Melatonin Treatment of Pediatric Residents for Adaptation to Night Shift Work

Anita Cavallo, MD; M. Douglas Ris, PhD; Paul Succop, PhD; Julie Jaskiewicz, MD

Background.—Night float rotations are used in residency training programs to reduce residents' sleep deprivation. Night shift work, however, is accompanied by deleterious effects on sleep, mood, and attention.

Objective.—To test whether melatonin reduces the deleterious effects of night shift work on sleep, mood, and attention in pediatric residents during night float rotation.

Design/Methods.—Double-blind, randomized, placebo-controlled crossover. Participants took melatonin (3 mg) or a placebo before bedtime in the morning after night shift; completed a sleep diary and an adverse-effects questionnaire daily; and completed the Profile of Mood States and the Conners Continuous Performance Test 3 times in each study week to test mood and attention, respectively.

Setting.—A university-affiliated, tertiary-care pediatric hospital.

Participants.—Healthy second-year pediatric residents working 2 night float rotations.

Outcome Measures.—Standardized measures of sleep, mood, and attention.

Results.—Twenty-eight residents completed both treatments; 17 completed 1 treatment (10 placebo, 7 melatonin). There was not a statistically significant difference in measures of sleep, mood, and 5 of 6 measures of attention during melatonin and placebo treatment. One measure of attention, the number of omission errors, was significantly lower on melatonin (3.0 ± 9.6) than on placebo (4.5 ± 17.5) ($z = -2.12$, $P = .03$).

Conclusions.—The isolated finding of improvement of 1 single measure of attention in a test situation during melatonin treatment was not sufficiently robust to demonstrate a beneficial effect of melatonin in the dose used. Other strategies need to be considered to help residents in adaptation to night shift work.

KEY WORDS: melatonin; night float rotation; night shift work; residency training

Ambulatory Pediatrics 2005;5:172–177

The imperative for around-the-clock work in health care professions has led to a system of night calls superimposed on a busy daytime workload for physicians in training (residents). Because of concerns about compromised patient safety secondary to resident fatigue from sleep deprivation attributed to frequent nights on call, many residency-training programs have adopted the night float rotation. The new work-duty hour standards recently developed by the Accreditation Council for Graduate Medical Education has led to further use of the night float rotation.[1] Typically, the night float resident relieves the daytime resident on night call of some of the responsibilities, thereby providing the daytime resident an opportunity for some rest during the night on call.[2,3] However, the sudden inversion of daytime work to night shift work may also have negative effects on the night float residents and, consequently, on patient safety.

Many biological functions (eg, body temperature, sleep propensity, hormonal secretions) are circadian and usually synchronized to the 24-hour solar cycle of alternating light and dark periods. Nocturnal work causes a misalignment of these biological functions with the 24-hour light-dark cycles, which leads to an array of symptoms of maladjustment, including sleep disturbances, mood disorders, and decline in alertness and performance.[4,5] We have recently shown that the night float rotation, albeit a time-limited night shift period, is indeed accompanied by these deleterious consequences.[6,7]

In many animal species and in humans, the pineal secretory product melatonin contributes to synchronization of circadian rhythms to the 24-hour solar cycle by translating environmental changes in the light-dark cycle to an internal pacemaker.[8] Treatment trials of melatonin to entrain phase-shifted circadian rhythms have been successful in some naturalistic studies of travelers experiencing jet lag[9] and in individuals with free-running rhythms secondary to blindness[10–12] or pinealectomy.[13] Moreover, melatonin treatment also accelerates adjustment to an inverted activity-sleep schedule in experimental shift work when light exposure, sleep and activity schedules are strictly controlled.[14] We hypothesized that treatment with exogenous melatonin might reduce symptoms of maladjustment to a sudden change in the activity-sleep cycle from daytime to night shift work in the actual work environment of night float residents by mediating the realignment of their biological functions to the inverted activity-sleep schedule. We report the results of a placebo-controlled treatment trial of melatonin during the night float rotation.

From the Cincinnati Children's Hospital Medical Center and the Departments of Pediatrics and Environmental Health, University of Cincinnati College of Medicine, Cincinnati, Ohio.

Address correspondence to Anita Cavallo, MD, Division of General and Community Pediatrics, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave, Cincinnati, OH 45229-3039 (e-mail: anita.cavallo@cchmc.org).

