FINAL PROGRESS REPORT

Practical Circadian Interventions for Night Shift Work

R01 OH003954 – years 4 to 8

Grant Period: 8/1/2003 – 4/30/2009

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List of Terms and Abbreviations

DLMO = dim light melatonin onset = a marker of the phase or time of the circadian clock

Tmin = temperature minimum = estimate for the sleepiest circadian time

TST = total sleep time

TMD = total mood disturbance

A. Abstract

Humans, like most of the plants and animals on the planet, have an internal circadian clock which produces daily (circadian) rhythms in almost all functions and variables such as body temperature, cognitive and physical performance, the secretion of hormones and neurotransmitters, etc. Our circadian clocks are synchronized to the 24 hour day primarily by the light and dark to which we are exposed, to the 24 hour light-dark cycle. As diurnal animals we are programmed by our circadian clocks to feel sleepy and to sleep at night, and to be awake and alert during the day. Body temperature, alertness and performance reach a low point around 4 to 6 am. This creates a problem for night shift workers who feel sleepy and are most prone to accidents at work, especially near the end of the night shift. This low point produced by the circadian clock persists even if the worker obtains enough sleep during the day. Furthermore, since we are programmed to be alert during the day, night shift workers often have shortened and disrupted sleep when they go home to sleep during the daytime after the night shift. This results in cumulative partial sleep deprivation which exacerbates the natural circadian dip in alertness during the night shift.

Aside from the obvious safety risks to the night worker and to the public, especially for critical jobs such as nuclear power plant operators and hospital intensive care nurses, there are long term health consequences for the workers. Night shift workers have a higher incidence of cancer, diabetes and heart disease. There are several factors that may account for this. One is the fact the night workers are forced to be awake, to eat meals and to sleep at the wrong times according to their internal circadian clock. Thus, the body is not properly prepared for these activities. This is called "circadian misalignment" because the daily activities and the internal circadian rhythms are not properly aligned. Another factor which could account for health problems is the shortened and disrupted sleep. Shorter sleep has been linked to obesity and diabetes. Finally, the higher incidence of cancer could be caused, in part, by light during the night shift. Light suppresses the secretion of the neurohormone melatonin which is an antioxidant. In any case, the International Agency for Research on Cancer has classified night work as a probable carcinogen. Millions of Americans, 15 to 20% of the workforce, work night shifts. This number will probably increase as we become even more of a 24/7 society.

For over 20 years the P.I. has been working on methods to trick the circadian clock of the night worker into aligning with the night work, day sleep schedule in order to eliminate circadian misalignment. She has shown that by creating a new 24 pattern of light and dark the circadian clock can be completely reset, or phase-shifted, to align with the night work, day sleep schedule. This is done by using bright light from light boxes during the night shift, dark sunglasses on the commute home and a regular, dark, daytime sleep period. Most of these studies, including those reported here, were simulated night shift studies in which volunteers "work" night shifts in the lab. But they sleep at home like real night shift workers. The circadian clocks of most real night workers do not phase shift to adjust to the night work schedule, because they are not exposed to an appropriate pattern of light and dark. For example, they do not have bright light at work, do not wear dark sunglasses on the way home, and do not maintain a regular dark sleep episode after work. One problem with introducing these methods into the workplace is that complete alignment to the night shift schedule leaves the individual misaligned with their friends and family on days off. We expect that night workers might not adhere to a program that makes them feel good during work days, but not on days off.

The 5 year project reported here was designed to assess the feasibility of achieving and maintaining a compromise circadian phase position for permanent night shift work. (This procedure could easily be expanded for slowly rotating shift work systems.) A compromise phase position is one in which the circadian clocks of night workers are *partially* aligned with a night work and day sleep schedule, so that their sleepiest time is delayed out of the night work period and into the first part of the daytime sleep episode. Because the sleepiest time is shifted out of the night work period, alertness and performance during the work period will improve. Because the sleepiest time of day is shifted into the daytime sleep period after work, sleep will improve. A late sleep schedule is maintained on days off, which is about half-way between the earlier sleep schedule of the non-shift working society and the very late (daytime) sleep schedule the night worker is forced to adopt after night

shifts. With this days-off sleep schedule, which is another compromise, the sleepiest time of day will occur near the end of the sleep period, producing fairly good sleep on days off. An added bonus is that the time for the secretion of melatonin is shifted from primarily during the night shift to primarily during the dark sleep periods, so that melatonin synthesis is not suppressed, thus reducing the cancer risk. Our overall goal was to produce a circadian phase position that is good for working at night and for both daytime sleep after night shifts as well as late nighttime sleep on days off.

These studies assessed the circadian phase of experimental groups and control groups during a series of blocks of night shifts (3-5 consecutive night shifts) alternating with 2 consecutive days off. Experimental subjects were exposed to intermittent bright light pulses during night shifts (usually only 15 minutes of bright light per hour, only 4 to 5 pulses per night shift). The light pulses were produced by light boxes usually sold for SAD or winter depression. The subjects had scheduled sleep episodes at home after night shifts and on days off. Bedrooms were made dark by covering the windows with black plastic. Subjects wore dark sunglasses during their morning commute home from night shifts. The dark sunglasses are commercially available, meeting the traffic signal color requirements of ANSI Z80.3-1996, and are general purpose sunglasses for driving and most outdoor activities. Subjects were required to go outside for afternoon light exposure following their daytime sleep after night work and their sleep on days off. This afternoon light exposure (a "light brake") was intended to keep their circadian clocks from completely adjusting to the night work and day sleep schedule, since partial adjustment was the goal of the compromise phase position. Like real night shift workers, control subjects remained in normal room light during their night shifts, and had unrestricted sleep and outdoor light exposure. They were given lightly tinted sunglasses.

These interventions reset the circadian clock of most of the experimental subjects to the target compromise phase position after about a week. This first week consisted of 3 night shifts, 2 days off and then more night shifts. When the circadian clocks of the subjects had shifted and were close to the compromise phase position, the subjects had improved alertness, performance, and mood during night shifts. In many subjects performance levels returned to daytime baseline levels, which is a vast improvement that cannot be matched even by the use of stimulants during the night shift. Experimental subjects were able to sleep for nearly all of the allotted time in bed on the prescribed schedule. In other words, they slept as long as permitted after the night shift (which was 7 hours) and as long as permitted on days off (which was 9 hours). In contrast to the experimental subjects, the sleepiest circadian time for most control subjects remained during night work, and was accompanied by impaired performance and mood, as well as decreased daytime sleep duration. A few control subjects adopted sleep schedules similar to those required of the experimental subjects, or even more extreme schedules with very late sleep on days off. Some of these subjects reset their circadian clocks as much as the experimental subjects even without bright light during the night shifts or very dark sunglasses during the commute home. However, the most reliable way to reduce circadian misalignment is to use bright light at work and wear dark sunglasses on the way home, along with the recommended sleep schedule.

These findings indicate that complete circadian adjustment to a night work and day sleep schedule is not necessary to produce substantial improvements in alertness and performance during night work. Instead, practical interventions that could be adopted by night workers with the cooperation of their employers can produce partial adaptation to a compromise circadian phase position. This will improve night shift alertness and performance while permitting sufficient sleep after work and on days off.

Future studies should implement these techniques into the workplace. This will take the cooperation of employers who would have to provide light boxes or overhead fixtures, but in return they could see increased productivity and reduced mistakes and accidents. It will also require some life style changes of the workers, including giving up morning activities after the night shift and on days off. Both employers and workers would have to agree to eliminate rapidly rotating shift work schedules, because such schedules do not permit circadian alignment. Finally, it will require a change in the culture to recognize the importance of obtaining enough sleep and getting it at the right time. Night shift workers need the cooperation of family and friends to be able to adopt the recommended sleep schedules. Fortunately, there are organizations such as the National Sleep Foundation, which have begun to educate the public about the importance of sleep. Their public awareness campaigns may be responsible for the increasing number of news stories about sleep. Adequate sleep has finally been recognized as important in the list of lifestyle changes that can improve the health of our nation, along with smoking cessation, diet and exercise.

B. Highlights\Scientific Findings

This grant included a series of studies designed to test whether a compromise circadian phase position could be produced and maintained in permanent night shift workers. The compromise we aimed for was to delay the sleepiest time of day out of the night work period and into the first half of the daytime sleep period. To delay it even further, into the second half of the daytime sleep episode, would be considered complete circadian adaptation, or complete reentrainment, because the normal phase relationship between the internal circadian rhythms and sleep, wake and meals would be restored. However, complete reentrainment leaves the worker out of phase on days off. Thus, a compromise circadian phase position is in between an ideal circadian phase position for night shift work (from a health and safety perspective) and an ideal circadian phase position on days off (from a social perspective). Experimental subjects received a number of interventions designed to promote phase delays (resetting to a later time) of their circadian clocks. These interventions included phase-delaying intermittent bright light pulses during night shifts, wearing dark sunglasses during the commute home from night shifts (to attenuate morning light that would hinder phase delays), scheduled daytime sleep episodes after work in a darkened bedroom, a late sleep schedule on days off, and scheduled outside light exposure upon awakening from daytime sleep (to prevent their circadian clocks from delaying past the compromise circadian phase position). Control subjects were exposed to conditions similar to what real night shift workers experience. They remained in normal dim room light during night shifts, wore lightly tinted sunglasses when outside, and had unrestricted sleep and light exposure.

The first specific aim was to determine whether the compromise phase position could be achieved and maintained in experimental subjects during alternations between blocks of night shifts and days off. We found that the compromise phase position was achieved on about day 7 to 9 of the schedule (after 3 night shifts, 2 days off and a few more night shifts), and that this phase position was maintained after a subsequent weekend off (after 12 days on the schedule).

Another specific aim was to determine whether experimental subjects performed and felt better than control subjects during night shifts. While we did observe some group differences in the predicted direction, these differences were not as robust as when we examined the individual differences in performance with respect to circadian phase. Independent of group assignment, those subjects whose circadian clocks delayed so that they were close to the compromise phase position performed and felt better during night shifts than subjects whose circadian clocks did not delay, or delayed only slightly.

Another specific aim was to determine if more experimental subjects than control subjects achieved the compromise phase position. Almost all of the experimental subjects achieved the compromise circadian phase position. Although there were large individual differences in circadian phase for control subjects, most had small phase delays such that the sleepiest circadian time remained during the night work period.

The final specific aim of this grant was to assess whether experimental subjects slept more than control subjects after night shifts and on days off. Experimental subjects were able to sleep for nearly all of the scheduled time in bed after night shifts and during the late nighttime hours on days off, indicating they tolerated the prescribed sleep schedule well. In contrast, the control subjects showed very large individual differences in sleep timing and duration. Control subjects who through their own means adopted sleep schedules similar to the experimental subjects, or even later, had circadian clocks that delayed to reach the compromise phase position, and these subjects had longer and more consolidated sleep bouts. Like many real night shift workers, control subjects who reverted to "normal" sleep times on days off showed little or no circadian adjustment to the night shift schedule and had shorter and more disrupted daytime sleep.

C. Translation of Findings

This series of studies demonstrated that a combination of practical interventions can be used to improve alertness and performance during a permanent night shift schedule. These interventions can be broken down into 4 categories: 1) intermittent bright light during the night shifts, 2) dark sunglasses for the commute home, 3) a specific sleep schedule after the night shifts and on days off in a very dark bedroom, and 4) afternoon bright light exposure after waking up from sleep.

