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Melatonin, Sleep, and Shift Work Adaptation

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Learning Objectives

- Recall, in this study of 165 employees at a facility making medical devices, any differences in the frequency of mental symptoms, sleep symptoms, or fatigue between those working the first (day) shift, the second (swing) shift, and the third (night) shift.
- Compare sleep-wakefulness patterns in employees working different shifts, as assessed by wrist actigraphy—a noninvasive means of monitoring ambient light exposure and physical activity.
- Summarize associations between alterations in melatonin (6-hydroxymelatonin sulfate, 6-OHMS) production and the diurnal variation in urinary 6-OHMS excretion on the one hand and, on the other, work shift, disrupted sleep, and symptoms.

Abstract

Background: *Night work is associated with disrupted circadian rhythms, fatigue, accidents, and chronic disease. Melatonin secretion helps regulate sleep and circadian rhythms.* ***Objective:*** *Melatonin, sleep disturbances, and symptoms (sleep, fatigue, mental) were compared among workers on permanent day, swing, and night shifts.* ***Methods:*** *Urinary 6-hydroxymelatonin sulfate (6-OHMS) was measured in postwork and postsleep samples. Disrupted circadian melatonin production was evaluated using the sleep:work 6-OHMS ratio. Wrist actigraphy characterized light exposures and sleep characteristics.* ***Results:*** *Night workers had altered melatonin, disrupted sleep, and elevated symptom prevalence. Subjects grouped by their sleep:work 6-OHMS ratio rather than shift had even greater symptom prevalence. Risks for two or more symptoms were 3.5 to 8 times greater among workers with sleep:work ratios ≤1 compared to those with ratios >1.* ***Conclusions:*** *This ratio may help identify workers at increased risk for accidents or injuries.* (J Occup Environ Med. *2005;47:893–901*)

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Many critical aspects of modern life, including medical care, power generation, the military, and law enforcement, depend on shift workers, as do important commercial sectors, such as manufacturing and public transportation. Approximately 20% of the US workforce participates in shift work, which corresponds to approximately 15 million workers.[1] Shift workers are plagued by disrupted lifestyles, sleep disturbances, increased accident and injury rates, and elevated risks for reproductive, gastrointestinal, and cardiovascular disease.[1–8] The costs of fatigue-related accidents attributable to shift work in the United States have been estimated at approximately $16 billion annually, resulting in decreased productivity exceeding $55 billion per year.[2]

Disruption and desynchronization of circadian rhythms are key factors mediating the adverse health and safety outcomes observed among shift workers.[1,2,5,6,9] Production of the hormone melatonin plays a key role in the circadian organization of sleep and other biological rhythms.[9–11] Melatonin typically exhibits a diurnal pattern of secretion, with peak concentrations occurring in the dark phase (0200–0400 hours) and lowest concentrations occurring during the light phase (1200–1800 hours) of the diurnal light:dark cycle.[10] The circadian melatonin rhythm is synchronized by ambient light and can be disrupted by artificial light exposures in the evening and night.[10–14]

Shift work can result in disrupted production and desynchronization of melatonin with sleep and other circadian rhythms.[5,9] There is considerable variability in the pattern of melatonin secretion among shift workers. Some night workers retain

the typical diurnal pattern of melatonin production whereas others shift the phase of their melatonin secretion to coincide with daytime sleep.[15–23] Elevated melatonin production is associated with increased sleepiness and performance decrements in laboratory-based human studies,[24–27] suggesting that synchronization of peak melatonin secretion to coincide with the sleep period should benefit workers on night shifts. In some studies, night workers who shifted their nocturnal melatonin rhythm had better shift work tolerance and improved sleep compared with those who did not.[14,17,18,28] In some cases, however, night workers who did not change their pattern of elevated melatonin secretion still obtained adequate sleep[19–21] or maintained a high degree of work satisfaction.[16] These inconsistencies highlight the need for more research on melatonin production and shift work tolerance. The purpose of this study was to compare ambient light exposures, melatonin production, sleep disturbances, and symptom prevalence among workers on permanent day, swing, and night shifts. We hypothesized that disrupted sleep, fatigue and mental symptoms would be associated with altered patterns of melatonin production, particularly among night workers.

