ELSEVIER

Sleep Medicine 8 (2007) 578–589

SLEEP MEDICINE

www.elsevier.com/locate/sleep

Working on atypical schedules

Diane B. Boivin [a,c,*], Geneviève M. Tremblay [a,b], Francine O. James [a,b]

[a] *Centre for Study and Treatment of Circadian Rhythms, Douglas Hospital Research Centre, 6875 LaSalle Boulevard, F-1127 Montreal, Que., Canada H4H 1R3*

[b] *Graduate Program in Neurological Sciences, Faculty of Medicine, McGill University, Montreal, Que., Canada*

[c] *Department of Psychiatry, Faculty of Medicine, McGill University, Montreal, Que., Canada*

Received 18 August 2006; received in revised form 13 March 2007; accepted 15 March 2007
Available online 3 May 2007

Abstract

Shift work has been associated with a number of health problems including cardiovascular disease, impaired glucose and lipid metabolism, gastrointestinal discomfort, reproductive difficulties, and breast cancer. The specific contributions of disturbed physiological rhythms, circadian misalignment, and sleep debt to the various medical problems encountered by shift workers remain to be clarified. Fatigue can be caused by extended on-duty and/or waking periods, inadequate sleep quantity, sleep disturbances, disruption of circadian rhythms, and difficult work and familial conditions. Fatigue-related accidents raise a safety concern for shift workers, especially at the end of the night when the circadian nadir of alertness interacts with increased time awake. Individuals vary greatly in their capacity to adjust to atypical work schedules and their tolerance to circadian misalignment. Predisposing individual and domestic factors have been identified, such as increasing age, being a single woman in charge of children, and split sleep patterns, all of which can affect the ability to adjust to atypical schedules. However, prior studies indicate that predisposing individual and social determinants are generally poor predictors of shift work tolerance in a given individual. In this manuscript, we review several countermeasures to improve adaptation to shift work.

Keywords: Shift work; Sleep; Vigilance; Circadian rhythms; Melatonin; Phototherapy; Nap; Caffeine; Hypnotics; Psychostimulants

1. The problem of shift work in modern society

In industrialized countries, it is estimated that between 15 and 30% of the workforce operates outside standard daytime hours [1–4]. Workers in developing countries may be more likely to be offered precarious work conditions characterized by irregular hours and nighttime work [5]. Shift work, early work start, compressed schedules with 12-h shifts, and counterclockwise rotations have been on the rise in all sectors, including the service industry [3,6]. Working on atypical shifts has important socioeconomic effects as it leads to an increased risk of accidents, worker impairment and danger to public safety, especially at night [7–10]. This is of particular concern in the transportation industry where irregular schedules and curtailed sleep are highly prevalent [9,11].

In addition to these safety concerns, shift work has been associated with a number of health problems including peptic ulcer disease, coronary heart disease, metabolic syndrome, certain cancers, undesirable pregnancy outcomes as well as increasing the likelihood of aggravating an existing medical condition [12–14]. Survey studies have shown that shift work and high variability of working hours negatively affect health, well-being, life satisfaction, and happiness [15,16]. Night

* Corresponding author. Address: Centre for Study and Treatment of Circadian Rhythms, Douglas Hospital Research Centre, 6875 LaSalle Boulevard, F-1127 Montreal, Que., Canada H4H 1R3. Tel.: +1 514 761 6131x2397; fax: +1 514 888 4099.
E-mail address: diane.boivin@douglas.mcgill.ca (D.B. Boivin).

1389-9457/$ - see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.sleep.2007.03.015

shift work is also associated with an increased perception of mental and physical fatigue [17].

The International Classification of Sleep Disorders describes a shift work sleep disorder that is associated with work on atypical schedules and is characterized by excessive sleepiness and/or sleep disruption [1]. Although the degree of tolerance to shift work varies greatly in the shift worker population, only a minority show an appropriate adaptation of physiological rhythms to atypical work schedules. Intolerance to shift work remains a complex problem that requires a comprehensive, multilevel approach, as it is simultaneously affected by several factors such as sleep–wake cycle disturbances, circadian misalignment, and predisposing individual and domestic factors [1,4,18].

2. Sleep–wake cycle disturbances

In a recent study, 32% of night shift workers reported symptoms of insomnia or excessive sleepiness, whereas these symptoms were reported in only 18% of day workers from the same sample population [19]. This is important since night shift workers who have a mean reported daytime sleep duration of 5.5 h or less are approximately three times more likely to report suffering from stomach ulcers than night shift workers who report sleeping at least 6.4 h during the day [19]. A meta-analysis of reported sleep times across different shift systems reveals that working at night, whether on a fixed or rotating schedule, is associated with shorter sleep duration than working during the day [20]. Analysis of continuous actigraphy data in night shift workers revealed daytime total sleep times between 4 and 6 h with sleep efficiencies below 80% [21–23]. These values are considerably less than nighttime sleep episodes of workers on day or evening shifts, which are easily 20% longer. Daytime sleep length may be particularly short if consecutive night shifts are planned [24].

In individuals living on a day-oriented schedule, it is hypothesized that a harmonious relationship between homeostatic and circadian processes serves to promote uninterrupted bouts of 8 h of sleep and 16 h of wakefulness per day [25]. When the sleep schedule is displaced, as is the case for shift workers, the normal temporal relationship between the sleep–wake cycle and the endogenous circadian pacemaker is perturbed, which can lead to reduced sleep duration [26].

Longer sleep episodes are observed in shift workers with a proper alignment between the endogenous circadian pacemaker and the shifted sleep schedule [27–31]. Interestingly, a study comparing two groups of 15 nurses with mild and severe daytime sleep complaints revealed that having a greater proportion of 6-sulfatoxy-melatonin excreted during daytime sleep was associated with better daytime sleep [32].

Acute and chronic sleep deprivation is likely to occur over a series of shifts between which daytime sleep is not restful [33]. The resultant decreases in vigilance and performance, together with the misalignment of the endogenous circadian pacemaker places the night shift worker at particular risk for sharp drops in performance and vigilance levels during the shift [34,35]. Indeed, significant vigilance impairments are associated with working on shifts where factors such as extended duration of the work period, night shifts, early morning shifts, and reduced prior sleep length increase the risk of significant sleepiness [36]. Electroencephalographic (EEG) and electrooculographic (EOG) measures of sleepiness increase at the end of the night and during the mid-afternoon hours [37,38]. These two times of day are characterized by a greater sleep propensity and a greater risk of serious work-related accidents [8,11]. Although the nature of work can affect alertness levels [37], physiological considerations such as sleep deprivation and circadian misalignment remain major determinants of fatigue in shift workers.

3. Circadian misalignment

It is well established that work on irregular schedules results in a misalignment between several physiological and hormonal rhythms that could have significant negative impacts on physical and mental health. Hormonal rhythms are influenced by an interaction of circadian and sleep–wake-dependent processes. Some hormones like cortisol and melatonin are more strongly influenced by the endogenous circadian pacemaker than by homeostatic processes and are thus often misaligned in workers with atypical work schedules. In daytime workers, cortisol levels reach their minimal values early in the night and their maximal values around the regular time of awakening, whereas melatonin levels peak at night during the middle of the sleep episode and are undetectable during the day (for a review see [39]). A lack of entrainment of cortisol and melatonin rhythms to a night-oriented schedule is reported in a number of studies even after a series of consecutive shifts [39–41]. In these cases, cortisol and melatonin secretion continue to peak in the early morning hours and at night, respectively, despite the significant change in the sleep–wake schedule. Cortisol levels are significantly higher during the daytime sleep episodes of shift workers than observed during nocturnal sleep in workers keeping a regular daytime schedule [41], and the reduction in cortisol levels achieved during daytime sleep is smaller than that observed during nighttime sleep [42]. Furthermore, cortisol levels are lower during nighttime waking episodes in shift workers than during daytime waking episodes in day workers [41]. A misalignment in the cortisol rhythm resulting in lower levels during the waking

episode could potentially contribute to the observed reduction in performance in the workplace [43].

