Review Article

Circadian-Based New Technologies for Night Workers

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Abstract: Night work is becoming increasingly common. Unfortunately, humans are physiologically unsuited to inverted schedules, leading to negative consequences for shift workers, employers, and society. The circadian and homeostatic processes which govern sleepiness and alertness are improperly aligned for night workers. We review a number of laboratory studies designed to treat circadian maladaptation to night work by shifting the circadian clock with light, exercise, or melatonin. There is substantial evidence that bright light treatments can successfully overcome the circadian misalignments associated with night work. The evidence for the efficacy of non-photic synchronizers such as exercise and exogenous melatonin is equivocal. Nevertheless, our expanding scientific understanding of the nature of the problem has generated a promising range of options for shift workers.

Key words: Shift work, Circadian rhythm, Light, Exercise, Melatonin, Sleep, Alertness

Introduction

Working at night has become an increasingly common experience in the developed world. Unfortunately, humans are physiologically unsuited to such inverted schedules, leading to negative consequences for shift workers, their employers, and society. The purpose of this paper is to review studies testing new technologies for maladaptation to shift work based on our understanding of the human circadian system. While field studies are of critical importance in understanding whether treatments can be successfully implemented in the real world, such applications must be based on sound basic science. Laboratory shift work simulations represent an intermediate step between studies aimed at elucidating the basic principles of circadian rhythms and field studies, where variables are more difficult to control. Our survey of laboratory simulations should be useful as a basis for developing applications of basic circadian science to the workplace.

Significance of Shift Work1

Working at night is prevalent in a wide variety of occupations, including police officers, truck drivers, air traffic controllers, airline pilots, and nuclear power plant operators1. In the United States, 17.1% of the workforce, or more than 15 million workers, are involved in shift work2, while a recent report from the Japanese Ministry of Labor estimated that approximately 5.8 million workers in Japan engaged in shift work3. However, shift work exacts many costs, from workers, employers, and from society. Shift workers suffer from a variety of health problems1, 4, 5. Additionally, shift work takes a toll on the social and emotional lives of workers1. Since the alertness, cognitive capacity, and vigilance of shift workers...
is impaired, on the job performance suffers as well, leading to decreased work rate, quality control errors and industrial accidents, and injuries.

**Psychophysiology of Alertness**

The difficulties involved in working at night have a neurophysiological basis. Alertness (and its complement, sleepiness) is primarily governed by two processes: the circadian clock, and the sleep homeostat.

**The circadian clock and the sleep homeostat**

The activity of all organisms on Earth demonstrates a near-24 hour cyclicity termed the *circadian rhythm*. In humans, as in other mammals, the circadian rhythm is generated by the suprachiasmatic nucleus of the brain (SCN), a structure which functions as a biological clock. The SCN produces a sinusoidal rhythm with a period of 24.2 h (standard error = .04 h), which governs a wide variety of physiological and psychological functions. This rhythm can be observed via a number of outputs, notably core body temperature (CBT), melatonin, and cortisol. The phase of the rhythm is typically aligned with the sleep/wake cycle. The nadir of the CBT rhythm (CBTmin) is usually located 1–2 h before habitual waketime, depending on the chronotype of the individual. The midpoint of the melatonin secretion episode is typically centered in the sleep episode, 2–3 h before CBTmin.

Alertness levels closely track the CBT function. All other things being equal, alertness will be lowest at CBTmin, just before awakening, and rise throughout the daytime, reach a maximum in the early evening, and then decline again in the late evening.

The sleep homeostat describes the monotonic decline in alertness with time awake. For practical purposes, alertness can be described as a linear function of time awake, though it is more precisely characterized as an exponential or gaussian function. Alertness recovers in a nonlinear fashion during sleep, so that the typical 7–9 hour sleep episode will allow recovery from 15–17 h of wakefulness.

**Interaction of the clock and the homeostat**

Maintaining daytime wakefulness and consolidated night time sleep: To a first approximation, the circadian clock and the sleep homeostat are additive. When people sleep at night and awake in the morning, constant alertness can be sustained throughout the day and consolidated sleep maintained at night. As described above, the circadian component of alertness is near its low point at awakening. However, homeostatic alertness it at its highest at this time. As homeostatic alertness falls, circadian alertness is rising, which compensates for the decline in homeostatic alertness throughout the first 10–12 hours of wakefulness. After this point, both component functions decline, and alertness follows, leading to evening bedtimes. Alertness rises exponentially during sleep as the homeostat recovers.

