Sleep Medicine Reviews, Vol. 6, No. 5, pp 407–420, 2002
doi:10.1053/smrv.2001.0215, available online at http://www.idealibrary.com on IDEAL®

SLEEP
MEDICINE
reviews

CLINICAL REVIEW

Bright light, dark and melatonin can promote circadian adaptation in night shift workers

Helen J. Burgess, Katherine M. Sharkey and Charmane I. Eastman

Biological Rhythms Research Laboratory, Rush-Presbyterian-St Luke's-Medical Center, 1645 W. Jackson Blvd,
Suite 425, Chicago IL 60612, USA

KEYWORDS
chronobiotic, phase, rhythm, sleep

Summary The circadian rhythms of shift workers do not usually phase shift to adapt to working at night and sleeping during the day. This misalignment results in a multitude of negative symptoms including poor performance and reduced alertness during night work and poor daytime sleep at home. After an introduction to circadian principles, we discuss the efficacy of appropriately timed bright light exposure (natural and artificial) and exogenous melatonin administration for producing circadian adaptation to night work. Interventions that generate alternative 24 h light/dark patterns that facilitate appropriate circadian phase shifting are discussed. Such interventions include minimizing night workers' exposure to the external light/dark cycle, and the use of intermittent and moving patterns of bright light at work. The efficacy of melatonin in phase shifting circadian rhythms in the field is also addressed and compared to that of bright light. We present sleep/light exposure schedules that could produce circadian adaptation in permanent night workers. We conclude this review by discussing the impact of individual differences on possible circadian interventions and issues associated with the use of bright light interventions in the field. © 2002 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

This review discusses field and simulated shift work studies that used bright light (defined here as artificial light more intense than ordinary room light) and/or exogenous melatonin to facilitate circadian adaptation to night work. Simulation shift work studies in which subjects were exposed to morning sunlight after "night shifts" were of most interest as these more realistically represent night work. Preference was also given to studies that used common measures of circadian phase such as endogenous melatonin and demasked core body temperature. This review focuses on permanent night work or slowly rotating schedules, rather than rapidly rotating schedules as circadian phase shifting is typically too slow for adaptation in such circumstances.

THE HUMAN CIRCADIAN SYSTEM AND PHASE RESPONSE CURVES

The circadian rhythms of core body temperature and the hormone melatonin are commonly used

---

Correspondence should be addressed to: Charmane Eastman, Biological Rhythms Research Laboratory, Rush-Presbyterian-St Luke's-Medical Center, 1645 W. Jackson Blvd, Suite 425, Chicago IL 60612, USA. E-mail: ceastman@rush.edu

1087–0792/02/$ – see front matter © 2002 Elsevier Science Ltd. All rights reserved.

markers of circadian phase in humans. The relationships between circadian rhythms and various stimuli or zeitgebers are described using phase response curves (PRCs). A PRC is derived by administering a stimulus at many different times or circadian phases and measuring the effect on the phase of the circadian clock. A schematic light PRC and an exogenous melatonin PRC illustrate that the timing of light or melatonin administration is crucial to the magnitude and direction of the subsequent phase shifts (Fig. 1).

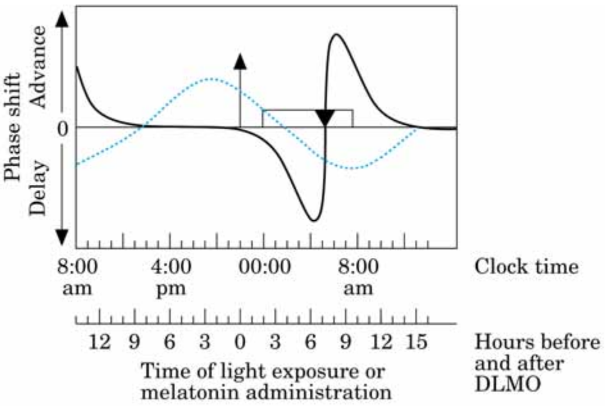

Figure 1 A schematic human phase response curve (PRC) to light (dark line) and a PRC to exogenous melatonin (dashed line). The y-axis shows the direction and relative magnitude of the phase shift produced by the administration of light or melatonin at various times, which are shown on the x-axis. The x-axis covers more than 24 h in order to better illustrate the PRCs. The rectangle represents sleep, the triangle represents the core body temperature minimum (Tmin) and the arrow represents the dim light melatonin onset (DLMO). The clock time axis shows the DLMO at about 10.00 p.m., sleep from about midnight to 8.00 a.m. and the Tmin at about 5.00 a.m. These represent typical times and phase relationships among these rhythms when the circadian clock is entrained to a 24 h day. For individuals with earlier or later circadian rhythms the local time axis should be adjusted accordingly. The light PRC is a schematic based on the results of numerous studies. The melatonin PRC is based on a single study using 0.5 mg doses of melatonin [21]. The PRCs show the phase shift to light or melatonin administration, but in a particular situation the overall 24 h LD pattern, which includes the dark time during sleep, is important in determining the direction and magnitude of the resulting phase shift. The magnitude of phase shifts on the melatonin and light PRCs should not be directly compared to each other as the magnitude will depend on the "dose" used and the magnitude of the shift of sleep/dark.

The schematic light PRC in Figure 1 is based on a synthesis of the results of numerous studies. In some, sleep time was held constant and high intensity light was applied before or after sleep ([1], see review [2]). In others the sleep schedule was shifted (up to 12 h) and the course of re-entrainment was studied while light "pulses" of several hours were applied at various circadian phases ([3, 4], see reviews [2, 5]). Finally, in two others, light pulses were applied to free-running individuals [6, 7]. The time of the minimum of core body temperature (T_{min}), near the middle to end of sleep, is currently used as an estimate for the crossover point of the human light PRC. Light before the T_{min} produces phase delays and light after the T_{min} produces phase advances. For long durations of light that fall on both the phase advance and delay portions of the PRC, the direction of the resulting phase shift is influenced by where most of the light falls [3, 5]. Light exposure close to the T_{min} produces the greatest phase shifts and so in humans the normal nighttime sleep period must be shifted to generate the largest phase shifts. When the sleep period is not shifted, light in the middle of the afternoon ("dead zone") does not produce phase shifts (e.g. [1]). The magnitude of phase shift increases with increasing intensity and duration of light [8] although this relationship is nonlinear (e.g. [9]). As the human circadian clock has a period slightly longer than 24 h [10, 11], it has a natural tendency to drift slightly later and later each day. For this reason phase delays are usually easier for humans than phase advances.

Melatonin is a hormone synthesized and released from the pineal gland with a circadian rhythm. Typically, melatonin levels begin to increase before sleep and peak in the early hours of the morning and decrease to daytime levels after waking (see Fig. 2).

Melatonin can be measured in plasma, urine and saliva but its secretion is suppressed by light [12], including ordinary indoor light [13, 14]. The time of the onset of melatonin secretion in dim light (DLMO, measured in plasma or saliva) and maximum (acrophase) are frequently used as markers for the phase of the circadian clock.