Received for publication July 26, 2004; accepted January 12, 2005.

METHODS

The Institutional Review Board approved the study, and participants gave written consent for participation. We have previously described the night float rotation at our institution.[6] Briefly, it consists of a 2-week period (14–15 days) in the second year of training, during which residents report to work at midnight and leave work in the morning between 0800 and 1000 hours. During this rotation, residents receive 1 night off during 1 week and 2 consecutive nights off during the other week. Hence, overall during this rotation is a total of 11–12 days when residents have the inverted activity-sleep schedule distributed over a 2-week period. During the remaining second year of training, residents usually work from 0630 or 0700 hours to 1700 or 1800 hours and have night calls every 4 days or less often. Most residents work 2 night float periods during the second year of residency training.

The design was a double-blind, placebo-controlled, randomized, crossover treatment trial of melatonin during night float rotations. For each night float rotation was a 2-week control period 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. We used the daytime data to examine the effect of night float per se on sleep, mood, and attention and reported the results in a separate study.[7] In addition, we used the daytime data in the statistical analysis of the present report.

Participants were pediatric residents. Inclusion criteria were being a second-year resident scheduled for 2 night float rotations and being willing to abstain from alcoholic beverages and sedative or hypnotic drugs during each period of the study. Exclusion criteria were presence of infants or toddlers in the household (because of greater potential of daytime sleep interruptions), chronic illness, pregnancy, present or past depression, use of sedatives or hypnotic drugs during 2 weeks preceding each period of the study, use of exogenous melatonin, and use of light-treatment devices. Sixteen men and 29 women, age 28.6 $\pm$ 1.9 years, participated. Of these 45 residents, 28 participated in the study during the 2 night float rotations, completing the 2 treatment arms of the crossover design. The other 17 residents completed only 1 treatment arm: 7 were assigned to take melatonin and 10 were assigned to take placebo. There was not a difference in demographic characteristics between the residents who completed 1 treatment arm and those who completed both treatment arms or between the residents who took melatonin and those who took placebo. The present study is based on a total of 73 treatment trials, of which 35 were melatonin and 38 placebo, and 73 daytime control periods.

The Food and Drug Administration gave consent to the principal investigator (A.C.) to use melatonin in human subjects (investigational New Drug Number 42 901). The hospital's investigational drug pharmacist used simple randomization with no restriction and prepared gelatin capsules of melatonin and placebo that were identical in appearance. The melatonin capsule contained 3 mg synthetic melatonin of high purity (Regis Chemical Co, Morton Grove, Ill) mixed in lactose. This preparation falls into the category of ''fast release'' melatonin, such as has been used in other treatment trials.[15] The placebo capsule contained lactose only. The pharmacist dispensed the capsules in a regular medication container for the first 8 participants and in a container fitted with an automated medication monitoring event system (Track Cap) for all subsequent participants to monitor compliance with treatment. For a total of 676 treatment days with capsules dispensed in track caps, there were 661 track cap data points and 660 diary data points, with both data points present concurrently in 645 entries (96%). For 15 diary treatment entry points (2%), there were no corresponding track cap data points, and data from these days were excluded from analysis.

Participants were instructed to take 1 capsule (placebo or melatonin) regularly in the morning of the days of night work and to go to sleep in a darkened room. 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 1300 hours because of concern about a possible hangover effect that might jeopardize their work during the immediately following night shift. They were allowed to sleep as long as desired without any concern about time of waking up.

Study procedures included completion of a daily sleep diary and performance of tests of attention and mood 3 days of each study week as previously described.[7] Briefly, each participant was oriented to all study procedures that included a practice run of the mood and attention tests. The diary included blanks for entry of number of naps and date and time of events related to the main sleep period (ie, going to bed, falling asleep, waking up, getting up, and number of sleep interruptions [awakenings]). In addition, it contained a 100-mm sleep analogue 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.[9] During the night float, participants also recorded the time of drug administration and completed a medication adverse-effects log daily that covered general symptoms (headaches, lightheaded), gastrointestinal symptoms (abdominal pain, nausea, vomiting), excessive sleepiness, and an open-ended question about other adverse effects. 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 Conners Continuous Performance Test, which is a brief and easy-to-follow computer program.[16] 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 States, a 65-item self-report pencil-and-paper questionnaire.[17] This test measures 6 general mood states: tension-anxiety, depres-