During night shifts we used four or five 15-minute intermittent bright light pulses delivered once per hour, and interspersed by normal room light. Bright light pulses were administered by light boxes that were positioned around a table. We used standard commercially available bright light boxes (about 2 feet wide and 1 foot tall) which are usually marketed for the treatment of winter depression. The setup of light boxes in the workplace could easily be adapted to meet the constraints of the given space (e.g. single or multiple portable light boxes could be set above or on the side of a desk or workstation, or permanent ceiling fixtures could be installed). The intermittent nature of our light treatment lends itself to use in the workplace. Several studies have demonstrated that intermittent bright light is a more efficient method of phase shifting the human circadian clock (Burgess et al. 2003; Gronfier et al. 2004; Rimmer et al. 2000). Intermittent light pulses were used in the studies reported here and in our previous simulated night shift studies (Crowley et al. 2003, 2004) to effectively phase delay the circadian clocks of our subjects during night shift work. Although in the studies reported here we used regular intermittent light pulses (once per hour), the regularity of the pulses in real world settings is probably not critical. Although our subjects usually only received a total of 1 hour of bright light per night shift, we recommend that workers receive as much bright light exposure as possible during their night shifts. However, we would not recommend that bright light exposure occur later than 4:00 am during a night shift, at least for those starting to work night shifts for the first time, because bright light that occurs after this time could tend to make the circadian clock earlier rather than later. Delaying the circadian clock, making it later, is necessary to reduce the circadian misalignment caused by working night shifts.

Another simple and practical intervention used in this study was to make the bedrooms of our experimental subjects completely dark by putting black plastic over their windows. This is something that night workers could do by covering their windows with any opaque material or buying special block-out shades. This is important for facilitating circadian phase delays for several reasons, including that daytime light exposure can cause a phase advance of the circadian clock and thus oppose the phase delays that are needed. It is important that a worker prioritize a regular sleep episode in a dark bedroom after the night shift.

The timing of the daytime sleep schedule is another important intervention that facilitates circadian phase delays during night work. Our simulated night shifts ended at 7:00 am, and the daytime sleep episode began at 8:30 am. However, we recommend that a worker go to bed as soon as possible after the night shift. This will permit the worker to get the most sleep, because their internal circadian clocks will wake them up when "morning wake time" on their circadian clock is reached. The phase delaying interventions delay their circadian clocks so that "morning wake time" is later, permitting later sleep. We required our subjects to stay in bed in the dark from 8:30 am until 3:30 pm. We chose a regular time for consistency in our experimental groups, but in practice this strict schedule could be more flexible, especially if bedtime could be even earlier. We chose a 7 hour time in bed because we did not think that real night shift workers would agree to spend more time in bed possibly missing family and social activities after 3:30 pm. But in practice workers might choose to sleep more than 7 hours, which would be preferable. After most night shifts our subjects had to stay in bed until 3:30 pm. However, after the last night shift in a series (e.g. at the end of a block of night shifts), they were required to wake up at 1:30 pm. The reason for this was to build up a little sleep pressure, a little sleep deprivation, to help the worker fall asleep earlier on the subsequent days off.

One of the most important factors for promoting circadian phase delays and thus achieving adaptation to night work was sleeping late on days off. In our studies sleep times on the weekends off were from 3:00 am to 12:00 noon. This was another compromise in our system. Days off sleep times were not as late as after the night shift, which would be ideal, but not as early as those of most non shift-workers. The days-off sleep schedule was late enough so that when the compromise circadian phase position was reached the sleepiest time of day would still fall within the sleep episode. For our control subjects who could sleep whenever they wanted, weekend wake time was strongly associated with the degree of circadian adaptation to the night shift schedule; the subjects who slept until 12:00 were much more likely to have a circadian clock that was in a favorable position for promoting night shift alertness. Consequently, we recommend that night workers sleep as late as is possible on their days off. This may be the most difficult intervention to institute in practice, because some people may not be willing to give up morning activities on their days off. It is more likely to be adopted after a worker tries the system and experiences the benefits.

Bright light exposure during the commute home from the night shifts will impede circadian adaptation to a night work and day sleep schedule. Dark "blue-blocker" sunglasses (15% average light transmission) were used in our experimental subjects to attenuate this light exposure. This intervention is important because attenuating bright morning light will facilitate the phase delaying necessary to adjust to a night work and daytime sleep schedule. However, in the days before the compromise phase position is reached, the sleepiest time of day may occur during the commute home. In fact, this is often the case for real night shift workers and is a driving hazard. Since bright light is alerting, dark sunglasses could reduce this alerting affect and exacerbate the problem. Therefore, we recommend that workers do not drive home until they have several, at least 5 or more, night shifts with bright light under their belt and have followed all the other recommendations designed to delay their circadian clocks, and don't feel drowsy at the end of the night shift. They should not drive hone while sleepy. They should wear the dark sunglasses and take public transportation or take taxis or get rides from non-shift workers until they feel alert during their commute home time. Drowsy driving after night shifts is currently a hazard for real night shift workers. The compromise schedule and interventions recommended here are designed to delay the sleepiest time out of the night shift and out of the commute time home and into the daytime sleep episodes. Remember, for permanent night shift workers, this transition from a normal diurnal circadian phase to the compromise circadian phase only has to be made once. Thereafter, the compromise circadian phase should be maintained through alternations between night shifts and days off. The transition would only have to be repeated if the worker goes on vacation and his or her circadian clock reverts back to the normal circadian phase position.

The final intervention, afternoon outdoor light exposure upon awakening from daytime sleep, was used to *maintain* the compromise circadian phase position. The purpose of this "light brake" was to keep the circadian clock from delaying too far, past the compromise phase position. Receiving a small amount of outside light exposure soon after awakening from the daytime sleep episodes prevents the circadian clock from achieving complete circadian adaptation, and instead facilitates the more socially acceptable partial circadian adaptation to a compromise phase position. In practice, if a worker does not want to go outside, a light box could be used instead. However, outside light is almost always more intense and powerful than a light box.

The specific schedule tested in these studies had 8 hour night shifts with the following sequence: 3 night shifts, 2 days off, 5 night shifts and finally 2 days off. But the basic principles could be applied to shifts of various lengths and with different sequences of night shifts and days off. A sleep and light schedule could be designed by some one who understands basic circadian rhythm principles including the light phase response curve (PRC). The most critical element for designing an acceptable schedule is the time the night shift ends, not when it starts. Night shift end time determines the time of day for sleep after night work. This in turn determines the time for sleep on days off. The earlier the night shift ends, the earlier sleep on days off can be while still having the sleepiest time of day fall within the days-off sleep episode.

D. Outcomes/Relevance/Impact

The outcomes of this research can be classified as potential outcomes, recommendations that could impact workplace risk if used. These studies were performed on volunteers who were not real shift workers, although they "worked" night shifts (in the lab) and slept at home like real night shift workers. Obviously, these interventions have to be tested with real shift workers while working their usual jobs. Previous research by us and other labs has shown that scheduled exposure to light and darkness (the type of interventions proposed here) is capable of completely aligning the circadian clock to a night work and day sleep schedule, thereby improving night shift alertness and daytime sleep quality.

Nevertheless, these types of interventions have not been widely adopted in the workplace. There are several reasons for this. The first is that much of the previous research has focused on producing complete alignment of circadian rhythms to the night work, day sleep schedule. While this is ideal for night work alertness and daytime sleep, it leaves the worker out of phase with friends and family on days off. However, we have shown here that complete alignment to a night work and day sleep schedule is not necessary. Instead, partial alignment to the compromise circadian phase position is sufficient for improving night shift alertness, performance, and mood while allowing adequate daytime sleep. Our system includes a days off sleep schedule that is a compromise between going to bed and waking up as early as most people with daytime jobs, but not as late as sleep is forced to be after night work. Real night workers may be willing to adopt this intervention strategy because it is associated with improvements in alertness, well-being and sleep duration, relative to the alternative of no circadian adaptation and its concomitant sleepiness, insomnia and general malaise. However, they would have to give up morning activities.

A second reason why the results of previous studies have not been widely adopted in the workplace is the perception that bright light exposure during the night shift is not feasible. However, we have shown here that only a total of one hour of bright light per night shift is enough, and it is possible that even less would be sufficient. Furthermore, the bright light can be intermittent so that workers could move away from brightly lit areas when needed. We used relatively inexpensive commercially available light boxes with fluorescent tubes. A variety of desk and floor stands are available to position the light boxes at different heights and at different angles, which should facilitate their use in various work places. More expensive installations of ceiling fixtures are also possible. The most elaborate example is the crew quarters the astronauts live in during the week before a space shuttle launch. There are many fluorescent ceiling fixtures in every room, including the conference room, exercise room, bathrooms and hallways. The bedrooms are light proof. The astronauts usually work shifts while on orbit. The P.I. designed the light and sleep schedules they use to shift their circadian clocks to the desired phase position before launch (Stewart and Eastman 1996; Stewart et al. 1995). Employers in more conventional businesses may be reluctant to spend money on light boxes or fixtures. However, they might be more receptive after a study in a real workplace shows an increase in productivity and a decrease in mistakes and accidents.

A third obstacle to the acceptance of the interventions proposed here is that many workplaces use rapidly rotating shift work systems, rotating between days, evenings, and nights with no more than a few, or even only one night shift at a time. These systems are based on the fact the since most real night shift workers on permanent or fixed night shifts do not adapt to night work, it is best to limit the number of consecutive night shifts to permit the worker to try to recuperate in between. However, rapid rotations do not permit any kind of circadian adaptation. Therefore, workers are almost always working and sleeping at the wrong circadian times when they work nights, and the night shifts are fraught with the usual dangers. It would be possible to modify the system tested here to work with very slowly rotating shift work systems. Ideally, each type of shift would be worked for a month or more. Appropriately timed light and dark could be used to shift the circadian clock from one shift to the next. Schedules of light, dark and sleep to accomplish this should be tested. One obstacle to our proposed system for *permanent* night work is that it requires workers to give up mornings. However, with a slowly rotating shift system, such as having shifts rotate once a month, workers could have some months in which they would be awake in the mornings.

E. Scientific Report

1. Background

Night shift work is associated with numerous problems and personal health risks (Costa 1996; Koller 1983). These include decreased sleep quantity and quality with subsequent sleepiness and fatigue (Akerstedt 2003; Pilcher et al. 2000), increased risk of cardiovascular dysfunction (Boggild and Knutsson 1999; Drake et al. 2004; Knutsson and Boggild 2000), gastrointestinal disturbance (Drake et al. 2004; Knutsson 2003; Scott 2000), reproductive dysfunction (Bisanti et al. 1996; Knutsson 2003) and cancer (Hansen 2006; Schernhammer et al. 2001; Viswanathan et al. 2007). Night shift work ahs been classified as a probable carcinogen by the International Agency for Research on Cancer (IARC), the cancer arm of the World Health Organization (Straif et al. 2007). Night shift work is also associated with decrements in psychological well being (Bohle and Tilley 1989; Scott et al. 1997) and disrupted social, family, and marital relationships (Staines and Pleck 1984; Walker 1985; White and Keith 1990). Drop-outs are common (Costa 1996), resulting in rehiring and retraining costs.

Alertness and performance during night work can be seriously impaired (Akerstedt et al. 1994; Dinges 1995; Mitler et al. 1988). While these decrements reduce worker productivity and in some jobs may endanger the individual night shift worker, the potential sequelae for a number of professions extend beyond the worker and the employer increasing the risk of accidents and injury for society as a whole. Examples of such professions include air traffic controllers and nuclear power plant operators. The problems with alertness and performance common to night shift work are due to misalignment between the circadian clock and the imposed sleep, wake and meal schedule. These problems arise because the circadian clocks of most night shift workers do not shift to align with a night work, day sleep schedule (Eastman et al. 1995). Consequently, workers are attempting to remain awake and functional around the sleepiest circadian time, which occurs during the night shift. Circadian misalignment may also be the etiology of some of the more serious health problems associated with night work, such as cancer, diabetes and cardiovascular disease (Martino et al. 2008; Martino et al. 2007).