While *endogenous* melatonin can be measured to estimate circadian phase, synthetic *exogenous* melatonin can phase shift circadian rhythms. Exogenous melatonin is readily available (at least in the

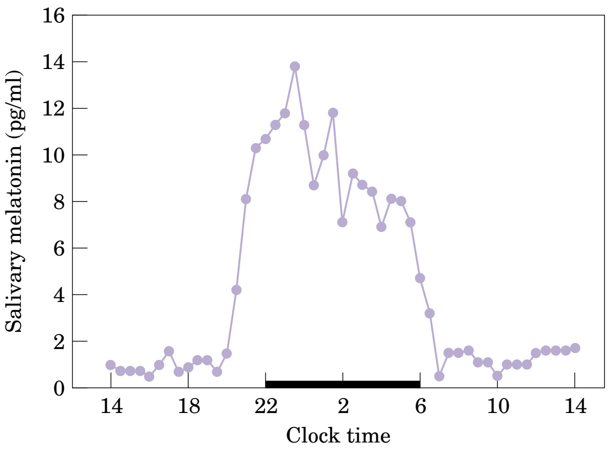

Figure 2 A typical 24 h profile of melatonin secretion. This individual, a 25-year-old male, slept from 10.00 p.m.–6.00 a.m. (indicated by the black bar) for one week before his melatonin profile was assessed. During the assessment, the subject remained awake in a semi-recumbent position in dim light (<10 lux) and saliva samples were collected at 30 min intervals and later assayed for melatonin [58].

USA), has a half-life of ~0.5 h [15] and has very low toxicity with mild side effects [16]. However, due to melatonin's potential influence on maturation and reproductive function, it is advised that children, pregnant and nursing women do not use exogenous melatonin. In general, oral melatonin doses ranging from 0.05 to ~0.3 mg are thought to produce serum melatonin levels comparable to physiological nocturnal levels, whereas doses of 0.5 mg and higher produce pharmacological or supraphysiological levels (see review [17]). Nonetheless, there is high interindividual variability in levels of nocturnal endogenous melatonin production (e.g. [18]) and in the metabolism of exogenous melatonin (e.g. [19]). Greater effects of exogenous melatonin generally occur with "pharmacological" doses as compared to "physiological" doses (e.g. [20]).

A PRC for orally administered exogenous melatonin has been generated (see Figure 1). Circadian phase delays are produced when melatonin is taken in the later hours of the sleep period and in the morning. Phase advances result when melatonin is taken in the afternoon and early evening. This PRC was generated by giving 0.5 mg of melatonin for 4 consecutive days to 6 subjects whose sleep schedule was not shifted (the subjects woke briefly if they had to take the pill during their sleep). Each subject participated in 12 trials in which the melatonin was taken at different circadian times. The resulting PRC (Figure 1 in [21]) was composed of many symbols showing data from all the individual subjects. In Figure 1 (this review), we show a line to better illustrate the general pattern. In the original paper [21] the x-axis was converted from hours before and after the DLMO to a version of circadian time (CT) in which CT14 was defined as the individual's baseline DLMO. To avoid confusion with other definitions of CT in humans [5], our Figure 1 does not have a CT axis. While it is often said that the light and melatonin PRCs are mirror images of each other, Figure 1 shows that this is true for much but not all of the circadian cycle. As the melatonin PRC is based on one dose of melatonin given to a few subjects, in only one type of protocol, more research is necessary to further delineate the melatonin PRC. Currently one of the most exciting uses of the phase shifting properties of melatonin is the entrainment of free-running blind people by phase advances (e.g. [22]).

SHIFT WORK AND THE NATURAL LIGHT/DARK CYCLE

Approximately 1 in 5 workers in the USA engage in some form of shift work (defined here as nonstandard work hours). Females are almost as likely as males to be shift workers (21% of working males versus 19% of working females) [23]. Shift work is associated with numerous negative effects, including shortened and disturbed sleep, fatigue, decreased alertness, cognitive deficits, increased injuries and accidents, reproductive disorders, and risks to cardiovascular and gastrointestinal health. These detrimental consequences pose threats to the health and safety of individual workers and to the general public (e.g. see [24] for review). This is particularly true for workers who can make high-risk mistakes (e.g. health care workers and nuclear power plant workers).

In part, night shift workers experience these symptoms and deficits because without intervention their circadian rhythms rarely phase shift to align with the sleep-wake schedule demanded by their occupations (see review [25]). This is because exposure to the 24 h LD cycle and possibly other 24 h time cues keep circadian rhythms synchronized for alertness during the day and sleep at night. As the circadian rhythms of most night workers do not phase shift, the workers are in a constant state of circadian misalignment and are forced to work at the "wrong" circadian phase (when their bodies are ready to sleep) and must try to sleep at the "wrong" circadian phase (when their physiology is primed for alertness). Typically in daytime workers, the DLMO is ~ 1–3 h before sleep onset and the Tmin and melatonin acrophase both occur during sleep (Figs 1 and 2). For circadian adaptation to daytime sleep to occur, the rhythms must phase shift to align with the new sleep period. Fortunately, the symptoms due to circadian misalignment can be reduced even if the original phase relationship is not completely reestablished. The magnitude of phase shift is positively related to the extent of improved performance and alertness during the night and better daytime sleep at home (e.g. [26–30]). However, it is beyond the scope of this review to address performance and sleep results – this review is limited to the phase shifting efficacy of light and melatonin. However, it should be remembered that greater realignment between circadian rhythms and the sleep period generally leads to better performance, alertness and daytime sleep. In this review we use the term "adaptation" to refer to phase shifts that place the T_{min} or melatonin acrophase within the sleep period [5, 31]. We will not discuss important non-circadian influences on the health and well being of shift workers, such as psychological and social factors.

The impact of natural light on circadian adaptation in night workers has been examined in two field studies. A study of 30 permanent night nurses who worked 3–9 consecutive nights (midnight to 8.00 a.m.), found that 5 of the nurses adapted by phase delaying (their melatonin rhythm and sleep were sufficiently realigned), 22 were "non-shifters" and 3 advanced (but only 1 of these adapted by our definition) [32]. This study illustrates that the circadian rhythms of most shift workers, even permanent night workers, do not phase shift. It also shows that when the LD cycle to which workers are exposed is reversed, circadian adaptation can occur. The overall 24 h pattern of light exposure for the nonshifters showed the normal diurnal pattern (brighter during the day than at night). The delayers had a reversed pattern; they received less light during the morning and afternoon (because they tended to stay in bed longer and their bedrooms were darker) than during the night shift. Another study was of 14 night watchmen who worked 5 consecutive night shifts (~ 6.00 p.m.–6.00 a.m.) [33]. Better circadian adjustment to night work and day sleep (phase delays) was significantly associated with less exposure to morning (6.00–9.00 a.m.) outdoor light. Earlier daytime sleep onset (and thus again less morning/early afternoon light) was also associated with greater phase delays.

The results from both of these studies (as well as another study to be reviewed later [27]), show that better circadian adaptation occurs when workers receive less morning/afternoon sunlight. However, most workers are exposed to this daylight after night work, and it produces a phase advance, or at least counters the phase delay required for circadian adjustment (see Fig. 1). This light exposure may occur while commuting home after a night shift, or while night workers attempt to sleep if their bedrooms are not sufficiently dark. Night workers can also receive phase advancing light if they have social/family commitments that force them to delay their sleep, rather than being free to sleep shortly after the night shift ends.