Table 1. Sleep Characteristics During Night Float on Placebo and Melatonin (Mean ± Standard Deviation)*

	All Days		Morning Treatment Days	
	Placebo	Melatonin	Placebo	Melatonin
Sleep duration (h)	6.3 ± 2.5	6.4 ± 2.4	6.3 ± 2.0	6.5 ± 1.9
No. of observations	538	486	336	292
Sleep quality	62.0 ± 20.3	64.1 ± 17.8	60.8 ± 19.6	62.6 ± 17.7
No. of observations	495	449	331	288
No. of awakenings	2.3 ± 1.9	2.2 ± 1.8	2.3 ± 1.9	2.3 ± 1.8
No. of observations	499	451	328	284

*All days includes mean of all study days, including days off. Morning treatment days includes mean of days when participants took melatonin or placebo during the morning (0800–1300 hours) after night shift work.

sion-dejection, anger-hostility, vigor-activity (generally referred to as ''vigor''), fatigue-inertia (generally referred to as ''fatigue''), and confusion-bewilderment. The residents completed the tests of attention and mood at the end of their work shift (ie, in the morning after a night shift during the night float rotations and at the end of a day shift during the control periods). Before implementation of the described study protocol, we conducted a pilot study of pediatric residents repeating the Conners Continuous Performance Test over 5 consecutive days. We found no systematic changes reflecting a practice effect. This observation supports previous observations that the test can be used for repeated sessions without concern of a practice effect.[16] Likewise, the Profile of Mood States can be used to rate mood on repeated days without concerns of practice effect.[17–19]

On the basis of preliminary results of a pilot study of 5 residents, a power of 80% for rejecting the null hypothesis of no difference in total sleep duration for the melatonin treatment required an increase in sleep duration of at least 30 minutes compared with placebo and required a sample size of 40. Repeated measure analysis of covariance models were performed by the general linear model procedure of SAS program version 8.20 (SAS Institute Inc, Cary, NC). A subject factor was added to each analysis of covariance model to account for within-subject variability. 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 2 variables were analyzed by Poisson regression (GENMOD 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. For the adverse effects we used the *z*-statistic derived from a GENMOD (repeat measure) model for Poisson outcomes. Results are given as mean ± standard deviation. We used a *P* value of .05 to determine statistical significance.

RESULTS

Of a total opportunity of 11 days for daytime melatonin administration, the mean number of days during which the bedtime and the time of drug administration were earlier than 1300 hours was 9.0 ± 1.7 for melatonin and 9.4 ± 1.8 for placebo ($F = 1.3$, $P = .26$). The time of drug administration during these days was 10.3 ± 1.3 hours for melatonin and 10.4 ± 1.2 hours for placebo ($F = 0.05$, $P = .82$).

Sleep Measures

We show 2 sets of results for the sleep measures during night float. The first set includes all days for each night float (ie, days of work and days off) (Table 1). The second set is limited to the workdays during which the participants took melatonin or placebo before 1300 hours, which were included in the statistical analysis (Table 1). There was not a statistically significant difference in the sleep measures during placebo and melatonin treatment. There was not a statistically significant effect of the respective daytime sleep measures, week, or drug by week on the measures of sleep during night float.

Attention Measures

There was not a statistically significant difference in the number of commission errors, mean reaction time, hit reaction time block change, attentiveness, and risk taking during placebo and melatonin treatment (Table 2). The number of omission errors was significantly lower on mel-

Table 2. Conners Continuous Performance Test During Night Float on Placebo and Melatonin (Mean ± Standard Deviation)

	Placebo	Melatonin	*F*	*P*
No. of observations	222	211		
No. of commission errors	10.3 ± 8.0	10.5 ± 7.4	0.0	(.95)
Mean reaction time (milliseconds)	339.3 ± 65.0	333.0 ± 59.8	0.01	(.93)
Hit reaction time block change	0.0016 ± 0.0259	0.0025 ± 0.0285	0.10	(.75)
Attentiveness	3.5 ± 1.1	3.6 ± 1.0	0.0	(.99)
			z	
Risk taking	0.3 ± 1.6	0.3 ± 1.6	−0.48	(.63)
No. of omission errors	4.5 ± 17.5	3.0 ± 9.6	−2.12	.03