Materials and Methods

The study population comprised workers at a medical device manufacturing facility in the western United States. Workers were studied during a 24-hour period beginning at the start of their Wednesday work shift (5-day workweek). This facility operates with three nonrotating work shifts: day (first shift: 6:00 AM to 2:00 PM), swing (second shift: 2:00 PM to 10:00 PM), and night (third shift: 10:00 PM to 6:00 AM). Urinary biological monitoring was used to assess melatonin production. Wrist actigraphy was used to characterize ambient light exposures and sleep characteristics. Symptom prevalence was ascertained via a questionnaire. The study protocol received Institutional Review Board approval, and participants provided informed consent. Data were collected from June 2001 through January 2002.

Melatonin production was assessed by radioimmunoassay of its major urinary metabolite, 6-hydroxymelatonin sulfate (6-OHMS; Stockgrand Ltd., Surrey, UK).[29,30] Urinary concentrations of 6-OHMS follow a diurnal pattern that is well correlated with circulating melatonin, and overnight 6-OHMS excretion represents an integrated measure of nocturnal melatonin production.[29–31] Each participant collected one postwork urine sample immediately after their shift and a second postsleep sample that included the entire urinary output after their sleep period, plus any voids that occurred during the sleep period. Samples were transported on ice and frozen at −70°C until analysis. The interassay coefficient of variation was 13% at 3 ng/mL, 17% at 20 ng/mL, and 6% at 38 ng/mL. The intraassay coefficient of variation was 12% and the limit of detection was 0.1 ng/mL. Melatonin production during sleep was estimated as the product of the post-sleep 6-OHMS concentration and the post-sleep urine sample volume. Post-work and post-sleep 6-OHMS concentrations normalized to urinary creatinine levels (6-OHMS/cr) also were evaluated. Sleep time melatonin levels are ordinarily 5 to 10 times greater than nonsleep, daytime values.[10,32] We reasoned that well-adapted shift workers with appropriate circadian melatonin production would exhibit a pattern of elevated melatonin during sleep and reduced melatonin levels during work, regardless of their work shift. Alternatively, workers with desynchronized melatonin production would not have a robust diurnal melatonin rhythm, and their postsleep and postwork 6-OHMS/cr concentrations would therefore be similar. The ratio of the postsleep and postwork 6-OHMS/cr concentrations was evaluated as a potential indicator of disrupted circadian melatonin production by comparing adjusted mean sleep:work 6-OHMS/cr ratios among workers on each shift. Symptom prevalence was compared among workers grouped by their sleep:work 6-OHMS/cr ratios (≤ 1 vs. >1, see end of this section).

Personal monitoring of ambient light exposures and physical activity was performed using the Actiwatch-L monitor (Mini Mitter, Inc., Bend, OR). The Actiwatch-L is similar in size, weight, and appearance to a wristwatch and uses an accelerometer, light sensor, and data-logging microprocessor to record gross motor activity and ambient light intensity. Wrist actigraphy is a reliable and noninvasive method for evaluating sleep–wake patterns in normal or sleep-disturbed individuals.[33–36] Participants wore the Actiwatch-L on their nondominant wrist over the entire 24-hour data collection period and data were logged at 15-second intervals. Each subject recorded the times they went to bed/awoke, arrived at/left work, and arrived at/left home. Ambient light exposure was evaluated as the time-weighted average light intensity (lux) during each period (home–morning, prework commute, work, postwork commute, home–evening, sleep) using a custom computer program.[37] The manufacturer's Actiware sleep analysis computer program was used to summarize each subject's sleep characteristics (total sleep time, sleep efficiency, sleep latency, and sleep movement and fragmentation index). Sleep efficiency is the total amount of time spent in bed divided by total sleep time. Sleep latency is the time elapsed between going to bed and falling asleep. The movement and fragmentation index is an indicator of sleep restlessness that is obtained by summing the percentage of minutes moving during sleep and the percentage of 1-minute immobility phases. Actiwatch-L data from five subjects were excluded because of equipment malfunction. Other data records were inspected for evidence

that the watch was not worn during the sleep period, and subjects without movement during the entire sleep interval were excluded ($n = 11$).

A self-administered questionnaire was completed at the end of each participant's 24-hour data collection cycle. The instrument solicited information on demographic, occupational, lifestyle, and medical characteristics (details available upon request), as well as other factors potentially related to melatonin production (eg, supplemental melatonin consumption, use of anti-inflammatory agents, antidepressants, pain medication). Questions on sleep symptoms and fatigue were obtained with permission from the Standard Shift Work Index.[38] Mental symptoms included difficulty remembering, difficulty concentrating, headache, and dizziness. Likert scale responses for sleep symptoms were dichotomized by combining the two most extreme levels of an answer to indicate the presence (eg, frequently or almost always = yes), and the three least extreme answers to indicate the absence (eg, almost never, rarely, or sometimes = no) of a symptom. Separate analyses evaluated whether "any" or combined symptoms (0, 1, ≥2) within each category (sleep, fatigue, mental) were linked with shift work or 6-OHMS ratios.