This balance between circadian and homeostatic components of alertness relies on a particular phase angle between the behavioral sleep/wake cycle and the environmental light/dark cycle. In diurnal animals such as humans, this means sleep during the night and wakefulness during the daytime. When this phase relationship is disturbed, due to transmeridien travel or shift work, sustained wakefulness and consolidated sleep become difficult to achieve. This is because the circadian system relies on the SCN (or *zeitgebers*) to maintain a normal phase relationship. The most powerful synchronizer is light, although there is clear evidence that other stimuli (non-photic synchronizers) can affect circadian phase, and some researchers argue that darkness has an effect on the system beyond the mere absence of light.

The phase response curve: The effect of a synchronizer on an oscillator such as the circadian clock can be described...
by sweeping out the *phase response curve* (PRC) of the oscillator to the stimulus. The PRC (see Fig. 2) plots the change in phase of the system generated by the stimulus against the phase that the stimulus is applied at. There are two basic classes of PRCs: Type 1, or weak resetting (maximal shift < 3 hours), and Type 0, or strong resetting (shifts up to 12 hours). With light, both Type 1 and Type 0 resetting can be observed in humans, depending on the intensity of the stimulus. Regardless of the type of the PRC, stimuli applied within a few hours before phase 0 (usually identified with CBTmin in humans) will delay the phase of the clock, while stimuli applied within a few hours after phase 0 will advance the phase of the clock. Stimuli applied around 180° (halfway through the cycle, or 12 hours after phase 0) generally have very little effect. In some species, there is a wide “dead zone” around this phase where stimuli have no discernable effect on phase, though humans are held not to display such a “dead zone.” The difference between Type 1 and Type 0 resetting is at phase 0. On a Type 1 PRC, stimuli applied at phase 0 have no effect, while Type 0 PRCs are characterized by a strong resetting response at phase 0.

Transmeridian travel: an example: The shape of the human PRC to light has important practical implications. Consider the case of transmeridian travel. An individual who travels from Boston to Tokyo finds that the environmental light/dark cycle is 10 hours ahead of her usual schedule. As a result, on arrival, her internal circadian rhythm is out of phase with the local schedule. Assume that her habitual sleep episode in Boston was from 0:00 to 8:00, and that her CBTmin occurred at 6:00. In Tokyo, her CBTmin would occur at 20:00. The circadian component of alertness would thus have its nadir in the evening and its peak in the late morning. If she attempted to maintain a standard Tokyo schedule, setting her alarm clock for 8:00, the homeostatic and circadian would both be at their peak at waketime, and proceed to decline throughout the morning and afternoon. As a result, she would become increasingly sleepy throughout the day (see Fig. 3), and at 20:00 would be significantly sleepier than at any time during her normal schedule back in Boston, since she is usually not awake at the circadian nadir. While it would be fairly easy to go to sleep at this point, it would be difficult for her to remain asleep, as both components of alertness were on the rise. This is the condition referred to as “jet lag”.

Fortunately, if she adopted the local schedule as described, her circadian system would adapt after a week or so. Since there would be more light in the delay region (the late afternoon and early evening hours before 20:00) than in the advance region (the late evening and early morning hours after 20:00), the net result would be a delay in the circadian rhythm so that CBTmin occurred at a later hour. Pushing CBTmin towards the sleep episode would then decrease the light in the advance region further, and the phase of the system would continue to delay until CBTmin reached 6:00 Tokyo time.

Night work: However, if our hypothetical traveler chose instead to keep to a Boston schedule, sleeping in her darkened hotel room during the Tokyo day and going out at night, she would never adapt to the local schedule, because the light-sensitive portions of the PRC would be shielded from light. The shift worker, particularly the night worker, is in a similar situation. Imagine a shift worker whose habitual
sleep/wake schedule, again, is to sleep from 0:00 to 8:00, resulting in a 6:00 CBT_{min}. On the night shift, however, he works during that time, and, typically, will sleep after the work shift, e.g. from 9:00 to 17:00. Wake time is now just an hour before the peak of the circadian component of alertness, so he becomes sleepier and sleepier throughout the evening, and arrives for his work shift with already substantially diminished alertness, compared to starting a day shift at 9:00 following a 0:00 to 8:00 sleep episode. Alertness continues to decline throughout the work shift, since the circadian nadir is near the end of the work shift. After leaving work, however, the circadian component of alertness is on the upswing, and while the accumulated homeostatic sleep pressure may allow the worker to initially fall asleep, consolidated sleep will be difficult to maintain as both circadian and homeostatic components of alertness rise throughout the sleep episode. The shift worker therefore experiences difficulty maintaining wakefulness, vigilance, and other aspects of performance on the job, and also experiences difficulty sleeping during the day, which in turns leads to chronic sleep deprivation throughout the rotation, which will compound the problem. Furthermore, the effects of homeostat and the circadian clock on alertness are not really additive. They interact, such that the effect of circadian phase is magnified when people are sleep deprived, and the effects of time awake are magnified near the circadian nadir. Thus, working at night near the nadir after sustained wakefulness and impaired sleep is a recipe for disaster. At this point, it should be noted that a number of major industrial disasters, such as the nuclear accidents at Three Mile Island and Chernobyl, the Union Carbide chemical disaster at Bhopal, India, and the explosion of the space shuttle Challenger, have all been blamed on poor judgement or performance due to night shift work.