Table 3. Profile of Mood States During Night Float on Placebo and Melatonin (Mean ± Standard Deviation)

	Placebo	Melatonin	*F*	*P*
No. of observations	235	209		
Tension-anxiety	6.8 ± 5.3	6.7 ± 5.5	0.01	(.93)
Depression-dejection	5.1 ± 8.4	5.2 ± 8.6	0.60	(.44)
Anger-hostility	3.9 ± 5.9	3.9 ± 7.3	0.39	(.53)
Vigor-activity	10.5 ± 6.9	10.8 ± 6.6	0.34	(.56)
Fatigue-inertia	9.0 ± 6.1	8.4 ± 5.9	0.03	(.87)
Confusion-bewilderment	6.5 ± 4.0	6.6 ± 3.9	0.29	(.59)

atonin (3.0 ± 9.6) than on placebo treatment (4.5 ± 17.5) ($z = -2.12$, $P = .03$). There was not a statistically significant effect of the respective daytime sleep measures, week, or drug by week on any of the measures of attention during night float.

Mood Measures

There was not a statistically significant difference in the mood measures during placebo and melatonin treatment (Table 3). Moreover, there was not a statistically significant effect of the respective daytime sleep measures, week, or drug by week on the measures of mood during night float.

Adverse Effects

Thirty-one residents completed the adverse-effects questionnaire during placebo and 28 completed the questionnaire during melatonin treatment; the other residents left the form blank. There was not a statistically significant difference between placebo and melatonin in the number of days with headache, abdominal pain, nausea, vomiting, diarrhea, or dizziness (Table 4). Excessive sleepiness was present 10 days in 6 residents on placebo and only 1 day in 1 resident on melatonin treatment, but the difference was not statistically significant ($z = -1.69$, $P = .09$). One resident reported 5 days with nightmares during daytime sleep while taking melatonin.

DISCUSSION

We have recently shown that, compared with daytime rotations, residents had shorter sleep duration during the night float rotation even though they had ample opportunity to sleep during the day after each night shift.[7] Furthermore, they had decreased vigor and increased fatigue during night float, and the fatigue scores correlated significantly with omission errors during the night float rotation but not during daytime rotations. In the present study we show that melatonin treatment improved attention, evidenced by fewer omission errors, but had no significant effect on measures of sleep or mood, particularly fatigue. Hence, one might conclude that a beneficial effect of melatonin on attention may occur independently of improved sleep or decreased fatigue. Alternatively, one might argue that the statistically significant improvement in 1 of 6 measures of attention tested in this study may not be of practical significance at all.

Melatonin treatment, however, did not improve sleep duration, vigor, or fatigue, which were all decreased during night float compared with daytime rotations. Possibly, a larger number of observations may have yielded more promising results. Although the number of observations was large for a study of this nature, it fell short of the target number of 40 in each treatment arm, as 35 residents completed the melatonin trial and 38 completed the placebo. The addition of a few more participants, however, would not have greatly changed the study's power for detecting differences between treatments.

Previous studies with experimental shift work models suggested a promising role for melatonin treatment of shift workers.[20,21] Experimental shift models, however, use rigid sleep-activity schedules in research laboratories where environmental light and other conditions are standardized, unlike the conditions of actual work places. Field studies are scarce and results are inconsistent. For example, 7 police officers had improved sleep and alertness while taking 5 mg of melatonin during 7 days of night work compared with placebo, but the benefit for performance was inconclusive.[22] In contrast, emergency-department physicians on rapidly rotating night shifts of 2–3 consecutive nights with 2–3 nights off did not benefit from melatonin administration compared with placebo when taking the drug in the morning after each night shift[23] or in the evening after completion of consecutive night shifts.[24]

Strengths of the present study include a larger number of participants than in most published melatonin trials and rigorous research methods. In fact, the design was placebo controlled and included standardized methods for assessment of sleep, mood, and attention; moreover, it included corresponding daytime control measures as well. Limitations of the study include those inherent to a field study (ie, uncontrolled light exposure and lack of rigorous

