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The Cincinnati Children's Hospital Medical Center
3333 Burnet Ave.
Cincinnati, OH 45229-3039

Project Title: Intervention to Mitigate Adverse Effects of Shift Work

Principal investigator: Anita Cavallo, MD

Co-investigators: Julie Jaskiewicz, MD
M. Douglas Ris, PhD
Paul Succop, PhD

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Abstract

Socio-economic pressures and customer needs render night work imperative in many occupations. Sleep deprivation, common in night workers, is a major cause of accidents and fatalities. Alertness and sleep are normally rhythmic events synchronized to the light and dark phases of the 24h solar cycle. Rotating or permanent night work cause dissociation of rhythms from the 24h light/dark phases with resultant poor sleep, diminished alertness and mood disturbances. Melatonin is effective in accelerating adjustment to alterations in the 24 h light/dark cycle in certain conditions, e.g., jet lag and blindness. The proposed project tested the hypothesis that melatonin accelerates the adjustment of workers to a reversal in the activity/sleep cycle from daytime to night work by synchronizing sleep to the desired schedule and consequently improving alertness and mood during the waking hours. The hypothesis was tested in an actual work place, a hospital. Subjects were residents, i.e., physicians in training, whose work requires

intense alertness and vigilance. The design included two treatment phases for each subject, melatonin and placebo, and two respective baseline phases, one for each treatment; each phase lasts two weeks. The treatment phases consisted of the night float rotation characterized by a sequence of 5-15 days of night work without any daytime duties, thereby involving an abrupt reversal of the wake-sleep schedule. During this work period the residents got 3 days off over 2 weekends. Residents were instructed to take the drug 30 minutes before their desired bedtime, but they omitted taking the drug if bedtime occurred after 1300h. Melatonin or placebo was be administered daily in the morning of the workdays during the night float rotation. On the days off, residents had the option of omitting the drug or taking it at the desired bedtime, which was usually in the evening. Outcome measures included: (1) sleep characteristics obtained by diary and wrist actigraphy; (2) attention assessed by the Conner's continuous performance test (Conners 1995); and (3) mood assessed by the Profile of Mood States (McNair, Lorr et al. 1992). Forty five subjects participated: 28 completed both treatment phases and 17 completed one treatment phase of whom 10 took placebo and 7, melatonin.

First, we examined the impact of the night float rotation on sleep, mood and attention of the 38 residents who took placebo, by comparing the outcome measures during the night float rotation with the respective daytime control measures. Residents completed sleep diaries daily and the tests of mood and attention 3 times a week during the two-week night float rotation and during equivalent blocks of time of their daytime rotations. We showed that, despite having ample opportunity to sleep during the day while on night float rotation, residents slept less during the night float rotation than during the nights of their usual daytime rotations, 6.3h $\pm$ 2.5h and 7.2h $\pm$ 1.7h, respectively, $p < 0.0001$. Also, during night float compared to daytime rotations residents had increased fatigue-inertia scores, 8.7 $\pm$ 4.1 and 4.8 $\pm$ 2.4, respectively, $p < 0.0001$, and decreased vigor-activity scores 10.7 $\pm$ 5.4 and 14.8 $\pm$ 5.3, respectively, $p = 0.02$. The scores for attention were not significantly different between night float and daytime rotations. The correlation coefficients of fatigue with measures of attention were not statistically significant for daytime rotations. However, for night float fatigue correlated with omission errors, $r = 0.51$, $p = 0.001$ and with attentiveness $r = -0.36$, $p = 0.03$. We concluded that the night float rotation caused deleterious effects on sleep, mood and attention as had been observed in other modalities of shift work. The proposed model of shift work and the outcome measures are not job-specific, hence, the results of the study can be generalized to other occupations which require high level of vigilance and alertness.

Next, we examined the effect of melatonin treatment on sleep, mood and attention in the 45 residents. There was no significant difference between melatonin and placebo treatment in measures of sleep, mood and attention of all 45 participants. In the 28 residents who each participated in both treatment conditions, melatonin and placebo, there were two distinct responses of sleep duration to melatonin: it increased by 0.89h$\pm$0.62h in 15 residents (responders) and decreased by 0.68h$\pm$0.55h in 13 (non-responders); also, there was a marginal beneficial effect of melatonin on vigor, $F_{(1,26)}=4$, $p=0.056$. Side effects were not statistically more frequent on melatonin than on placebo and they were not unusual other than nightmares in one resident taking melatonin. We propose the following explanations for the finding of responders and non-responders: pharmacogenetic characteristics, individual tolerance to shift work, and a relationship of response to melatonin with tolerance to shift work. Further studies are needed to identify factors that will predict a favorable response to melatonin treatment.

The results suggest that melatonin treatment may be beneficial in adaptation to night shift in some workers. The expected benefits of melatonin treatment may lead to development of new strategies for adjustment to night work, resulting in increased safety and reduced accidents and fatalities related to sleep deprivation in night workers.

Significant findings

The night float rotation used in this project as a model of a field study of night shift work caused disruptions of sleep, and alterations of mood and attention similar to those reported in other modalities of night shift work. The findings have been published recently (Cavallo, Ris et al. 2003) and are summarized below, along with the results of melatonin treatment.

Sleep

First, the sleep diary confirmed that during the night float residents slept during daytime when working at night and reverted to night sleep on days off work, a behavior that is commonly encountered in other types of night shift work.

A comparison of sleep measures during the night float rotation of residents who took placebo with their respective daytime rotations showed that the duration of the main sleep event was significantly lower during the night float rotation, 6.3h $\pm$ 2.5h, than during the daytime rotations, 7.2h $\pm$ 1.7h, (F (1, 1451) = 45.45, $p<0.0001$). The frequency of awakenings was significantly higher during the night float rotation when residents had 0 or 1 awakening in only 38% of the main sleep periods and 2 or more awakenings in 62% of the main sleep periods, in contrast to the daytime rotations when residents had 0 or 1 awakening in 48% of the main sleep periods and 2 or more awakenings in 52% of the main sleep periods, x^2 (1, 1377) = 11.5, p=0.0007.

A comparison of the sleep measures during the night float rotations when residents took placebo with those when they took melatonin showed no significant effect of melatonin treatment on the sleep measures during the night float morning treatment days. These measures were respectively for placebo and melatonin: sleep duration 6.3h$\pm$2.0h and 6.5h$\pm$1.9h, F=0.18, p=0.67; sleep quality 60.8mm$\pm$19.6mm and 62.6mm$\pm$17.7mm, F=0.53, p=0.47, and number of awakenings 2.27$\pm$1.87 and 2.34$\pm$1.82, x^2=1.19, p=0.27.

However, a comparison of sleep duration in the 28 residents who participated in each of the two treatments, melatonin and placebo, showed two types of response: a positive response, with sleep duration 0.9h$\pm$0.6h longer on melatonin than on placebo in 15 residents, and a negative response, with sleep duration 0.7h$\pm$0.6h shorter on melatonin than on placebo in 13 residents (Fig. 1). The former residents were considered melatonin-responders and the latter, melatonin-non responders.

Mood

A comparison of the mood measures during the night float rotation of residents who took placebo with their respective daytime rotations (Table 1) showed that the scores for tension-anxiety, depression-dejection, anger-hostility and confusion-bewilderment were not significantly different between daytime shift and night float. Of note is that these scores were in the range seen in healthy young adult college students (McNair, Lorr et al. 1992). In contrast, the score for vigor-activity for daytime shift, 14.8 ± 5.3, was significantly higher than that for night float, 10.7 ± 5.4, $F (1, 600) = 6.15$, $p = 0.02$ (Fig. 1). In addition, the scores for fatigue-inertia for daytime shift, 4.8 ± 2.4, was significantly lower than for night float, 8.7 ± 4.1, $p < 0.0001$ (Fig. 2).