Exceptions to the general rule that shift workers do not adapt to night work occur when night workers work and sleep at unusual locations, such as offshore oilrigs or Antarctic stations (e.g. [34, 35]). In these unusual work environments, workers can be less exposed to the external LD cycle and competing social demands. Circadian adaptation can also occur in a few night workers in more populated areas (e.g. [32, 36, 37]). Such relatively rare adaptation is probably due to various factors that contribute to a reversed LD cycle. These factors include early bedtimes after the night shift, later bedtimes on days off, and the commute home occurring in dim morning light (for example in winter and/or before sunrise).

Preventing inappropriate light exposure (even before using melatonin or artificial bright light) is an important first step in improving circadian adaptation in the shift worker. As pioneered by Eastman [3], night workers can easily overcome inappropriate morning light exposure by wearing dark sunglasses and putting black material over their bedroom windows or using light-tight shades (some already do [38]). Getting to bed as early as possible after the night shift and allowing a long enough time in a dark bedroom is also important. While welder's goggles were originally used to minimize morning light exposure [39], fashionable, inexpensive dark sunglasses (12% light transmission) approved for driving are now available ("Bandito" frames with "espresso" lenses, Uvex Safety Inc., RI, USA).

IMPROVING CIRCADIAN ADAPTATION WITH ARTIFICIAL BRIGHT LIGHT

The appropriate use of nocturnal high intensity light can increase the rate of circadian adaptation even further than simple shielding from the external LD cycle. Several simulation studies have successfully used such light to phase shift rhythms to realign with a shifted sleep period. In a few of these studies the bright light was very intense (5000–12 000 lux), the duration of exposure very long (6–7.5 h) and the light was administered on at least 4 consecutive nights. The "workers" were also shielded from inappropriate external light – they spent 8 h in darkened bedrooms [3, 29, 30] and used goggles during their commute home [3]. In one study sleep was shifted 12 h and light produced delays and advances of 1–2 h/day in the first few days (the phase shifts diminished thereafter) ([3] and see review [5]). Shifts of this magnitude indicate the extent to which the circadian system can be "pushed" in night workers.

Several field studies conducted at NASA with astronauts and ground crew also used long high intensity light exposures to produce adaptation to shift work ([40–42], see review [43]). In these studies, 3–9 h of light (3000–12 000 lux) were administered for about a week prior to each launch along with a slow or rapid shift in sleep to pre-adapt the workers to the shift schedules required during the missions. Urinary melatonin results indicated complete adaptation to shift work, and bright light has become a permanent part of the Space Shuttle program. While impressive, there were several factors in these studies (aside from the bright light and the shift in sleep schedule) that facilitated the circadian adaptation: quiet and dark sleeping quarters, reduced social demands and the enthusiasm and motivation of the workers.

Few of these factors were present when more typical night workers were studied at an Exxon Chemical Company [38]. Here, the considerable methodological problems associated with most field research on real shift workers occurred. Thirteen workers followed a work schedule that rotated between day and night shifts: 4 day shifts (6.00 a.m.–6.00 p.m.), 4 days off, 4 night shifts (6.00 p.m.–6.00 a.m.), 4 days off. After a baseline "lights off" period, high intensity light (4000–8000 lux) was used during the night shifts for 3 months, followed by another "lights off" period. Blackout curtains were also distributed to help darken bedrooms at home. Unfortunately the timing and duration of the light was not clear and it varied among workers due in part to varying tasks. Compliance to the experiment was low (some workers wore hats or sunglasses inside to avoid the light, or used the light during the last "lights off" period). Furthermore, as the circadian marker (urinary melatonin) was probably masked by exposure to indoor and outdoor high intensity light, it remains uncertain how much, if at all, the workers phase shifted. Nonetheless, the light probably did shift some workers as the greatest complaint regarding the lights was that it was difficult to adjust back to a daytime schedule after the night shifts (no attempt was made to make this adjustment easier such as applying bright light to phase advance circadian rhythms). This study is important as it demonstrates the difficulties that can be encountered when introducing high intensity light in an industrial workplace.

In contrast bright light was successfully used for nurses who worked permanent night shifts [44]. Some of the nurses received bright light (2000–7000 lux) during the first 6 h of each night shift and wore dark goggles on the commute home while others continued to work in normal indoor light and did not use goggles. All of the nurses maintained regular 8 h sleep/dark periods during the day after night work. Rectal temperature recordings (constant routine procedure) made before and after the night shifts showed that both groups phase delayed. However, only the bright light group delayed enough so that the average T_{min} was properly aligned with the daytime sleep period. These results illustrate that bright light, dark goggles and regular sleep/dark can promote circadian adaptation in real night shift workers.

Long exposures of high intensity light do not necessarily produce greater phase shifts than shorter periods of such light. One simulated shift work study found no difference between 3 versus 6 h of $\sim$5000 lux light exposure during 8 consecutive "night shifts". With 6 h of the light, 69% of the subjects phase shifted by at least 8 h, while after 3 h of light on each night 65% phase shifted by at least 8 h (with only dim light, none of the subjects shifted this much [30]). Thus a shorter duration of high intensity light can be as effective as long (>6 h) durations, but only if timed appropriately.

When bright light is administered at the same clock time on each night, the largest phase shifts tend to occur during the first few nights of bright light exposure and diminish in size thereafter (e.g. [3]). One reason this occurs is because as the circadian clock shifts in response to light, its PRC also shifts. For example, light initially timed to produce a large phase delay will, with subsequent exposures at the same clock time, progressively "hit" the PRC at a section that produces progressively smaller phase delays (see Fig. 1). To overcome this and maximize the desired phase shifts, light exposure has been moved later and later in time (for a phase delay) or earlier and earlier in time (for a phase advance) during each night shift (e.g. [3, 28, 45]). Such "moving" bright light is an approach to ensuring that the administration of light continues to "hit" the correct portion of the PRC.

Figure 3 illustrates how moving bright light could be used to promote circadian adaptation to night work. Moving light is also a very effective way of correctly timing light exposure when an individual's circadian phase has not been measured, or one is trying to simultaneously shift a group of individuals with different circadian phases. Moving light is effective and "safe" because it can be started far from the T_{min} and gradually moved closer. Thus the risk of light falling on the wrong side of the T_{min} and accidentally shifting the circadian rhythms of some individuals in the wrong direction is minimized. Moving high intensity light has also been used successfully on real shift workers at NASA [40, 41, 43, 46] and on an oil rig in the North sea [47].

High intensity artificial light ($\sim$2000–10 000 lux) is often considered aversive even though it is not nearly as intense as outdoor light (which can be 100 000 lux or more). Indeed, some shift workers try and avoid high intensity light [38] and one simulation study started a period of high intensity light exposure by slowly increasing the light intensity during a 15 min transition period [29]. The aversive nature of artificial high intensity light is probably due to the contrast between the light source (typically small) and the surrounding area. Thus it is best to use larger light boxes that cover more of the visual field. For example, by covering the ceilings of the astronauts' crew quarters in Houston with fluorescent fixtures, the aversive nature of a small light box on a desk was avoided.