Several approaches have been studied as possible ways to improve night shift alertness and performance, thereby attenuating the risks of preventable accidents and errors. Hypnotic medication can increase sleep duration in the daytime after night shifts, but do not eliminate the nadir in alertness and performance that occurs during night work (Schweitzer et al. 1991; Walsh et al. 1995). Stimulants such as caffeine (Schweitzer et al. 2006; Walsh et al. 1995) and modafinil (Czeisler et al. 2003; Walsh et al. 2004), bright light exposure during night shifts used for its direct alerting effects (Campbell et al. 1995), and prophylactic naps (Schweitzer et al. 2006) can all improve alertness and performance during night shifts when used alone or in combination, but do not restore alertness and performance to daytime levels.

Scheduled exposure to bright light from light boxes or fixtures and scheduled dark/sleep episodes are established methods of shifting the circadian clock, and have been used in laboratory and field studies to facilitate entrainment to a night work, day sleep schedule [e.g. (Boivin and James 2002; Campbell 1995; Crowley et al. 2003; Czeisler et al. 1990; Dawson et al. 1995; Eastman 1987; Revell and Eastman 2005)]. Phase shifting the circadian clock to phase delay and completely align with a night work, day sleep schedule is the most effective way to normalize nighttime alertness and performance and to maximize daytime sleep quality and duration. However, this approach has limited utility for the majority of night shift workers, because complete entrainment to a day sleep schedule would preclude shifting back to a nighttime sleep schedule on days off. Thus, the worker would have difficulty sleeping at night and would feel sleepy during the day on days off, which is a sacrifice that few shift workers would be willing to make.

Eastman and Martin (1999) proposed the idea of a compromise circadian phase position for permanent night shift work in which the circadian clock is delayed to partially entrain to a night work, day sleep schedule. The goal was to delay the temperature minimum (Tmin, the sleepiest circadian time) into the daytime sleep periods. Delaying the Tmin [calculated by adding 7 h to the dim light melatonin onset (DLMO)] out of the night work period and into the first half of the daytime sleep period was shown to improve night shift alertness and performance (Crowley et al. 2004). Furthermore, when the Tmin is delayed into the daytime sleep period, day sleep is hypothesized to be lengthened for those who would otherwise have trouble sleeping during the day because of circadian misalignment. Importantly, a compromise phase position is also hypothesized to facilitate late nighttime sleep and subsequent daytime alertness on days off.

The somewhat flexible timing of human sleep with respect to the phase of the circadian clock permits good quality sleep in a compromise phase position. Under entrained conditions, the Tmin falls in the latter half of a sleep episode, several hours before awakening (Benloucif et al. 2005; Czeisler et al. 1990; Mongrain et al. 2004; Strogatz et al. 1987; Wever 1979). In contrast, when free running, a main sleep bout is typically initiated at about the Tmin (Strogatz et al. 1987; Wever 1979, 1992; Zulley et al. 1981). Studies of sleep under an ultradian light-dark cycle (Akerstedt et al. 1997; Lavie 1986) also suggest that sleep is most likely for several hours before and after the Tmin. Thus, for most people sufficient good quality sleep can probably be obtained as long as the Tmin falls anywhere within the sleep period. Eastman & Martin (1999) estimated a phase tolerance interval for good sleep from 6 h before to 6 h after the Tmin, which would vary depending on previous time awake and other factors such as age.

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

In this project we conducted a series of studies to find a balance between phase delaying light from light boxes during the night shifts plus the delay of the sleep/dark episode and phase advancing light after sleep (the light brake) to achieve and maintain a target compromise phase position during alternations between blocks of night shifts and days off. Our goal was to achieve and maintain a target compromise phase position, defined as a DLMO of about 3:00 am. At this circadian phase position, the Tmin, an estimate for the sleepiest circadian time, which occurs about 7 hours after the DLMO (Benloucif et al. 2005; Cagnacci et al. 1996; Cajochen et al. 2000; Eastman et al. 2000; Goel 2005, 2006; Griefahn 2002; Griefahn et al. 2002; Mongrain et al. 2004), will fall at about 10:00 am. In this series of studies the sleep episodes for experimental groups started at 8:30 am after night shifts and at 3:00 am on days off. Thus, a Tmin of about 10:00 am puts the sleepiest circadian time early in the sleep period after night shifts and late in the sleep period on days off, but always within the sleep episode and never during night work.

2. Specific Aims

This grant had four specific aims: 1) To determine whether the compromise phase position could be achieved and maintained in subjects during alternations between blocks of night shifts and days off; 2) To determine if more experimental subjects (that receive interventions) achieve and maintain the compromise phase position than do control subjects (who do not receive an intervention, and are similar to real night shift workers); 3) To assess whether experimental subjects perform and feel better than control subjects during night shifts; 4) To assess whether experimental subjects sleep more than control subjects after night shifts and on days off. We conducted a series of studies to evaluate these specific aims. These specific aims are described here so that the reader can consider them when reviewing the methods and results. An evaluation of the outcome of each specific aim will be described at the end of the Scientific Report section, below.

3. Methodology

This grant consisted of 5 studies numbered 0 through 4 (see Fig 1, see the Study Numbers on the right side of the diagram). All the studies had the same sequence of 3 weeks of baseline with day shifts on days 17, 18 and 21 followed by alternating blocks of night shifts and days off. The difference among the studies is that each successive study ended on a later day within the night shift section (days 23-35). The last day of each study consisted of a final 24 hour circadian phase assessment. That ended the study for those groups of subjects because they were not allowed to sleep during the phase assessments. If they had then continued with the sequence of night shifts and days off, it would not have been a fair test of what would have happened if they went straight through without the sleep deprivation required during the phase assessments. Each study's final phase assessment took a "snapshot" of circadian phase at successively later days within the schedule to determine when the compromise circadian phase position was reached, and if it could be maintained during subsequent alternations of night shifts and days off. New groups of experimental and control subjects were run for each study. Each group started with the 3 weeks of baseline. Studies 1-4 in this series were between-subjects designs with each study having different control and experimental groups than the other studies. Study 0 only had one group because it ended before the night shifts began and this there was no need for separate experimental and control groups.

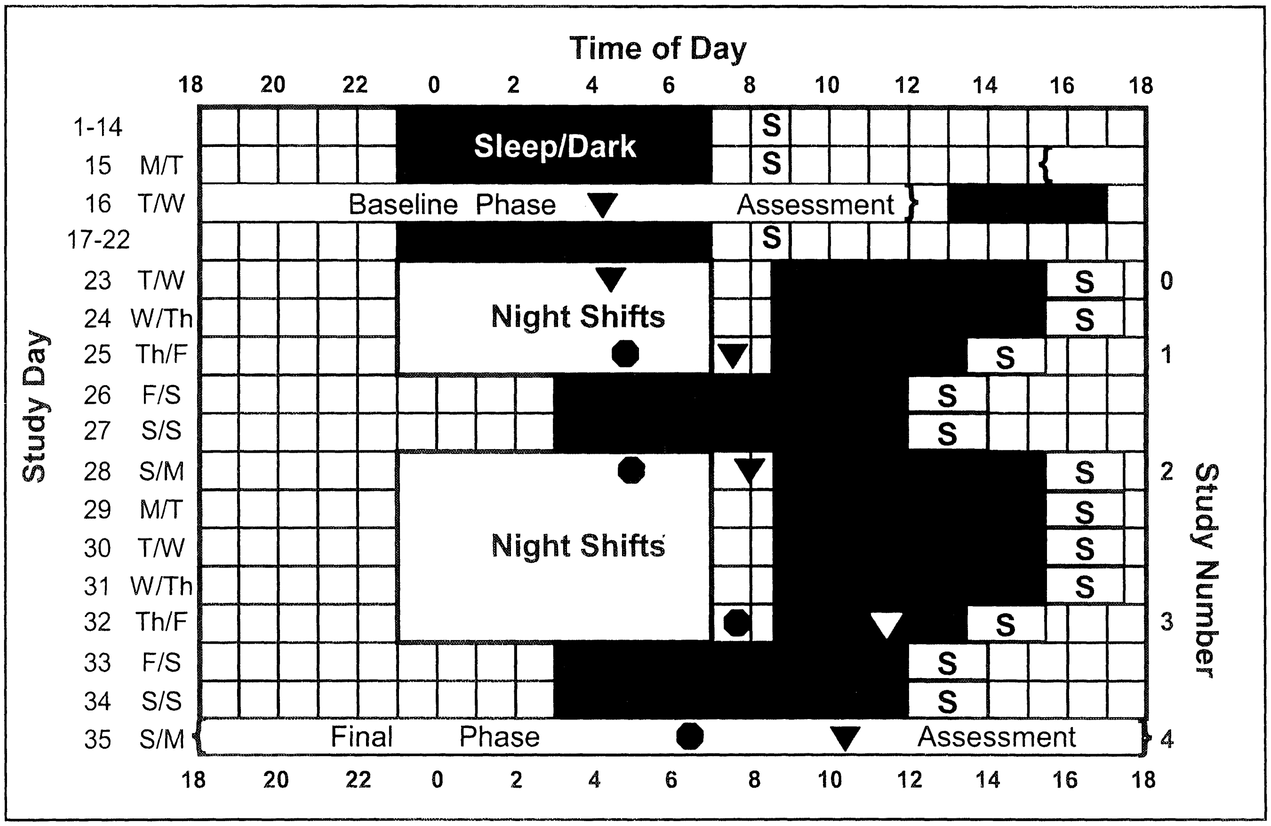


Figure 1. Diagram illustrating the protocol for all five studies in this grant. Study numbers on the right correspond to the day of the final phase assessment for each study. Each study ended immediately after the final phase assessment. For example, Study 0 had a final phase assessment in lieu of the night shift depicted on day 23, and Study 1 included two night shifts on days 23-24, and had a final phase assessment in lieu of the night shift depicted on day 25. The schedule of sleep (black areas) and light exposure ("S") on days 1-22 are for all subjects. The "S" on days 1-22 indicates that all subjects were required to go outside for at least 15 minutes of sunlight between 8:00 and 9:00 am. When the series of night shifts began (day 23), all subjects were in the laboratory for the night shifts, but the indicated sleep and light exposure schedule was for experimental subjects only. Experimental subjects slept at home during the black areas in the diagram. Control subjects chose when to sleep at home on days 23-34, and had unrestricted light exposure on those days. Experimental subjects received bright light pulses during each of the night shifts, timed to delay circadian rhythms, while control subjects remained in room light. The "S" on days 23-34 depicts the "light brake" for experimental subjects, designed to keep circadian rhythms from delaying too far. The average Tmin (estimated by adding 7 hours to the measured DLMO) during the baseline phase assessment for all subjects in all studies is shown on day 16, and the average Tmin for the subjects in Study 0 is shown on day 23. The Tmin for the experimental groups (triangles) and control groups (circles) at the end of studies 1-4 are depicted separately on days 25, 28, 32, and 35. On day 28, the average Tmin for the two experimental groups of study 2 is depicted. In the text, day numbers correspond to the rows shown in the figure, the 24 h from 18:00 to 18:00.