A comparison of the mood measures during the night float rotations when residents took placebo with those when they took melatonin showed no significant effect of melatonin treatment on any of the mood measures (Table 2). However, further analysis of the mood measures in the 28 residents who participated in each of the two treatments, melatonin and placebo, showed no statistically significant effect of treatment by response to sleep (responders and non-responders) on tension-anxiety, depression-dejection, confusion-bewilderment, anger-hostility and fatigue, but a marginally significant effect on vigor $F (1, 26)=4.0$, $p=0.056$.

Attention

A comparison of attention measures during the night float rotation of residents who took placebo with their respective daytime rotations (Table 3) showed that the number of omission errors in the daytime shift, 1.6 ± 3.8, was in the normal range of published normal controls (Walker, Shores et al. 2000). The number of omission errors during night float, 3.9 ± 11.7, was somewhat higher and more variable than during daytime, however, there was no statistically significant difference between the shifts. The number of commission errors for daytime shift, 9.8 ± 6.6 and for night float, 10.2 ± 6.8 were not significantly different. Likewise, the mean hit reaction time was not significantly different between daytime shift and night float. Moreover, there was no statistically significant difference in the hit reaction time block change between daytime shift and night float. Of note, however, the negative slope for daytime shift, -0.002 ± 0.028, suggests quicker reaction times as the test progressed while the positive slope for night float, 0.0017 ± 0.026, suggests a slowing reaction over time. There was no statistically significant difference between daytime and night shift in attentiveness and risk taking.

A comparison of the attention measures during the night float rotations when residents took placebo with those when they took melatonin showed no significant effect of treatment on the number of commission errors, mean reaction time, hit reaction time block change, attentiveness and risk taking during the night float morning treatment days

(Table 4). However, the number of omission errors was significantly lower on melatonin than on placebo treatment, 4.5±17.5 and 3.0±9.6, respectively, Z=-2.12, p=0.03.

A comparison of the attention measures during the night float rotations when residents took placebo with those when they took melatonin showed no statistically significant effect of treatment by response to sleep (responders and non-responders): commission errors F (1, 26)=0.67, p=0.42, mean reaction time F (1, 26)=0.37, p=0.54, hit reaction time block change F (1, 26)=0.75, p=0.39, attentiveness F (1, 26)=0.76, p=0.39, risk taking Z=1.5, p=0.13 and omission errors Z=0.39, p=0.69.

Usefulness of findings

The present report shows that melatonin administration is useful in adaptation to short term night shift work in some individuals. The challenges ahead before attempting widespread use of melatonin for shift workers include methods to identify workers at risk of maladjustment to shift work and to determine factors that may predict a favorable response to melatonin treatment. Moreover, dose-response studies and comparisons of responses to fast release melatonin as used in the present study with slow release preparations of melatonin also should be conducted. Finally, measures need to be developed to assess the safety of melatonin for long-term use.

Scientific report

Background: More than 7 million people in the US work at night, either as permanent night workers or in alternating shifts that often include night work. Sleep deprivation is a major cause of on the job or on the road accidents and fatalities (Mitler, Carskadon et al. 1988). The goals of "Healthy People 2,000" include that of improving occupational safety and health by reducing work-related injuries and deaths. Development of strategies to reduce the negative impact of shift on workers' safety and health will contribute to these goals. Sleep and other human physiological rhythms are synchronized to the alternating light and dark phases of the 24h solar cycle and are designated "circadian". Nocturnal work causes desynchronization of circadian rhythms resulting in symptoms of maladjustment characterized by poor quality of sleep and decline in alertness and performance (Czeisler, Johnson et al. 1990). The pineal hormone melatonin contributes to the synchronization of circadian rhythms to the 24 h solar cycle by translating environmental changes in the light/dark cycle to an internal pacemaker in animals and humans (Reiter 1991).

Hypothesis: Treatment with exogenous melatonin will accelerate adjustment or prevent maladjustment to a sudden change in the activity/sleep cycle from daytime to night work in an actual work environment, by improving sleep and consequently improving alertness and mood. The hypothesis will be tested using a model of night work that requires high level vigilance and alertness, the night float rotation, which is a 2-week period of night work by physicians in training followed by a return to daytime work.

Specific goals: To determine whether, compared to placebo, melatonin will: (1) significantly improve the quality and efficiency of daytime sleep, (2) improve vigilance/alertness during wake hours, and (3) improve mood.

This study will contribute to a better understanding of the impact of night work on sleep, vigilance/alertness and mood. The expected benefits of melatonin treatment in the proposed model of night work may be generalized to other occupations that require high levels of vigilance and alertness. Ultimately, interventions that prevent maladjustment or facilitate adjustment of workers to shift changes will lead to improved productivity and increased safety, with reduction of shift-related accidents.

Methods

The Institutional Review Board approved the study and participants gave written consent for participation. Study participants were healthy pediatric residents. The design was a double blind, placebo-controlled crossover treatment trial of melatonin during night float rotations. The night float rotation at our institution consists of a 2-week period (14-16 days) in the second year of training, during which residents report to work at midnight and leave work in the morning between 0800h and 1000h. During this rotation they get one night off during one week and 2 consecutive nights off during the other week. During the remaining second year of training residents usually work from 0630h or 0700h to 1700h or 1800h and have night calls every 4 days or less. Most residents work 2 night float periods during the second year of residency training. For each night float rotation the study included a 2-week control phase of daytime work scheduled within 3 months of the respective night float. During the weeks of daytime control the residents did not receive any treatment but completed similar study steps.

Forty-five residents age 28.6 $\pm$ 1.9 years participated in the study: 16 were male and 29, female. Of these, twenty-eight residents participated in the study during the 2 night float rotations, taking melatonin in one rotation and placebo in the other. Seventeen residents participated in the study during one night float; of these, 7 residents were assigned to take melatonin and 10 were assigned to take placebo. Hence, of the 45 participants 35 took melatonin and 38, placebo.

The Food and Drug Administration gave consent to the principal investigator to use melatonin in human subjects (IND # 42,901). The hospital's investigational drug pharmacist prepared gelatin capsules of melatonin and placebo that were identical in appearance. The melatonin capsule contained 3 mg synthetic melatonin of high purity (Regis Technologies, Inc.) mixed in lactose, and the placebo capsule contained lactose only. This preparation falls into the category of 'fast release' melatonin, such as has been used in other treatment trials (Arendt, Skene et al. 1997). For the first 9 participants the capsules were dispensed in a regular medication container and for the subsequent 36 participants the capsules were dispensed in a container fitted with an automated medication monitoring event system (Track Cap™) that recorded the date and time of opening the cap. Discrepancies between diary and Track Cap^{TM} entries lead to record review and data editing.

Participants were instructed to take one capsule (placebo or melatonin) regularly in the morning of the days of night work and to go to sleep in a darkened room. During the days off, they had the option to omit treatment or to take the drug at the desired bedtime. Bedtime was not prescribed because this was a naturalistic study that should be applicable to a wide range of night shift workers. However, participants were instructed to skip taking the capsule if they went to sleep after 1300h, because of concern about a possible hangover effect that might jeopardize their work during the immediately following night shift.

Study procedures included completion of a sleep diary daily and performance of tests of attention and mood 3 days of each study week. The diary included blanks for entry of number of naps and date and time of events related to the main sleep period, i.e., going to bed, falling asleep, waking up, getting up and number of sleep interruptions (awakenings). In addition, it contained a multiple choice question to determine the state of alertness upon awaking and a 100 mm sleep analog scale in which the opposite extremes were "best sleep for a long time" (100 mm) and "most rotten sleep for a long time" (0 mm) to estimate sleep quality (Arendt, Aldhous et al. 1987). During the night float participants also recorded the time of drug administration and completed a medication side effects log daily that covered general symptoms (headaches, lightheaded), gastrointestinal symptoms (abdominal pain, nausea, vomiting), excessive sleepiness, and an open-ended question about other side effects. Thirty six participants also wore a wrist activity monitor, the actigraph, at bedtime (Sadeh, Hauri et al. 1995). Successful actigraphy recordings available in 28 participants were used to validate the sleep diary entries. The following measures of sleep obtained from the diaries were used in data analysis: sleep duration defined as the time interval from time asleep to wake up time, number of awakenings and sleep quality.