As with our stubborn traveler, most shift workers never adapt to the night shift, even after extended tours of duty. This is because the pattern of light exposure they receive is not consistent with the sleep/wake schedule they are maintaining. Consider again our hypothetical shift worker, sleeping from 9:00 to 17:00. Upon awakening, he will be exposed to relatively bright late afternoon light. However, this light falls on the relatively insensitive portion of the PRC near 180°. At work, he is exposing the delay region of the PRC to the relatively dim indoor light, which will shift his clock slightly later. However, upon leaving work, he experiences the bright light of the commute home, which is a powerful stimulus in the advance region, counteracting the small delaying effect of the work shift light. As a result, his circadian clock will probably not adapt to the new schedule. If, however, our worker were in an isolated environment, such as an oil platform, in which there was no exposure to natural light, he would probably be able to adjust as quickly as a Boston to Tokyo traveler who adopts the local schedule.

**Phase-shifting shift work experiments**

Properly treating a condition requires an understanding of the underlying physiological causes. Our expanding understanding of the neurophysiological underpinnings of maladaptation to shift work has led to a number of experiments designed to overcome this problem. The common diagnosis is that night workers are suffering from a circadian maladaptation to shift work. Their circadian rhythms are misaligned with their sleep/wake schedules, and therefore the primary strategy has been to shift the circadian system into proper alignment.

The circadian system has evolved to detect the prevailing pattern of night and day and adjust sleep and waking behaviors accordingly. Shift work provides the system with two competing schedules: the environmental day/night cycle and the artificial schedule of work and sleep. Maladaptation to night work occurs when the artificial schedule is weak in comparison to the natural schedule. All of the successful manipulations described in this paper serve to reverse this situation, whether by boosting the strength of the artificial schedule with appropriately timed bright light, or by diminishing the strength of the natural schedule by dark goggles.

**Light**

Since light has been identified as the primary synchronizer of the circadian system, several studies have employed strategically timed exposure to bright light to shift the circadian rhythm into alignment with the sleep/wake schedule. Czeisler et al. developed a two week long shift work simulation protocol. The first week consisted of baseline ambulatory recordings of temperature and activity, during which subjects were required to maintain regular sleep/wake schedules, verified by actigraphy. During the second week, subjects slept at home during the day and commuted to the laboratory for “work shifts”. The work shifts, scheduled from 0:00 to 8:00, consisted of computerized alertness and mood tests. Circadian phase was assessed before and after the night shift segment via the constant routine (CR) procedure. The CR was designed to measure CBT without the masking effect of sleep (which depresses temperature) and activity (which can increase temperature). Subjects were confined to bed, in a semirecumbent position, for 24 to 48
hours (CRs longer than 24 hours occurred only after the night shift segment, not before). The experimental manipulation was as follows: for treatment studies, subjects were required to be in bed from 9:00 to 17:00 during the night shift segment (again monitored via actigraphy), and were given lightproof material to cover their windows. During the night work shifts, they were exposed to bright light (7000 to 12000 lux). For control studies, subjects were not given lightproof material, were allowed to sleep ad lib, and were exposed to only normal room light (~150 lux) during the night work shifts. The study was conducted with subjects.

Czeisler, et al. found that the circadian rhythms of subjects during the control studies (measured in urine production, plasma cortisol, and CBT) shifted only 1.1 hours from the first CR to the second, while the treatment studies produced a 9.6 hour shift, sufficient to restore a normal phase angle between sleep and the circadian rhythm. Subjective alertness and cognitive performance rhythms shifted as well.