Medium intensity light may also be as useful as high intensity light, as the dose response relationship between light intensity and the magnitude of subsequent phase shifts is nonlinear (e.g. [9]). A simulation study used a moving pattern of medium intensity light ($\sim$ 1230 lux for 3 h) during the night shift with a 10 h delay in the sleep period [28]. The subjects wore dark sunglasses ($\sim$ 7% transmission) to reduce the advancing effect of morning light. Compared to ordinary room light (<250 lux), medium intensity light significantly increased the percentage of subjects who adapted to the "night shift" from 42–85%. High intensity light ($\sim$ 5700 lux for the same 3 h) increased this percentage to 100% but this increase was not significant. Thus providing morning light exposure is minimized, and regular sleep/dark periods occur shortly after the end of night work, medium intensity light can be just as effective as brighter light at shifting circadian rhythms. Medium intensity light is also more easily tolerated and less expensive.

The work arrangements of many shift workers do not make it feasible for them to receive long durations of high intensity light. In such circumstances, intermittent high intensity light is an effective alternative. An intermittent high intensity light pattern was first used in a simulation night work study to hasten circadian adaptation to a 9 h delay in the sleep period [26]. The light pattern was 6 pulses of $\sim$ 5000 lux, each 40 min long, alternating between 20 min of room light (<500 lux). This light pattern was within the first 6 h of the first 3 night "shifts". All subjects slept (or at least remained) in darkened bedrooms for 8 h after each "shift" and wore dark sunglasses ($\sim$ 7% transmission) whenever they went outside. The high intensity light facilitated circadian adaptation: 100% of the subjects who received the light adapted by the fourth to eighth "night shifts", while only 50% of subjects in a control group who received only room light adapted. Furthermore, the phase shifts with intermittent light were similar in magnitude to the phase shifts observed following eight nights of 3 h/night of appropriately timed continuous high intensity light [45]. The effectiveness of intermittent high intensity light may be due to a nonlinear relationship between the degree of phase shifting and light duration. The human circadian system may be most sensitive to bright light at the beginning of a pulse [48]. Thus installing bright lights into work or rest areas such that night workers receive bright light while performing certain tasks or during breaks is likely to be an effective way of administering light (cf. [49]).

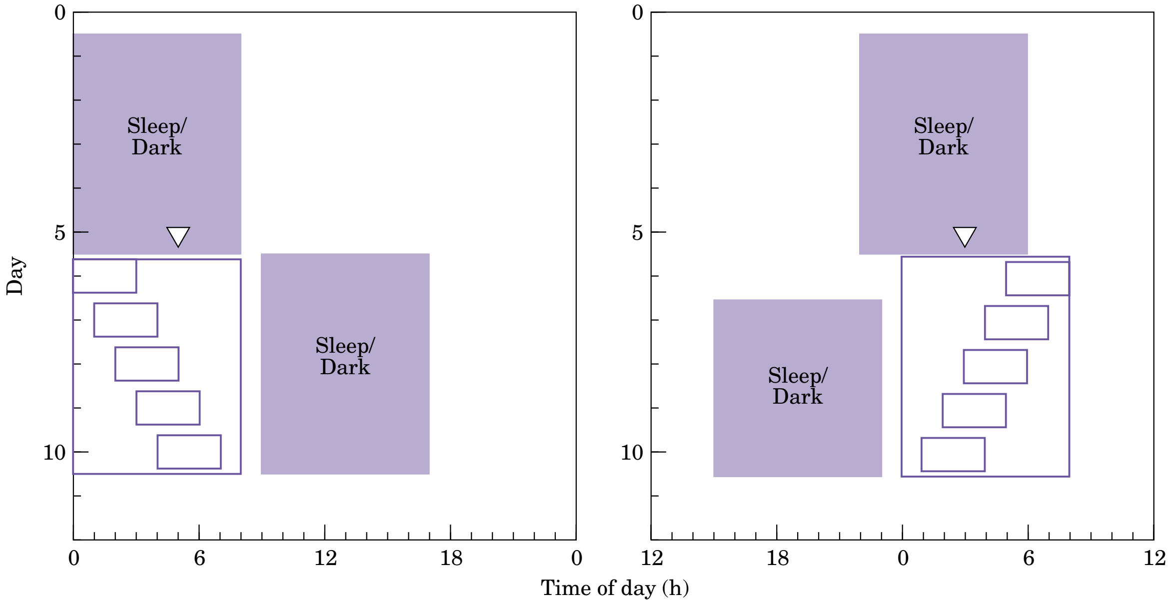

Figure 3 An example of a sleep-work-light-dark schedule using moving bright light to shift circadian rhythms in the direction of the shifted sleep/dark period (represented by shaded boxes). There are 5 days with nocturnal sleep, followed by 5 consecutive night shifts (represented by large white boxes). The left panel illustrates sleep taken after the night shift (a 9 h delay of sleep/dark), while the right panel illustrates sleep taken before the night shift (a 7 h advance of sleep/dark). The small white rectangles during night work show a 3 h bright light exposure on each night, shifted later in time for a phase delay (left) or earlier in time for a phase advance (right). The triangles represent the typical Tmin during baseline. The delaying sleep pattern corresponds to what most night shift workers do, but the advance could be used in special circumstances, such as a change from an early morning shift or for "early birds".

Morning light exposure can impair circadian adaptation in night workers, even if they receive high intensity light during the night shift. For example, in a simulation study 50 subjects maintained a daytime schedule (baseline) for 10 days, and then worked 8 "night shifts" followed 2 h later by a 8 h sleep/dark period at home [27]. There were 4 groups run in a 2 x 2 design (dark goggles versus no goggles during the commute home; 6 h of ~5000 lux light on the first 2 "night shifts" versus ordinary room light). By comparing the average Tmin in the last 7 baseline days to the average Tmin in the last 4 "night shifts", the effects of the light and goggles were determined. The shift of sleep/dark was 12 h, and the light during the night shift (bright or dim) covered both the delay and advance portions of the PRC. Thus goggles were especially important to the direction of circadian adaptation. The goggles were necessary for phase delays (a faster means to adaptation); without goggles morning light exposure "tipped the scales" in favor of phase advances. Goggles increased the mean phase shift by 2.4 h with only ordinary room light during the "night shifts" and 1.9 h with high intensity light. Thus goggles during the commute home improved circadian adaptation regardless of whether bright light was applied during the night shift.

Incorrectly timed bright light exposure (with respect to the T_{min}) during the night shift can also prevent circadian adaptation. This principle was evident in a simulation study where the sleep/dark schedule was advanced or delayed by 9 h and high intensity light was timed to either facilitate or conflict with the required circadian adjustment [45]. After 8 days 88% of the subjects in the "facilitating light" group shifted at least 6 h, whereas only 38% of subjects in the "conflicting light" shifted as far. These results point to the careful attention that must be paid to the timing of bright light during night work.

Finally, while bright light has circadian phase shifting effects, it is also beneficial to workers as it has an acute alerting effect and improves cognitive performance (see review [50]). Indeed, several field studies have reported that high intensity light improved alertness, mood, productivity, safety and decreased absences in workers (e.g. [43, 46, 51–53]). Such beneficial effects are probably due to the immediate effects of bright light and in some cases to circadian phase shifting.