The test of attention was the Conner's continuous performance test, which is a brief and easy to follow computer program (Conners 1995). This program generates a report of several measures of attention: number of omission errors, number of commission errors, mean hit reaction time, hit reaction time block change, attentiveness and risk taking. The test of mood was the Profile of Mood Symptoms, a self-report pencil and paper questionnaire consisting of 65 items (McNair, Lorr et al. 1992). This test measures six general mood states: tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. The residents completed the tests of attention and mood at the end of their work shift, i.e., in the morning after a night shift during the night float rotation and the end of a day shift during the control periods.

Data analysis was performed using the General Linear Model (GLM) procedure of SAS program version 8.20. For outcomes that did not follow a normal distribution data analysis was performed after logit transformation. Because there were many values '0' for number of omission errors and risk taking, these two variables were analyzed by the Poisson regression procedure. The following independent variables were included in the model: participant, drug (melatonin, placebo), the mean value of the respective dependent measures of the daytime periods, study week (week 1, week 2) and the interaction of drug with study week. The Pearson product moment correlation was used to examine relationships among variables. A p value of 0.05 was used to determine statistical significance.

Results

The results are presented in the section 'significant findings' above.

Discussion

Although there was no statistically significant difference in the sleep measures between melatonin and placebo treatment for the 45 participants, there was considerable individual variability in responses. In fact, among the 28 residents who participated in two night float sessions, 15 residents had improved sleep duration on melatonin compared to placebo. Moreover, the trend for increased vigor in this subset of participants further suggests a beneficial effect of melatonin.

The results of the present field study support previous suggestions of a promising role for melatonin treatment of actual shift workers that was based on experimental shift work models (Deacon and Arendt 1996; Sharkey, Fogg et al. 2001). Experimental shift studies are conducted using rigid sleep/activity schedules in research laboratories where environmental light and other conditions are standardized. These strict laboratory conditions do not match the variable schedules and environmental conditions encountered by shift workers in the field.

Actual field studies are scarce and results are inconsistent. For example, 7 police officers had improved sleep and alertness while taking 5 mg melatonin over 7 days of night work compared to placebo, but the benefit over performance was inconclusive (Folkard, Arendt et al. 1993). In contrast, emergency room physicians on rapidly rotating night shifts of 2 to 3 consecutive nights with 2 to 3 nights off did not benefit from melatonin administration compared to placebo neither when taking the drug in the morning after each night shift (Jorgensen and Witting 1998) nor in the evening after completion of consecutive night shifts (Wright, Lawrence et al. 1998).

The significantly lower number of omission errors on melatonin treatment than on placebo might suggest a beneficial effect of melatonin on attention. One must note, however, that all attention measures during both treatments were in the range considered normal and they were not significantly different from the attention measures during the daytime rotations (Cavallo, Ris et al. 2003). These findings are similar to the results of a placebo controlled melatonin treatment trial of adaptation to night shift of nurses who had significantly increased sleep duration but no significant change in alertness or performance on melatonin (Yoon and Song 2002). One explanation for these observations is that the testing methods were not sufficiently sensitive to detect a deleterious effect of night shift on attention. Alternatively, however, one might assume that health care workers have a higher motivation and heightened sense of responsibility on the job that maintains their attention at a high level. Nevertheless, the concern remains that the night float residents are at high risk for decreased attention linked to two factors: sleep deprivation and shift of the activity/sleep cycle. Thus, the finding in the present study of significantly improved sleep duration with melatonin treatment in some participants is important.

A possible limitation of the present study is that the days off work in the middle of the night float period might have masked any emerging benefit from melatonin treatment over the entire duration of the night shift period. This consideration would be valid if the therapeutic effect of melatonin were limited to resetting the internal circadian pacemaker (Lewy, Ahmed et al. 1992; Czeisler 1997). However, melatonin also appears to have a hypnotic effect that might benefit workers during transitions from dayshift to night shift (Zhdanova, Wurtman et al. 1995). In fact, the hypnotic property may explain the positive result of melatonin treatment on sleep on the first day of an inverted wake/sleep schedule in an experimental shift work study (Sharkey and Eastman 2002).

Three main factors may explain the variability in responses in the present study and the inconsistency of results among other studies: pharmacogenetic characteristics, individual tolerance to shift work, and a relationship of response to melatonin with tolerance to shift work. The first factor, pharmacogenetics, consists of genetically determined characteristics that vary among individuals and influence steps involved in drug action, from absorption to transport, to interaction with targets, to metabolism and elimination (Weinshilboum 2003). Overall, genetic characteristics may account for 20–95 percent of variability in drug disposition and effects (Evans and McLeod 2003). To our knowledge, pharmacogenetics of melatonin has not been investigated.

The second factor, tolerance to shift work, also varies considerably among individuals and is seldom considered in the interpretation of results of studies of shift workers (Ashkenazi, Reinberg et al. 1997). A search for practical predictors of tolerance to night work has not been successful (Knauth and Harma 1992; Ashkenazi, Reinberg et al. 1997).

The third factor, the link of response to melatonin with individual tolerance to shift work has been highlighted in a recent study of rotating shift workers on a schedule of 7 consecutive 10h night shifts alternating with 7 days off. Some workers spontaneously adapted their internal rhythm to shift change and did not have additional benefit from taking melatonin compared to placebo. In contrast, among the workers who did not adapt spontaneously to shift change, only a subset benefited from melatonin treatment, although there were no predictive indicators of which individuals might have a favorable response (Sack and Lewy 1997).

Generally, therapeutic trials of melatonin have not reported methodology for monitoring the safety of this drug, seeming to rely on spontaneous reports of undesirable effects. The present study included a daily side effects checklist that covered most systems that might be affected by melatonin. Of interest, the association of melatonin with nightmares or vivid dreams in some individuals in the present study has been previously noted (Guardiola-Lemaitre 1997). Otherwise, the results suggest that melatonin given for a short period of time of 2 weeks is well tolerated.

In summary, the present report shows that melatonin administration is useful in adaptation to short term night shift work in some individuals. Measures need to be developed to assess the safety of melatonin for long-term use.

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Table 1. Profile of Mood States (mean ± SD) in 38 residents during daytime and night float (placebo) rotations

	Daytime	Night Float	F (df)	p
Tension-Anxiety	5.8 ± 3.9	6.8 ± 4.3	0.69 (1, 600)	0.41
Depression-Dejection	4.0 ± 5.1	4.9 ± 7.3	0.26 (1, 600)	0.61
Anger-Hostility	3.3 ± 4.0	4.0 ± 5.1	0.30 (1, 599)	0.59
Vigor-Activity	14.8 ± 5.3	10.7 ± 5.4	6.15 (1, 601)	0.02
Fatigue-Inertia	4.8 ± 2.4	8.7 ± 4.1	19.54 (1, 602)	<0.0001
Confusion-Bewilderment	5.2 ± 3.2	6.4 ± 3.1	1.95 (1, 601)	0.17

Table 2. Profile of Mood States (mean ± SD) in 45 residents during night float on placebo and melatonin treatment

	Night Float Placebo	Night Float Melatonin	F	p
Tension-Anxiety	6.83±5.29	6.67±5.45	0.01	0.93
Depression-Dejection	5.06±8.36	5.2±8.55	0.60	0.44
Anger-Hostility	3.92±5.89	3.92±7.34	0.39	0.53
Vigor-Activity	10.48±6.92	10.79±6.57	0.34	0.56
Fatigue-Inertia	8.99±6.06	8.41±5.91	0.03	0.87
Confusion-Bewilderment	6.46±3.98	6.6±3.87	0.29	0.59