Table 4. Number of Days With Adverse Effects on Placebo and Melatonin Treatment During Night Float

Adverse Effect	Placebo (31)*	Melatonin (28)*	*z*	*P*
Headache	49 (19)	33 (14)	−0.64	(.52)
Abdominal pain	6 (3)	12 (5)	0.79	(.43)
Nausea	6 (4)	14 (8)	1.46	(.15)
Vomiting	0 (31)	6 (4)		
Diarrhea	3 (2)	7 (2)	0.91	(.36)
Dizziness	1 (1)	1 (1)	0.08	(.93)
Excessive sleepiness	10 (6)	1 (1)	−1.69	(.09)

*The numbers in parentheses indicate the number of residents who reported the respective symptom; for vomiting, statistical comparison was not possible because all residents on placebo had no event.

schedule for sleep-wake periods). In fact, bright light exposure on the way home after night shift may hinder the shift of circadian rhythms toward the desired daytime sleep.[25] As for schedule, residents did have regular work hours during the night float rotation and had ample opportunity to sleep during the day after the night shift, but sleep was not prescribed or regulated by a rigid schedule, unlike studies of experimental shift work. Another possible concern is the unequal number of participants in each treatment cell, as some participants did not complete the crossover treatment period. This issue is not a true limitation of the study because the statistical method that was used—repeated measure analysis of covariance with the general linear model that included the participant as an independent variable—removed any concern about the unequal size of the treatment cells and controlled for subject effects. Another limitation of the study also inherent to its naturalistic design 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.

Three other 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 individual tolerance to shift work. The first factor, pharmacogenetic characteristics, 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.[26] Overall, genetic characteristics may account for 20%–95% of variability in drug disposition and effects.[27] The second factor, individual tolerance to shift work, also varies considerably among individuals.[28] Regrettably, no predictors of tolerance to night work exist.[28,29] The third factor, relationship 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 10-hour 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 with 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.[30]

Generally, therapeutic trials of melatonin have not reported methods for monitoring the safety of this drug, seeming to rely on spontaneous reports of undesirable effects. The present study included a daily adverse-effects checklist that covered most systems that might be affected by melatonin. Of interest, the association of melatonin with nightmares or vivid dreams in 1 individual in the present study has been previously noted.[31] Otherwise, the results suggest that melatonin given for a short period of time of 2 weeks is well tolerated.

The present study shows that melatonin administration had a limited effect on adaptation to short-term night shift work by improving 1 tested measure of attention. Possibly, a higher dose of melatonin may be more effective in improving sleep, attention, and mood during night shift work. Directors of residency-training programs must be aware that the night float rotation may carry deleterious effects on residents' sleep, mood, and attention that will not be counteracted by melatonin use alone.

ACKNOWLEDGMENTS

The authors thank Stephen Gay for excellent support in study coordination and data management. This study was supported by grant R18 OH03533 from the Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health to A.C.; and grant RR-08084 from the National Center for Research Resources, General Clinical Research Centers Program, National Institutes of Health.