3a. Methodology Common to All Studies

Baseline Sleep and Light Schedule

All studies began with 15 days on a 23:00-7:00 sleep schedule on weekdays (Fig 1). On weekends subjects were permitted to go to bed as late as 0:00 and wake as late as 8:00 am to simulate what many people do on weekends. Each morning subjects were required to go outside for ≥ 15 minutes between 8:00 – 9:00. The purpose of this morning light was to stabilize the position of the circadian clock, and to mimic the morning light exposure that most people who are not shift workers might get on the way to work. A baseline phase assessment lasted from 15:30 on day 15 until 12:00 on day 16. Subjects then resumed the same baseline sleep schedule with morning light exposure during days 17-22.

Circadian Phase Assessments

During phase assessment sessions subjects' saliva was sampled every 30 minutes under controlled posture and lighting conditions. Saliva samples were assayed for the hormone melatonin. By collecting saliva samples sequentially several hours, an entire profile of the circadian rhythm of melatonin is determined (Fig 2). The time that the melatonin levels exceed a threshold level is known as the dim light melatonin onset (DLMO). We measured melatonin because it is the most reliable marker of the phase (or time) of the circadian clock, but we are also interested in the sleepiest circadian time. The body temperature minimum (Tmin) coincides with the sleepiest circadian time. The Tmin occurs ~ 7 hours after the DLMO (Benloucif et al. 2005; Cagnacci et al. 1996; Cajochen et al. 2000; Eastman et al. 2000; Goel 2005, 2006; Griefahn 2002; Griefahn et al. 2002; Mongrain et al. 2004). In this series of studies we thus measured the DLMO and estimated the time of the Tmin by adding 7 hours to the DLMO.

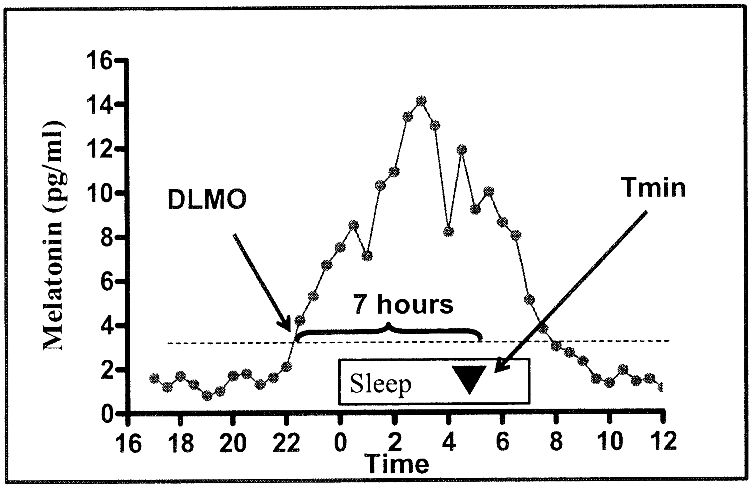


Figure 2. A typical profile of the circadian rhythm of melatonin production. The time that the melatonin level exceeds a threshold (dotted horizontal line) is referred to as the dim light melatonin onset (DLMO). Under entrained conditions the DLMO occurs 2-3 hours before the habitual sleep period (rectangle containing "Sleep"). The temperature minimum (Tmin) coincides with the time of peak circadian sleepiness, and occurs ~ 7 hours after the DLMO.

Bright light pulses

Experimental subjects were exposed to bright intermittent light pulses during night shifts. Light pulses were produced by four light boxes with fluorescent tubes (5,095 Kelvin) arranged around the circumference of a table at which the subjects sat. The light boxes (SunRays, Sun Box Co,) were about 22" wide and 15" high. At a typical distance and angle of gaze, the illuminance of the light boxes was ~ 3600 lux, the irradiance was ~ 1125 $\mu W/cm^2$, and the photon density was ~ 2.9×10^{15} $photons/cm^2/second$. The duration and pattern of the light pulses for each study are described below. All bright light pulses were interspersed by normal dim room light (< 50 lux, overhead fluorescent fixtures on a dimmer, 4,100 Kelvin).

Performance and Mood Batteries

To measure performance and alertness, subjects completed a test battery on desktop computers 4 times during three day shifts (days 17, 18, and 21) and during each night shift. During day shifts, the test battery was administered beginning at 10:05, 12:05, 14:05, and 16:05. During night shifts, it was administered beginning at 00:05, 2:05, 4:05, and 6:05 [see Fig 2 in (Smith et al. 2008)]. The test battery was typically completed about half past the hour. As part of each test battery, subjects completed the Profile of Mood States (POMS) (McNair et al. 1971) three 10-point scales assessing tiredness and mental and physical exhaustion, and the Automated Neurophysiological Assessment Metrics (ANAM) (Cernich et al. 2007). For the POMS, data for the fatigue-inertia subscale and total mood disturbance were analyzed. Endpoints of the scales assessing tiredness and exhaustion were 1) "fresh as a daisy" versus "tired to death", 2) "physically exhausted" versus "energetic", and 3) "mentally exhausted" versus "sharp".

The ANAM included simple reaction time, procedural reaction time, mathematical processing, delayed matching to sample, code substitution, and the Stanford Sleepiness Scale (Hoddes et al. 1973). The simple reaction time task is similar to the Psychomotor Vigilance Task (PVT) (Dinges and Powell 1985). In the ANAM version, an asterisk appeared in the middle of the computer screen at variable intervals and the subjects pressed the left mouse button which recorded reaction time (RT). Lapses were defined as RT > 500 msec. The procedural reaction time task assessed processing efficiency and reaction time when following a defined set of mapping rules. The basic block version of this test was administered. In it a single digit number between 2 and 5 was displayed within a box on the screen. Subjects indicated whether the number was 2 or 3 (left mouse click), or 4 or 5 (right mouse click). The mathematical processing task measured computational skills and working memory. This task entailed adding and subtracting three digits between 1 and 9, and indicating whether the answer was greater than 5 (right mouse click) or less than 5 (left mouse click). The delayed matching to sample task measured visuo-spatial working memory and spatial processing. Subjects viewed a sample pattern produced by a 4x4 grid of light and dark squares. After a 5 second delay in which the screen was blank, two comparison grids were displayed side by side on the screen, and the subject indicated which of the two grids matched the previously shown grid (left or right mouse click). The code substitution task measured sustained attention and visual search capacity and is similar to the Digit Symbol Substitution Test (DSST) (Stone 1984). Subjects viewed a "key" across the top of the screen pairing nine digits with nine symbols. A single digit-symbol pair was presented at the bottom of the screen and the subject indicated whether the pair matched (left mouse click) or didn't match (right mouse click) the pair in the key above. Subjects received immediate feedback after each response for incorrect responses on the code substitution task. Further details on these tests have been published (Reeves et al. 2007).

To account for large individual differences during day shifts (baseline), all data were transformed into difference-from-baseline scores. The data from the first day shift was excluded as practice. Scores on the second and third day shifts were averaged to form a baseline value. This baseline value was subtracted from scores on each night shift test bout to obtain difference-from-baseline scores.

Sunglasses

All subjects wore sunglasses when outside during daylight hours. Control subjects in studies 1-4 wore lighter sunglasses (36% average transmission, ranging from 0% transmission at 400 nm to about 55% at 650 nm). Subjects in study 0 and the experimental subjects in studies 1-4 wore dark sunglasses (15% average transmission, ranging from 0% at 400 nm to about 25% at 650 nm) that more strongly attenuated short wavelength light, to which the circadian system is most sensitive. All the studies were run during the summer months in Chicago (between May and Oct). We have previously shown that morning light on the commute home from the night shift can keep the circadian clocks of night shift workers from adjusting (Eastman et al. 1994). This can be explained by the fact that morning light coincides with the phase advance portion of the light phase response curve (PRC) and inhibits the phase delays needed for adjustment. Thus, testing subjects in the summer was the strictest test of whether our system could work.

Night Shift Section Sleep Schedule

After night shifts began on day 23, experimental subjects were required to be in bed, in the dark, at scheduled times after night shifts and on weekends off (Fig 1). These times were from 8:30 - 15:30 after night shifts (7 hours), except after the last night shift in a block, when sleep was from 8:30 – 13:30 (5 hours). Sleep was cut short on these days to build up some sleep pressure to make it easier to fall asleep earlier on the next night, which was a day off. Sleep times on the weekend off were from 3:00 to 12:00. Within the first two hours after awakening from these scheduled sleep episodes, experimental subjects were required to go outside for ≥ 15 minutes of light exposure ("S" on days 23-34 in Fig 1). The purpose of this light exposure was to keep the circadian clock of experimental subjects from delaying too far, past the compromise circadian phase position. After the first night shift, on day 23, control subjects had unrestricted sleep and light exposure.

3b. Study 0

Study 0 was designed to test whether the position of the circadian clock in phase assessments one week apart was similar when maintaining the baseline sleep schedule and morning outdoor light exposure. This was important because the baseline phase assessment in studies 1-4 occurred 1 week before the series of night shifts began. We wanted to make sure that the circadian phase position (the DLMO) was the same on day 23 as on day 16, because phase on day 16 would be used in the subsequent studies as the baseline measure. In studies 1-4, the intervening week was intended to allow subjects to recover from sleep deprivation caused by the baseline phase assessment before beginning the series of night shifts. A group of 11 subjects completed study 0. A final phase assessment session was conducted on day 23 (Fig 1). It was hypothesized that the time of the DLMO on day 23 would be similar to the time of the DLMO on day 16.

3c. Study 1

Study 1 assessed circadian phase in a control group (n= 12) and 2 experimental groups. Experimental group 1 (n=11) used the traditional white light boxes and experimental group 2 used blue-enriched light boxes (n=10). After two consecutive night shifts, a final phase assessment was conducted on day 25 (Fig 1).

Experimental subjects received five 15-minute intermittent light pulses during the night shifts, one per hour, with 45 min of room light in between the pulses. The first pulse began at 00:45 and the last pulse ended at 5:00.

3d. Study 2

Study 2 assessed circadian phase in a control (n= 12) and two experimental groups. The final phase assessment occurred on day 28 after 3 night shifts and 2 days off (Fig 1).

Experimental group 1 (n = 9) received five 15-minute intermittent light pulses. The first began at 00:45 and the last pulse ended at 5:00. Because the final circadian phase of experimental group 1 was not as late as desired (see results), an additional group of subjects was studied to determine if increasing the duration and number of nocturnal bright light pulses would be associated with a later final DLMO. Consequently, experimental group 2 (n = 10) received six 20-minute intermittent light pulses, one per hour. The first began at 00:40 and the last pulse ended at 6:00.

3e. Study 3

Study 3 assessed circadian phase in a control (n = 12) and an experimental (n = 12) group. After 3 night shifts, 2 days off, and 4 more night shifts, a final phase assessment was conducted on day 32 (Fig 1).

Experimental subjects received five 15-minute intermittent light pulses, one per hour. The first began at 00:45 and the last pulse ended at 5:00.

3f. Study 4

Study 4 assessed circadian phase in a control (n = 10) and an experimental (n = 9) group. After 3 night shifts, 2 days off, and 5 more night shifts, and 2 more days off, a final phase assessment was conducted on day 35 (Fig 1).

Because final circadian phase in study 3 was slightly later than predicted (see results), experimental subjects in study 4 were exposed to only four 15-minute intermittent light pulses, one per hour. The first began at 00:45 and the last pulse ended at 4:00.

4. Results & Discussion

Table 1. Circadian phase. Time of dim light melatonin onset (DLMO) and temperature minimum (Tmin) in clock time with (SD) in minutes for all groups in all studies. The Tmin = DLMO + 7 hours = estimated sleepiest time of day.