Table 3. Conner's Continuous Performance Test (mean ± SD) in 38 residents during daytime and night float (placebo) rotations

	Daytime	Night Float	F (df)	X^2	p
No. Omission Errors	1.6 ± 3.8	3.9 ± 11.7		0.85	0.36
No. Commission Errors	9.8 ± 6.6	10.2 ± 6.8	0.04 (1, 582)		0.85
Mean Reaction time (msec)	332.4 ± 54.1	336.7 ± 52.6	0.12 (1, 582)		0.73
Hit Reaction Time Block Change	-0.0013 ± 0.0149	0.0025 ± 0.0135	0.03 (1, 582)		0.86
Attentiveness	3.7 ± 0.8	3.5 ± 0.9	0.30 (1, 582)		0.59
Risk Taking	0.19 ± 0.34	0.30 ± 0.68		0.21	0.65

Table 4. Conner's Continuous Performance Test (mean ± SD) in 45 residents during night float on placebo and melatonin treatment

	Night Float Placebo	Night Float Melatonin	F	p
No. Commission Errors	10.3±8.0	10.5±7.4	0.0	0.95
Mean Reaction Time (msec)	339.3±65.0	333.0±59.8	0.01	0.93
Hit Reaction Time Block Change	0.0016±0.0259	0.0025±0.0285	0.10	0.75
Attentiveness	3.5±1.1	3.6±1.0	0.0	0.99
			Z	p
Risk Taking	0.3±1.6	0.3±1.6	-0.48	0.63
No. Omission Errors	4.5±17.5	3.0±9.6	-2.12	0.03

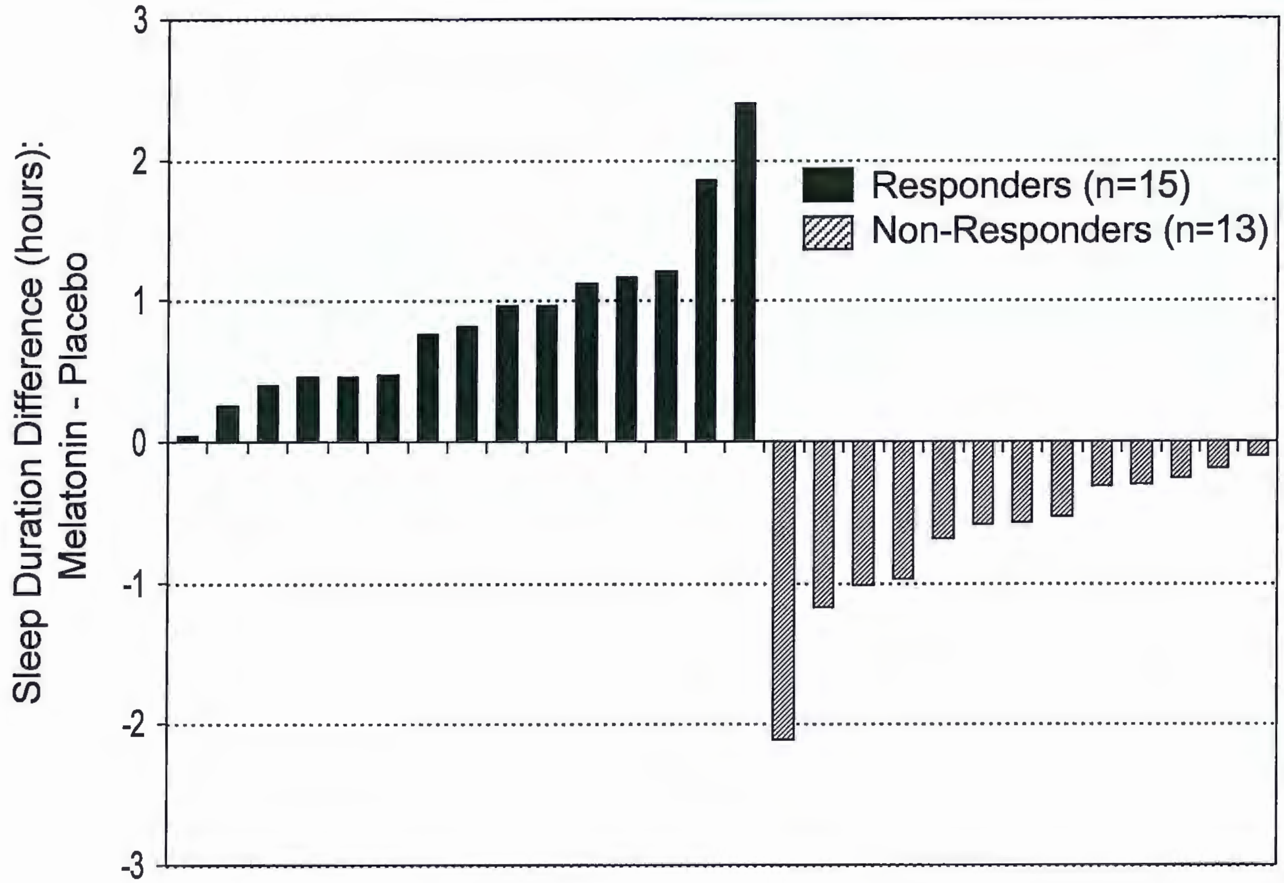

Fig. 1 Individual difference in the mean sleep duration on melatonin and placebo treatment in 28 residents during the night float rotations