Personal exposures to volatile organic compounds (VOCs) used at this facility (tetrahydrofuran or THF, isopropanol, and cyclohexanone) were assessed for each participant using a passive dosimeter (SKC 575-001 passive sampler, SKC, Inc., Eighty-Four, PA) clipped to the lapel or shirt pocket for the duration of their work shift. The start/stop times, date, and sample identification number were recorded and dosimeters were transported on ice in plastic bags and frozen at −8°C before analysis. VOC analyses were performed at the Trace Organics Analysis Center, Department of Environmental Health, University of Washington, Seattle, WA. Dosimeters were desorbed separately with 2.0 mL of 10% isobutanol in carbon disulfide and analyzed using an HP5890 gas chromatograph with a 30-m RTX-wax column and a flame ionization detector. Quantitation limits were 1.8 μg per sample for THF, 3.2 μg per sample for isopropanol, and 2.4 μg per sample for cyclohexanone. Standards and samples analyzed in duplicate had <15% variation on average. Mean recoveries from two laboratory-spiked samples were 106%, 91%, and 95% for THF, isopropanol and cyclohexanone, respectively. Results uncorrected for desorption efficiency were reported as the time-weighted average in mg per cubic meter air (mg/m^3).

Data were analyzed using the Statistical Analysis System (SAS) computer program (version 8.1, SAS Institute, Cary, NC). Melatonin metabolite variables (total sleep period 6-OHMS production, postsleep and postwork 6-OHMS/cr concentrations, and sleep:work 6-OHMS/cr ratios) and ambient light exposures were log-transformed for analysis. Total sleep time, sleep efficiency, and sleep fragmentation were not transformed. Sleep latency was analyzed using a square root transformation. Results were transformed back to original units for presentation. A screening procedure identified questionnaire items associated with 6-OHMS and Actiwatch-L outcomes using the generalized linear models procedure in SAS. Screened variables were included as potential confounding factors in subsequent multivariate statistical analyses if at least 10% of the study subjects were available for analysis and the variable was associated with a 6-OHMS or Actiwatch-L variable at a $P \leq 0.10$ level of significance. Differences in 6-OHMS excretion and Actiwatch-L sleep parameters among shift workers were evaluated using the generalized linear model procedure in SAS. Least squares means adjusted for selected confounding factors were calculated for workers on each shift and compared using the least significant differences statistic.

The proportion of workers with sleep, fatigue, or mental symptoms, or sleep:work 6-OHMS/cr ratios ≤1 was compared among shifts using the Mantel-Haenszel χ^2 statistic and Fisher's exact P-value. To evaluate circadian desynchronization among shift workers, the percentage of sleep, fatigue, or mental symptoms were compared among workers grouped according to their sleep:work 6-OHMS/cr ratios (≤1, $n = 21$ or >1, $n = 144$). The risk of having mental, sleep, or fatigue symptoms among workers with sleep:work 6-OHMS/cr ratios ≤1 was estimated by calculating odds ratios with 95% confidence intervals. Differences between groups were evaluated with using the Mantel-Haenszel χ^2 statistic and Fisher's exact P-value. A total of 53 participants (32%) operated radiofrequency (27 MHz) heat sealing devices. Separate analyses performed after excluding these subjects did not alter the interpretation of the results. Results presented are for all subjects combined.

Results

A total of 171 workers were studied between June 2001 and January 2002 (participation rate: 51%). Complete biomonitoring data were available for 165 (96%) of the participants (two subjects left work due to illness, three subjects did not collect urine samples, one subject dropped out). Most of the participants were women (65%) and were of Hispanic (28%) or Asian (23%) ethnicity. Characteristics of subjects on the first (43%), second (38%), and third (19%) shifts are presented in Table 1. The average age of workers on the third shift was 7 to 9 years younger than workers on the first shift or second shift. The average work duration on the currently assigned shift was approximately 2 to 3 years shorter among subjects on the second and third shifts compared with those on the first shift. However, there were no differences in the career total duration of time spent working on swing or night shifts.