This basic finding has been replicated a number of times in different laboratories. Eastman conducted a three week shift work simulation. Subjects maintained a regular eight-hour nocturnal sleep schedule for 10 days, followed by a 12-hour shift in the sleep/wake schedule. From Day 11 to Day 20, subjects slept during the day, and spent eight hours indoors in simulated night work. The night shift started six hours after wake time, leaving a two hour “commute period” between the end of the shift and the start of the next sleep episode. A five-hour bright light pulse (5000 lux) was administered during the night shift. Subjects’ bedrooms were covered in lightproof plastic material. When going outdoors during the last 10 days of the study, subjects wore dark welder’s goggles which reduced light intensity by 99%. This was intended to reduce the resetting effect of bright outdoor light, especially during the “commute period”. Ambulatory temperature was monitored and CBT used as the phase marker. The data were later reanalyzed using a “demasking” technique which mathematically compensates for the reduction of temperature due to sleep. For a cautionary note about demasking techniques, see. As predicted by the PRC, light applied after CBT advanced the clock, and light applied before CBT delayed the clock. In this particular study, delays produced greater shifts (9.6 h over the first four days) than advances (6.2 h). After 8 days, delayed subjects had completely adapted, while advanced subjects’ average CBT was just before wake time.

Eastman et al. demonstrated the efficacy of the dark goggles in a similar protocol using a factorial design crossing light (bright, ~5000 lux vs. dim) and goggle use (yes or no). They found that, as expected, the circadian rhythms of the dim light, no goggle subjects did not shift substantially, while the bright light group with goggles adapted well to the 2-hour shift in schedule. Interestingly, bright light, no goggle subjects did exhibit shifts of the clock, but only in the advance direction, presumably because of the countervailing effect of the environmental bright light during the commute, which should fall in the advance region of the PRC.

There are of course many questions to be asked about the optimal strategy for shifting the clock with bright light. What is the ideal light level? The ideal timing and duration of the light? Should light pulses be delivered at the same time each night or gradually delayed (or advanced) to match the expected change in the rhythm, and the accompanying PRC? For a comparison of the latter two strategies, see Eastman. Dawson & Campbell have shown that a single (6000 lux) four-hour light pulse delivered on the first day of the night shift can be effective in improving adaptation to night work. Following a baseline day on which subjects slept from 0:00 to 8:00 and then trained on a computerized data entry task from 8:00 to 16:00, subjects returned to the laboratory for three consecutive days of night shift work, working from 0:00 to 8:00 and sleeping from 8:00 to 16:00. Alertness during the night shifts was assessed via the repeated test of sustained wakefulness (RTSW). Treatment subjects were exposed to the bright light from 0:00 to 4:00 on the first night shift. Lighting at all other times (and for all control subjects) was <500 lux. Demasked CBT data was used to assess phase. Dawson & Campbell found that, while both groups shifted significantly by the third night shift day, the treatment group exhibited a greater shift (5.9 h) than the control group (2.4 h), which meant that only the treatment group’s CBT moved into the daytime sleep episode. Accordingly, the treatment group was found to have better quality daytime sleep than the controls, as well as superior alertness as measured by the RTSW.

As the Dawson & Campbell study suggests, it is not necessary to expose subjects to bright light throughout the night shift. Indeed, as Eastman & Martin’s study indicates, it is the timing of the light pulse within the night shift which is critical. How long must the duration of the light pulse be? Eastman et al. tested six hour and three hour pulses of 5000 lux against a dim (<500 lux) control group (the control group was actually the dim light, no goggles group) in an 18-day study. Ten baseline days of eight hours of nocturnal sleep at the subjects’ habitual sleep times were followed by eight night shift days. During the night shift days, the sleep episodes were shifted by 12 hours, and night shifts occurred during the time of the baseline sleep episodes.
Subjects in this study were not given goggles to block outdoor light during the night shift segment. Ambulatory CBT was continually measured throughout the study, and the bright light pulses were centered around the baseline CBT\textsubscript{min}, which was derived from demasked data. In this study, phase advances were predominant over phase delays, presumably because of exposure to bright morning light during the commute. Subjects in the dim light group exhibited an average phase shift 3.2 hours over the course of the study, which was inadequate to move CBT\textsubscript{min} out of the night shift, much less into the day sleep episode. Subjects in the three-hour bright light group shifted by an average of 8.1 hours, compared to 9.4 hours for the six-hour bright light group. The magnitude of the phase shifts, which was sufficient to bring CBT\textsubscript{min} into the sleep episode, did not differ significantly between these groups. These large phase shifts were associated with improved mood at night and improved sleep during the daytime.