Glucose and lipid metabolism varies according to the time of day, and greater serum triglycerides, cholesterol, and impaired glucose metabolism were found in the shift worker population [44–46]. Altogether, these studies suggest that disturbed metabolism of carbohydrates and lipids can increase the risk of cardiovascular diseases in shift workers.

4. Predisposing individual and domestic factors

It has been suggested that predisposing factors, including a morning-type chronotype, sleep disturbances, medical and psychiatric conditions, and reduced family support, may impair workers' ability to adjust to shift work [18,47–49]. Larger phase delay shifts were observed in subjects with greater eveningness scores [50] and subjects presenting late temperature minima seem to better re-entrain to night shifts regardless of the intervention [51]. However, a longitudinal study found that baseline sleep and circadian indices such as greater circadian amplitude, later circadian acrophase, and shorter sleep duration were poor predictors of psychological symptoms associated with shift work [52].

Other individual factors such as marital status, number of children in the household, and age may have a profound effect on the shift worker's quality of life. Women continue to bear most of the house and familial responsibilities, and their total daily hours of sleep following shifts may be severely diminished as a result [53,54]. Nurses living with a partner and children report less leisure time and engage in more domestic tasks than their male partners [55]. This is also true for women working at home with preschool children [56]. This might explain why more female night shift workers with children at home tend to adopt part-time jobs in comparison with female workers without children [18]. It is well known that tolerance to sleep at an unusual circadian phase deteriorates with age [57]. Nevertheless, youth has also been identified as a risk factor for sleepiness at work and accident risks, especially in the transportation industry [58]. This observation suggests that older operators might have developed better sleep hygiene and lifestyle habits.

The worker's spontaneous selection of a pattern of light and darkness exposure is also a key factor affecting circadian adaptation to a given sleep–wake schedule [30,59]. Namely, the percentage of subjects who adapt completely to a shift of their sleep schedule during the day was found to increase with the intensity of light exposure during the night [50]. It was shown that nurses working permanent nights who presented adaptive phase delays also tended to preferentially expose themselves to light in the evening and night and reduce their daytime light exposure compared to non-adapted nurses [30]. Night workers on offshore oil rigs showed greater circadian phase advances and shorter daytime sleep in March than in November [60]. This study suggests that, in this environment, changes of season can affect circadian adjustment secondary to a change in the pattern of light–dark exposure of the workers.

5. Countermeasures

Given the serious medical and societal impacts associated with shift work, several countermeasures have been proposed and developed. These include the planning of strategic naps, exposure to bright light, and pharmacological agents.

5.1. Strategic napping

One approach shown to counteract sleep deprivation and achieve an acceptable amount of sleep per 24-h day is to plan naps of 20–120 min in duration [22,24,61–65]. Strategic napping can efficiently improve alertness and performance levels at work [63], even when naps are planned during the day, prior to night shifts [62]. Two types of strategic napping have been identified, namely "prophylactic naps" planned in the evening prior to the shift to limit anticipated sleep deprivation, and "recuperative naps" taken at night to temporarily relieve sleepiness. Individual differences among shift workers are observed in napping behavior, where morning-types and older workers are more likely to schedule naps earlier than younger workers and evening-types [65].

Besides their beneficial effects, naps can negatively affect the level of alertness and vigilance in the minutes immediately following the awakening from sleep. This phenomenon is referred to as "sleep inertia" and its duration varies according to time of day with a worsening for naps planned at the end of a night shift [65]. Recuperative naps scheduled at night can lead to shorter daytime main sleep episodes, with reduced abilities to fall asleep and remain asleep [64]. This situation contrasts with longer daytime sleep episodes in workers who do not nap at work [66]. Regardless of these limitations, the planning of naps at night can be seen as beneficial since they allow workers to spend more time in social and domestic activities during the day, while limiting the resultant cumulative sleep deprivation [65].

5.2. Bright light exposure

Circadian adaptation to the work shift appears beneficial to the night shift worker, especially when on a regular night schedule. Exposure to bright light (~1230–12,000 lux), often in the first half of the night, has been proposed as a countermeasure to physiological maladaptation to shifted sleep–wake schedules based on a

number of previous laboratory investigations [51,67–72] and field studies [59,73–78]. The schedule of light and darkness is based on the phase response curve (PRC) to light [79,80]. Namely, exposure to bright light in the late evening/early night will induce greater phase delays, whereas exposure in the late night/early morning will induce greater phase advances. Thus, phototherapy sessions are generally scheduled 3–6 h prior to the expected nadir of the core body temperature cycle (which occurs 1–2 h prior to the morning time of awakening) in order to produce significant delays in the body temperature, plasma melatonin, plasma cortisol, and subjective alertness rhythms of shift workers. Since the precise timing of the temperature minimum is generally unknown in field conditions, one approach consists of starting the light exposure early at night and progressively delaying it over successive days [50]. Progressively delaying pulses of bright light at night and bright light exposure in the early afternoon on days off was used successfully in workers on an oil platform in the North Sea [59].

In a previous investigation [43,73], we demonstrated that an intervention combining intermittent exposure to bright light at work (~2000 lux) during the first 6 h of night shifts, shielding from morning bright light with the use of goggles, and maintenance of a stable diurnal sleep/darkness schedule can promote circadian adaptation in nurses working permanent night shifts (Fig. 1 and Table 1). Circadian phase was assessed by a constant routine (CR) procedure before and after a series of ~12 night shifts worked over a ~3-week period. Following the intervention, temperature, and salivary melatonin and cortisol rhythms phase delayed by $-9{:}19 \pm 1{:}04$, $-11{:}18 \pm 1{:}08$, and $-11{:}26 \pm 1{:}26$, respectively, such that these rhythms were completely realigned to the new daytime sleep schedule. This indicates that sustained periods of intensely bright light are not necessary for resetting the human circadian system and that complete circadian adaptation to night work is possible despite the intervening presence of days off. Our results are consistent with studies by Baehr et al. [81] who described the phase shifting effect of ~5000 lux light interrupted with room light of <500 lux in simulated shift work experiments and with those of Bougrine et al. [71] who described that bright-light induced circadian adaptation to night work was stable despite the intervening presence of days off.

Prior studies have demonstrated that the timing of sleep/darkness episodes can also contribute to the circadian adaptation of salivary melatonin and temperature rhythms to simulated night work, possibly through its effect on the timing of background room light [67]. These results are consistent with the known sensitivity of the human circadian pacemaker to light of lower intensity [82–85]. Inappropriate exposure to room light could have contributed to the unsuccessful intervention in one of our nurses who did not comply with a regular sleep/darkness schedule on work days (Fig. 2). The shielding from morning sunlight by wearing dark goggles can also elicit adaptative phase delays independently of bright light exposure at night [86]. The combination of bright light at night to morning goggles during the day induced greater phase delays [51,86].

Not all field studies support the use of bright light for shift workers. One major complaint of shift workers exposed to bright light is difficulty readjusting to a day-oriented schedule on rest days [87]. However, a recent study of operators in a truck production plant in Sweden revealed a beneficial effect of bright light on reducing sleepiness and melatonin levels during night shifts and no detrimental effects on sleep on days off [88].