		DLMO		T MIN	
	N	Baseline	Final	Baseline	Final
Study 0	11	21:00 (35)	21:30 (28)	04:00	04:30
Study 1					
Experimental (white)	11	21:24 (48)	00:36 (84) *	04:24	07:36
Control	12	21:00 (60)	21:48 (78)	04:00	04:48
Experimental (blue)	10	21:02 (50)	00:18 (108) *	04:02	07:18
Study 2					
Experimental 1 (15 min)	9	20:48 (48)	00:59 (72) *	03:48	07:59
Control	12	20:59 (48)	22:00 (108)	03:59	05:00
Experimental 2 (20 min)	10	20:09 (42)	23:55 (102) *	03:09	06:55
Study 3					
Experimental	12	20:58 (60)	04:34 (96) *	03:58	11:34
Control	12	21:04 (48)	00:39 (174)	04:04	07:39
Study 4					
Experimental	9	21:18 (66)	03:22 (120) *	04:18	10:22
Control	10	20:39 (36)	23:24 (228)	03:39	06:24

* $p < 0.001$ vs. control group

4a. Study 0

The results of study 0 have been published (Revell et al. 2005). The average position of the DLMO during the baseline phase assessment was 21:00 (Table 1). During the final phase assessment 1 week later the average DLMO was similar (21:30). The estimated final Tmin (DLMO + 7 h) derived from this is shown by the triangle on day 23 in Fig 1. The position of the DLMO was slightly but significantly later during the final phase assessment (paired t-test, $p < 0.01$), but the mean absolute change in the position of the DLMO was only 34 ± 18 min. Thus, when the prescribed sleep and light exposure schedule is followed on the intervening days (i.e. days 17-22), circadian phase is reproducible in phase assessments conducted 1 week later (e.g. compare the position of the Tmin triangles on days 16 and 23 in Fig 1). This similarity permits the baseline phase assessment (day 16) to be used as a good estimate of the position of the circadian clock when beginning the sequence of night shifts one week later.

4b. Study 1

The results of study 1 have been published (Lee et al. 2006). This particular manuscript has many details about the methods and is intended to serve as a reference for all the papers from this series of studies.

During the baseline phase assessment the average time of the DLMO for the experimental (white light boxes) and control groups was similar (21:24 and 21:00, respectively, Table 1). After the two night shifts, the average final DLMO for the experimental group (00:36) was significantly later than the control group (21:48). Thus, the average Tmin (the sleepiest time of day) for the control group (circle on day 25 in Fig 1) had moved very little from its baseline position, but the average Tmin for the experimental group (triangle on day 25 in Fig 1) had delayed out of the night work period. Thus, the circadian snapshot after 2 night shifts showed that the experimental group was delaying as expected, by about 1 1/2 hours per day. Therefore, we could continue as planned with the next study in the series.

As expected, the experimental subjects did not delay far enough to reach the target compromise phase position (DLMO of ~ 3:00; Tmin of ~ 10:00) after just two night shifts. Despite this, there was a group difference in the amount of daytime sleep obtained after night shifts. On day 24, the experimental group slept significantly longer than the control group ($p < 0.01$).

At the time study 1 was being conducted, exciting new research indicated that the human circadian clock was most sensitive to short wavelength (blue) light (Brainard et al. 2001; Thapan et al. 2001; Wright and Lack 2001). This was due to newly discovered circadian photoreceptors in the retina, called intrinsically photosensitive retinal ganglion cells (ipRCGs), which are distinct from the rods and cones (Berson et al. 2002; Fu et al. 2005). The light box manufacturers jumped on this discovery and began producing and marketing light boxes with more blue light or predominately blue light (monochromatic blue light). Therefore, we thought it was important to test whether blue light could help the experimental subjects reach the compromise circadian phase position faster.

We tested whether polychromatic lamps that were enriched in the blue portion of the visible light spectrum would be any more effective for producing phase delays than the "white" lamps used in study 1, described above. This was done in the exact same protocol for study 1, but different light boxes were used to administer the bright light pulses during the night shifts. Measured at the subject's eyes at a typical distance from the light boxes and angle of gaze, the illuminance of the white light boxes (5095K, SunRay The SunBox Company Inc., Gaithersburg, MD, USA) was ~3600 lux, the irradiance was ~1125 $\mu W/cm^2$, the photon density was ~2.9×10^{15} $photon/cm^2/sec$. The illuminance of the blue-enriched light boxes (17,000K, Philips Lighting, Eindhoven, The Netherlands) was ~3900 lux, the irradiance was ~1600 $\mu W/cm^2$, and the photon density was ~4.1×10^{15} $photon/cm^2/sec$. Between 400-490nm, the blue-enriched light boxes emitted more than twice as many photons as the white light boxes (1.95 versus 0.76×10^{15} $photon/cm^2/sec$). Thus, the blue-enriched light boxes delivered about 25% more total photons, and about twice as many in the blue portion of the visible light spectrum. The spectral power distributions have been published for both the white (Lee et al. 2006) and blue-enriched (Smith et al. 2009b) light boxes.

During the baseline phase assessment the average time of the DLMO for the blue experimental group was 21:02, which was similar to the white experimental group (21:24, Table 1). After the two night shifts the average final DLMO for the blue-enriched group (00:18) was similar to the white experimental group (00:36). We concluded that bright blue-enriched polychromatic light was not more effective in producing circadian phase delays in this protocol than bright white light. This study has been published as a conference abstracts (Smith et al. 2006a; Smith et al. 2006b), and the manuscript is in preparation (Smith et al. in preparation). We decided to continue the series of studies with the original white light boxes because they were more commonly available and less expensive.

4c. Study 2

For more details see the publication describing Study 2 (Smith et al. 2008).

During the baseline phase assessment the average time of the DLMO for experimental group 1 and the control group was similar (20:48 and 20:59, respectively, Table 1). After three consecutive night shifts and two days off, the average final DLMO of experimental group 1 (00:59) was significantly later than that of the control group (22:00). However, the final DLMO of experimental group 1 (00:59) was about the same as the final DLMO of the white light experimental group in study 1 (00:36). In other words, after an additional night shift (on day 25) and 2 days off, circadian phase was about the same. At least we showed that the weekend off did not cause the progress made in delaying the circadian clock to be reversed. However, we had expected there to be more of a delay between the 2 snapshots of circadian phase.

Consequently, we tested another group of subjects, experimental group 2, to determine if additional light exposure during night shifts could delay the circadian clock faster. We increased the duration of the light pulses from 15 to 20 minutes and added a sixth light pulse at the end of the train of pulses (from 5:40 to 6:00 am). Experimental group 2 had an average baseline DLMO of 20:09, which was similar to that of experimental group 1. The final DLMO of experimental group 2 (23:55) was similar to that of experimental group 1 (00:59). Thus, the extra bright light during the night shifts did not help delay the circadian clock. Therefore, in the next study of the series we used the original light pattern of 5, 15 minute light pulses. The average Tmin for both experimental groups combined and for the control group is shown on Day 28 in Fig 1.

There were some differences in performance between the experimental and control groups. On the second and third night shifts, the number of lapses (defined as a reaction time > 1500 milliseconds on a simple reaction time task) was significantly elevated for control subjects compared to both of the experimental groups ($p < 0.05$). In addition, the experimental groups had reaction times that were very close to their daytime baseline levels.

Although circadian phase after the two days off (day 28) was not as late as hoped for the experimental groups, we cannot be sure that the experimental subjects did not achieve the compromise phase position after three night shifts. We did not have a group with a final circadian phase snapshot on day 26 which could have answered this question. The grant was designed to have a limited number of phase assessments to conserve time and money. It is possible that the experimental subjects did delay far enough to have a DLMO close to the target phase (3:00 am) after 3 night shifts, but due to the effect of the earlier sleep schedule on days off and the "light brake" on days 26-28, they advanced back to the position we observed on day 28.

Similar to study 1, although the final phase position was not as late as the targeted compromise phase position, the experimental groups appeared better off than the control subjects in that they had improved levels of alertness during their night shifts.

4d. Study 3

For more details see the publication describing Study 3 (Smith and Eastman 2008).

During the baseline phase assessment the average time of the DLMO for the experimental group and the control group was similar (20:58 and 21:04, respectively, Table 1). After three consecutive night shifts, two days off, and four more consecutive night shifts the average final DLMO of the experimental group (04:34) was significantly later than that of the control group (00:39). The final circadian phase position of the Tmin for the experimental group (11:34) was slightly later than the target compromise phase position (10:00). However, our goal of having the Tmin occur within the sleep episodes after night shifts as well as within the sleep episodes on days off was reached. The Tmin for the experimental group (white triangle on day 32 in Fig 1) would occur during the first half of daytime sleep episodes after night shifts and at the end of the sleep episode on days off.

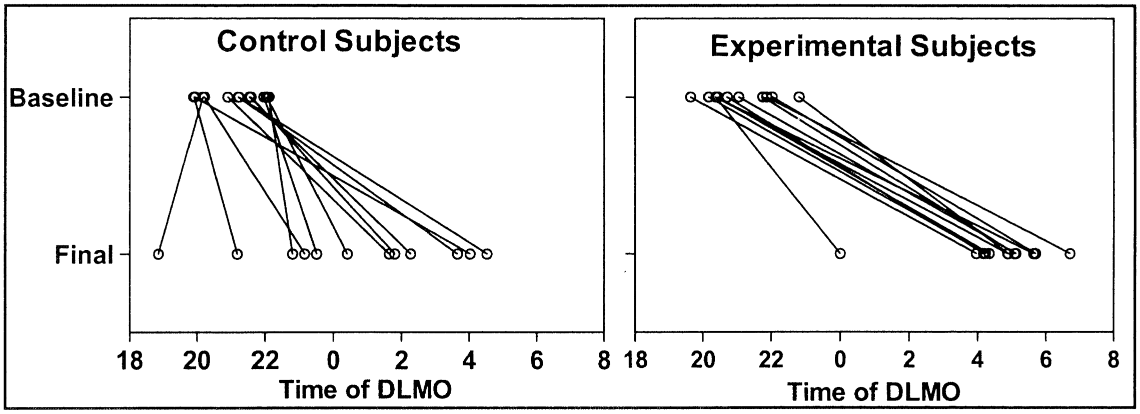


Figure 3. Position of the DLMO for individual subjects at the baseline and final phase assessments during study 3. Lines are included to connect the DLMOs of each subject.

Experimental subjects were more likely than controls to show substantial circadian phase delays (Fig 3). There were large individual differences in final circadian phase for control subjects. Some control subjects delayed as much as the experimental group, but others showed little or no phase delay. This was related to the sleep pattern they adopted on days off. Those who went to bed later and woke up later had later final DLMOs. The correlation between average days off wake time and final DLMO was r=0.84, p < 0.01, and between average days off bedtime and final DLMO was r=0.63, p=0.03.

Experimental subjects performed better during their night shifts than control subjects. On the first night shift (before experimental subjects' circadian clocks had shifted towards a compromise phase position), the performance of all subjects was impaired (Fig 4). On successive night shifts, reaction time for the experimental group decreased and remained low, while reaction time for the control group increased and remained elevated.