The light intensity levels used in these studies are quite bright by the standards of indoor light. Intensity levels in the studies we have described so far range from 5000 to 12000 lux, which is one or two orders of magnitude greater than the intensity of typical indoor light\textsuperscript{59}. This may be necessary to counter the effects of sunlight during the daytime (which can be yet another order of magnitude brighter), at least for subjects not wearing protective goggles. However, this can be quite expensive, and there is some evidence that lower light intensities may be equally effective. A number of intensity response curves (IRC) have been constructed, measuring the phase shifting response of the circadian system as a function of light intensity\textsuperscript{60, 61}. These studies indicate that the phase shifting response to light is a nonlinear, compressive function of intensity, asymptoting around 600 lux. In other words, light intensities above 600 lux have only a small additional effect on the pacemaker. Of course, the IRC is measured in the absence of competing stimuli, so the minimum light intensity required for adaptation to night work remains an empirical question. Martin & Eastman\textsuperscript{62} compared three levels of light intensity: low (<250 lux), medium (1230 lux), and high (5700 lux) in an 18-day study. Following seven days of sleeping at home (in bedrooms darkened with lightproof plastic) for eight hours at night (monitored by actigraphy), subjects’ sleep/wake schedule was delayed by 10 hours so that they were sleeping during the daytime, and coming to the laboratory for a night work shift at the time of their baseline sleep episode. This schedule was maintained for six days, and was followed by four days of recovery, when subjects returned to their original (night sleep) schedule. The light exposure episodes were 3 hours long, and administered on each of the first 5 days of the night shift. The light exposure episodes on the first day of the night shift began with the start of the night shift, and then delayed one hour each night to follow the presumed shift of the circadian rhythm. Subjects were given goggles to wear when outside during the night shift segment. Circadian phase was estimated from demasked ambulatory CBT data. For the low intensity group, CBT\textsubscript{min} delayed only 3.7 hours from the baseline days to the last three night shift days. The high intensity group shifted 8.3 hours, and the medium intensity group shifted 7.1 hours. There was no significant difference observed between the high and medium intensity groups, and the magnitude of the shifts in these two groups was sufficient to place CBT\textsubscript{min} in the daytime sleep episode. Whether even weaker light pulses will suffice to adapt subjects to night work is still an empirical question.

The duration of light pulses is another important parametric question. The studies described above have used light pulses in the range of three to six hours. How brief can the pulse be and still be considered effective? By analogy to the PRC and the IRC, we would ideally refer to the duration response curve (DRC), which would indicate the relationship between pulse duration and phase shift for a given intensity of light delivered at a given phase. Unfortunately, the relevant DRCs have not been constructed, even for a single intensity at a single phase. In an attempt to circumvent this problem, Thessing et al.\textsuperscript{63} directly compared zero, two, and four hour pulses of bright light in a two-night simulated shiftwork study. All bright light exposures were delivered on the first night, while performance and alertness tests were administered on the second night, a design which neatly avoids confounding the effects of acute light exposure with the phase shifting effects of light. Subjects were divided into three groups. The four-hour group was exposed to bright light (~9000 lux) from 0:00 to 4:00 and dim light (~350 lux) from 4:00 to 8:00; the two-hour group received bright light only from 2:00 to 4:00, with dim light the rest of the time; while the zero-hour group was in dim light for the entire 0:00 to 8:00 episode. On the second night, all subjects were under <300 lux conditions. Performance was assessed via a simulated assembly line task (SALT) and alertness using visual analog scales and the multiple sleep latency test (MSLT).\textsuperscript{64} Performance and alertness generally declined over the night, showing significant or marginal advantages for the four-hour group over the other two groups, which were indistinguishable on these measures. Thessing et al. concluded that the four-hour pulse induced a phase delay of the circadian rhythm, which underlay improvements in the performance and alertness of the four-hour group. The
two-hour pulse was apparently insufficient to produce such a delay shift. These conclusions should be viewed as tentative. As a DRC study, it is lacking in several ways, not the least of which is the lack of any measure of circadian phase. Furthermore, the background “dim” light levels are relatively high for indoor light, and bright enough to induce significant phase shifts, according to existing IRCs. This would tend to compress differences between groups, which could explain why the two-hour group showed no advantage over the zero-hour group. Furthermore, the four-hour pulse was centered at 2:00, while the two-hour pulse was centered at 3:00. As a result, these two pulses are hitting the PRC at different locations, so we would expect different phase shifts, even if four hours and two hours were otherwise equivalent. Nevertheless, this study points the way toward a more systematic exploration of this important parameter space.