In the night shift worker, circadian adjustment to the work schedule may translate into an increase in sleep duration and quality during the day [32,89]. It has been reported that bright light exposure at night can improve daytime sleep when circadian realignment occurs [68,70,90,91]. In personnel working in special environments such as an Antarctic base during winter, circadian adaptation and improved daytime sleep duration can also occur spontaneously throughout a series of night shifts [92].

In addition to its phase shifting effect, bright light exposure can exert a direct alerting effect leading to improved performance levels, reduced sleepiness scores, increased vigilance levels as well as an increase in beta and reduction in alpha–theta EEG activity [23,88,93]. It was proposed that melatonin suppression at night contributed to the alerting effect of bright light [94]. However, this interpretation is inconsistent with the significant improvements in sleepiness and performance levels induced by bright light exposure during the day when melatonin levels are undetectable [95].

Studies have also demonstrated the greater efficacy of light of short wavelengths (440–480 nm) for suppressing melatonin at night [96], advancing human circadian rhythms [97], and decreasing subjective sleepiness and increasing performance at night [98]. Glasses fitted with orange lenses blocking the transmittance of all wavelengths below 540 nm can counteract the melatonin-suppressing effect of nocturnal bright light exposure [99].

5.3. Pharmacological interventions

About 8–32% of workers on nights or rotating schedules present severe difficulties adapting to their atypical schedules [100]. The shift work sleep disorder (SWSD) is closely associated with the work schedule, which is out of synchrony with the endogenous circadian system.This leads to excessive sleepiness at work and/or disturbed daytime sleep [1]. Use of pharmaceutical agents such as psychostimulants, hypnotics, melatonin, or caffeine can be considered in these impaired workers to either enhance vigilance at work or promote daytime sleep.

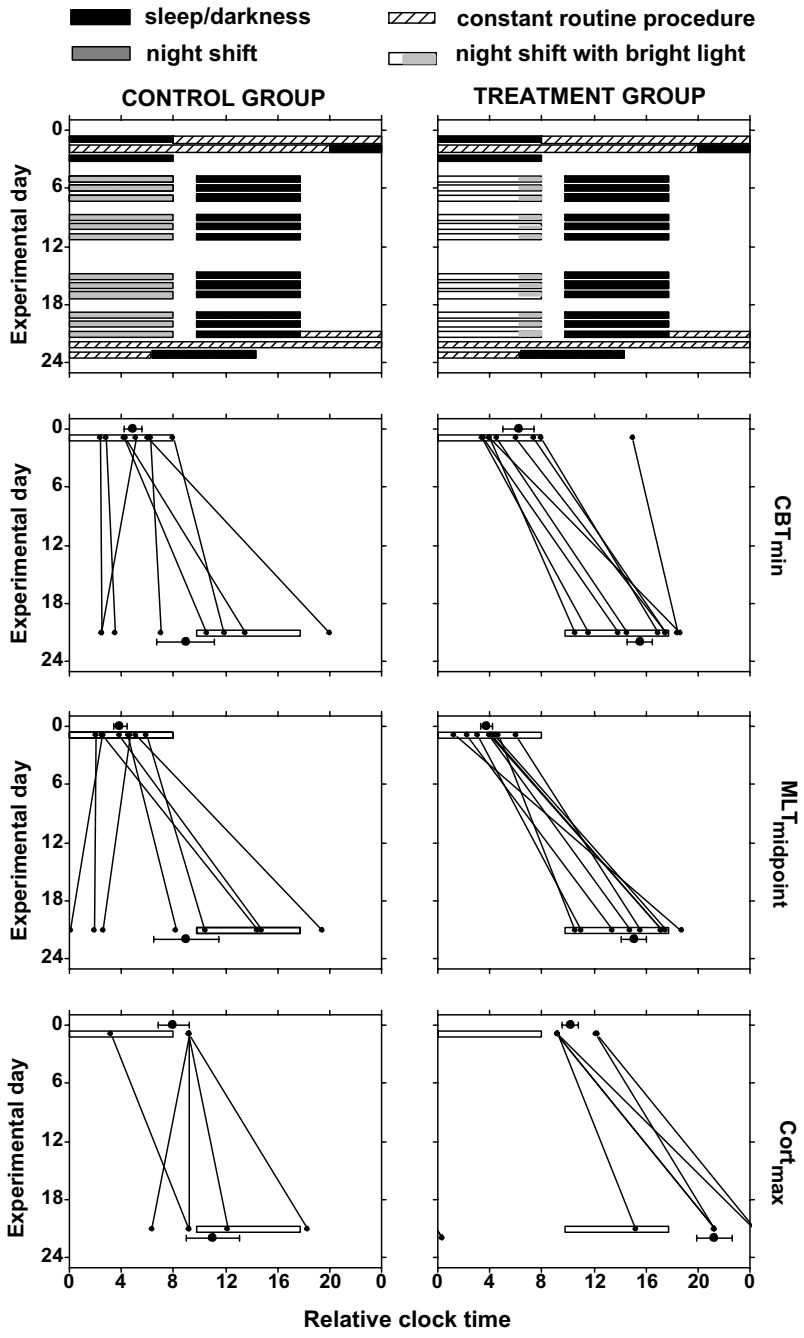

Fig. 1. Top two panels represent the experimental protocol. A hypothetical succession of experimental days is shown along the *y*-axis. Workers, following a vacation period, entered the laboratory on the first experimental day and slept on their habitual schedule. Upon awakening, workers underwent a 36-h CR for the determination of the endogenous circadian phase and amplitude. This was followed by an *ad libitum* sleep episode. Workers then returned to their regular schedule of night shifts, for a total of ~12 shifts. They were instructed to remain in the dark and to attempt to sleep during a single 8-h period beginning 2 h after the end of the shift. Sleep episodes on nights off are not shown. A final 36-h CR was performed in the laboratory following the period of night work and was followed by an *ad libitum* sleep episode. On night shifts, treatment group workers were intermittently exposed to bright light during the first 6 h of their night shifts and spent the remainder of the shifts in ordinary indoor illumination. Relative bedtimes of 00:00 and 10:00 have been assigned for nighttime and daytime sleep periods, respectively. CBT data obtained during the initial and final CRs are shown for each subject in the second row of panels. Closed circles represent the time of fitted temperature minimum (CBTmin). Melatonin data obtained during the initial and final CRs are shown for each subject in the third row of panels. Closed circles represent the melatonin midpoint. Cortisol data obtained during the initial and final CRs are shown for each subject in the bottom row of panels. Closed circles represent the cortisol maximum. Control group, $n = 8$; treatment group, $n = 9$ for CBT and melatonin. Control group, $n = 5$ and treatment group, $n = 6$ for cortisol. Group mean physiological data is shown in each panel (closed circle) ±SEM. CR, constant routine; CBT, core body temperature; SEM, standard error of the mean.