TABLE 1
Study Population Characteristics

Characteristic	First Shift (n = 71)	Second Shift (n = 62)	Third Shift (n = 32)
Gender (%)			
Female	21 (30)	23 (37)	14 (44)
Male	50 (70)	39 (63)	18 (56)
Age (years)	38 ± 12	36 ± 11	29 ± 9†
Education (%)			
High school or less	3 (4)	2 (3)	3 (10)
High school graduate	47 (67)	28 (46)	13 (42)
High school and more	20 (29)	31 (51)	15 (48)
Ethnicity (%)			
White, non-Hispanic	29 (41)	20 (32)	16 (50)
Hispanic	30 (42)	9 (15)	7 (22)
Black, African-American	2 (3)	5 (8)	5 (16)
Asian, Pacific Islander	8 (11)	26 (42)	4 (12)
Native American or Alaskan	1 (1)	2 (3)	0 (0)
Work duration, present shift (years)	4.7 ± 5.4	2.7 ± 4.1†	1.3 ± 2.0†
Work duration, any night or swing shift (years)	2.0 ± 3.3	3.3 ± 4.3	2.5 ± 3.7
Duration in current residence (years)	6.4 ± 7.4	4.6 ± 5.4	1.7 ± 1.7†
Body mass index (kg/m^2)	26 ± 6	25 ± 6	25 ± 5
Cigarette smoking (%)			
Smokers	14 (20)	13 (22)	8 (26)
Nonsmokers	57 (80)	47 (78)	23 (74)
Cigarette consumption (cigarettes/day)	5 ± 11	7 ± 15	8 ± 15
Alcohol consumption (beverages/week)	2 ± 4	3 ± 7	1 ± 2
Caffeine consumption (beverages/day)	2 ± 1	3 ± 2	2 ± 1
Exercise (days/week ≥30 min)	2 ± 2	1 ± 2	2 ± 2
TWA volatile organic chemical exposure (mg/m^3)	21.2 ± 14.5	15.3 ± 5.6†	25.2 ± 18.5
24-hour TWA ambient light exposure (lux)	770 ± 495	1338 ± 1260*	427 ± 347

Volatile organic chemicals include tetrahydrofuran, isopropanol, and cyclohexanone.
*$P \leq 0.05$ and †$P \leq 0.01$ compared with first shift.
TWA indicates time-weighted average.

Workers on the second shift had higher 24-hour ambient light and lower work shift VOC exposures compared with those on the first or third shifts. Consumption of alcohol, caffeine, and cigarettes was similar among shifts, and there were no differences in body mass index or weekly exercise regimen (Table 1).

The prevalence of two or more sleep symptoms was greater among workers on the third shift (37% vs. 12% on first shift, $P = 0.02$). This stemmed from complaints of poor sleep quality (22% vs. 4% on first shift, $P < 0.01$), difficulty waking (38% vs. 19% on first shift, $P = 0.05$), and difficulty falling asleep (19% vs. 4% on first shift, $P = 0.02$). Workers on the second shift were more likely to report difficulties falling asleep (16% vs. 4% on first shift, $P = 0.04$), dizziness (18% vs. 4% on first shift, $P = 0.02$), and a lack of alertness (41% vs. 19% on first shift, $P < 0.01$), but were less likely to feel drained than first shift workers (20% vs. 37% on first shift, $P = 0.05$). There were no differences in the prevalence of "any symptom" grouped by sleep, fatigue, or mental categories among the three shifts studied, and no statistically significant differences in the prevalence of two or more mental or fatigue symptoms among workers on the three shifts. Workers reporting a lack of alertness had higher THF exposures compared with those without this symptom (0.62 vs. 0.46 mg/m^3, $P = 0.04$), although there were no other statistically significant differences in mean VOC exposures among workers with or without sleep, fatigue, or mental symptoms (data not shown). No VOC exposures exceeded occupational standards (data not shown).

Sleep actigraphy outcomes are presented in Table 2 for workers on each shift. Workers on the second shift had more adjusted mean sleep fragmentation ($P = 0.02$) than first shift workers. Night workers had shorter adjusted mean sleep times ($P = 0.002$), reduced sleep efficiency ($P = 0.001$), longer sleep latency ($P = 0.04$), and a higher movement and fragmentation index ($P = 0.01$) compared with those on the first shift (Table 2).