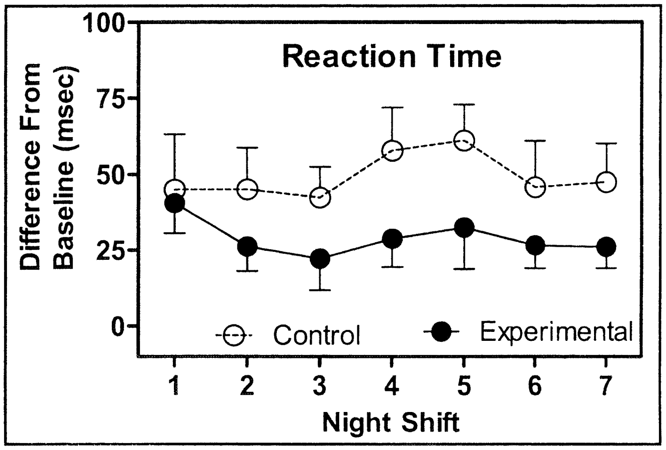


Figure 4. Simple reaction time on each night shift. The average reaction time for 4 test bouts on each night shift is shown. Error bars = SEM.

Experimental subjects slept for nearly the entire allotted time in bed. Although the average sleep duration for the control group was nearly as long as the experimental group on many days (i.e. the groups were only significantly different on 3 of 9 days), control subjects showed large individual differences in the duration and pattern of sleep episodes (see Fig 5). Some control subjects selected a pattern of sleep and light exposure similar to that of the experimental group, initiating daytime sleep soon after night shifts, and adopting late bed and wake times on the two weekend days off. Like real shift workers, other control subjects had a more erratic sleep pattern, with shorter and more disrupted sleep after night shifts, and earlier bed and wake times on the weekend days off.

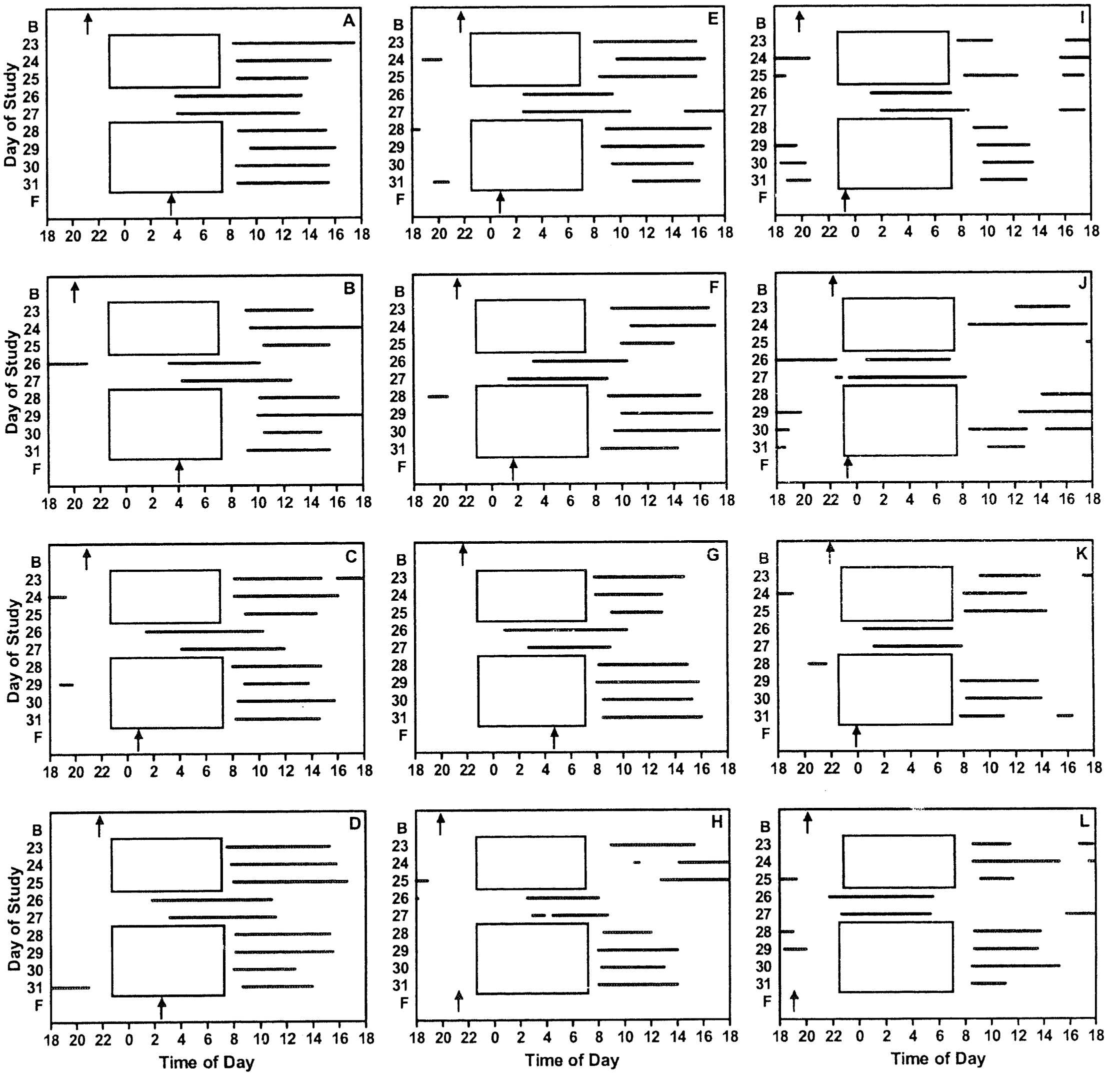


Figure 5. Sleep times (horizontal lines) after night shifts and on the weekend off for all of the control subjects in Study 3 arranged according to average wake up time on the weekend (study days 26-27). Latest weekend wake time shown in top left (subject A), with progressively earlier wake times plotted down the left column (B, C, D), then from the top down the middle column (E, F, G, H), then from the top down the right column (I, J, K, L). Boxes indicate times of night shifts. Upward arrows indicate the time of the DLMO during the baseline (B) and final (F) phase assessments. Note that the final DLMO is later in the subjects with the latest weekend wake times.

Average total sleep time (TST) for control subjects was positively correlated with the time of the final DLMO (r =.65, p = 0.02). Those control subjects who (through their own devices) delayed so far that their final DLMO was close to a compromise phase position (2:00 – 4:00) averaged 7 h or more TST across days 23-31, while control subjects with final DLMOs before 00:00 averaged 5-6 h TST (Fig 6).

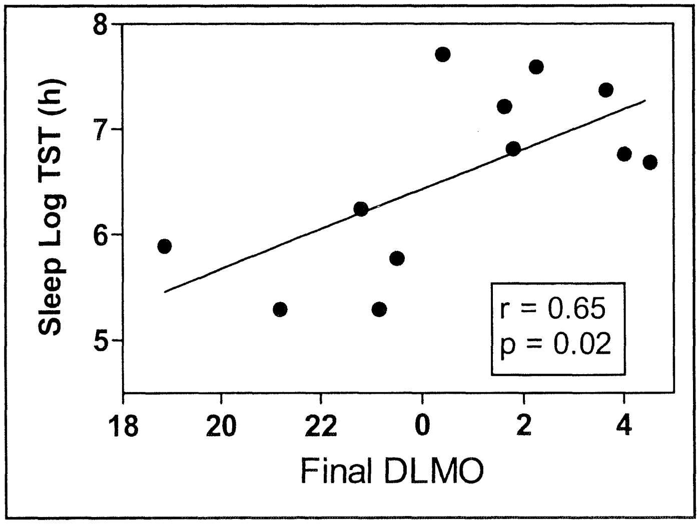


Figure 6. Scatterplot of average total sleep time (days 23-31) versus final DLMO for control subjects in Study 3.

We conclude that scheduled exposure to light and darkness was effective for producing a compromise circadian phase position in the experimental subjects, and that some control subjects who slept late on days off also reached the compromise phase position. For the experimental subjects, it appears that the compromise phase position (Tmin ~ 10 am) was achieved in between days 28 and 32 (see Fig 1 and imagine a line connecting the triangles on days 28 and 32). In other words, the compromise phase was reached by days 7 to 9 on the night work, days off sequence.

To summarize, performance and alertness was better for experimental subjects than for control subjects. Experimental subjects tolerated the prescribed sleep schedule well, sleeping for nearly the entire amount of scheduled time in bed. For the control group, there were robust associations between sleep duration and final circadian phase and between bed and wake times on days off and final circadian phase. Some control subjects slept at later times on weekends and delayed so that their final DLMO was close to a compromise phase position. Those subjects slept as long as experimental subjects, while those subjects whose circadian clocks showed little or no phase delay obtained less sleep.

4e. Study 4

For more details see the publication describing Study 4 (Smith et al. 2009a).

During the baseline phase assessment the average time of the DLMO for the experimental group and the control group was similar (21:18 and 20:39, respectively, Table 1). After three consecutive night shifts, two days off, five more consecutive night shifts, and two more days off, the average final DLMO of the experimental group (03:22) was significantly later than that of the control group (23:24). The final circadian phase position of the Tmin for the experimental group (10:22) was very close to the target compromise phase position (10:00), and would occur during the first half of the sleep episode during daytime sleep after night work, and at the end of the sleep episode on days off (see triangle on day 35 in Fig 1). The average final Tmin for the control group (6:24) occurred much earlier, and would fall within the night work episode (circle on day 35 in Fig 1).

Experimental subjects had somewhat earlier and more variable final DLMOs in study 4 than in study 3 (compare Figs 3 and 7). Some of this might be due the fact that we used 4 instead of 5 phase-delaying nocturnal bright light pulses in study 4. The final DLMO for experimental subjects in study 4 was related to the "light brake". When controlling for baseline DLMO, the partial correlation between final DLMO and total light exposure (minutes > 10 lux) during the first 2 hours after awakening from sleep episodes on days 23-34 was -.72, p = .04. Subjects with greater afternoon light exposure had relatively earlier final DLMOs, indicating that this afternoon light exposure, the "light brake," was effective for keeping the circadian clock from delaying past the compromise circadian phase position.

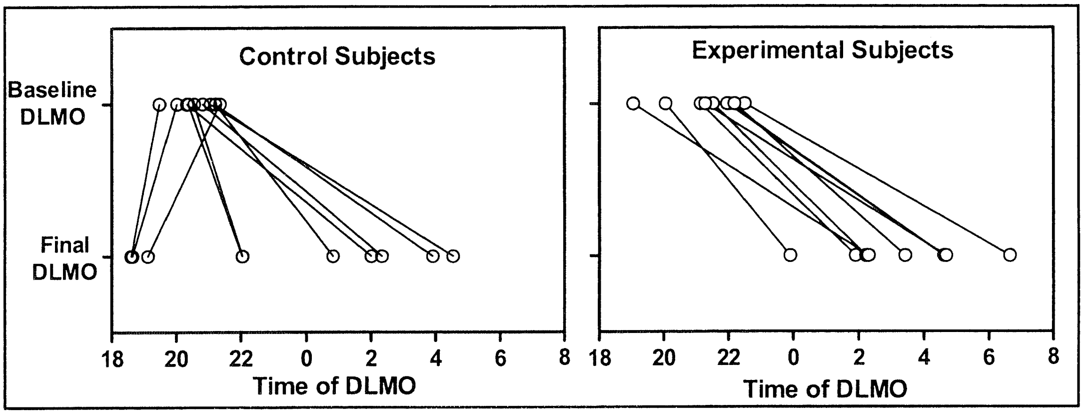
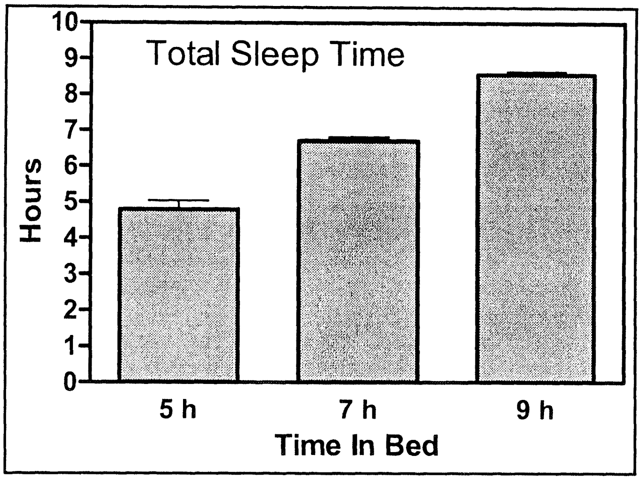


Figure 7. Position of the DLMO for individual subjects at the baseline and final phase assessments during study 4. Lines are included to connect the DLMOs of each subject.