It is clear from these studies that properly timed light is a powerful tool for overcoming circadian maladaptation to night work. Techniques continue to be refined in the laboratory. However, this treatment may not work for all populations. The studies described so far have typically used younger subjects. Campbell examined the efficacy of phase shifting via bright light in middle-aged (40 to 60 y.o.) subjects. Subjects spent two baseline nights sleeping in the laboratory from 0:00 to 8:00 and training on the SALT from 8:00 to 17:00 during the day. Following the second baseline day, subjects shifted to a schedule of working 0:00 to 8:00 and sleeping between 9:00 and 17:00. There were three night shifts. On the first night shift, the treatment group was exposed to >4000 lux bright light from 0:00 to 4:00, followed by four hours of dim (<100 lux) light. On the second and third night shift, illumination was ~1000 lux for the entire shift. The control group experienced only dim light for all three night shifts. Phase estimates were derived from demasked ambulatory temperature data. The treatment group exhibited a 6.25 hour delay, compared with 2.51 hours for the control group. This difference was significant, and sufficient to move the CBT_{min} of the treatment subjects into the daytime sleep episode. However, surprisingly, Campbell found that successful phase shifting was not accompanied by improved psychological adaptation to night work for these subjects. Measures of sleep quality and on shift performance and alertness did not differ significantly between the two groups. Campbell suggested that this discrepancy with results from younger subjects may be due to a reduced tolerance for sleeping out of phase with age. While the average CBT_{min} moved into the sleep episode for the treatment group, sleep and CBT were still out of phase when compared to the baseline period. Laboratory studies of sleep in older and younger individuals supports this hypothesis; older subjects have more trouble sleeping out of phase than younger subjects. Therefore, more sophisticated treatments, including more careful timing of light pulses, may be required for older populations.

**Exercise**

Light is not the only synchronizer of the circadian system. Given the ability of activity to reset the circadian rhythms of animals, some investigators have proposed that appropriately timed exercise can serve the same purpose in humans. Eastman et al. hypothesized that exercise could be used to induce adaptation to the night shift schedule. The design was similar to previously described studies by Eastman’s group. Seven baseline days of regular sleep at the subjects’ habitual nocturnal bedtimes was followed by eight night shift days with night shifts scheduled at the time of the baseline sleep episode, followed one hour later by an eight hour daytime sleep episode. Subjects’ bedrooms were lightproofed with black plastic, and the subjects were given goggles to shield them from outdoor light during the night shift segment. The goggles were particularly important in this study, because subjects spent only the first three days of the night shift segment in the laboratory, and the remaining five days at home. Light levels in the laboratory were relatively dim (<500 lux). Exercise was administered during the first three night shifts (those spent in the laboratory). Subjects in the treatment group spent 15 minutes on a stationary bicycle during each hour of the night shift. The intensity of the exercise was calibrated so that subjects reached 50% to 60% of their (previously measured) maximum heart rate for an average of 12.3 minutes during each exercise episode. Control subjects were sedentary during these night shifts, and all subjects were required to abstain from exercise outside of the laboratory. Circadian phase was estimated from demasked ambulatory temperature data. By the last four days of the night shift, both groups’ CBT_{min} had delayed towards the daytime sleep episode, and these shifts were marginally greater (6.6 h) for the treatment group than the control group (4.2 h). This difference became significant when morningness-eveningness score was used as a covariate.

Following up on Eastman et al., Baehr et al. compared the efficacy of exercise and bright light in a 2 × 2 factorial design. The study procedures were identical to that in Eastman et al., except for the experimental treatments. Bright light was administered over the first six hours of the first three night shifts in intermittent fashion: 40 minutes of
were not given goggles. After waking from the third daytime work shift and sleeping from 9:00 to 17:00. This schedule was maintained for three days, accompanied by a similarly delaying pulse of bright (~5000 lux) light each day, until subjects were sleeping from 9:00 to 17:00. This schedule was maintained for three days, and then subjects were returned to their baseline schedule for five days. During the last five days of the study, subjects were divided into four different treatment groups in a 2 × 2 factorial design crossing bright light treatment and melatonin vs. placebo administration. The bright light consisted of 4 hours of 2000 lux administered after awakening (8:00 to 12:00) on the first two days of readaptation, accompanied by dark goggles to reduce exposure to outdoor sunlight. For the melatonin groups, 5 mg of melatonin was administered at 23:00 just before the first two sleep episodes of the readaptation days. An important feature of this study is that the bright light and the melatonin were set in opposition to one another: the light was timed to delay phase, and the melatonin timed to advance. The primary phase marker in this study was urinary 6-