A diurnal variation in mean urinary 6-OHMS excretion was observed among all subjects combined; mean postsleep concentrations were 24.6 ± 31.2 ng/mg cr, and mean pos-work concentrations were 5.3 ± 4.3 ng/mg cr. The mean sleep:work 6-OHMS/cr ratio was 7.1 ± 16.9. The average amount of total sleeptime 6-OHMS excretion was 13.3 ± 25.6 μg. Differences in melatonin

production were observed among workers with disrupted sleep. Workers in the lowest tertile of total sleep time had adjusted mean total sleep period 6-OHMS excretion that was 45% lower (5.3 vs. 9.7 μg, $P = 0.02$), and an adjusted mean sleep: work 6-OHMS/cr ratio that was 36% lower (3.5 vs. 5.5, $P = 0.05$) than subjects in the highest tertile. Subjects in the highest tertile of sleep movement and fragmentation had higher adjusted mean post-work 6-OHMS/cr concentrations compared to those in the lowest tertile (4.3 vs. 3.1 ng/mg cr, $P = 0.04$). No other statistically significant differences in adjusted mean 6-OHMS levels were observed among tertiles of the actigraphic sleep parameters (data not shown).

Workers on night shifts had altered 6-OHMS production in comparison with first shift participants (Table 3). Adjusted means for sleep period total 6-OHMS production ($P = 0.08$) and 6-OHMS/cr concentrations ($P = 0.26$) tended to be lower and postwork 6-OHMS/cr concentrations ($P = 0.09$) higher among night workers compared with those on the first shift (Table 3). A statistically significant reduction in adjusted mean sleep:work 6-OHMS/cr ratios was observed among workers on the third shift ($P = 0.02$ vs. first shift, Table 3). Altered circadian melatonin production was evaluated by comparing the distribution of workers on each shift with sleep:work 6-OHMS/cr ratios ≤1. The proportion of workers on the night shift with sleep:work 6-OHMS/cr ratios ≤1 was more than three times greater than that observed among first shift workers (25% vs. 8%, $P = 0.03$). The proportion of workers on the second shift with low sleep: work 6-OHMS/cr ratios was also elevated compared with those on the first shift, although the difference was not statistically significant (11% vs. 8%, $P = 0.77$).

The risk of self-reported insomnia, lack of sleep, or difficulty falling asleep was more than doubled among workers with low sleep:work 6-OHMS/cr ratios compared to those with ratios greater than one (Table 4). Subjects with sleep:work 6-OHMS/cr ratios ≤1 were 3.8 times more likely to have 2 or more sleep symptoms compared with those with 6-OHMS/cr ratios >1 (Table 4). The risk of feeling drained or exhausted was 30% and 80% greater, respectively, among workers with low sleep: work 6-OHMS/cr ratios (Table 5). The risk of reporting 2 or more fatigue symptoms was 3.5 times

TABLE 2
Sleep Actigraphy Among Shift Workers

Work Shift	Sleep Time (Hours)	Sleep Efficiency (%)	Sleep Latency (Minutes)	Movement and Fragmentation Index (%)
Crude				
First shift	5.7 ± 1.3	86.0 ± 8.6	7.8 ± 7.3	8.6 ± 5.1
Second shift	6.2 ± 1.3*	80.6 ± 10.4‡	12.2 ± 8.4	11.8 ± 6.4‡
Third shift	4.8 ± 1.9‡	73.0 ± 14.6‡	16.0 ± 8.4*	13.0 ± 8.2‡
Adjusted§				
First shift	5.7 ± 1.3	84.1 ± 8.6	10.0 ± 7.4	9.4 ± 5.1
Second shift	6.1 ± 1.3	81.3 ± 10.4	14.9 ± 8.1	12.1 ± 6.5†
Third shift	4.7 ± 1.9‡	75.3 ± 14.6‡	20.4 ± 8.5†	13.1 ± 8.4‡

*$P \leq 0.10$, †$P \leq 0.05$, and ‡$P \leq 0.01$ compared with first shift.

§Least squares means adjusted for potential confounding factors: sleep time (gender, stress, alcoholic beverages per day); sleep efficiency (gender, ethnicity, years in current residence); sleep latency (gender, aspirin use); movement and fragmentation index (gender, education).

