift work.

Publications:

Lee C, Tseng CY, Crowley SL, Fogg LF, and Eastman CI, Alignment of Circadian Rhythims to Daytime Sleep Improves Performance and Alertness in Night Shift Workers. Sleep, 26: A97,

Crowley SL, Lee C, Tseng CY, Fogg LF, and Eastman CI, Combinations of Bright Light, Scheduled Dark, Sunglass and Melatonin to Facilitate Circadian Entrainment to Night Shift Work, J. Biol Rythms, in 2003

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