REFERENCES

1. Report of the ACGME Work Group on Resident Duty Hours, June 11, 2002. Paper presented at: Accreditation Council for Graduate Medical Education, 2002; Chicago, Ill. Available at http://www.acgme.org/DutyHours/dutyhoursCommonPR.asp. Accessed September 16, 2003.
2. Lieu TA, Forrest CB, Blum NJ, et al. Effects of a night-float system on resident activities and parent satisfaction. *Am J Dis Child.* 1992;146:307–310.
3. Rosenberg M, McNulty D. Beyond night float? The impact of call structure on internal medicine residents. *J Gen Intern Med.* 1995;10:95–98.
4. Czeisler CA, Johnson MP, Duffy JF, et al. Exposure to bright light and darkness to treat physiologic maladaptation to night work. *N Engl J Med.* 1990;322:1253–1259.
5. Costa G. The problem: shiftwork. *Chronobiol Int.* 1997;14: 89–98.
6. Cavallo A, Jaskiewicz J, Ris MD. Impact of night-float rotation on sleep, mood, and alertness: the resident's perception. *Chronobiol Int.* 2002;19:893–902.
7. Cavallo A, Ris MD, Succop P. The night float paradigm to decrease sleep deprivation: good solution or a new problem? *Ergonomics.* 2003;46:653–663.
8. Reiter RJ. Pineal gland: interface between the photoperiodic environment and the endocrine system. *Trends Endocrinol Metab.* 1991;2:13–19.
9. Arendt J, Aldhous M, English J, et al. Some effects of jet-lag and their alleviation by melatonin. *Ergonomics.* 1987;30:1379–1393.
10. Arendt J, Deacon S. Treatment of circadian rhythm disorders—melatonin. *Chronobiol Int.* 1997;14:185–204.
11. Cavallo A, Good WV, Ris MD, Succop P. Dose response to melatonin treatment for disordered sleep rhythm in a blind child. *Sleep Med.* 2002;3:159–161.
12. Sack RL, Lewy AJ, Blood ML, et al. Melatonin administration to blind people: phase advances and entrainment. *J Biol Rhythms.* 1991;6:249–261.
13. Petterborg LJ, Thalen BE, Kjellman BF, Wetterberg L. Effect of melatonin replacement on serum hormone rhythms in a patient lacking endogenous melatonin. *Brain Res Bull.* 1991;27: 181–185.
14. Sharkey KM, Eastman CI. Melatonin phase shifts human circadian rhythms in a placebo-controlled simulated night-work study. *Am J Physiol Regul Integr Comp Physiol.* 2002;282: R454–R463.
15. Arendt J, Skene DJ, Middleton B, et al. Efficacy of melatonin treatment in jet lag, shift work, and blindness. *J Biol Rhythms.* 1997;12:604–617.
16. Conners CK. *Conners' Continuous Performance Test Computer Program User's Manual.* North Tonawanda, NY: Multi-Health Systems Inc; 1995.

17. McNair DM, Lorr M, Droppleman LF. *Profile of Mood States.* San Diego, Calif: Educational and Industrial Testing Service; 1992.
18. Eastman CI. High-intensity light for circadian adaptation to a 12-h shift of the sleep schedule. *Am J Physiol.* 1992;263(2 pt 2):R428–R436.
19. Florida-James G, Wallymahmed A, Reilly T. Effects of nocturnal shiftwork on mood states of student nurses. *Chronobiol Int.* 1996;13:59–69.
20. Deacon S, Arendt J. Adapting to phase shifts, II. Effects of melatonin and conflicting light treatment. *Physiol Behav.* 1996; 59:675–682.
21. Sharkey KM, Fogg LF, Eastman CI. Effects of melatonin administration on daytime sleep after simulated night shift work. *J Sleep Res.* 2001;10:181–192.
22. Folkard S, Arendt J, Clark M. Can melatonin improve shift workers' tolerance of the night shift? Some preliminary findings. *Chronobiol Int.* 1993;10:315–320.
23. Jorgensen KM, Witting MD. Does exogenous melatonin improve day sleep or night alertness in emergency physicians working night shifts? *Ann Emerg Med.* 1998;31:699–704.
24. Wright SW, Lawrence LM, Wrenn KD, et al. Randomized clinical trial of melatonin after night-shift work: efficacy and neuropsychologic effects. *Ann Emerg Med.* 1998;32(3 pt 1):334–340.
25. Eastman CI, Stewart KT, Mahoney MP, et al. Dark goggles and bright light improve circadian rhythm adaptation to night-shift work. *Sleep.* 1994;17:535–543.
26. Weinshilboum R. Inheritance and drug response. *N Engl J Med.* 2003;348:529–537.
27. Evans WE, McLeod HL. Pharmacogenomics—drug disposition, drug targets, and side effects. *N Engl J Med.* 2003;348:538–549.
28. Ashkenazi IE, Reinberg AE, Motohashi Y. Interindividual differences in the flexibility of human temporal organization: pertinence to jet lag and shiftwork. *Chronobiol Int.* 1997;14:99–113.
29. Knauth P, Harma M. The relation of shift work tolerance to the circadian adjustment. *Chronobiol Int.* 1992;9:46–54.
30. Sack RL, Lewy AJ. Melatonin as a chronobiotic: treatment of circadian desynchrony in night workers and the blind. *J Biol Rhythms.* 1997;12:595–603.
31. Guardiola-Lemaitre B. Toxicology of melatonin. *J Biol Rhythms.* 1997;12:697–706.