TABLE 3
Melatonin Metabolite Excretion Among Shift Workers

Shift	Total Sleep Period 6-OHMS Excretion (μg)	Post-Sleep 6-OHMS Concentration (ng/mg cr)	Post-Work 6-OHMS Concentration (ng/mg cr)	Sleep:Work 6-OHMS/cr Ratio
Crude				
First shift	8.7 ± 3.5	17.5 ± 2.5	4.1 ± 2.3	4.2 ± 2.5
Second shift	5.4 ± 4.0†	17.8 ± 2.5	3.8 ± 2.2	4.6 ± 2.4
Third shift	4.6 ± 4.6†	9.1 ± 2.9‡	4.0 ± 2.2	2.3 ± 5.1‡
Adjusted§				
First shift	8.7 ± 3.5	13.1 ± 2.5	3.8 ± 2.3	4.2 ± 2.5
Second shift	5.3 ± 4.0	8.9 ± 2.5	3.1 ± 2.2	4.5 ± 2.4
Third shift	4.8 ± 4.7*	10.0 ± 3.0	5.2 ± 2.2*	2.3 ± 5.1†

*$P \leq 0.10$, †$P \leq 0.05$, and ‡$P \leq 0.01$ compared with first shift.

§Least squares means adjusted for potential confounding factors. Total 6-OHMS: month, gender, smoking, alcohol consumption. Postsleep concentration: month, second hand smoke, EMF concern, eye color, body mass index. Postwork concentration: month, gender; Ratio: gender, recent missed work, tetrahydrofuran exposure.

TABLE 4
Sleep:Work 6-OHMS/cr Ratios and Sleep Disruption

No. Subjects With Symptom	Sleep:Work 6-OHMS ≤ 1 (n = 21)	Sleep:Work 6-OHMS > 1 (n = 144)	Odds Ratio	95% CI (Fisher's Exact P Value)
Insomnia	6 (30%)	8 (6%)	7.3	2.2–24.0 (<0.01)
Not enough seep	8 (40%)	34 (24%)	2.1	0.8–5.5 (0.17)
Poor sleep quality	2 (9%)	14 (10%)	1.0	0.2–4.6 (1.0)
Not rested after sleep	1 (5%)	5 (4%)	1.4	0.1–12.2 (0.57)
Difficulty falling asleep	5 (24%)	14 (10%)	2.9	0.9–9.0 (0.07)
Wake up early	5 (24%)	38 (27%)	0.8	0.3–2.5 (1.0)
Any sleep symptom	15 (71%)	70 (49%)	2.6	0.9–7.0 (0.07)
Sleep symptoms combined				
None	6 (32%)	71 (51%)	1.0	–
One symptom	5 (26%)	44 (31%)	1.3	0.4–4.7 (0.75)
Two or more symptoms	8 (42%)	25 (18%)	3.8	1.2–12.0 (0.03)

6-OHMS/cr indicates creatinine adjusted 6-hydroxymelatonin sulfate; CI, confidence interval.

TABLE 5
Sleep:Work 6-OHMS/cr Ratios and Fatigue

No. Subjects With Symptom	Sleep:Work 6-OHMS ≤ 1 (n = 21)	Sleep:Work 6-OHMS > 1 (n = 144)	Odds Ratio	95% CI (Fisher's Exact P Value)
Lack of energy	11 (52%)	88 (63%)	0.6	0.2–1.6 (0.34)
Feeling drained	7 (35%)	40 (29%)	1.3	0.5–3.6 (0.60)
Not alert	12 (60%)	107 (75%)	0.5	0.2–1.3 (0.18)
Exhausted	9 (45%)	44 (31%)	1.8	0.7–4.7 (0.31)
Any fatigue symptom	17 (85%)	86 (60%)	3.8	1.0–13.4 (0.04)
Fatigue combined				
None	3 (15%)	55 (41%)	1.0	–
One symptom	7 (35%)	27 (20%)	4.7	1.1–19.8 (0.03)
Two or more symptoms	10 (50%)	53 (39%)	3.5	0.9–13.3 (0.07)

6-OHMS/cr indicates creatinine adjusted 6-hydroxymelatonin sulfate; CI, confidence interval.