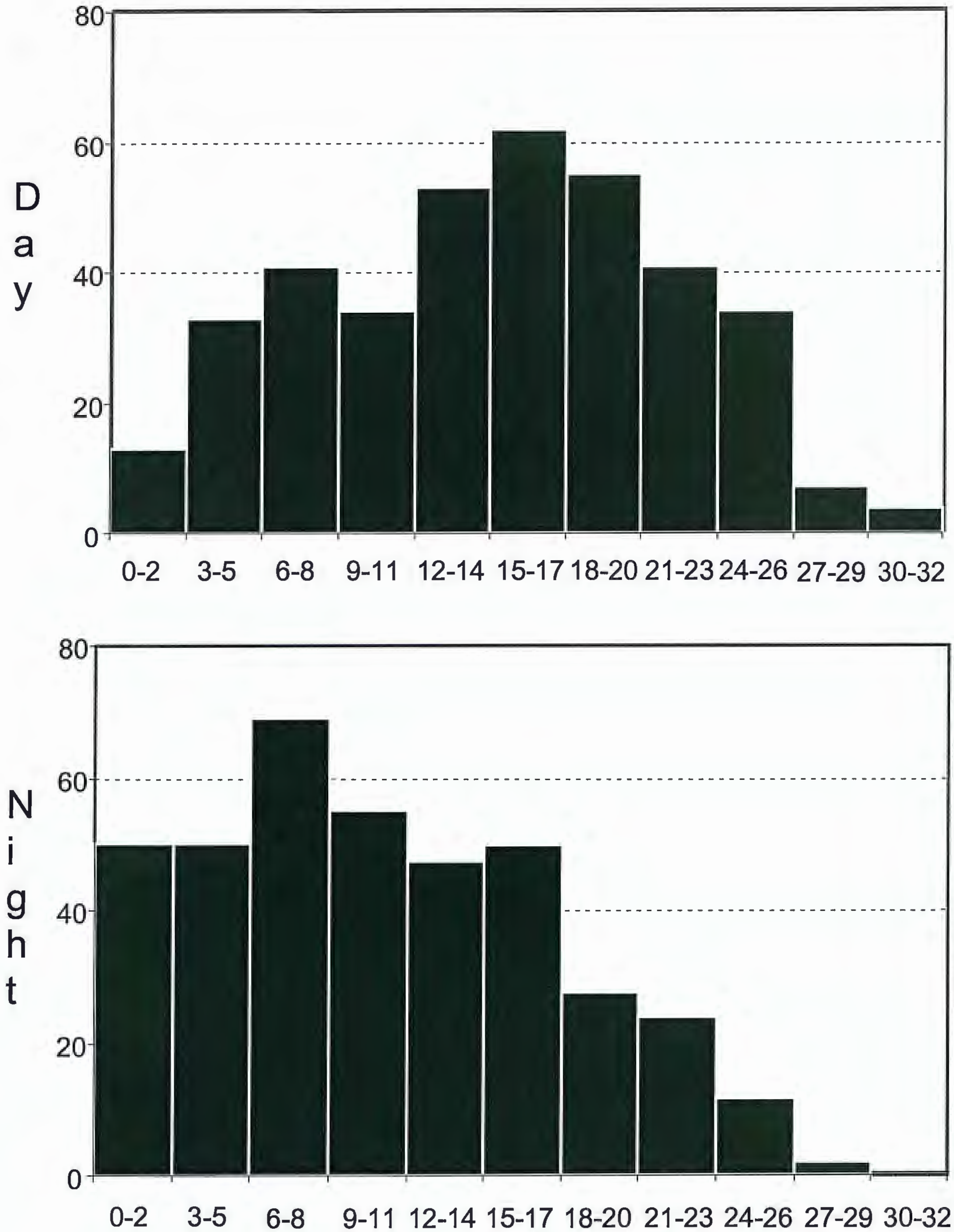

Fig. 2 Vigor-activity in 38 residents during night float on placebo treatment and during the control daytime rotation

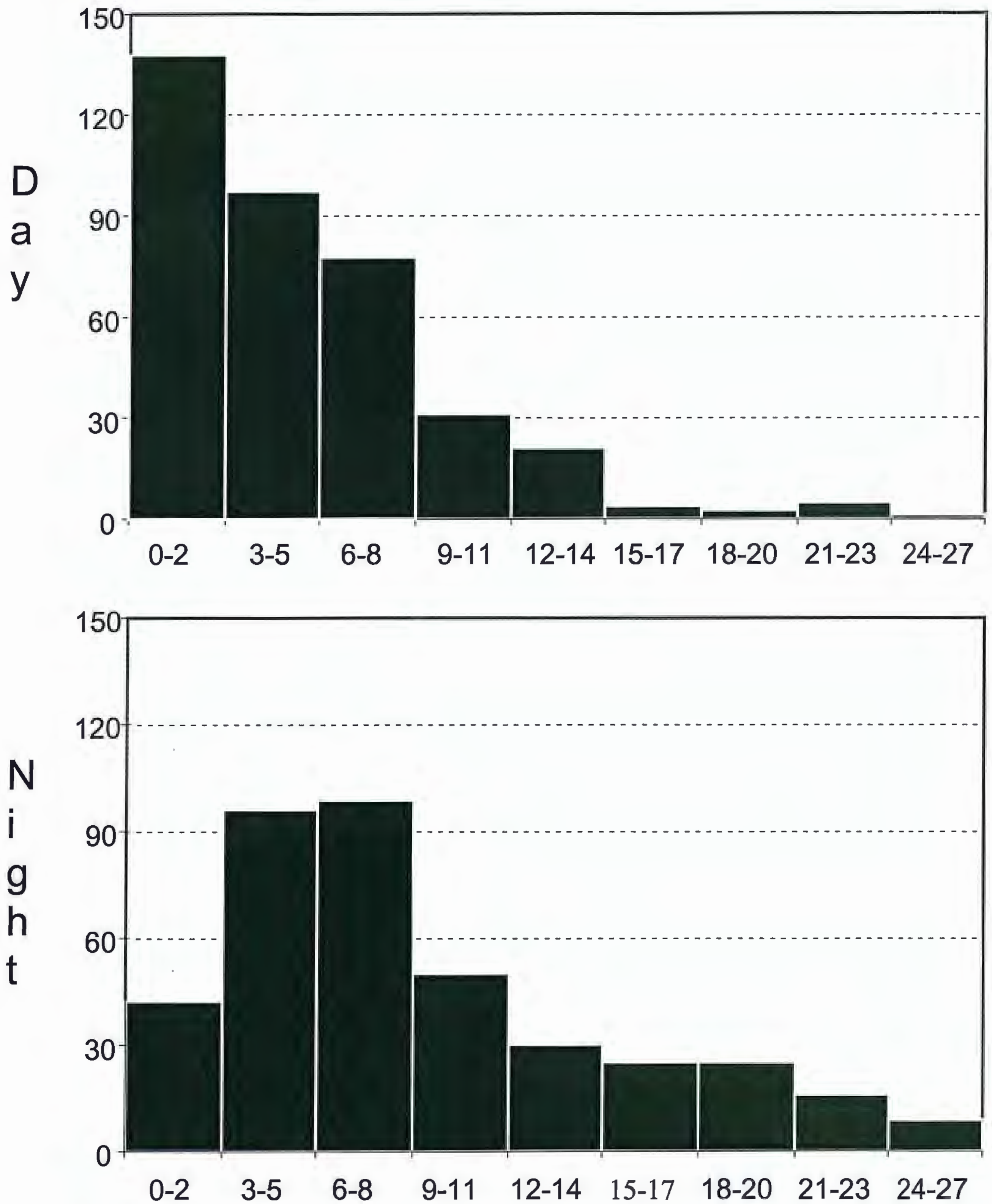

Fig. 3 Fatigue-inertia in 38 residents during night float on placebo treatment and during the control daytime rotation

2. Financial Status Report

A final report has been submitted previously.

3. Equipment Inventory

Not applicable. No equipment was acquired under this grant.

4. Final Invention Statement

Not applicable. No inventions were conceived under the grant.

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IMPACT OF NIGHT-FLOAT ROTATION ON SLEEP, MOOD, AND ALERTNESS: THE RESIDENT'S PERCEPTION

Anita Cavallo,* Julie Jaskiewicz, and M. Douglas Ris

Division of General and Community Pediatrics, Department of Pediatrics, Children's Hospital Medical Center, 3333 Burnet Ave. Cincinnati, OH 45229-3039

ABSTRACT

Night-float rotations were designed to alleviate the workload of residents on night call and thereby improve patient safety. However, the impact of the night float on residents is yet to be surveyed. We assessed the impact of the night-float rotation on pediatric residents using an anonymous questionnaire that covered topics, based on recall, about sleep, mood, alertness, adjustment, and others. The study was conducted in a major tertiary pediatric teaching hospital in the United States. Participants were pediatric residents who had completed one or two night-float rotations and were in active training at our teaching hospital at the time of the study. Fifty-two of 60 eligible residents (87%) responded. Sleep duration during the night-float rotation was shorter than during day-shift work in 24 residents (46%), longer in 20 (38%), and unchanged in eight (15%). A higher proportion of residents took longer to fall asleep, had more difficulty falling asleep, had more sleep interruptions, and felt less rested upon awakening. Twenty-four residents (46%) felt that their bodies never adjusted to the night shift. Also, 22 residents (43%) felt moody or depressed in contrast to seven (14%) who felt depressed during the daytime rotation ($p = 0.0001$). Twenty-one residents (41%) felt they were slower in their thinking during the night float than daytime rotations. The results suggest that disturbances of sleep and mood and decreased alertness,

*Corresponding author. Fax: (513) 636-4402; E-mail: anita.cavallo@chmcc.org

typical of night shift, are present in the night-float rotation. Residency programs should monitor closely the impact of the night-float rotation on resident well being and patient safety. The impact of night-shift work should be considered in the design of night-float schedules, and teaching should be provided for residents to learn coping strategies for night-shift work. (*Chronobiology International, 19(5), 893–902, 2002*)

Key Words: Circadian rhythm; Medical residents; Night-float shift; Shift work

INTRODUCTION

Night-float rotations are utilized in many residency-training programs in an effort to reduce housestaff stress and performance problems related to sleep deprivation and sleep disturbance.[1] Doctors in training (residents) usually provide around-the-clock coverage for patient care in teaching hospitals. Generally, the residents on inpatient ward rotations provide patient care during the daytime. In addition, they provide overnight coverage as "on-call" residents every 3–5 nights. Until the late 1980s, the on-call resident covered patients already hospitalized and also admitted new patients who required hospitalization during the night. The workload during the call night usually prevented the resident from getting enough rest before resuming usual daytime duties commencing the next morning. Resultant resident fatigue leads to impaired performance and serious errors in patient care.[2,3] The death of a patient and the ensuing lawsuit led training programs to acknowledge the residents' excessive workload and sleep deprivation.[4] Consequently, the night-float rotation was created and adopted by many training programs. This rotation consists of night-shift coverage performed by residents who do not have any daytime duties and provides coverage of inpatient services in addition to the "on call-resident" who is a daytime worker. Inherent in the night-float rotation is an abrupt reversal of the sleep–wake cycle.