Table 1
CBT, melatonin, and cortisol rhythm measured during CR1 and CR2

	CR1 control	CR1 treatment	CR2 control	CR2 treatment
CBT min	4:52 ± 0:39	6:12 ± 1:14	8:57 ± 2:12[a]	15:32 ± 1:00[ab]
CBT Ψ	−4:38 ± 0:28	−5:54 ± 1:07	+0:40 ± 2:15[a]	−5:58 ± 0:57[b]
CBT shift			−4:05 ± 1:56	−9:19 ± 1:04[b]
CBT amplitude	0.18 ± 0.02	0.25 ± 0.03	0.20 ± 0.03	0.23 ± 0.04
Melatonin midpoint	3:55 ± 0:29	3:47 ± 0:28	9:00 ± 2:27[a]	15:06 ± 0:58[ab]
Melatonin Ψ	−3:42 ± 0:17	−3:30 ± 0:18	+ 0:37 ± 2:32[a]	−5:32 ± 0:55[b]
Melatonin shift			−5:05 ± 2:19	−11:18 ± 1:08[b]
Melatonin AUC	67.30 ± 12.15	80.68 ± 32.72	62.73 ± 10.69	75.58 ± 26.25
Cortisol max	8:00 ± 1:13	10:13 ± 0:38	11:03 ± 2:02	21:17 ± 1:21[ab]
Cortisol Ψ	−8:32 ± 1:37	−9:51 ± 0:18	−1:15 ± 2:10[a]	−11:38 ± 1:22[b]
Cortisol shift			−3:41 ± 2:09	−11:26 ± 1:26[b]
Cortisol amplitude	0.06 ± 0.01	0.05 ± 0.01	0.07 ± 0.02	0.07 ± 0.02

Circadian phase is defined as the time for best fit to the temperature minimum, the midpoint of peak melatonin concentration, and the fitted cortisol maximum. Phase angles are calculated as: (bedtime − circadian phase). For the calculation of phase angles, bedtimes in the first CR are based on mean sleep times during the preceding vacation period, scaled to 8-h length. Phase angle for the second CR are based on scheduled bedtimes during the night shift work period. Significant intra-group differences are marked with a, and between-group differences with b. For CBT and melatonin, control group: $n = 8$; treatment group: $n = 9$. For cortisol, control group: $n = 5$; treatment group: $n = 6$. For p-values for CBT and melatonin see [73] and for cortisol see [43]. Data are express as mean ± SEM. CBT, core body temperature; CR, constant routine; SEM, standard error of the mean.

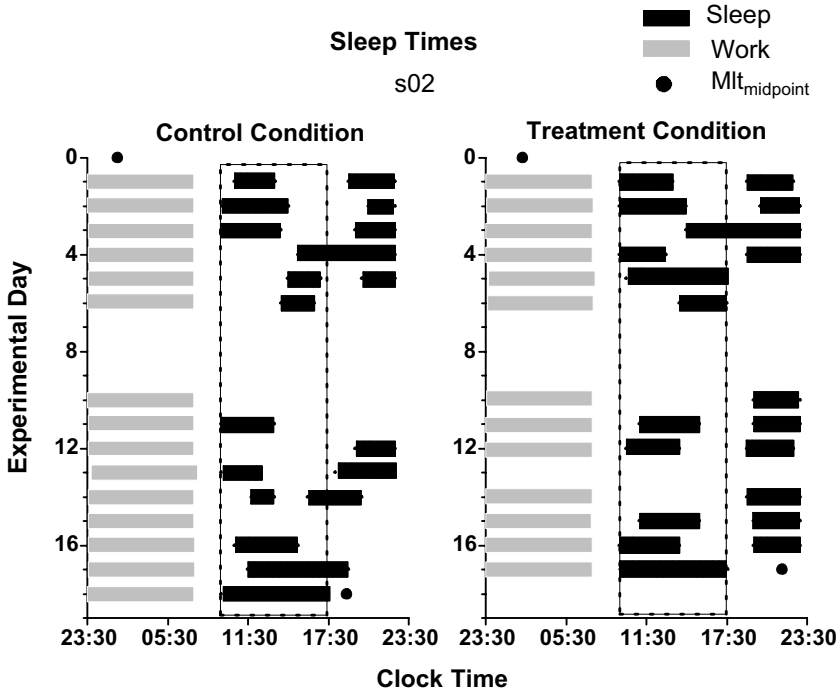

Fig. 2. Sleep–wake cycle of a nurse working regular night shifts. This nurse participated in the control and treatment conditions described in Fig. 1, although her results were excluded due to non-compliance with the study directives. After each night shift, she was requested to sleep for a single 8-h period scheduled from 9:30 to 17:30 but did not follow this requirement. Sleep episodes on nights off are not shown. Closed circles illustrate midpoint between the melatonin onset and offset, based on a 36-h CR performed before and after the series of night shifts. In the control condition, the melatonin peak was observed at 02:14 and 20:37 during the initial and final CR, respectively. In the treatment condition, the melatonin peak was observed at 02:48 and 22:10 during the initial and final CR, respectively. In both conditions, a misalignment persisted between the circadian rhythm of salivary melatonin and the shifted sleep schedule. Moreover, a phase advance rather than a phase delay seemed to have occurred. CR, constant routine.

5.4. Psychostimulants

In January 2004, modafinil, a non-amphetamine psychostimulant, recognized for its efficacy in the treatment of sleepy narcoleptic patients and its prevention of the cognitive decline induced by sleep deprivation [101], was approved by the US Food and Drug Administration (FDA) for the treatment of SWSD. The precise mechanism of action of modafinil is unknown but evidence suggests it could increase glutamate release in

the thalamus, reduce gamma-aminobutyric acid (GABA) release in the nucleus accumbens, modulate wake-promoting hypocretin neurons, and increase the noradrenergic inhibition of sleep-promoting ventrolateral preoptic (VLPO) neurons. Some studies have reported modafinil-induced Fos expression in the anterior hypothalamus and suprachiasmic nucleus (SCN), although others have not [101]. The action of modafinil on dopaminergic transmission is minimal as opposed to amphetamines, explaining its relatively low potential for addiction [101,102]. Modafinil exerts most of its effects centrally, explaining its greater cardiovascular safety profile compared to classical psychostimulants such as dextroamphetamine and methylphenidate. Thus, there is poor clinical justification for using classical psychostimulants for SWSD even though they exert a robust alerting effect [100]. So far, modafinil is the only approved prescription stimulant drug for this disorder.

A multicentric double-blind study conducted in 209 workers with SWSD revealed that modafinil administered at the dose of 200 mg prior to night shifts resulted in significant improvements of subjective and objective measures of sleepiness compared to placebo [103]. The latter was evidenced by increased sleep latencies during the multiple sleep latency test (MSLT), especially in the first half of the shift, and reduced attention lapses on the psychomotor vigilance test at night. A reduction in the risk of accidents while commuting back home in the morning was also reported. However, nighttime improvements were modest since sleepiness remained high and the reported number of mistakes, accidents, or near-accidents at work remained unchanged [103]. It appears more useful in this context to measure the capacity of workers to remain awake during the maintenance of wakefulness test (MWT) than their ability to fall asleep rapidly during the MSLT. Significant reduction of sleep onset on nighttime MWT was reported in a double-blind study of 107 workers using modafinil (200 mg) compared to placebo [104]. The therapeutic benefits of modafinil were maintained throughout a 12-month open label trial in SWSD [105].

At the clinically recommended single dose of 200 mg, no polysomnographic change of daytime sleep was reported, although more workers on modafinil reported insomnia [103]. Daytime sleep disruption is also observed when modafinil is given too late in the morning following a night shift [106].

5.5. Caffeine

Caffeine administered just before night work can be used to counteract the drop of vigilance and performance levels throughout the night [107–111]. A total daily dosage of 600 mg of caffeine in a slow-release formulation attenuates nighttime increases in microsleep duration and slows the disintegration of attention task scores when compared to placebo [112]. Caffeine administration at the dose of 100–300 mg demonstrates similar benefits for cognitive performance under conditions of sleep deprivation in intensive military training [113]. Considering the efficacy of caffeine together with its wide availability in over-the-counter medications and in foods, it is understandable that caffeine is one of the most widely self-administered stimulants [114].

Caffeine's mode of action is considered to be via its blockade of adenosine receptors whose substrate accumulation has been associated with increased homeostatic sleep pressure throughout wake periods [114,115]. The time of caffeine administration must be carefully considered in light of its detrimental effects on sleep consolidation [111]. At the dose of 200 mg (equivalent to approximately two cups of brewed coffee), caffeine administered in the 3 h preceding a nighttime sleep opportunity is sufficient to increase time to fall asleep and reduce both total sleep time and sleep efficiency in young and middle-aged subjects [116].