greater among subjects with low sleep:work 6-OHMS/cr ratios, although confidence intervals were imprecise (Table 5). The risks for poor memory, difficulty concentrating, headaches, and dizziness were each approximately 3 times greater among workers with sleep:work 6-OHMS/cr ratios ≤1, and this group was about 8 times more likely to have 2 or more mental symptoms (Table 6). Workers with sleep:work 6-OHMS/cr ratios ≤1 had higher THF exposures (0.47 vs. 0.30 mg/m^3, $P < 0.01$). However, there were no other statistically significant differences in the distribution of demographic or other characteristics (age, gender, participation month, work duration, smoking, alcohol or caffeine consumption, body mass index, exercise, stress, recent travel, or missed work) among workers with sleep:work 6-OHMS/cr ratios ≤1 compared with the remaining subjects. A somewhat-greater proportion of these participants were women (81% vs. 62%), and were of Asian (24% vs. 5%) or Hispanic (38% vs. 26%) ethnicity. This group was more likely to have participated in December (43% vs. 24%), and they had somewhat-lower mean light exposure at home before work (939 ± 2783 vs. 1730 ± 5296 lux) and at work (634 ± 261 vs. 878 ± 628 lux) compared with subjects with sleep:work 6-OHMS/cr ratios >1. However, light exposures varied considerably among workers and there were no statistically significant differences in mean light exposures between these groups.

Discussion

Modern society relies on shift workers to perform crucial tasks and maintain critical technological systems around the clock. Workers on night shifts must frequently maintain vigilance at times when their bodies are signaling a need for sleep. Sleep loss, fatigue, and circadian desynchronization among night workers leads to increased risks for accidents, injuries, and chronic disease.[1–8] Numerous strategies have been suggested to reduce these risks, although the benefits and limitations of the various approaches are still debated.[13,26,39,40] A central question is whether it is desirable for workers to shift the phase of the endogenous circadian pacemaker to coincide with their altered schedule (ie, to facilitate

TABLE 6
Sleep:Work 6-OHMS/cr Ratios and Mental Symptoms

No. Subjects With Symptom	Sleep:Work 6-OHMS ≤ 1 (n = 21)	Sleep:Work 6-OHMS > 1 (n = 144)	Odds Ratio	95% CI (Fisher's Exact P Value)
Difficulty remembering	6 (30%)	18 (13%)	3.0	1.0–8.7 (0.08)
Difficulty concentrating	4 (20%)	11 (8%)	3.0	0.8–10.5 (0.09)
Headache	8 (40%)	25 (17%)	3.1	1.2–8.5 (0.03)
Dizziness	4 (20%)	12 (8%)	2.7	0.8–9.5 (0.11)
Any mental symptom	14 (70%)	46 (32%)	4.9	1.8–13.6 (<0.01)
Mental symptoms combined				
None	6 (30%)	97 (67%)	1.0	–
One symptom	7 (35%)	32 (22%)	3.5	1.1–11.3 (0.04)
Two or more symptoms	7 (35%)	14 (10%)	8.1	2.4–27.5 (<0.01)

6-OHMS/cr indicates creatinine adjusted 6-hydroxymelatonin sulfate; CI, confidence interval.

daytime sleep and nighttime vigilance). Because many night workers revert back to a regular daytime schedule on their days off, some argue that shifting the phase of the endogenous pacemaker is impractical. Alternatively, when workers are on fast rotating shifts, they tend not to shift their rhythm and must perform work tasks when they are out of phase with sleep and other endogenous rhythms. The key to resolving this issue is to determine what scheduling approaches are most protective of worker's health and safety. Research strategies that implement melatonin biomonitoring and wrist actigraphy can help address this issue by studying shift workers and health or safety outcomes in actual work and home environments.

Self-reported sleep disturbances in the present study were more common on the second and third shifts, and a statistically significant increase in the prevalence of sleep disturbances was observed among night workers. Results obtained using wrist actigraphy supported these observations. Increases in adjusted mean sleep fragmentation and sleep latency, and decreases in total sleep time and sleep efficiency were observed among night-shift workers compared with those on the day shift. However, there were no differences in the prevalence of fatigue or mental symptoms between workers on the night and day shifts. This suggests some degree of adaptation among night workers participating in this study.

Although melatonin is not required for sleep, the circadian melatonin rhythm plays a role in the timing of sleep, and elevated melatonin production typically coincides with the sleep period.[11] The onset of increased diurnal melatonin production likely increases sleepiness and sleep propensity by influencing thermoregulatory neural processes.[11] Actigraphically determined bed times coincide with the nocturnal melatonin onset and increased sleep propensity.[41] Human laboratory-based and shift work intervention studies indicate that elevated melatonin production occurring during a period of desired wakefulness is associated with increased sleepiness, decreased alertness, and reduced performance.[13,14,24–27] In a controlled study of sustained wakefulness in 10 healthy men 21–31 years old, indicators of sleepiness (slow eye movements, slow-wave EEG activity) and decrements in neurobehavioral performance were in phase with, and preceded by, the onset of nocturnal melatonin production.[25] Results from the current study support previous observations. Sleep period total 6-OHMS excretion and sleep:work 6-OHMS/cr ratios were lower among workers with the shortest sleep durations, and those with the most sleep fragmentation had elevated post-work 6-OHMS/cr concentrations. The results are consistent with research indicating that sleep disruption occurs when melatonin production is out of phase with the sleep cycle.