Within both the control and experimental groups, there were large individual differences in final circadian phase (Fig 7). Several control subjects had final DLMOs that were close to or later than the compromise phase position. Likely due to this heterogeneity, we did not observe group differences in sleep duration or night shift alertness and performance. Correlation analyses were thus conducted to assess the association between final circadian phase and sleep duration or performance, with the hypothesis that those subjects with later final DLMOs would perform better during the night shift and sleep longer during the daytime.



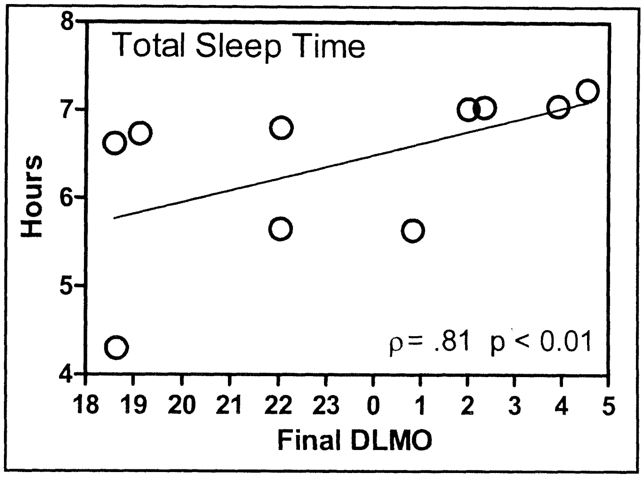


Figure 8. Total sleep time for experimental subjects in Study 4. The left bar shows the average TST (+ SD) when subjects were given 5 h time in bed (TIB) (days 25 and 32). The middle bar shows TST when subjects were given 7 h TIB (days 23-24 & 28-31). The right bar shows TST on weekend days (26-27 & 33-34) when subjects were given 9 h TIB.

Figure 9. Study 4 average total sleep time during the day following night shifts (days 23-25 & 28-32) versus final DLMO for control subjects. A Spearman correlation was used because the total sleep time data were not normally distributed.

As in study 3, experimental subjects in study 4 tolerated the sleep schedule well, and were able to sleep for nearly the entire allotted time in bed (Fig 8). Sleep duration for control subjects was more variable and was associated with final circadian phase position (Fig 9). Control subjects with later final DLMOs that were close to or later than the compromise phase position averaged about 7 hours of daytime sleep after night shifts, while some control subjects with earlier final DLMOs obtained less daytime sleep (Fig 9).

The variability in the pattern of sleep for the control subjects in shown in Fig 10 on the next page. As for the control subjects in Study 3, it is easy to see that later days off sleep times were associated with later final DLMOs, and thus better circadian alignment.

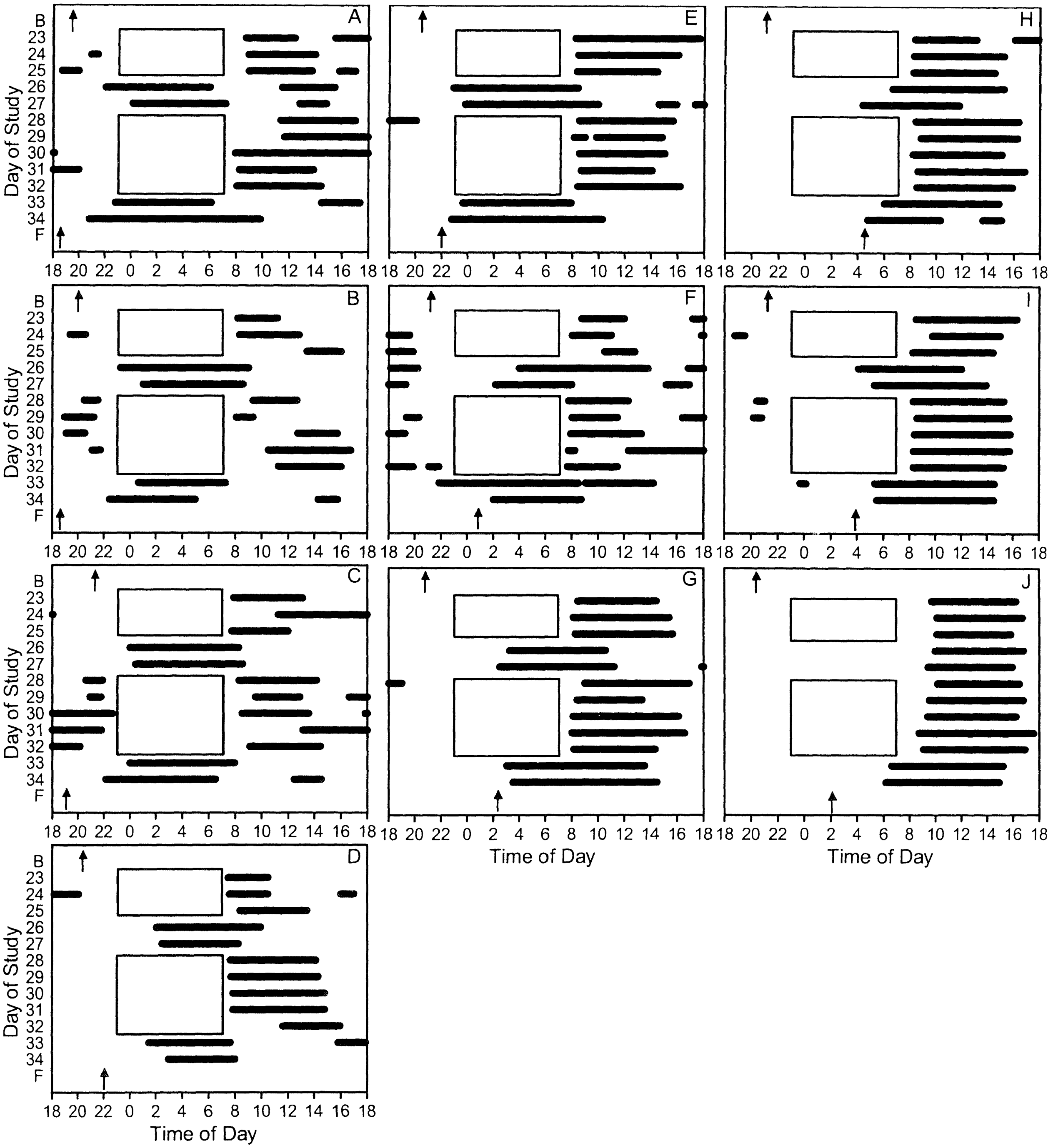


Figure 10. Sleep times (dark horizontal lines) for all the control subjects in Study 4 arranged according to average weekend (days off) wake up time (study days 26-27 and 33-34). Earliest average weekend wake time shown in top left panel (A), with progressively later wake times plotted down the left column (B, C, D), and then from the top down the middle column (E, F, G), and top down the right column (H, I, J). Boxes indicate times of night shifts. Upward arrows indicate the time of the DLMO during the baseline and final phase assessments (B and F on y-axis, respectively). Note that the final DLMO tends to be later in the subjects with later weekend wake times.

When beginning the sequence of night shifts, all subjects performed more poorly than at baseline, with prolonged reaction times and an increase in the frequency of lapses. By the end of the second block of night shifts (days 30-32), there was a consistent relationship between night shift performance and final circadian phase (Fig 11). In this graph we show data from the last 2 test bouts, which began at 4:05 and 6:05 am, because real night shift workers typically have to most trouble at this time during their night shifts. Subjects with final DLMOs that were close to the compromise phase position (at 2:00 or later) had faster reaction times than subjects with earlier final DLMOs (left panel of Fig 11). Despite this significant association, some of the subjects that had final DLMOs as late as the targeted position of 3:00 am had reaction times that were slightly above baseline levels. However, subjects with final DLMOs close to the compromise phase position did not have an increased frequency of lapses late in their night shifts (right panel of Fig I). In other words, they did not have more lapses during the end of those night shifts than they did during the baseline day shifts.

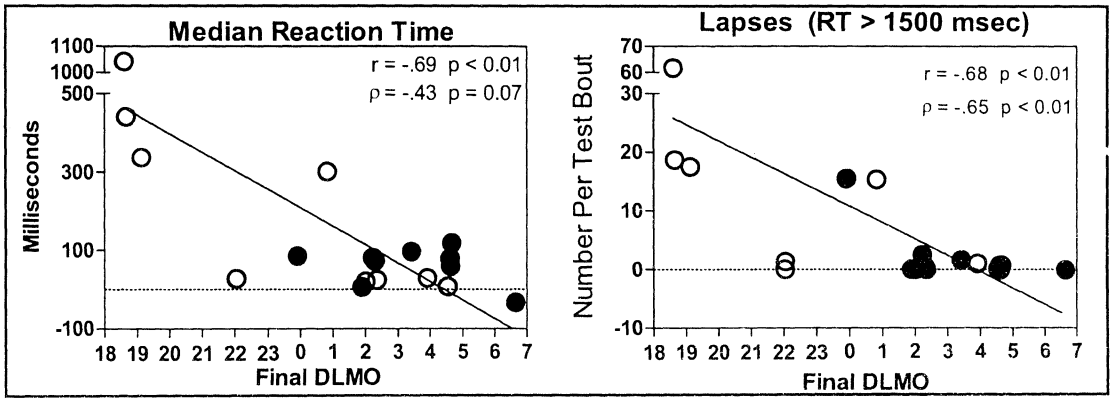


Figure 11. Performance on a simple reaction time task for experimental subjects (filled circles) and control subjects (open circles) versus final DLMO in study 4. The average performance for the 4:05 and 6:05 test bouts on the last three night shifts is shown. Data are difference-from-baseline scores where each subjects' baseline mean is depicted by the dashed horizontal line at 0 on the y-axis. Higher scores indicate poorer performance.

Combined Data from Studies 3 and 4

During night shifts, those subjects that had later final DLMOs in studies 3 and 4 also had improved mood, subjective fatigue and performance on a number of other components in the test battery. For these analyses, data from studies 3 and 4 were combined, and subjects were divided up into 3 categories based on their final circadian phase position. Subjects with a final DLMO earlier than 1:30 were classified as "not re-entrained" (open circles in Fig 12) because their final Tmin (earlier than 8:30) would not have occurred within the daytime sleep episode that began at 8:30 (for the experimental groups). Subjects with a final DLMO between 1:30 and 5:00 were classified as "partially re-entrained" (filled squares in Fig 12) because their final Tmin (between 8:30 and 12:00) would fall in the first half of the daytime sleep episode after night shifts (for experimental subjects). Subjects with a final DLMO later than 5:00 were classified as "completely re-entrained" (filled triangles in Fig 12) because their final Tmin (later than 12:00) would fall in the second half of the daytime sleep episode after night shifts (for experimental subjects). Subjects that were not re-entrained at the time of their final phase assessment began night shifts on days 29-31 with increased total mood disturbance (TMD). Subjects that were partially or completely re-entrained began these night shifts near baseline levels (top panel of Fig 12, at 00:05). At later times during the night shifts total mood disturbance increased for all subjects, but was consistently greater for the subjects that were not re-entrained. Mood ratings for subjects that achieved partial or complete re-entrainment were similar to each other and were closer to baseline levels. The bottom panel of Fig 12 shows total mood disturbance ratings for subjects on the last night shift (day 32). Only the subjects in study 4 are included in this figure because subjects in study 3 had a final phase assessment session instead of a night shift on day 32. In addition, the 1 subject that achieved complete re-entrainment is excluded from this figure. On day 32, subjects who did not re-entrain had elevated levels of total mood disturbance early in the night shift, with increasing levels of total mood disturbance as the night shift progressed. In contrast, subjects that achieved partial re-entrainment showed a stable level of total mood disturbance that was close to their baseline levels. The results of subjective alertness and performance scales showed a similar pattern, and are in press (Smith et al. in press).