Melatonin

The ability of the hormone melatonin to shift the circadian clock makes it a promising potential treatment for circadian maladaptation problems arising from jet lag and shift work. The human PRC to melatonin is apparently 180° out of phase with the PRC to light75,76, so that melatonin administered before CBTmin will advance the clock. Dawson et al.77 took advantage of this fact in designing their study, which compared the efficacy of bright light and melatonin. The six day study began with two baseline days of nocturnal sleep and training on performance tests from 9:00 to 17:00. Additionally, from 17:30 to 2:00, venous catheters were inserted and blood was drawn hourly in order to measure the dim light melatonin onset (DLMO78). On the third day, subjects changed to a night shift schedule, working from 23:00 to 7:00 and sleeping from 9:00 to 17:00. In between work shift and sleep, subjects were kept indoors in < 50 lux of light. Subjects were allowed to leave the laboratory between wake time and the start of the next work shift, and were not given goggles. After waking from the third daytime sleep episode, venous catheters were inserted and blood was drawn hourly for 24 hours. There were four groups, two treatment groups, each with its own control group. The bright light subjects were exposed to 4000 to 7000 lux of light from 0:00 to 4:00 during each of the three night shifts. A control group received 50 lux of dim red light during this time. Melatonin subjects were given the hormone orally during their sleep episodes in three doses, at 8:00, 11:00, and 14:00. The control group for melatonin were administered a placebo at the same times. The primary measure of circadian phase in this study was the onset of melatonin secretion. The first two DLMO measurements were averaged for initial phase, and the final phase was estimated from the onset of the 24-hour profile. All groups showed significant phase shifts. However, phase shifts in the melatonin group (4.7 h) did not differ significantly from the combined control groups (4.2 h). The bright light group delayed significantly further (8.8 h), sufficient to place most of the melatonin secretion episode into the day sleep episode. Interestingly, both treatment groups showed improvements on measures of sleep quality. Performance measures showed broadly the same pattern as phase shift.

However, more promising results came from a study by Deacon & Arendt79,80. Their methodology was somewhat different from the typical shift work simulation. In a two week study, they phase delayed their subjects nine hours, then returned them to a normal schedule. The protocol seems to model recovery from a few days of night work, or perhaps recovery from a brief trip across time zones. The study began with 4 baseline days of sleep from 0:00 to 8:00. Their controlled schedule then gradually delayed by nine hours over three days, accompanied by a similarly delaying pulse of bright (1200 lux) light each day, until subjects were sleeping from 9:00 to 17:00. This schedule was maintained for three days, and then subjects were returned to their baseline schedule for five days. During the last five days of the study, subjects were divided into four different treatment groups in a 2 × 2 factorial design crossing bright vs. dim light treatment and melatonin vs. placebo administration. The bright light consisted of 4 hours of 2000 lux administered after awakening (8:00 to 12:00) on the first two days of readaptation, accompanied by dark goggles to reduce exposure to outdoor sunlight. For the melatonin groups, 5 mg of melatonin was administered at 23:00 just before the first two sleep episodes of the readaptation days. An important feature of this study is that the bright light and the melatonin were set in opposition to one another: the light was timed to delay phase, and the melatonin timed to advance. The primary phase marker in this study was urinary 6-
sulphatoxymelatonin rhythm, which showed delays for the bright light only group, but primarily advances in the melatonin only and bright light + melatonin groups. However, only the two groups who received melatonin showed improvements in measures of sleep quality, performance, and alertness over the full five days. The bright light treatments apparently only improved alertness acutely. The authors conclude that the beneficial effects of melatonin do not derive entirely from its phase-shifting effect, and that it may be the disruption of sleep, rather than circadian maladaptation per se, which is the primary cause of reduced alertness and performance in shift work and jet lag.

**Sleep schedules and napping**

Of course, disruption of sleep and circadian misalignment are not independent factors. Circadian misalignment may disrupt sleep, and sleep behavior may affect circadian alignment. In contrast to the findings of Czeisler, et al.\(^6\), many of the studies we have described showed modest phase shifts for control groups\(^62, 73, 74, 77\). We believe that this is due to the fact that the later studies have typically fixed sleep and wake times for both control and treatment groups. This predictability of sleep timing would tend to strengthen the artificial schedule in the control groups as well as in the treatment groups. Work in our laboratory supports the notion that a fixed sleep schedule contributes significantly to circadian adaptation to night shift work\(^81\). Additionally, irregular sleep schedules are likely to reduce total sleep time\(^62\).