The usefulness of caffeine must be considered in terms of circadian phase as well. A forced desynchrony study of the effects of caffeine administration revealed that caffeine administration can effectively limit the decrease in cognitive throughput, vigilance and reaction time observed towards the end of 28.57-h wake periods [110]. However, caffeine administration results in a significant decrease in sleep efficiency particularly when sleep occurs at inappropriate circadian phases (i.e., times of low endogenous melatonin concentration) [110]. Of particular interest for the night shift worker, 200 mg of caffeine administered in the 3 h preceding a daytime sleep episode following 25 h of sleep deprivation further reduces total sleep time and sleep efficiency than when administered before a nighttime sleep episode [117]. This situation is analogous to that of a night shift worker who remains awake for comparable periods on the first night shift worked. Such a worker who ingests two cups of coffee in the late hours of the night shift, or on the drive home, for example, may expect that the combined influence of sleeping at an unfavorable circadian phase and caffeine consumption results in more disrupted sleep.

Effective dosages for the immediate beneficial effects of caffeine vary greatly [109]. Doses in the range of 50–300 mg are considered moderate, although larger doses have been studied. Because of the tendency for caffeine to be self-prescribed, additional care should be taken to contraindicate excessive consumption of caffeine from dietary sources and pharmacological formulations in addition to sensitizing individuals to the effects of caffeine on sleep and alertness. Carefully planning caffeine use in tandem with other countermeasures such as naps [107,118] may increase the likelihood of positive outcomes. A combination therapy of 300 mg caffeine plus a 1–2 h nap situated 3–4 h before night

shifts reduces nighttime decrements in performance on the psychomotor vigilance task (PVT) [107]. Although daytime sleep episodes were shorter in the presence of a nap, the total minutes of assumed sleep per day were larger in the nap and caffeine condition [107].

5.6. Hypnotics

In a survey of Air New Zealand pilots, just under 19% reported use of prescribed hypnotics in the previous two months [119]. Benzodiazepines (e.g., temazepam, triazolam) and non-benzodiazepines (e.g., zopiclone, zolpidem, zaleplon) have been approved for use in the treatment of insomnia [120] and have also been investigated for their sleep-promoting capacity in shift workers. The night shift worker may be more likely to have difficulty maintaining sleep rather than initiating it, such that these compounds useful in extending daytime sleep duration appear more interesting [121]. When temazepan is administered before an afternoon sleep opportunity, polysomnographically recorded total sleep time is longer compared to placebo, with an increase in stage 2 sleep [122]. Interestingly, by the end of a series of consecutive simulated night shifts, the difference in daytime sleep duration in participants receiving 0.25 mg triazolam or placebo became smaller as sleep durations increased in the placebo group. The circadian adaptation that may have occurred and contributed to the increase in daytime sleep duration in the placebo group would appear to undermine the usefulness of these agents over consecutive shifts, at least in laboratory conditions.

The drug-induced extension in daytime sleep can translate into improved alertness levels at night [121]. Nighttime alertness levels were higher in groups attempting daytime sleep with 20 mg temazepam [122], 0.5 mg triazolam [123], or 10 mg zolpidem [124,125] than in groups attempting sleep with placebo. Careful evaluation of the severity of the shift-associated sleep disorder is warranted before prescribing the short-term use of these hypnotics.

5.7. Melatonin

Melatonin phase shifting and sleep-promoting effects, although not totally understood, are thought to come from melatonin binding to MT1 and MT2 receptors (for a review see [126]). The chronobiotic effect of melatonin in humans has been plotted in a phase response curve (PRC) with phase advances and delays induced by exogenous melatonin given for several consecutive days in the late afternoon/early evening, or in the morning, respectively [127]. Although a PRC has been proposed for melatonin, there remains some unpredictability in effective dosages and formulation [128].

In addition to its phase shifting effect, melatonin can directly promote daytime sleep, increasing both reported levels of sleepiness [129] and polysomnographically recorded total sleep time [130]. Interestingly, it was observed that this effect was greater in subjects having lower initial sleep efficiencies [131]. This is consistent with the study by Wyatt et al. [132], using the forced desynchrony protocol. This study revealed that melatonin increased sleep efficiency only when given at times when endogenous melatonin was low. However, many studies in actual shift workers do not show a significant effect of exogenous melatonin on daytime sleep quality and duration based on sleep diary measures [133–135].

Melatonin agonists are also of interest because they can be developed to have more selectivity and affinity for MT1 and/or MT2 receptors than melatonin itself. Ramelteon, a high-affinity agonist of MT1 and/or MT2 receptors, is approved by the US FDA for the treatment of transient and chronic primary insomnia characterized by trouble falling asleep [136–138]. However, night shift workers do not typically have trouble falling asleep.

6. Conclusion

Several countermeasures to the shift work sleep–wake disorder have been proposed, such as judicious exposure to light and darkness (either by the use of phototherapy lamps, goggles, scheduled sleep/darkness), the strategic planning of naps (either prophylactic or recuperative), and pharmacological interventions (either stimulants or hypnotics). Other countermeasures, not reviewed in the present manuscript, are described elsewhere and include technological devices and education programs. Although each specific approach can lead to some reduction of fatigue in a given worker, no single one represents a unique, comprehensive and sufficient solution to the complex problem of working on atypical schedules.

Acknowledgements

This study was supported by a grant from the *Institut de recherche Robert-Sauvé en santé et en sécurité du travail* (IRSST), the Canadian Institutes of Health Research (CIHR), and the *Fonds de la Recherche en Santé du Québec* (FRSQ). G.M.T. was supported by a fellowship from the IRSST. D.B.B. was supported by career awards from the CIHR and the FRSQ.

References

[1] American Academy of Sleep Medicine. International classification of sleep disorders. Diagnostic and coding manual. 2nd ed. Westchester (IL): American Academy of Sleep Medicine; 2005.