IMPROVING CIRCADIAN ADAPTATION WITH EXOGENOUS MELATONIN

In addition to appropriate manipulations of light, exogenous melatonin may be an effective method of enhancing circadian rhythm phase shifts to a shifted sleep schedule. To date, there are only a few published studies that have examined the use of melatonin during shift work. Three studies with real night workers did not measure circadian phase, but workers did make subjective ratings of their daytime sleep and nighttime alertness. Overall, melatonin administration resulted in modest improvements. In two of the studies [54, 55], 5.0 or 10.0 mg of melatonin (or placebo) was administered to workers at bedtime after the night shift for 2–6 consecutive days. Daytime sleep durations increased by ~25 min and some measures showed improved nocturnal alertness. In another study [56], workers took 6.0 mg of melatonin (or placebo) before daytime sleep for 4 consecutive days. Melatonin decreased the number of self-reported awakenings but had no effect on total sleep time. As these studies did not use a measure of circadian phase, it is impossible to determine whether the slight improvements were due to the realignment of circadian rhythms with daytime sleep or to the soporific effect of melatonin. However, it is unlikely that circadian rhythms phase shifted very much as no effort was made to shield subjects from morning light after the night shifts.

A recent shift work simulation study from our laboratory tested placebo, 0.5 mg and 3.0 mg of exogenous melatonin to try and hasten phase advances to a 7 h advance in the sleep schedule [57, 58]. There were 7 baseline days, followed by a 26 h phase assessment period in dim light (<10 lux), and then 7 "night shifts" in ordinary room light (<250 lux). Subjects slept (or at least remained) in their specially darkened bedrooms for 8 h in the afternoon/evening before each "night shift". After a final eighth daytime sleep episode, there was another phase assessment period. Subjects took a pill 30 min before each of the first 4 daytime sleep periods. This was the equivalent of 7.5 h before their baseline bedtime and thus was timed to hit the beginning of the phase advance portion of the melatonin PRC (see Fig. 1). The DLMOs from the phase assessments indicated that the magnitude of the desired phase advance was greater with larger doses of melatonin. Consequently more subjects who took melatonin adapted to the shifted sleep schedule (56% of subjects with 0.5 mg, 73% of subjects with 3.0 mg) than those who took placebo (0%). These results suggest that melatonin is likely to prove an effective tool for shift workers who choose to sleep in the afternoon/evening before night work. However, simulation studies examining melatonin's efficacy at phase delaying are also needed (most night workers choose to sleep in the morning and so their circadian rhythms need to delay rather than advance).

To date, there is only one field study that has tested melatonin for night work (and measured circadian phase) in real shift workers. This study by Sack and colleagues (summarized in [59]) examined the effects of melatonin on the circadian rhythms of nurses and hospital clerical staff alternating between 7 consecutive night shifts (9.30 p.m.–7.30 a.m.) and 7 days off. A low dose of melatonin (0.5 mg) or placebo was taken at bedtime after the night shifts and then at bedtime during the week off (for 2 consecutive weeks in a double-blind crossover design). The DLMO was measured at the end of each week. The results of this study are unusual in that some subjects had an adaptive phase shift in their circadian rhythms after the week of night work on placebo. This group corresponds to the rare group of shift workers who probably adapt because their commute home occurs prior to sunrise, or in relatively dim outdoor light during northern winters [37]. Melatonin produced larger phase delays than placebo in 7 of 24 subjects studied. A further 9 subjects phase delayed equally well with melatonin or placebo, 3 phase advanced on both, and the remaining 5 had little or no phase shift on either pill. As this was a field study, there was less control of the timing of melatonin administration and the subjects' sleep schedules (the workers took the melatonin whenever they decided to go to bed). Nevertheless, the results are encouraging because melatonin appeared to help a subgroup of night workers.

Table 1 A comparison of two simulated night work studies that used high intensity light or melatonin to facilitate a phase advance in circadian rhythms

	Sharkey and Eastman [57, 58]	Mitchell and colleagues [45]
Stimulus dose	3.0 mg melatonin	3 h of ~5000 lux light
Shift in sleep	7 h advance	9 h advance
Stimulus timing	0.5 h before advanced day sleep	Moving pattern during night shift
Number of treatment days	First 4 night shifts	All 8 night shifts
Average T_{min} from	5–7th night shifts	5–8th night shifts
Phase advance	4.0 ± 1.2 h	6.7 ± 0.8 h
% of reentrainment	57%	74%

All core body temperature data was demasked. The percentage of reentrainment equals the phase advance divided by the shift in the sleep period (4/7 = 57%, 6.7/9 = 74%).

To our knowledge there is only one study that has compared the effectiveness of high intensity light versus melatonin in improving circadian adaptation during simulated night work [60]. However, this was an in-lab study and subjects were shielded from outside morning light. Furthermore, the timing of the light (4000–7000 lux, from midnight–4.00 a.m. during 3 night shifts) was good for phase delaying circadian rhythms, but as discussed in the paper, the timing of the melatonin before and during daytime sleep (2 mg at 8.00 a.m., 1 mg at 11.00 a.m. and 1 mg at 2.00 p.m.) was not optimal to facilitate phase delays (see Fig. 1). Thus it is not surprising that in this study melatonin proved no more effective for promoting phase delays than placebo. Further studies are required to assess the effectiveness of bright light versus melatonin in facilitating adaptation to shifts in sleep schedules.

Nonetheless, there is a tendency to assume that light is a much more powerful phase-shifting agent than melatonin. This may stem from a cursory comparison of the maximum phase shifts (~1 h) obtained with melatonin by Lewy *et al.* [21], with the maximum phase shifts obtained in bright light studies (~12 h) [3, 4]. As sleep was not shifted in the melatonin study but was shifted by as much as 12 h in the high intensity light studies, this comparison is not reasonable. Here we compare the effects of melatonin versus high intensity light from simulation shift work studies in which sleep was phase advanced. The efficacy of melatonin appears to be similar to that of high intensity light (see Table 1). In the study by Sharkey and Eastman, melatonin taken before afternoon/evening sleep (during the phase advance portion of the melatonin PRC) helped advance the Tmin by 57% of the total advance required for complete reentrainment [57, 58]. By comparison in the study by Mitchell and colleagues, high intensity light during the night shift (during the phase advance portion of the light PRC) helped advance Tmin by 74% of that required for complete reentrainment [45]. Thus the phase shifting effect of melatonin appears comparable to that of high intensity light, especially as the light exposure treatment occurred on 8 nights, while the melatonin treatment was only on 4 nights. Clearly however a proper comparison of melatonin and light would require the two to be tested in an identical protocol and even then only specific light patterns (intensity, duration, timing of administration) could be compared with specific melatonin administrations (dose, timing of administration). In any case, it is unlikely that melatonin would facilitate a phase delay shift if conflicting bright light exposure (such as morning sunlight after the night shift) occurred. Whether the administration of exogenous melatonin can significantly facilitate circadian adaptation above and beyond that achieved with appropriate bright light (and shielding from the external LD cycle) has yet to be determined and is currently under investigation in our laboratory.

INDIVIDUAL DIFFERENCES

Individual differences in the ability to adapt to a shift in the sleep period may be due to several factors. First, there is variability in individuals' circadian phase. Evening types (whose T_{min} occur at a later clock time) generally make better night workers as they have later bedtimes and so do not have to shift their sleep as much when they sleep after the night shift. They may also be capable of larger phase delays [45]. The converse of this is that morning people will find it easier to adapt to early morning shifts.