The advent of night-float rotations has had a positive impact on residency training programs, with residents reporting increased satisfaction with on-call responsibilities and increased sleep during on-call nights.[1,5] However, the impact of the night-float experience, particularly the sudden reversal from daytime to nighttime activities, on the residents has not been evaluated. Shift work has been associated with sleep disturbances, mood alteration including irritability and depression, and diminished alertness[6–8] that may have serious consequences. We report results of a study designed to investigate residents' perception of the impact of the night-float rotation on their sleep, mood, and alertness.

METHODS

The Institutional Review Board approved the study and participation was entirely voluntary. The study consisted of an anonymous pencil and paper questionnaire distributed on a single day to all available pediatric residents in training at that time. All 60 pediatric residents, who had completed at least one night float and were actively in training at the time of the study, were eligible to participate. Hence, all first and second-year residents who had not done a night float rotation were excluded. Included were second, third, and fourth-year residents who had done the night-float rotation during the second year of training. A voucher for an ice cream at the hospital diner was given to each resident who returned a completed questionnaire.

The night-float rotation at the Children's Hospital Medical Center, Cincinnati, Ohio is a consecutive 2wk rotation during the second year of pediatric residency. This rotation consists of night-shift work from 24:00 to 08:00h, without any daytime work obligations, giving residents the opportunity to sleep during the day. During this 2wk period residents get scheduled time off, usually a 2d weekend block plus a separate single day. These off periods are usually spaced to occur once in the middle and once towards the end of the rotation. Generally, residents revert to night sleep during these off work periods. The night-float residents have direct responsibility for inpatient admissions, management of these patients throughout their shift, and sign-out of the patients to the inpatient ward resident team in the morning. Most residents do two night-float rotations, usually separated by several months time.

Other rotations during the training program consist mostly of daytime duties, generally starting at 07:00h and lasting until 16:00–18:00h. During certain daytime rotations, residents also have night-call duty at least every four nights. On these days, they work the usual day shift and remain on site on night call until the next morning. They are then in charge of admissions to their service until 24:00h, when the night-float resident assumes the task of new admissions. However, the "on-call" daytime residents continue to be responsible for the patients admitted to the service before 24:00h. Hence, the amount of sleep they get during the "on-call" night is variable, depending on patient load, the severity of medical conditions, and related intercurrent problems during the night.

The questionnaire was anonymous and consisted of 52 items related to six main categories: demographics, sleep, mood, alertness, adjustment to change from daytime shift to night shift, and voluntary written comments (Table 1). The questionnaire relied on participants' recall; the time lapse from the experience in question to the day of completion of the survey instrument varied from a few weeks to several months. Most questions were categorical multiple-choice, some open-ended, and some yes/no type. Some questions related to the night-float rotation, others to representative daytime rotations during the same academic year, and others related to the resident's experience during night-float vs. daytime rotations. We pre-tested the questionnaire for clarity with a few residents. The full questionnaire is available upon written request to the corresponding author.

We used the SAS program version 8.20 for data analysis applying published methodologies.[9] Frequencies of responses were calculated as percentages. When applicable, comparisons of responses between night-float and daytime rotations were made by analysis of variance techniques (ANOVA). Relationships between questionnaire distributed on a single day to all available pediatric residents in training at that time. All 60 pediatric residents, who had completed at least one night float and were actively in training at the time of the study, were eligible to participate. Hence, all first and second-year residents who had not done a night float rotation were excluded. Included were second, third, and fourth-year residents who had done the night-float rotation during the second year of training. A voucher for an ice cream at the hospital diner was given to each resident who returned a completed questionnaire.

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Table 1. Questionnaire Topics

Demographics
Age
Sex
Current residency year
Number of completed night float rotations
Sleep
Duration of main sleep event
Difficulty falling asleep
Time to fall asleep
Number of spontaneous sleep interruptions
Feeling rested after main sleep event
Use of prescription/nonprescription sleep medication
Adjustment to change from daytime to night-float shift
Overall experience of night float
Eventual overall adjustment
Number of days for body to adjust
Need to readjust to night-float shift following weekend off
Mood
Feeling depressed or moody
Difficulty interacting with nursing staff
Difficulty interacting with peers
Alertness
Perception of mental "quickness"
Perception of proficiency with procedures
Voluntary written comments

responses were tested with the χ^2 procedure. McNemar's test for paired samples, or test of symmetry. Multi-factorial interactions were tested using logistic regression technique.

RESULTS

Participants: Fifty-two of the 60 eligible residents (87%) responded. Seventeen were male and 35 female. Some 41 residents were between 25 and 30 yr of age, eight were 30–35 yr of age, and three were 35–40 yr of age. Fifteen residents had completed one night float, and 37 had completed two night-float rotations. At the time of the study, 21 residents were in the second year of training (PL-2), 28 were in the third year of training (PL-3), and three were chief residents (PL-4).

Complete data are available for 51 of the 52 responders and partial data for one, because this resident did not complete eight questions due to inadvertently skipping one page of the questionnaire. Data analysis took into account the number of responses to each question. Results are given as mean ± SD.

Sleep duration: During typical daytime rotations in the PL-2 year, when not on night-call, the group mean sleep duration on weeknights was 6.9 ± 0.8 h. Most residents 41/52 (79%) tended to sleep longer on off-work weekends. The group mean sleep duration on these weekend nights was 8.6 ± 1.3 h, which was significantly different from the sleep duration on weeknights ($p < 0.0001$; ANOVA). During the night float the group mean sleep duration was 6.8 ± 2.1 h on days following night-shift work, which was not significantly different from the sleep duration of the weeknights during daytime rotations ($p = 0.63$; ANOVA). Of note, compared to their daytime rotations, 20 residents (38%) reported they slept longer during night float while 24 (46%) slept less during night float, and only eight (15%) reported no appreciable change. This comparison had a high concordance of 75% with the average sleep duration that the residents reported for their daytime and night-float shifts.

Difficulty falling asleep: During typical daytime rotations in the PL-2 year when not on call, most residents, 46/51 (90%), reported difficulty falling asleep no more than once a week, and only five residents (10%) reported difficulty falling asleep two or more times a week. In contrast, during the night float 38 residents (75%) reported difficulty falling asleep in the first 1–5 d of the night float, and 13 (25%) reported difficulty falling asleep most days (McNemar's test: night-float vs. daytime rotations: $p = 0.02$).

Sleep onset latency: During typical daytime rotations when not on call in the PL-2 year, 24/52 residents (46%) took less than 10 min to fall asleep, 24 (46%) took 10–30 min, and only four (8%) took longer than 30 min. In contrast, during the night float fewer residents, 16 (31%), took less than 10 min to fall asleep, 24 (46%) took 10–30 min, and 12 (23%) took longer than 30 min (test of symmetry—night float vs. daytime rotations: $p = 0.055$). The questionnaire also inquired if sleep aids were used when working daytime rotations: 51/52 residents responded. None ever took prescription sleep medications, and only five took nonprescription sleep medication twice a week or less. Unfortunately, inquiry about sleep medications use during the night-float rotation was inadvertently excluded from the questionnaire.