[2] Beers TM. Flexible schedules and shift work: replacing the '9-to-5' workday? Mon Labor Rev 2000:33–40.
[3] Shields M. Shift work and health. Health Rep 2002;13:11–33.
[4] Rosekind MR. Managing work schedules: an alertness and safety perspective. In: Saunders, editor. Principles and Practice of Sleep Medicine. 4th ed. 2005. p. 680–90.
[5] Bohle P, Quinlan M, Kennedy D, Williamson A. Working hours, work-life conflict and health in precarious and "permanent" employment. Rev Saude Publica 2004;38 Suppl:19–25.
[6] Akerstedt T, Kecklund G. The future of work hours – the European view. Ind Health 2005;43:80–4.
[7] Akerstedt T, Fredlund P, Gillberg M, Jansson B. A prospective study of fatal occupational accidents – relationship to sleeping difficulties and occupational factors. J Sleep Res 2002;11:69–71.
[8] Folkard S, Tucker P. Shift work, safety and productivity. Occup Med (Lond) 2003;53:95–101.
[9] Philip P. Sleepiness of occupational drivers. Ind Health 2005;43:30–3.
[10] Folkard S, Lombardi DA, Tucker PT. Shiftwork: safety, sleepiness and sleep. Ind Health 2005;43:20–3.
[11] Boivin DB. Best practices compendium of fatigue countermeasures in transport operations. Montreal (Que.), Canada: Transportation Development Center; 2000. Report No.: TP 13620E. 42 p.
[12] Karlsson B, Knutsson A, Lindahl B. Is there an association between shift work and having a metabolic syndrome? Results from a population based study of 27,485 people. Occup Environ Med 2001;58:747–52.
[13] Schernhammer ES, Laden F, Speizer FE, et al. Night-shift work and risk of colorectal cancer in the nurses' health study. J Natl Cancer Inst 2003;95:825–8.
[14] Knutsson A. Health disorders of shift workers. Occup Med (Lond) 2003;53:103–8.
[15] Janssen D, Nachreiner F. Health and psychosocial effects of flexible working hours. Rev Saude Publica 2004;38(Suppl):11–8.
[16] Kaliterna LL, Prizmic LZ, Zganec N. Quality of life, life satisfaction and happiness in shift- and non-shiftworkers. Rev Saude Publica 2004;38(Suppl):3–10.
[17] Tepas DI, Barnes-Farrell JL, Bobko N, Fischer FM, Iskra-Golec I, Kaliterna L. The impact of night work on subjective reports of well-being: an exploratory study of health care workers from five nations. Rev Saude Publica 2004;38(Suppl):26–31.
[18] Monk TH. Shift work: basic principles. In: Saunders, editor. Principles and practice of sleep medicine. 4th ed. 2005, p. 673–9.
[19] Drake CL, Roehrs T, Richardson G, Walsh JK, Roth T. Shift work sleep disorder: prevalence and consequences beyond that of symptomatic day workers. Sleep 2004;27:1453–62.
[20] Pilcher JJ, Lambert BJ, Huffcutt AI. Differential effects of permanent and rotating shifts on self-report sleep length: a meta-analytic review. Sleep 2000;23:155–63.
[21] Burch JB, Yost MG, Johnson W, Allen E. Melatonin, sleep, and shift work adaptation. J Occup Environ Med 2005;47:893–901.
[22] Park YM, Matsumoto PK, Seo YJ, Cho YR, Noh TJ. Sleep–wake behavior of shift workers using wrist actigraph. Psychiatry Clin Neurosci 2000;54:359–60.
[23] Yoon IY, Jeong DU, Kwon KB, Kang SB, Song BG. Bright light exposure at night and light attenuation in the morning improve adaptation of night shift workers. Sleep 2002;25:351–6.
[24] Akerstedt T. Shift work and disturbed sleep/wakefulness. Occup Med (Lond) 2003;53:89–94.
[25] Dijk DJ, Czeisler CA. Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. J Neurosci 1995;15:3526–58.
[26] Ursin R, Bjorvatn B, Holsten F. Sleep duration, subjective sleep need, and sleep habits of 40- to 45-year-olds in the Hordaland Health Study. Sleep 2005;28:1260–9.
[27] Quera-Salva MA, Guilleminault C, Claustrat B, et al. Rapid shift in peak melatonin secretion associated with improved performance in short shift work schedule. Sleep 1997;20:1145–50.
[28] Roden M, Koller M, Pirich K, Vierhapper H, Waldhauser F. The circadian melatonin and cortisol secretion pattern in permanent night shift workers. Am J Physiol 1993;265:R261–7.
[29] 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;16:127–35.
[30] Dumont M, Benhaberou-Brun D, Paquet J. Profile of 24-h light exposure and circadian phase of melatonin secretion in night workers. J Biol Rhythms 2001;16:502–11.
[31] Hennig J, Kieferdorf P, Moritz C, Huwe S, Netter P. Changes in cortisol secretion during shiftwork: implications for tolerance to shiftwork? Ergonomics 1998;41:610–21.
[32] Benhaberou-Brun D, Lambert C, Dumont M. Association between melatonin secretion and daytime sleep complaints in night nurses. Sleep 1999;22:877–85.
[33] Ahsberg E, Kecklund G, Akerstedt T, Gamberale F. Shiftwork and different dimensions of fatigue. Int J Ind Ergon 2000;26:457.
[34] Fathallah FA, Brogmus GE. Hourly trends in workers' compensation claims. Ergonomics 1999;42:196.
[35] Hanecke K, Tiedemann S, Nachreiner F, Grzech-Sukalo H. Accident risk as a function of hour at work and time of day as determined from accident data and exposure models for the German working population. Scand J Work Environ Health 1998;24(Suppl 3):43–8.
[36] Sallinen M, Harma M, Mutanen P, Ranta R, Virkkala J, Muller K. Sleepiness in various shift combinations of irregular shift systems. Ind Health 2005;43:114–22.
[37] Sallinen M, Harma M, Akila R, et al. The effects of sleep debt and monotonous work on sleepiness and performance during a 12-h dayshift. J Sleep Res 2004;13:285–94.
[38] Kecklund G, Akerstedt T. Sleepiness in long distance truck driving: an ambulatory EEG study of night driving. Ergonomics 1993;36:1007–17.
[39] Boivin DB, James FO. Light treatment and circadian adaptation to shift work. Ind Health 2005;43:34–48.
[40] Sack RL, Blood ML, Lewy AJ. Melatonin rhythms in night shift workers. Sleep 1992;15:434–41.
[41] Weibel L, Brandenberger G. Disturbances in hormonal profiles of night workers during their usual sleep and work times. J Biol Rhythms 1998;13:202–8.
[42] Pietrowsky R, Meyrer R, Kern W, Born J, Fehm HL. Effects of diurnal sleep on secretion of cortisol, luteinizing hormone, and growth hormone in man. J Clin Endocrinol Metab 1994;78:683–7.
[43] James FO, Walker CD, Boivin DB. Controlled exposure to light and darkness realigns the salivary cortisol rhythm in night shift workers. Chronobiol Int 2004;21:961–72.
[44] Nagaya T, Yoshida H, Takahashi H, Kawai M. Markers of insulin resistance in day and shift workers aged 30–59 years. Int Arch Occup Environ Health 2002;75:562–8.
[45] Simon C, Weibel L, Brandenberger G. Twenty-four-hour rhythms of plasma glucose and insulin secretion rate in regular night workers. Am J Physiol Endocrinol Metab 2000;278:E413–20.
[46] Lund J, Arendt J, Hampton SM, English J, Morgan LM. Postprandial hormone and metabolic responses amongst shift workers in Antarctica. J Endocrinol 2001;171:557–64.
[47] Taylor E, Folkard S, Shapiro DA. Shiftwork advantages as predictors of health. Int J Occup Environ Health 1997;3:S20–9.
[48] Breithaupt H, Hildebrandt G, Dohre D, Josch R, Sieber U, Werner M. Tolerance to shift of sleep, as related to the individual's circadian phase position. Ergonomics 1978;21:767–74.