A person's age will also affect the degree to which they adapt. Older people tend to sleep and wake earlier with respect to clock time (e.g. [61]). Thus older workers will need to phase shift more in order to adapt to night work (even if their phase shifting capacity is not reduced). Furthermore, middle-aged [62, 63] and older people (e.g. [61]) are also likely to be less "phase tolerant" than younger people. Phase tolerance refers to the range of phase relationships between rhythms and sleep that can be "tolerated" [31]. For example, in one laboratory study high intensity light phase shifted circadian rhythms to produce a partial realignment with daytime sleep [63]. Middle-aged subjects phase shifted as much as young subjects, but their daytime sleep and nighttime alertness and performance did not improve to the same extent. Thus they were less phase tolerant than the younger subjects. Therefore, middle-aged and older workers will have to shift their circadian rhythms more in order to reap the same benefits as younger people. The decreased phase tolerance in older workers is probably why shift workers find night work increasingly difficult as they get older. As the population of shift workers is likely to parallel society and become progressively older, the problems of the aging shift worker will become more pressing. Already in 1986 in the USA 24% of shift workers were middle aged or older ($\geq$35 years) [24]. Clearly, more research is required to investigate the effectiveness of light and melatonin in phase shifting older shift workers as they are most likely to need such circadian interventions.

OTHER ISSUES WITH BRIGHT LIGHT INTERVENTIONS

Many of the findings from laboratory studies have yet to be systematically introduced into workplace settings. As previously mentioned, the appropriate timing of light (according to the PRC) is crucial in producing appropriate phase shifts and thus increasing adaptation to night work. In the field it is often difficult and costly to measure an individual's circadian phase in order to ensure the correct timing of light. Thus, in shift work settings, the use of moving light will minimize the number of workers, who because of their extreme phase (early or late) may otherwise receive the light during the wrong portion of their PRC. Intermittent and medium intensity light are also likely to be more practical and less expensive.

With information about circadian principles and work place incentives, shift workers may eventually use light during work with success similar to NASA's. Indeed, despite their exposure to long pulses of high intensity light during some of their night shifts, and the difficulty in returning to a daytime schedule on their days off, 54% of workers in one previously discussed field study still reported that the "bright light program was an overall improvement compared to the baseline period" (p. 777, [38]). This result suggests that medium intensity intermittent light is likely to be well received by the majority of shift workers. Clearly however, as shift workers themselves have reported [38], the implementation of circadian principles needs to be tailored to each separate work environment. Glare is a common problem [38] that can be overcome by the installation of nonreflective surfaces and ensuring that light originates from a large indirect source.

A major complaint about the use of bright light in the field was that it makes the readjustment to a daytime schedule after night work more difficult [38]. This presumably interferes with workers' social and family commitments during their time off. If workers must return to a daytime schedule (e.g. because of family responsibilities and can not choose to sleep later), they may take a few days to reentrain [28] and so will be "out of sync" during their time off. To hasten the readaptation back to a normal daytime schedule, some workers at NASA successfully self-administered bright light at home or went outside into daylight (e.g. [46]). A self-administered moving pattern of bright light was also used to help oil rig workers delay back to days off at home after working nights [47]. Indeed several workers reported continued use of bright light on their days off 2 years after the study.

WORK-LIGHT-SLEEP-DARK SCHEDULES FOR SHIFT WORK

An example of a sleep schedule to help shift workers adjust to a fortnightly alteration between day and night shifts has been developed [39]. Around the transitions from day to night shifts and from night to day shifts, the sleep period is gradually delayed by 1–3 h/day. Another "sleep plan" was designed for workers on a weekly rotation from day to evening to night shifts [2]. Here, the sleep period delayed by up to 2 h/day. In both of these delaying schedules the use of high intensity light or sunlight was encouraged in the hours immediately before sleep and was to be avoided after sleep. There is also a sleep schedule for permanent night workers that uses a medium intensity moving light pattern (fig. 5 in [5]). In this review, we present a new plan for permanent night workers that uses medium or high intensity intermittent light during just 2 night shifts. It also makes use of afternoon daylight to advance circadian rhythms when workers need to wake up earlier on their days off because of personal commitments (Fig. 4).

The schedule in Figure 4 is a compromise between the ideal alignment of circadian rhythms (represented by the T_{min}) with the sleep period during work days versus days off. The T_{min} is earlier within the sleep period than ideal during some day sleep periods, and later within the sleep period than ideal during day off sleep. However, the intent is to keep the T_{min} within all the sleep periods after it has crossed the travel home time and thereafter to keep it from delaying around the clock by using afternoon light. The shaded areas within the sleep boxes show when good sleep might be expected, from 6 h before to 6 h after the Tmin [5] that will vary according to each worker's individual phase tolerance. Night workers using this plan may also consider taking exogenous melatonin before their daytime sleep periods. While data are scarce on whether melatonin can facilitate phase delays in night workers, melatonin's soporific action is likely to improve daytime sleep (e.g. [64]).

TO SHIFT OR NOT TO SHIFT

It has been suggested that multiple phase shifts may not be healthy [65]. For example, hamsters exposed to a constantly shifting LD cycle had a shorter life expectancy than hamsters kept in a constant LD cycle [66]. However, if circadian rhythms do not phase shift, then the increased sleepiness at work and decreased sleep during the day need to be addressed. Again, this is particularly true for workers who can make high-risk mistakes (e.g. health care workers and nuclear power plant workers). One approach to overcome such decrements is to use stimulants to stay alert (e.g. caffeine, amphetamines) and sleeping pills (e.g. benzodiazepines) to sleep during the day. Such stimulants and sleeping pills typically have hangover effects and health risks

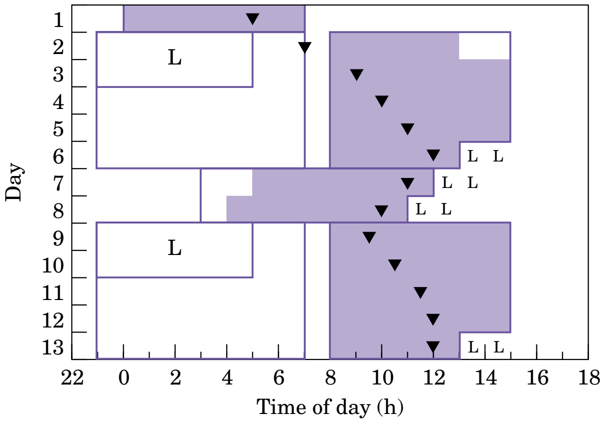

Figure 4 A light and sleep schedule designed to produce partial circadian adaptation to permanent night work. Day 1 shows a typical sleep time (midnight–7.00 a.m.) and temperature minimum (T_{min} at 5.00 a.m., triangle) for an individual before starting night work. A typical night work schedule is shown on days 2–6 (5 night shifts, 11.00 p.m.–7.00 a.m.) followed by 2 days off and then 5 more night shifts. The shaded large rectangles surround the sleep/dark (S/D) periods, when the worker should be in bed. Following the night shift the S/D period is shown as 8.00 a.m. to 3.00 p.m. but the sooner sleep occurs after the night shift the better. The "L" symbols show appropriate times for light exposure. During the first two night shifts this light could be medium *or* high intensity intermittent light depending on which is best suited to the work environment and tasks. The Tmin phase delays in response to the night shift light and the delayed S/D period. On the days off the S/D period is shown as 3.00–11.00 a.m. or 12 noon, but the later in time sleep occurs during days off the better. The day sleep following the last night shift (day 6) is shortened to enable light exposure that should help advance the circadian clock. This light (outdoor brighter light is better) and the small sleep deprivation should facilitate earlier sleep during the two days off. Dark sunglasses should be worn during the travel home time after the night shifts. This will facilitate the delaying of the Tmin through the travel home time during the first few night shifts by reducing the exposure to advancing sunlight. After the Tmin reaches the S/D period, the sunglasses will reduce the impact of delaying sunlight, which could delay the Tmin too far and make it more difficult to sleep earlier on days off. The shaded areas show the time when good sleep might be expected.