Spontaneous sleep interruptions: During typical daytime rotations when not on call in the PL-2 year, 44/51 residents (86%) awoke spontaneously no more than once a night and only seven (14%) awoke more than once a night. In contrast, during the night float 30 (59%) spontaneously awoke only once from daytime sleep while 21 (41%) awoke more than once (McNemar's test: night float vs. daytime rotation: $p = 0.001$).

Feeling rested: During typical daytime rotations in the PL-2 year when not on call, 24/52 residents (46%) felt rested most of the time upon awakening while 28 (54%) felt rested only sometimes or rarely. In contrast, during night-float work only 11 residents (21%) felt rested upon awakening while 41 (79%) felt more tired compared to their daytime rotations ($p = 0.007$; McNemar's test).

Sleep duration and fatigue: Of the 32 residents who slept about the same duration or less when on the night float than daytime rotations, five (16%) felt well rested upon awakening during the night float while 27 (84%) felt more tired. Of the 20 residents who reported longer sleep duration when on the night float than daytime rotations, six (30%) felt well rested upon awakening during night float while 14 (70%) felt more tired upon awakening compared to daytime rotations ($p = 0.22$; χ^2 test).

Adjustment to night-float rotation: Almost half the residents, 24/52 (46%), felt their bodies never adjusted to the night-float shift. The average number of days it took to adjust to the first night-float rotation was up to 2 d in 14 residents (27%), 3–7 d in 27 (52%), and 8 or more days in 11 (21%). These figures were similar for the second night-float rotation that had been completed by 37 residents. Moreover, 33 residents (63%) felt that they had to readjust again to the night-float schedule after the 2d weekend off period at mid-rotation.

Feeling depressed: Overall, during the daytime rotations in the PL-2 year, 44/51 residents (85%) never or rarely felt depressed while only seven (14%) felt depressed about half the time, and none felt depressed most of the time. In contrast, during the night-float shift 29 (57%) residents never or rarely felt depressed or moody while 22 (43%) felt depressed or moody (McNemar's test—night-float vs. daytime rotations: $p = 0.0001$). Moreover, 19 of the 44 residents (43%) who were never or only rarely depressed overall during the PL-2 year reported feeling depressed during night float.

Depressed mood and fatigue: Of the 41 residents who were more tired during night-float than daytime rotations, 22 (54%) reported feeling depressed or moody during the night float while 19 (46%) reported not feeling depressed or moody. In contrast, of the 11 residents who were well rested during night float, only one (9%) reported being depressed or moody during night float while 10 (91%) were not depressed or moody (McNemar's test: $p = 0.033$).

Depressed mood and demographics: When on the night-float rotation, 19/41 (46%) of those feeling depressed or moody were younger than 30 yr of age, and 4/11 (36%) 30 yr of age or older (χ^2 test: $p = 0.55$). There was no significant relationship between depressed mood during the night float with gender (χ^2 test: $p = 0.37$) or with overall adjustment to the night-float rotation (χ^2 test: $p = 0.38$). Logistic regression procedure for depressed mood during the night float also showed there was no significant relationship with adjustment to night float ($p = 0.15$), age ($p = 0.27$), depressed mood during overall during the PL-2 year ($p = 0.37$), gender ($p = 0.82$), or sleep duration during the night-float vs. daytime rotations ($p = 0.62$).

Alertness: Compared to daytime rotations in the PL-2 year, during night-float work 21/52 residents (41%) felt their thinking was slower. Only 9 (17%) felt that their thinking was slower during the night float than on night-call during daytime rotations.

Performance: Compared to daytime rotations in the PL-2 year, 9/51 (18%) of the residents experienced slower speed of performance of procedures during the night-float shift. Three residents (6%) experienced slower speed in performance of procedures during the night float than when on night-call during daytime rotations.

Personal interactions: Compared to typical daytime rotations in the PL-2 year, most residents reported their interactions during the night float were not more difficult with peers (96%) or with nursing staff (88%).

Overall rating: Two of the 52 residents (4%) rated the overall experience of the first night-float rotation as terrible, 11 (21%) as bad, 17 (33%) as indifferent, 16

(31%) as good, and six (12%) as great. The distribution of the ratings was similar for the second night-float rotation completed by 37 of the same residents.

Voluntary remarks: Twenty-four residents offered 25 written comments. Ten comments described sleep problems and fatigue during the night-float shift. Some comments consisted of statements about feeling tired all the time during the night float, and others described never adjusting to the night float, including one resident who took 2 wk to readjust to the daytime work schedule. Some described strategies to combat these problems, e.g., keeping the room dark for daytime sleep, taking a nap before the night shift, and going to sleep immediately after the end of the night shift. Six comments were positive about the night shift: one resident described himself as a "night owl."

DISCUSSION

The present study provides insight into a previously unexplored aspect of residency training. Even though there is general awareness of the negative impact of night-shift work, potential problems were not taken into account when the night-float rotation was created. Possibly, training programs assumed that the transient nature of the rotation would obviate the negative effects of night-shift work. The present results, however, show the night-float rotation is indeed accompanied by sleep problems, mood change, decreased alertness, and overall poor adjustment to the inverted wake-sleep schedule. These problems are common in night-shift workers in many services and industries.[8,10–13] The potential repercussions of these problems are severe. For example, night work has been associated with increased rate of accidental exposure to blood-borne pathogens among residents,[14] and sleep deprivation has been associated with increased risk for motor vehicle accidents among residents[15,16] and nurses.[17]

The present study was based on subject recall. As noted in the presentation of the results, there was good internal consistency for the questions related to sleep duration. Although memory about past events may change over time, there was no trend related to year of training in the responses given. The study warrants follow-up prospective studies utilizing objective measures. Strong points of this study include the high completion rate (87%), the comprehensive and extensive set of questions related to the topics under investigation, and the source of respondents—a large and well-established pediatric residency training program with a longstanding, stable night-float rotation. Even though the participants of this study were pediatric residents, the problems are not specific to pediatrics, and thus the conclusions of this study may be applicable to other training programs that utilize a night-float system.

The sleep problems associated with the night-float rotation encompassed difficulty falling asleep after the night shift, prolonged sleep onset latency, and increased number of spontaneous sleep interruptions. It is unknown whether residents resorted to sleep medications when assigned to the night float; however, their use was rare when on daytime rotations. Interestingly, during the night-float rotation many residents did not feel rested upon awakening regardless of whether they slept less or more than during daytime shifts. This finding is consistent with the complexity of physiological changes that occur with inverted sleep–wake schedules. It is possible that residents also were sleep-deprived during their daytime rotations since they reported only 6.9 h of sleep per night on average. The nature of the present study precludes further inquiry into this issue, and prospective studies are needed to determine whether sleep-deprivation constitutes a problem during residency training overall, despite the creation of the night-float rotation.

Another striking finding is that during the night-float rotation almost half the residents felt moody or depressed while few residents reported depressed mood during their daytime rotations. Depressed mood and increased fatigue may be linked, at least in part, to sleep deprivation. In fact, a study of first-year residents in internal medicine showed a significant relation of sleep-deprivation with higher mood scores (depression) on a self-report inventory of mood state.[18] Sleep deprivation, however, may not be the main cause of fatigue or mood change during the night float. The effect of night-shift work on mood and fatigue is multifactorial, insomnia being just one of the contributing factors.