However, Deacon & Arendt’s argument\(^79\) that sleep disruption is the proximate cause of night shift alertness and performance decrements suggests that dealing with disrupted sleep directly might be a better strategy than attempting to shift the pacemaker. One obvious solution to disrupted sleep is napping. Shift workers tend to nap much more frequently on evening, night, and extended 12-hour shifts than they do on the day shift\(^83\). We do not know what the precise function of this behavior is. Naps may be prophylactic, to ward off expected declines in alertness, they may compensate for lost sleep\(^83\), or they may function as “anchor sleep”\(^49, 85\) to help maintain synchronization with a day-active schedule\(^66\). The primary question here is whether naps, taken either before or during a night shift, can mitigate the sleepiness and performance decrements observed during night work. Some field studies have shown improvements in performance and alertness due to naps\(^87\), while others have found the opposite\(^83\). One reason for this confusion is that all naps are not created equal. The timing and duration of naps is important. For instance, nappers often experience transient grogginess, or “sleep inertia”\(^88–90\) upon awakening from a nap, which may temporarily mask the beneficial effects of the nap. Sleep inertia tends to increase with increased nap length\(^91\), so shorter naps may actually be preferable. Sallinen et al.\(^52\) looked at the timing of naps during the workshift (early vs. late) and the length of naps (30 min. vs. 50 min.), in comparison to a no-nap control group. Each nap was studied on one night shift (23:00 to 7:10), followed by daytime sleep (8:00 to at least 13:30) in the laboratory. Individual shifts were separated by at least 16 days, so this is a study of purely first night shift effects. Naps produced modest improvements in alertness and performance relative to the napless control condition, at the cost of a modest reduction in slow wave sleep during the following daytime sleep episode. The length and timing of naps made little difference, though early naps were somewhat more effective at reducing physiological measures of sleepiness. 10–15 minutes of sleep inertia were observed. Matsumoto & Harada\(^93\) studied night time naps in workers on a rapid clockwise (day to evening to night) rotation at two factories. Workers at one factory were forbidden to nap during the night shift, while workers at the other factory were allowed two nap for up to two hours during one of two napping opportunities: 1:00 to 3:00, or 3:00 to 5:00. They found that naps during the night shift decreased sleep duration during the subsequent daytime sleep episode, such that total sleep time (nap plus daytime sleep) was constant. Sleepiness at the end of the night shift was reduced for workers who napped relative to those who didn’t, though not without some post-nap sleep inertia.

**Rapid rotation schedules**

It may not always be advisable to shift the circadian clock in a shift work situation, depending on the type of rotation. Given that the experimental studies indicate that at least three days are required for sufficient adaptation to the night shift schedule though not necessarily three days of treatment\(^86\), phase shifting is clearly a suboptimal strategy if the duration of the night shift rotation is less than three days. Furthermore, workers must then readapt to a normal diurnal schedule following the night shift rotation, which may require additional treatments\(^94, 95\). Therefore, night shift rotations of less than a week or so may call for a different strategy. A number of promising methods have been proposed to improve night shift alertness without a shift of the clock. Bright light has an acute effect on alertness\(^96\), independent of its phase-shifting effect, which makes it useful for this purpose, especially in combination with caffeine\(^97–99\). The stimulant modafinil has shown promise in alleviating the
effects of sleep deprivation). For a review of pharmacological treatments for shift work, see Åkerstedt et al. Naps, may be particularly useful on rapid rotation schedules, because they may increase alertness and performance during the night shift while helping to maintain circadian synchronization to a day-active schedule.

Conclusions

The studies we have reviewed demonstrate the tremendous potential for our expanding knowledge of the human circadian and sleep/wake systems to be translated into practical applications. Phase shifting the circadian clock into proper phase alignment with the shifted sleep/wake cycle does seem to overcome, or at least alleviate, the problems associated with shift work, as far as alertness, performance, and sleep are concerned. Whether such treatments will also ameliorate the health problems associated with shift work is not yet known.

Appropriately timed bright light treatments remain the most promising and best understood method for resetting the clock in the shift work setting. While non-photic synchronizers such as exogenous melatonin or exercise also have potential to overcome circadian misalignment, evidence from laboratory shift work simulations is still scarce and equivocal.

Different shift work situations have different requirements, and there is no single solution to the problems caused by night shift work. Nevertheless, a thorough scientific understanding of the nature of the problem has generated a promising range of options for shift workers.

References