associated with chronic use, and even pharmacologically increased sleep during the day will not prevent the decrease in performance during night work due to circadian misalignment (e.g. [64, 67, 68]). Furthermore night workers who fail to adequately shift their circadian rhythms will typically develop cumulative sleep debts. Recent work in humans has suggested that a cumulative sleep debt can lead to significant health concerns, such as a decrease in glucose tolerance which may in turn lead to an increased risk for diabetes [69]. Thus while the long term health effects of regular phase shifting remains uncertain, on the current evidence phase shifting in order to adapt to a new sleep schedule is clearly a healthier strategy for the shift worker and one that will increase public safety.

Practice Points

Circadian adaptation to night work will be enhanced by:

1. Several consecutive night shifts followed shortly by long undisturbed dark periods for sleeping during the day.
2. Dark sunglasses when traveling home from the night shift, especially if the time of the commute falls after the body temperature minimum (T_{min}).
3. Appropriately timed patterns of medium intensity and/or intermittent light during night work.
4. Exogenous melatonin (if phase advances are needed).

Research Agenda

1. Determine optimal patterns and intensities of intermittent bright light during the night shift.
2. Determine the intensity and duration of bright light exposure during the commute home from the night shift that will hinder adaptative circadian phase delays given various bright light treatments during the night shift.
3. Determine the efficacy of exogenous melatonin in phase delaying night workers.
4. Determine the degree of alignment of circadian rhythms with sleep necessary to improve daytime sleep and night work alertness in middle-aged and older shift workers.
5. Improve workplace and public education about shift work, such as the benefits of slowly rotating or permanent night work schedules. Such schedules combined with appropriate interventions such as dark undisturbed periods for daytime sleep could produce circadian adaptation and thus improve night workers' performance, sleep and health and public safety.

ACKNOWLEDGEMENTS

We thank Stacy Martin for preparing some of the figures and her comments on the manuscript. This review was supported by NIH grants R01 NS35695, R01 OH03954 and R01 NR07677 to CIE and F31 MH 11239 to KMS.

REFERENCES

1. Dumont M, Carrier J. Daytime sleep propensity after moderate circadian phase shifts induced with bright light exposure. *Sleep* 1997; **20**: 11–17.

*2. Eastman CI. Circadian rhythms and bright light: recommendations for shift work. *Work & Stress* 1990; **4**: 245–260.

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

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

*5. Eastman CI, Martin SK. How to use light and dark to produce circadian adaptation to night shift work. *Ann Med* 1999; **31**: 87–98.

6. Minors DS, Waterhouse JM, Wirz-Justice A. A human phase-response curve to light. *Neurosci Lett* 1991; **133**: 36–40.

7. Honma K, Honma S. A human phase response curve for bright light pulses. *Jpn J Psychiatry Neurol* 1988; **42**: 167–168.

8. Johnson CH. Forty years of PRCs-What have we learned? *Chronobiol Int* 1999; **16**: 711–743.

9. Zeitzer JM, Dijk DJ, Kronauer RE, Brown EN, Czeisler CA. Sensitivity of the human circadian pacemaker to nocturnal light: melatonin phase resetting and suppression. *J Physiol* 2000; **526.3**: 695–702.

10. Wever RA. The Circadian System of Man. New York-Heidelberg-Berlin: Springer-Verlag 1979.

---

* The most important references are denoted by an asterisk.

11. Czeisler CA, Duffy JF, Shanahan TL, Brown EN, Mitchell JF, Rimmer DW, Ronda JM, Silva EJ, *et al.* Stability, precision, and near-24-hour period of the human circadian pacemaker. *Science* 1999; **284**: 2177–2181.
12. Lewy AJ, Wehr TA, Goodwin FK, Newsome DA, Markey SP. Light suppresses melatonin secretion in humans. *Science* 1980; **210**: 1267–1269.
13. Trinder J, Armstrong SM, O'Brien C, Luke D, Martin MJ. Inhibition of melatonin secretion onset by low levels of illumination. *J Sleep Res* 1996; **5**: 77–82.
14. McIntyre IM, Norman TR, Burrows GD, Armstrong SM. Human melatonin suppression by light is intensity dependent. *J Pineal Res* 1989; **6**: 149–156.
15. Vakkuri O, Leppaluoto J, Kauppila A. Oral administration and distribution of melatonin in human serum, saliva and urine. *Life Sci* 1985; **37**: 489–495.
16. Arendt J. Safety of melatonin in long-term use? *J Biol Rhythms* 1997; **12**: 673–681.
17. Sack RL, Hughes RJ, Edgar DM, Lewy AJ. Sleep-promoting effects of melatonin: At what dose, in whom, under what conditions, and by what mechanisms? *Sleep* 1997; **20**: 908–915.
18. Arendt J. Melatonin. *Clin Endocrinol* 1988; **29**: 205–229.
19. Aldhous M, Franey C, Wright J, Arendt J. Plasma concentrations of melatonin in man following oral absorption of different preparations. *Br J Clin Pharmacol* 1985; **19**: 517–521.
20. Deacon S, Arendt J. Melatonin-induced temperature suppression and its acute phase-shifting effects correlate in a dose-dependent manner in humans. *Brain Res* 1995; **688**: 77–85.

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

22. Sack RL, Brandes RW, Kendall AR, Lewy AJ. Entrainment of free-running circadian rhythms by melatonin in blind people. *N Engl J Med* 2000; **343**: 1070–1077.
23. Presser HB. Toward a 24-hour economy. *Science* 1999; **284**: 1778–1779.
24. U.S. Congress, Office of Technology Assessment. *Biological Rhythms: Implications for the Worker*. Washington, DC: U.S. Government Printing Office, 1991.

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

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

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

28. Martin SK, Eastman CI. Medium-intensity light produces circadian rhythm adaptation to simulated night-shift work. *Sleep* 1998; **21**: 154–165.

*29. Czeisler CA, Johnson MP, Duffy JF, Brown EN, Ronda JM, Kronauer RE. Exposure to bright light and darkness to treat physiologic maladaptation to night work. *N Engl J Med* 1990; **322**: 1253–1259.