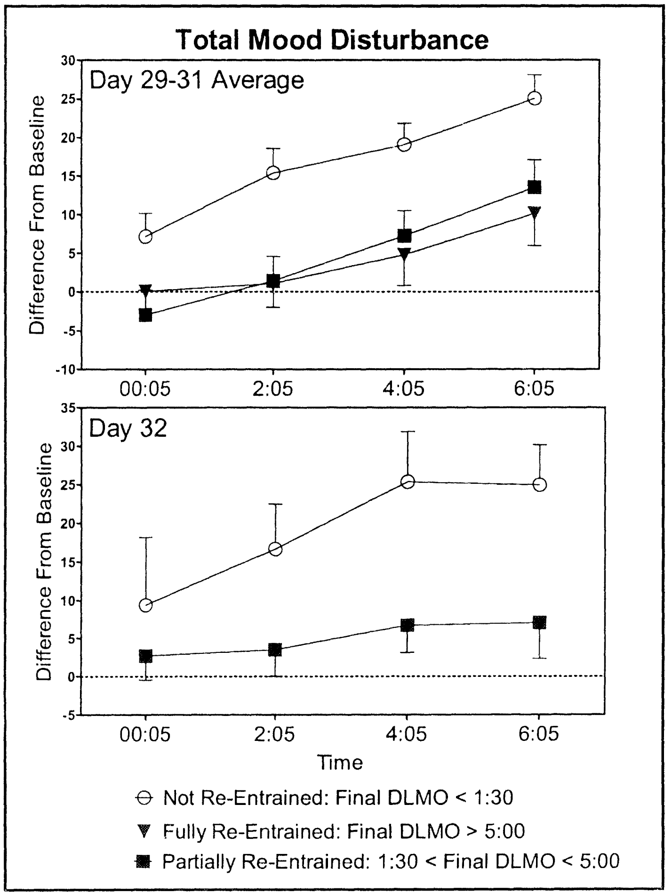


Figure 12. Profile of Mood States (POMS) scores for subjects achieving different degrees of circadian adaptation to night shifts. Higher scores indicate a higher level of mood disturbance relative to subjects' daytime levels (horizontal line at zero). The top panel shows data for all subjects from studies 3 and 4. The bottom panel shows data for subjects from study 4, since these were the only subjects that had a night shift on day 32.

4f. Achievement of the Specific Aims

Our first specific aim was to determine whether the compromise phase position could be achieved and maintained in experimental subjects (treatment groups) during alternations of night shifts and days off. The compromise position was achieved after about a week of the night work, days off sequence and was maintained even after a second weekend off.

The second specific aim was to determine if more experimental subjects achieved and maintained the compromise phase position than did control subjects. Experimental subjects consistently had larger phase delays than control subjects and had final circadian phase positions that were closer to the compromise phase position. In studies 3 and 4, there were also some control subjects that adopted a pattern of sleep very similar to that of the prescribed schedule for experimental subjects, and these control subjects achieved phase delays as large as the experimental group.

The third specific aim was to assess whether experimental subjects performed and felt better than control subjects during night shifts. In studies 1, 2, and 3 there was clear evidence that experimental subjects performed better than controls. For studies 3 and 4 performance and mood at the end of the series of night shifts was consistently associated with circadian phase, such that subjects that achieved a final circadian phase position close to or later than the compromise phase position performed and felt better than subjects that did not phase shift as much.

The final specific aim was to assess whether experimental subjects slept more than control subjects after night shifts and on days off. We did not find strong evidence in support of this aim. However, experimental subjects were able to sleep for nearly all of their scheduled sleep episodes. Many control subjects were also able to sleep well. One reason for the lack of group differences is that some control subjects in studies 3 and 4 adopted sleep schedules even more conducive for delaying circadian rhythms than we required of our experimental subjects, and had large phase delays that would be conducive for obtaining good daytime sleep. Consistent with this hypothesis are the observed associations in studies 3 and 4 showing that control subjects who had later final DLMOs had longer daytime sleep.

5. Conclusions

Complete circadian adaptation (complete reentrainment) to a night work and day sleep schedule is not necessary to reduce the performance, mood, and sleep problems associated with night work. Partial reentrainment can produce benefits similar to those derived from complete reentrainment. Scheduled exposure to light and darkness can be used to partially delay the circadian clock to a compromise circadian phase position for a permanent night shift schedule. A few brief (15 min) light pulses during the night shift, the use of dark sunglasses during the commute home, sleep in the dark soon after night shifts and sleep on a late sleep schedule during days off is the most reliable way to produce the compromise phase position. A few control subjects who worked in ordinary room light during the night shifts and wore lightly tinted sunglasses on the way home were able to achieve the compromise phase position by adopting late sleep schedules on days off. The compromise phase position was associated with increased night shift alertness, performance and mood, as well as sufficient daytime sleep after night shifts. Importantly, the compromise phase position is also compatible with afternoon wakefulness on days off.

F. Publications

Publications from Years 1 to 3 of the Grant

1. **Crowley SJ, Lee C, Tseng CY, Fogg LF, Eastman CI** 2003 Combinations of bright light, scheduled dark, sunglasses, and melatonin to facilitate circadian entrainment to night shift work. Journal of Biological Rhythms 18:513-523

2. **Crowley SJ, Lee C, Tseng CY, Fogg LF, Eastman CI** 2004 Complete or partial circadian re-entrainment improves performance, alertness, and mood during night shift work. Sleep 27:1077-1087

3. **Smith MR, Lee C, Crowley SJ, Fogg LF, Eastman CI** 2005 Morning melatonin has limited benefit as a soporific for daytime sleep after night work. Chronobiology International 22:873-888

Publications from Years 4 to 8 of the Grant

4. **Lee C, Eastman CI** 2004 Initial steps towards a circadian compromise for night shift workers. Abstracts of the Ninth Meeting of the Society for Research on Biological Rhythms:34-35

5. **Revell VL, Kim H, Tseng CY, Crowley SJ, Eastman CI** 2005 Circadian phase determined from melatonin profiles is reproducible after 1 wk in subjects who sleep later on weekends. Journal of Pineal Research 39:195-200

   This is the full report of Study 0.

6. **Revell VL, Eastman CI** 2005 How to trick mother nature into letting you fly around or stay up all night. Journal of Biological Rhythms 20:353-365

7. **Lee C, Smith M, Eastman C** 2006 A compromise phase position for permanent night shift workers: circadian phase after two night shifts with scheduled sleep and light/dark exposure. Chronobiology International 23:859-875

   This is the full report of Study 1.

8. **Smith MR, Lee C, Revell VL, Eastman CI** 2006 Blue-enriched versus white light for circadian phase delays. Abstracts of the Society for Research on Biological Rhythms:131

9. **Smith M, Revell V, Lee C, Eastman C** 2006 Bright blue-enriched light did not produce larger phase delays than bright white light. Soc Light Treatment Biol Rhythms Abstracts 18:30

10. **Smith MR, Fogg LF, Lee C, Eastman CI** in preparation Bright blue-enriched and white polychromatic light differentially phase shift the DLMO and DLMOff during simulated night shift work.

11. **Smith M, Eastman C** 2007 Scheduled bright light and darkness to achieve a compromise phase position for permanent night shift work. Sleep 30:A49

12. **Smith MR, Cullnan EE, Eastman CI** 2008 Shaping the light/dark pattern for circadian adaptation to night shift work: Study 2. Physiology and Behavior 95:449-456

    This is the full report of Study 2.

13. **Smith M, Eastman C** 2008 Achieving a compromise phase position for permanent night shift work using scheduled bright light and darkness. Sleep:A43

14. **Smith MR, Eastman CI** 2008 Night shift performance is improved by a compromise circadian phase position: Study 3. Circadian phase after 7 night shifts with an intervening weekend off. Sleep 31:1639-1645
    This is the full report of Study 3.

15. **Smith MR, Fogg LF, Eastman CI** 2009 A compromise circadian phase position for permanent night work improves night shift alertness and is compatible with late nighttime sleep on days off. Sleep 32:A44

16. **Smith M, Fogg L, Eastman C** 2009 Practical interventions to promote circadian adaptation to permanent night shift work: Study 4. Journal of Biological Rhythms 24:161-172
    This is the full report of Study 4.

17. **Smith MR, Fogg LF, Eastman CI** in press A compromise circadian phase position for permanent night work improves mood, fatigue, and performance. Sleep
    This is the analysis of combined data from Studies 3 and 4.

Publications that used Baseline Data for Reports Not Related to the Specific Aims

18. **Burgess HJ, Eastman CI** 2005 The dim light melatonin onset following fixed and free sleep schedules. Journal of Sleep Research 14:229-237

19. **Burgess H, Alderson D, Fogg L, Eastman C** 2007 Why do some people secrete more melatonin than others? Sleep 30:A49

20. **Burgess H, Fogg L** 2008 Individual differences in the amount and timing of salivary melatonin secretion. PLoS One 3:e3055

G. Inclusion/Enrollment Report

Principal Investigator/Program Director (Last, First, Middle): EASTMAN, Charmane I.

Inclusion Enrollment Report

This report format should NOT be used for data collection from study participants.

Study Title: Practical Circadian Interventions for Night Shift Work

Total Enrollment: 151 **Protocol Number:**

Grant Number: R01 OH003954 years 4 to 8

PART A. TOTAL ENROLLMENT REPORT: Number of Subjects Enrolled to Date (Cumulative) by Ethnicity and Race

	Sex/Gender			
Ethnic Category	**Females**	**Males**	**Unknown or Not Reported**	**Total**
Hispanic or Latino	7	4		11 **
Not Hispanic or Latino	72	68		140
Unknown (individuals not reporting ethnicity)				
Ethnic Category: Total of All Subjects*	79	72		151 *
Racial Categories				
American Indian/Alaska Native	3	1		4
Asian	17	12		29
Native Hawaiian or Other Pacific Islander				
Black or African American	14	11		25
White	40	47		87
More Than One Race	4	1		5
Unknown or Not Reported	1			1
Racial Categories: Total of All Subjects*	79	72		151 *

PART B. HISPANIC ENROLLMENT REPORT: Number of Hispanics or Latinos Enrolled to Date (Cumulative)

Racial Categories	**Females**	**Males**	**Unknown or Not Reported**	**Total**
American Indian or Alaska Native	2			2
Asian				
Native Hawaiian or Other Pacific Islander				
Black or African American				
White	2	4		6
More Than One Race	2			2
Unknown or Not Reported	1			1
Racial Categories: Total of Hispanics or Latinos**	7	4		11 **

* These totals must agree.
** These totals must agree.

Inclusion of Children

Children between the ages of 18 and 21 were included in these studies.

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