[49] Steele MT, McNamara RM, Smith-Coggins R, Watson WA. Morningness–eveningness preferences of emergency medicine residents are skewed toward eveningness. Acad Emerg Med 1997;4:699–705.
[50] 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.
[51] Crowley SJ, Lee C, Tseng CY, Fogg LF, Eastman CI. Combinations of bright light, scheduled dark, sunglasses, and melatonin to facilitate circadian entrainment to night shift work. J Biol Rhythms 2003;18:513–23.
[52] Bohle PL. Sleep and circadian rhythm characteristics as predictors of adjustment to shiftwork. Int J Occup Environ Health 1997;3:S30–4.
[53] Knutsson A, Nilsson T. Job strain in shift and daytime workers. Int J Occup Environ Health 1997;3:S78–81.
[54] Kurumatani N, Koda S, Nakagiri S, et al. The effects of frequently rotating shiftwork on sleep and the family life of hospital nurses. Ergonomics 1994;37:995–1007.
[55] Loudoun RJ, Bohle PL. Work/non-work conflict and health in shiftwork: relationships with family status and social support. Int J Occup Environ Health 1997;3:S71–7.
[56] Sasaki T, Matsumoto S. Actual conditions of work, fatigue and sleep in non-employed, home-based female information technology workers with preschool children. Ind Health 2005;43:142–50.
[57] Brugere D, Barrit J, Butat C, Cosset M, Volkoff S. Shiftwork, age, and health: an epidemiologic investigation. Int J Occup Environ Health 1997;3:S15–9.
[58] Harma M, Sallinen M, Ranta R, Mutanen P, Muller K. The effect of an irregular shift system on sleepiness at work in train drivers and railway traffic controllers. J Sleep Res 2002;11:141–51.
[59] Bjorvatn B, Stangenes K, Oyane N, et al. Subjective and objective measures of adaptation and readaptation to night work on an oil rig in the North Sea. Sleep 2006;29:821–9.
[60] Barnes RG, Forbes MJ, Arendt J. Shift type and season affect adaptation of the 6-sulphatoxymelatonin rhythm in offshore oil rig workers. Neurosci Lett 1998;252:179–82.
[61] Wright Jr KP. Modeling the effectiveness of naps as a countermeasure to driver sleepiness and accidents. Comment on Garbarino et al. professional shift-work drivers adopting prophylactic naps can reduce the risk of car accidents during night work. Sleep 2004;27(7):1295–302. Sleep 2004;27:1446–1448.
[62] Macchi MM, Boulos Z, Ranney T, Simmons L, Campbell SS. Effects of an afternoon nap on nighttime alertness and performance in long-haul drivers. Accid Anal Prev 2002;34:825–34.
[63] Takeyama H, Matsumoto S, Murata K, et al. Effects of the length and timing of nighttime naps on task performance and physiological function. Rev Saude Publica 2004;38(Suppl):32–7.
[64] Pilcher JJ, Popkin SM, Adkins K, Roether L. Self-report naps in irregular work schedules. Ind Health 2005;43:123–8.
[65] Takeyama H, Kubo T, Itani T. The nighttime nap strategies for improving night shift work in workplace. Ind Health 2005;43:24–9.
[66] Daurat A, Foret J. Sleep strategies of 12-hour shift nurses with emphasis on night sleep episodes. Scand J Work Environ Health 2004;30:299–305.
[67] Horowitz TS, Cade BE, Wolfe JM, Czeisler CA. Efficacy of bright light and sleep/darkness scheduling in alleviating circadian maladaptation to night work. Am J Physiol Endocrinol Metab 2001;281:E384–91.
[68] 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;322:1253–9.
[69] Campbell SS. Effects of timed bright-light exposure on shift-work adaptation in middle-aged subjects. Sleep 1995;18:408–16.
[70] 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.
[71] Bougrine S, Mollard R, Ignazi G, Coblentz A. Days off and bright light: effects on adaptation to night work. International Journal of Industrial Ergonomics 1998;21:187.
[72] Burgess HJ, Sharkey KM, Eastman CI. Bright light, dark and melatonin can promote circadian adaptation in night shift workers. Sleep Med Rev 2002;6:407–20.
[73] Boivin DB, James FO. Circadian adaptation to night-shift work by judicious light and darkness exposure. J Biol Rhythms 2002;17:556–67.
[74] Samel A, Gander P. Bright light as a chronobiological countermeasure for shiftwork in space. Acta Astronaut 1995;36:669–83.
[75] Gibbs M, Hampton S, Morgan L, Arendt J. Adaptation of the circadian rhythm of 6-sulphatoxymelatonin to a shift schedule of seven nights followed by seven days in offshore oil installation workers. Neurosci Lett 2002;325:91–4.
[76] Hakola T, Harma MI, Laitinen JT. Circadian adjustment of men and women to night work. Scand J Work Environ Health 1996;22:133–8.
[77] 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;8:105–12.
[78] Stewart KT, Hayes BC, Eastman CI. Light treatment for NASA shiftworkers. Chronobiol Int 1995;12:141–51.
[79] Czeisler CA, Kronauer RE, Allan JS, et al. Bright light induction of strong (type 0) resetting of the human circadian pacemaker. Science 1989;244:1328–33.
[80] Khalsa SB, Jewett ME, Cajochen C, Czeisler CA. A phase response curve to single bright light pulses in human subjects. J Physiol 2003;549:945–52.
[81] Baehr EK, Fogg LF, Eastman CI. Intermittent bright light and exercise to entrain human circadian rhythms to night work. Am J Physiol 1999;277:R1598–604.
[82] Boivin DB, Duffy JF, Kronauer RE, Czeisler CA. Dose–response relationships for resetting of human circadian clock by light. Nature 1996;379:540–2.
[83] Boivin DB, James FO. Phase-dependent effect of room light exposure in a 5-h advance of the sleep–wake cycle: implications for jet lag. J Biol Rhythms 2002;17:266–76.
[84] Duffy JF, Wright Jr KP. Entrainment of the human circadian system by light. J Biol Rhythms 2005;20:326–38.
[85] Zeitzer JM, Dijk DJ, Kronauer R, Brown E, Czeisler C. Sensitivity of the human circadian pacemaker to nocturnal light: melatonin phase resetting and suppression. J Physiol 2000;526(Pt 3):695–702.
[86] 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;17:535–43.
[87] 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;27:771–82.
[88] Lowden A, Akerstedt T, Wibom R. Suppression of sleepiness and melatonin by bright light exposure during breaks in night work. J Sleep Res 2004;13:37–43.
[89] James FO, Chevrier E, Boivin DB. Improvement of daytime sleep in shift workers by judicious light exposure. Sleep 2002;25:A156–7.
[90] Dawson D, Campbell SS. Timed exposure to bright light improves sleep and alertness during simulated night shifts. Sleep 1991;14:511–6.
[91] Kelly TL, Kripke DF, Hayduk R, Ryman D, Pasche B, Barbault A. Bright light and LEET effects on circadian rhythms, sleep and cognitive performance. Stress Med 1997;13:251–8.