30. Eastman CI, Liu L, Fogg LF. Circadian rhythm adaptation to simulated night shift work: Effect of nocturnal bright-light duration. *Sleep* 1995; **18**: 399–407.
31. Dawson D, Campbell SS. Timed exposure to bright light improves sleep and alertness during simulated night shifts. *Sleep* 1991; **14**: 511–516.
32. Dumont M, Benhaberou-Brun D, Paquet J. Profile of 24-h light exposure and circadian phase of melatonin secretion in nightworkers. *J Biol Rhythms* in press.
33. Koller M, Harma M, Laitinen JT, Kundi M, Piegler B, Haider M. Different patterns of light exposure in relation to melatonin and cortisol rhythms and sleep of night workers. *J Pineal Res* 1994; **16**: 127–135.
34. Barnes RG, Deacon SJ, Forbes MJ, Arendt J. Adaptation of the 6-sulphatoxymelatonin rhythm in shiftworkers on offshore oil installations during a 2-week 12-h night shift. *Neurosci Lett* 1998; **241**: 9–12.
35. Midwinter MJ, Arendt J. Adaptation of the melatonin rhythm in human subjects following night-shift work in Antarctica. *Neurosci Lett* 1991; **122**: 195–198.
36. Weibel L, Spiegel K, Gronfier C, Follenius M, Brandenberger G. Twenty-four-hour melatonin and core body temperature rhythms: their adaptation in night workers. *Am J Physiol* 1997; **41**: R948–R954.
37. Sack RL, Blood ML, Lewy AJ. Melatonin rhythms in night shift workers. *Sleep* 1992; **15**: 434–441.
38. Budnick LD, Lerman SE, Nicolich MJ. An evaluation of scheduled bright light and darkness on rotating shiftworkers: trial and limitations. *Am J Ind Med* 1995; **27**: 771–782.
39. Eastman CI. Bright light in work-sleep schedules for shift workers: Application of circadian rhythm principles: In Rensing L, an der Heiden U, Mackey MC (eds). *Temporal Disorder in Human Oscillatory Systems*. Berlin-Heidelberg-New York: Springer-Verlag, 1987; 176–185.
40. Whitson PA, Putcha L, Chen YM, Baker E. Melatonin and cortisol assessment of circadian shifts in astronauts before flight. *J Pineal Res* 1995; **18**: 141–147.

41. Stewart KT, Chapman JC, Nimmagudda RR, Putcha L. Light treatment shifts salivary melatonin rhythms in NASA shiftworkers. *Soc Light Treatment Biol Rhythms Abst* 1995; **7**: 16.
42. Czeisler CA, Chiasera AJ, Duffy JF. Research on sleep, circadian rhythms and aging: Applications to manned spaceflight. *Exp Gerontol* 1991; **26**: 217–232.
43. Stewart KT, Eastman CI. The light stuff: Shiftwork, circadian rhythms, and manned spaceflight: In Holick MF, Jung EG (eds). *Biologic Effects of Light 1995*. Berlin/New York: Walter de Gruyter & Co. 1996; 340–347.

*44. James FO, Boivin DB. Circadian adjustment to night shift work with a bright light intervention regimen in the workplace. *Sleep* 2001; **24**: A88.

45. Mitchell PJ, Hoese EK, Liu L, Fogg LF, Eastman CI. Conflicting bright light exposure during night shifts impedes circadian adaptation. *J Biol Rhythms* 1997; **12**: 5–15.
46. Stewart KT, Hayes BC, Eastman CI. Light treatment for NASA shiftworkers. *Chronobiol Int* 1995; **12**: 141–151.
47. Bjorvatn B, Kecklund G, Akerstedt T. Bright light treatment used for adaptation to night work and re-adaptation back to day life. A field study at an oil platform in the North Sea. *J Sleep Res* 1999; **8**: 105–112.
48. Rimmer DW, Boivin DB, Shanahan TL, Kronauer RE, Duffy JF, Czeisler CA. Dynamic resetting of the human circadian pacemaker by intermittent bright light. *Am J Physiol* 2000; **279**: R1574–R1579.
49. Lowden A, Akerstedt T, Wibom R. Light exposure during rests on the night shift. *J Sleep Res* 2000; **9 Supp 1**: 122.
50. Campbell SS, Dijk D-J, Boulos Z, Eastman CI, Lewy AJ, Terman M. Light treatment for sleep disorders: consensus report. III. Alerting and activating effects. *J Biol Rhythms* 1995; **10**: 129–132.
51. Costa G, Gaffuri E, Ghirlanda G, Minors DS, Waterhouse JM. Psychophysical conditions and hormonal secretion in nurses on a rapidly rotating shift schedule and exposed to bright light during night work. *Work & Stress* 1995; **9**: 148–157.
52. Van Kerkhove E. Bright light technology: A field evaluation of its use in night and shiftwork. *Shiftwork International Newsletter* 1999; **16**: 27.
53. Costa G, Ghirlanda G, Minors D, Waterhouse JM. Effect of bright light on tolerance to night work. *Scand J Work Environ Health* 1993; **19**: 414–420.
54. Folkard S, Arendt J, Clark M. Can melatonin improve shift workers' tolerance of the night shift? Some preliminary findings. *Chronobiol Int* 1993; **10**: 315–320.
55. Jorgensen KM, Witting MD. Does exogenous melatonin improve day sleep or night alertness in emergency physicians working night shifts? *Ann Emerg Med* 1998; **31**: 699–704.
56. James M, Tremea MO, Jones JS, Krohmer JR. Can melatonin improve adaptation to night shift? *Am J Emerg Med* 1998; **16**: 367–370.
57. Sharkey KM, Eastman CE. Melatonin phase shifts human circadian rhythms in a simulated night work study. *J Sleep Res* 2000; **9 Suppl 1**: 173.
58. Sharkey KM. *Melatonin administration to phase shift circadian rhythms and promote sleep in human models of night shift work*. Unpublished doctoral dissertation, Rush University 2000.
59. Sack RL, Lewy AJ. Melatonin as a chronobiotic: Treatment of circadian desynchrony in night workers and the blind. *J Biol Rhythms* 1997; **12**: 595–603.
60. Dawson D, Encel N, Lushington K. Improving adaptation to simulated night shift: Timed exposure to bright light versus daytime melatonin administration. *Sleep* 1995; **18**: 11–21.
61. Dijk DJ, Duffy JF, Riel E, Shanahan TL, Czeisler CA. Ageing and the circadian and homeostatic regulation of human sleep during forced desynchrony of rest, melatonin and temperature rhythms. *J Physiol* 1999; **516.2**: 611–627.
62. Moline ML, Pollak CP, Monk TH, Lester LS, Wagner DR, Zendell SM, Graeber RC, Salter CA, *et al.* Age-related differences in recovery from simulated jet lag. *Sleep* 1992; **15**: 28–40.

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

64. Sharkey KM, Fogg LF, Eastman CI. Effects of melatonin administration on daytime sleep after simulated night shift work. *J Sleep Res* 2001; **10**: 181–192.
65. Aschoff J. Problems of re-entrainment of circadian rhythms: Asymmetry effect, dissociation and partition: In Assenmacher I, Farner DS (eds). *Environmental Endocrinology.* Berlin-Heidelberg-New York: Springer-Verlag, 1978; 185–195.
66. Penev PD, Kolker DE, Zee PC, Turek FW. Chronic circadian desynchronization decreases the survival of animals with cardiomyopathic heart disease. *Am J Physiol* 1998; **275**: H2334–H2337.
67. Walsh JK, Muehlbach MJ, Schweitzer PK. Hypnotics and caffeine as countermeasures for shiftwork-related sleepiness and sleep disturbance. *J Sleep Res* 1995; **4**: 80–83.
68. Sharkey KM, Fogg LF, Eastman CI. Effects of melatonin administration on daytime sleep after simulated night shift work. *J Sleep Res* 2001; **10**: 181–192.

*69. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet* 1999; **354**: 1435–1439.