The overall impact of an inverted sleep–wake schedule has far reaching effects on biological functions other than sleep and mood. They include disruptions in hormonal secretions, cardiovascular and digestive system dysfunction, etc.[6,11,12,19] The global manifestations of maladjustment are well captured in the residents' response to the present survey in which almost half the group felt their bodies never adjusted to the work-shift change. Abrupt change from day to night-shift work causes desynchronization of the activity/sleep schedule from the internal circadian system. Generally, it takes about 1 wk for complete adjustment of the circadian time structure to the inverted schedule, although many workers never adjust completely.[19,20] The designation of weekend off time in the middle of the night-float rotation may have contributed to or even aggravated the adjustment problems because residents usually reverted to night sleep then. Hence, the residents had to undergo an adjustment phase to night shift not only at the beginning of the rotation, but also after the weekend off in the middle of the rotation.

The night-float rotation did not alter the residents perceived performance despite their self-rating of decreased alertness compared to daytime shifts in almost half the residents. This finding is at variance with the reported effects of night-shift work on alertness and performance in services and industries. In fact, the most vulnerable period of the 24h day is between 01:00 and 08:00h, during which catastrophes related to fatigue and decreased performance are more likely to occur.[7,14] Perhaps, the residents overestimated their performance in this survey. Alternatively, one might propose that because of their responsibilities, physicians in training have higher motivation to maintain a high performance level in contrast to night-shift workers that perform other types of activities. This explanation is supported by studies of physicians in training. For example, a study of surgery residents who were sleep-deprived by frequent night-calls during dayshifts showed that sleep-deprivation did not affect cognitive or motor performance evaluated by psychometric tests.[21] Another study reported only relatively mild cognitive impairment of internal medicine residents who were sleep-deprived because of night-call during daytime rotations in comparison to nonsleep-deprived residents.[18] One must note, however, that cognitive and motor tests may not reflect actual work performance capability of on-call physicians. Moreover, studies of sleep-deprived residents on daytime rotations cannot be extrapolated to the night-float rotation, because as stated earlier the overall effect of sleep–wake schedule reversal is broader than sleep-deprivation alone.

In summary, the present report suggests the night-float rotation may have important negative impact on residents. In all likelihood, night-shift work, a necessity in many spheres of modern society, particularly health care, will remain an integral component of many residency-training programs. Currently, much research is in progress aiming at strategies to enhance adaptation to sudden shift change.[22–24] In the future, such strategies may become applicable to night-float rotations. Meanwhile, training programs should acknowledge this problem and consider a design of night-float schedules that minimizes the negative impact of shift work on residents.[20] In addition, they should instruct residents on strategies to cope with the required shift work.[25,26]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
Centers for Disease Control
and Prevention (CDC)

Memorandum

Date: October 28, 2003

From: Michael J. Galvin, Ph.D., Program Official
Office of Extramural Programs, NIOSH, E-74

Subject: Final Report Submitted for Entry into NTIS for Grant 5 R18 OH003533-03.

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

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

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

Attachment
cc: Sherri Diana, EID, P03/C13

List of Publications

Cavallo A, Ris MD, et al.: The Night Float Paradigm to Decrease Sleep Deprivation: Good Solution or A New Problem? Ergonomics, in press, 2003

Cavallo A, Jaskiewicz J, Ris MD: Impact of Night-Float Rotation on Sleep, Mood, and Alertness: The Resident's Perception. Chronobiology International 19(5):893-902, 2002

Title: Intervention of Mitigate Adverse Effects of Shift Work
Investigator: Anita Cavallo, M.D.
Affiliation: Children's Hospital Medical Center
City & State: OH
Telephone: (513) 636-4583
Award Number: 5 R18 OH003533-03
Start & End Date: 9/1/1998–8/31/2002
Total Project Cost: $542,770
Program Area: Intervention Effectiveness Research Methods
Key Words:

Final Report Abstract:
Socio-economic pressures and customer needs render night work imperative in many occupations. Sleep deprivation, common in night workers, is a major cause of accidents and fatalities. Alertness and sleep are normally rhythmic events synchronized to the light and dark phases of the 24h solar cycle. Rotating or permanent night work cause dissociation of rhythms from the 24h light/dark phases with resultant poor sleep, diminished alertness and mood disturbances. Melatonin is effective in accelerating adjustment to alterations in the 24 h light/dark cycle in certain conditions, e.g., jet lag and blindness. The proposed project tested the hypothesis that melatonin accelerates the adjustment of workers to a reversal in the activity/sleep cycle from daytime to night work by synchronizing sleep to the desired schedule and consequently improving alertness and mood during the waking hours. The hypothesis was tested in an actual work place, a hospital. Subjects were residents, i.e., physicians in training, whose work requires intense alertness and vigilance. The design included two treatment phases for each subject, melatonin and placebo, and two respective baseline phases, one for each treatment; each phase lasts two weeks. The treatment phases consisted of the night float rotation characterized by a sequence of 5-15 days of night work without any daytime duties, thereby involving an abrupt reversal of the wake-sleep schedule. During this work period the residents got 3 days off over 2 weekends. Residents were instructed to take the drug 30 minutes before their desired bedtime, but they omitted taking the drug if bedtime occurred after 1300h. Melatonin or placebo was be administered daily in the morning of the workdays during the night float rotation. On the days off, residents had the option of omitting the drug or taking it at the desired bedtime, which was usually in the evening. Outcome measures included: (1) sleep characteristics obtained by diary and wrist actigraphy; (2) attention assessed by the Conner's continuous performance test (Conners 1995); and (3) mood assessed by the Profile of Mood States (McNair, Lorr et al. 1992). Forty five subjects participated: 28 completed both treatment phases and 17 completed one treatment phase of whom 10 took placebo and 7, melatonin.

First, we examined the impact of the night float rotation on sleep, mood and attention of the 38 residents who took placebo, by comparing the outcome measures during the night float rotation with the respective daytime control measures. Residents completed sleep diaries daily and the tests of mood and attention 3 times a week during the two-week night float rotation and during equivalent blocks of time of their daytime rotations. We showed that, despite having ample opportunity to sleep during the day while on night

float rotation, residents slept less during the night float rotation than during the nights of their usual daytime rotations, 6.3h ± 2.5h and 7.2h ± 1.7h, respectively, $p < 0.0001$. Also, during night float compared to daytime rotations residents had increased fatigue-inertia scores, 8.7 ± 4.1 and 4.8 ± 2.4, respectively, $p < 0.0001$, and decreased vigor-activity scores 10.7 ± 5.4 and 14.8 ± 5.3, respectively, $p = 0.02$. The scores for attention were not significantly different between night float and daytime rotations. The correlation coefficients of fatigue with measures of attention were not statistically significant for daytime rotations. However, for night float fatigue correlated with omission errors, $r = 0.51$, $p = 0.001$ and with attentiveness $r = -0.36$, $p = 0.03$. We concluded that the night float rotation caused deleterious effects on sleep, mood and attention as had been observed in other modalities of shift work. The proposed model of shift work and the outcome measures are not job-specific, hence, the results of the study can be generalized to other occupations which require high level of vigilance and alertness.

Next, we examined the effect of melatonin treatment on sleep, mood and attention in the 45 residents. There was no significant difference between melatonin and placebo treatment in measures of sleep, mood and attention of all 45 participants. In the 28 residents who each participated in both treatment conditions, melatonin and placebo, there were two distinct responses of sleep duration to melatonin: it increased by 0.89h ± 0.62h in 15 residents (responders) and decreased by 0.68h ± 0.55h in 13 (non-responders); also, there was a marginal beneficial effect of melatonin on vigor, $F(1,26)=4$, $p=0.056$. Side effects were not statistically more frequent on melatonin than on placebo and they were not unusual other than nightmares in one resident taking melatonin. We propose the following explanations for the finding of responders and non-responders: pharmacogenetic characteristics, individual tolerance to shift work, and a relationship of response to melatonin with tolerance to shift work. Further studies are needed to identify factors that will predict a favorable response to melatonin treatment.

The results suggest that melatonin treatment may be beneficial in adaptation to night shift in some workers. The expected benefits of melatonin treatment may lead to development of new strategies for adjustment to night work, resulting in increased safety and reduced accidents and fatalities related to sleep deprivation in night workers.

Publications:

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