[92] Ross JK, Arendt J, Horne J, Haston W. Night-shift work in Antarctica: sleep characteristics and bright light treatment. Physiol Behav 1995;57:1169–74.
[93] Daurat A, Foret J, Benoit O, Mauco G. Bright light during nighttime: effects on the circadian regulation of alertness and performance. Biol Signals Recept 2000;9:309–18.
[94] Lavoie S, Paquet J, Selmaoui B, Rufiange M, Dumont M. Vigilance levels during and after bright light exposure in the first half of the night. Chronobiol Int 2003;20:1019–38.
[95] Phipps-Nelson J, Redman JR, Dijk DJ, Rajaratnam SM. Daytime exposure to bright light, as compared to dim light, decreases sleepiness and improves psychomotor vigilance performance. Sleep 2003;26:695–700.
[96] Lockley SW, Evans EE, Scheer FA, Brainard GC, Czeisler CA, Aeschbach D. Short-wavelength sensitivity for the direct effects of light on alertness, vigilance, and the waking electroencephalogram in humans. Sleep 2006;29:161–8.
[97] Warman VL, Dijk DJ, Warman GR, Arendt J, Skene DJ. Phase advancing human circadian rhythms with short wavelength light. Neurosci Lett 2003;342:37–40.
[98] Cajochen C, Munch M, Kobialka S, et al. High sensitivity of human melatonin, alertness, thermoregulation, and heart rate to short wavelength light. J Clin Endocrinol Metab 2005;90:1311–6.
[99] Sasseville A, Paquet N, Sevigny J, Hebert M. Blue blocker glasses impede the capacity of bright light to suppress melatonin production. J Pineal Res 2006;41:73–8.
[100] Schwartz JR, Roth T. Shift work sleep disorder: burden of illness and approaches to management. Drugs 2006;66:2357–70.
[101] Keating GM, Raffin MJ. Modafinil: a review of its use in excessive sleepiness associated with obstructive sleep apnoea/hypopnoea syndrome and shift work sleep disorder. CNS Drugs 2005;19:785–803.
[102] Ballon JS, Feifel D. A systematic review of modafinil: potential clinical uses and mechanisms of action. J Clin Psychiatry 2006;67:554–66.
[103] Czeisler CA, Walsh JK, Roth T, et al. Modafinil for excessive sleepiness associated with shift-work sleep disorder. N Engl J Med 2005;353:476–86.
[104] Dinges DF, Arora S, Darwish M, Niebler GE. Pharmacodynamic effects on alertness of single doses of armodafinil in healthy subjects during a nocturnal period of acute sleep loss. Curr Med Res Opin 2006;22:159–67.
[105] Rosenberg R, Corser B. Patient functional status, safety and tolerability of modafinil in a 12-month open-label study in patients with chronic shift work sleep disorder. Sleep 2004;27:A57–8.
[106] Gill M, Haerich P, Westcott K, Godenick KL, Tucker JA. Cognitive performance following modafinil versus placebo in sleep-deprived emergency physicians: a double-blind randomized crossover study. Acad Emerg Med 2006;13:158–65.
[107] Schweitzer PK, Randazzo AC, Stone K, Erman M, Walsh JK. Laboratory and field studies of naps and caffeine as practical countermeasures for sleep–wake problems associated with night work. Sleep 2006;29:39–50.
[108] Wright Jr KP, Badia P, Myers BL, Plenzler SC. Combination of bright light and caffeine as a countermeasure for impaired alertness and performance during extended sleep deprivation. J Sleep Res 1997;6:26–35.
[109] Walsh JK, Muehlbach MJ, Schweitzer PK. Hypnotics and caffeine as countermeasures for shiftwork-related sleepiness and sleep disturbance. J Sleep Res 1995;4:80–3.
[110] Wyatt JK, Cajochen C, Ritz-De Cecco A, Czeisler CA, Dijk DJ. Low-dose repeated caffeine administration for circadian-phase-dependent performance degradation during extended wakefulness. Sleep 2004;27:374–81.
[111] Jay SM, Petrilli RM, Ferguson SA, Dawson D, Lamond N. The suitability of a caffeinated energy drink for night-shift workers. Physiol Behav 2006;87:925–31.
[112] Beaumont M, Batejat D, Pierard C, et al. Slow release caffeine and prolonged (64-h) continuous wakefulness: effects on vigilance and cognitive performance. J Sleep Res 2001;10:265–76.
[113] Lieberman HR, Tharion WJ, Shukitt-Hale B, Speckman KL, Tulley R. Effects of caffeine, sleep loss, and stress on cognitive performance and mood during US. Navy SEAL training. Sea-Air-Land.. Psychopharmacology (Berl) 2002;164:250–61.
[114] Nehlig A. Are we dependent upon coffee and caffeine? A review on human and animal data. Neurosci Biobehav Rev 1999;23:563–76.
[115] Benington JH, Kodali SK, Heller HC. Stimulation of A1 adenosine receptors mimics the electroencephalographic effects of sleep deprivation. Brain Res 1995;692:79–85.
[116] Drapeau C, Hamel-Hebert I, Robillard R, Selmaoui B, Filipini D, Carrier J. Challenging sleep in aging: the effects of 200 mg of caffeine during the evening in young and middle-aged moderate caffeine consumers. J Sleep Res 2006;15:133–41.
[117] Carrier J, Fernandez-Bolanos M, Robillard R, et al. Effects of caffeine are more marked on daytime recovery sleep than on nocturnal sleep. Neuropsychopharmacology 2006;32:964–72.
[118] Bonnet MH, Arand DL. Impact of naps and caffeine on extended nocturnal performance. Physiol Behav 1994;56:103–9.
[119] Petrie KJ, Powell D, Broadbent E. Fatigue self-management strategies and reported fatigue in international pilots. Ergonomics 2004;47:461–8.
[120] Morin AK, Jarvis CI, Lynch AM. Therapeutic options for sleep-maintenance and sleep-onset insomnia. Pharmacotherapy 2007;27:89–110.
[121] Simons R, Koerhuis CL, Valk PJ, Van den Oord MH. Usefulness of temazepam and zaleplon to induce afternoon sleep. Mil Med 2006;171:998–1001.
[122] Porcu S, Bellatreccia A, Ferrara M, Casagrande M. Performance, ability to stay awake, and tendency to fall asleep during the night after a diurnal sleep with temazepam or placebo. Sleep 1997;20:535–41.
[123] Walsh JK, Schweitzer PK, Anch AM, Muehlbach MJ, Jenkins NA, Dickins QS. Sleepiness/alertness on a simulated night shift following sleep at home with triazolam. Sleep 1991;14:140–6.
[124] Hart CL, Ward AS, Haney M, Foltin RW. Zolpidem-related effects on performance and mood during simulated night-shift work. Exp Clin Psychopharmacol 2003;11:259–68.
[125] Caldwell Jr JA, Caldwell JL. Comparison of the effects of zolpidem-induced prophylactic naps to placebo naps and forced rest periods in prolonged work schedules. Sleep 1998;21:79–90.
[126] Dubocovich ML, Markowska M. Functional MT1 and MT2 melatonin receptors in mammals. Endocrine 2005;27:101–10.
[127] Lewy AJ, Ahmed S, Jackson JM, Sack RL. Melatonin shifts human circadian rhythms according to a phase–response curve. Chronobiol Int 1992;9:380–92.
[128] Revell VL, Burgess HJ, Gazda CJ, Smith MR, Fogg LF, Eastman CI. Advancing human circadian rhythms with afternoon melatonin and morning intermittent bright light. J Clin Endocrinol Metab 2006;91:54–9.
[129] Rogers NL, Kennaway DJ, Dawson D. Neurobehavioural performance effects of daytime melatonin and temazepam administration. J Sleep Res 2003;12:207–12.
[130] Rajaratnam SM, Middleton B, Stone BM, Arendt J, Dijk DJ. Melatonin advances the circadian timing of EEG sleep and directly facilitates sleep without altering its duration in extended sleep opportunities in humans. J Physiol 2004;561:339–51.
[131] Sharkey KM, Fogg LF, Eastman CI. Effects of melatonin administration on daytime sleep after simulated night shift work. J Sleep Res 2001;10:181–92.

[132] Wyatt JK, Dijk DJ, Ritz-de Cecco A, Ronda JM, Czeisler CA. Sleep-facilitating effect of exogenous melatonin in healthy young men and women is circadian-phase dependent. Sleep 2006;29:609–18.
[133] Cavallo A, Ris MD, Succop P, Jaskiewicz J. Melatonin treatment of pediatric residents for adaptation to night shift work. Ambul Pediatr 2005;5:172–7.
[134] James M, Tremea MO, Jones JS, Krohmer JR. Can melatonin improve adaptation to night shift? Am J Emerg Med 1998;16:367–70.
[135] 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.
[136] Roth T, Stubbs C, Walsh JK. Ramelteon (TAK-375), a selective MT1/MT2-receptor agonist, reduces latency to persistent sleep in a model of transient insomnia related to a novel sleep environment. Sleep 2005;28:303–7.
[137] Erman M, Seiden D, Zammit G, Sainati S, Zhang J. An efficacy, safety, and dose–response study of Ramelteon in patients with chronic primary insomnia. Sleep Med 2006;7:17–24.
[138] Karim A, Tolbert D, Cao C. Disposition kinetics and tolerance of escalating single doses of ramelteon, a high-affinity MT1 and MT2 melatonin receptor agonist indicated for treatment of insomnia. J Clin Pharmacol 2006;46: 140–8.