Considerable variation exists in human melatonin production in response to shift work. Sack and coworkers[15] found that the nocturnal melatonin onset was out of phase with sleep initiation in eight out of nine permanent night workers. Some workers shifted the phase of their melatonin rhythm to coincide with daytime sleep whereas others did not.[15] Differences in the circadian pattern of melatonin production in response to shift work have since been confirmed by others.[16–23] In support of previous research, results from this study indicated that melatonin production and sleep patterns were altered among permanent night workers. A screening procedure was used to identify factors other than shift work that could have explained the results. Differences between crude and adjusted means of 6-OHMS and actigraphic sleep outcomes were minimal, providing little evidence for confounding in these analyses.

A critical question for shift workers is whether "circadian adaptation" (ie, phase-shifted melatonin secretion) is associated with better and safer performance at work. In a group of 40 registered nurses, improved shift work tolerance as measured by neurobehavioral performance (reaction time and memory

test), sleep parameters, and self-reported job satisfaction were associated with the ability to rapidly shift the onset of nocturnal melatonin production to the daytime sleep period.[18,28] Those who did not shift their melatonin rhythm had impaired sleep, poorer neurobehavioral performance, and lower self-reported shift work tolerance.[18,28]

However, changes in melatonin production have not always coincided with improved work performance or better sleep, particularly when melatonin is altered over short time periods.[16,19,22,42] To evaluate the effects of shift work on melatonin production and potential influences on work performance, we calculated sleep:work 6-OHMS/cr ratios among participants and hypothesized that workers with disrupted circadian melatonin production would have reduced sleep:work 6-OHMS/cr ratios and an increased prevalence of symptoms related to sleep disruption, fatigue, and poor mental state. Night workers in this study had both a reduction in adjusted mean sleep:work 6-OHMS/cr ratios and a higher degree of self-reported or actigraphic sleep disruption, which is consistent with other studies indicating desynchronization between melatonin production and the sleep cycle among night workers.[15,17,18,21,28]

Grouping subjects according to their sleep:work 6-OHMS/cr ratios rather than work shift resulted in a much higher prevalence of sleep, fatigue, and mental symptoms. Risks for two or more of these symptoms were 3.5 to 8 times greater among workers with sleep:work 6-OHMS/cr ratios ≤ 1 compared with those without altered circadian melatonin production. These differences are not likely to be explained by other factors because there were no major differences in demographic or other characteristics between groups with or without low sleep:work 6-OHMS/cr ratios. Higher THF exposures were noted among workers with a low sleep:work 6-OHMS/cr ratio. However, no symptoms were associated with THF or other VOCs except for the relationship between THF and a lack of alertness. Because a lack of alertness was not more prevalent among workers with a low sleep:work 6-OHMS/cr ratio (Table 5), differences in THF exposure between groups with low and high sleep:work 6-OHMS/cr ratios are not likely to explain the results.

The time of melatonin's nocturnal rise to levels above the daytime mean, referred to as the dim light melatonin onset, and the time of maximum melatonin secretion, or acrophase, have been used to characterize the phase of the endogenous circadian pacemaker.[13,43] Although the sleep:work 6-OHMS/cr ratio likely only approximates the phase of the endogenous circadian pacemaker, results from this study showed a clear association between low sleep:work 6-OHMS/cr ratios and increased mental symptoms, sleep disturbances and fatigue. Longitudinal studies are needed to confirm these observations and determine whether increased accident or injury risks among shift workers are specifically linked with disrupted circadian melatonin production. In summary, results from this study indicate that workers on permanent night shifts had altered melatonin production and disrupted sleep compared with day shift workers. Workers with an altered rhythm of circadian melatonin production were more frequently identified on the second and third shifts, and they had a higher prevalence of sleep, fatigue, and mental symptoms. Biological monitoring of melatonin production using urine or saliva to characterize the sleep:work 6-OHMS/cr ratio may help identify shift workers at increased risk for accidents and injuries.

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