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HUNGER RATINGS CHANGE WITH CIRCADIAN MISALIGNMENT AND SLEEP DEPRIVATION

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Introduction: Increased risk of obesity and other metabolic diseases observed in shiftworkers is thought to be related to consumption of the majority of calories at adverse circadian times. How the circadian system influences appetite at night is largely unknown and was therefore examined in two studies: a simulated shiftwork (SW) protocol with feeding at night and a total sleep deprivation (TSD) protocol with fasting at night.
Methods: Ten healthy adults (4 males) aged 26.3 ± 4.8 y, BMI 22.3 ± 1.7 participated in SW and seven healthy adults (5 males) aged 22 ± 5 y, BMI 22.9 ± 2.4 participated in TSD. Participants maintained ~8 h/night habitual sleep schedules the week prior to study. SW was a 5 day in-laboratory protocol simulating three consecutive nightshifts with Day 2 as baseline, Day 3 as transition to night work, which occurred Nights 3-5. TSD was a 3 day in-laboratory protocol with Day 1 as baseline and Days 2-3 40 h of TSD. Participants were fed meals meeting their daily caloric needs and in both studies, meals were given at approximately 1.5 h, 5.5 h, 10.5 h and 14.5 h awake. Thus, participants were fed at night during SW and fasted at night during TSD. Hunger ratings were assessed every 1-2 h with visual analog scales. Data were analyzed by Mixed Model ANOVA and planned comparisons.
Results: Hunger ratings for sweets, fruits, dairy, meats, and vegetables were lower when food was consumed during the nightshift compared to daytime levels at baseline ($p < 0.05$). Hunger ratings for these foods were also lower when fasting at night during TSD ($p < 0.005$) compared to when feeding during the daytime.
Conclusion: Although shiftworkers are reported to eat the majority of their calories at night, findings from the current study suggest that this pattern is not due to increased hunger at night, rather the circadian clock appears to reduce hunger at night regardless of food intake.
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CIRCADIAN MISALIGNMENT INCREASES CARDIOVASCULAR RISK INDEPENDENTLY OF SLEEP LOSS

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Introduction: Shift work, characterized by irregular schedules resulting in sleep loss and misalignment of circadian rhythms, is associated with increased incidence of cardiovascular disease. We tested whether circadian misalignment has an adverse impact on cardiovascular function independently of sleep loss.
Methods: 19 healthy adults were studied using a parallel group design comparing two interventions. Both interventions involved 3 inpatient days with 10-h bedtimes (B1-B3) followed by 8 inpatient days with 5 hours in bed (D4-D10), either with fixed nocturnal bedtimes (circadian alignment, n = 8, 3 women, 24.5 ± 2.7 years old, 23.6 ± 2.5 kg/m^2) or with bedtimes delayed by 8.5 hours on 4 of the 8 days (circadian misalignment, n = 11, 4 women, 22.5 ± 1.6 years old, 22.1 ± 2.6 kg/m^2). Both interventions were followed by 3 nights of recovery sleep, 2 nights with 12-h bedtimes (R12-13) and 1 night with 10-h bedtimes (R14). During each night, heart rate (HR) and cardiac sympathovagal balance (assessed via the ratio of low frequency to high frequency [LF:HF] in the ECG) were estimated over a 5-min period during stable NREM stage 2, slow wave sleep (SWS) and REM sleep. Only 5-min-periods free from artifacts, arousals, leg movements, breathing instability and ectopic beats were analyzed. A generalized linear model for repeated measures was used to examine between-group differences after adjusting for age and BMI.
Results: Total sleep time during the intervention was almost identical in the two groups (4h49min [4 min] vs. 4h46min [6 min]). When compared to the aligned condition, the increase of HR from baseline (B2) was 8 to 10 bpm higher in the misaligned condition during stage 2 (p:0.0009), SWS (p:0.0492) and REM sleep (p:0.0083). LF:HF was higher in the misaligned condition during stage 2 (p:0.0284), SWS (p:0.0450) and REM sleep (p:0.0338).
Conclusion: Circadian misalignment as occurs in shift work may impair autonomic cardiac modulation and increase cardiovascular risk, independently of sleep loss.
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DIFFERENTIAL SLEEP DISTURBANCES IN TWO PHENOTYPES OF SHIFT WORK DISORDER

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Introduction: Most patients meeting diagnostic criteria for Shift Work Disorder (SWD) report insomnia, but only a portion of these insomniacs also report excessive sleepiness. We hypothesize that two phenotypes of SWD, characterized by the presence or absence of excessive sleepiness, experience similar diurnal sleep but different nocturnal sleep.
Methods: 35 night workers completed a sleep diary for two weeks before an overnight phase assessment. Subjects with a history of insomnia or other sleep disorders prior to shift work were excluded. At 17:00, each subject completed an Insomnia Severity Index specific to daytime sleep (ISI-D) and an Epworth Sleepiness Scale (ESS). 12 subjects with normal scores on both scales were classified as controls. 12 subjects with ESS < 10 and ISI-D > 10 were classified "alert insomniacs" (AI). 11 subjects with ISI-D > 10 and ESS > 10 were classified "sleepy insomniacs" (SI). We used t-tests to compare diary-reported sleep parameters between subgroups.
Results: Dim-light melatonin onset was significantly ($p < 0.01$) delayed in controls (04:54 ± 3.7 h) than in both SWD groups: AI (22:45 ± 4.9 h) and SI (20:55 ± 4.6 h). For daytime sleep, both SWD groups reported lower sleep efficiency (82.35% AI; 88.71% SI) and more awakenings (1.62 AI; 1.79 SI) than controls (95.78%; 0.54 awakenings, $p < .05$). The AI group also reported longer daytime latencies than controls (34.59 vs. 13.73 minutes, $p < .05$). At night, however, only the AI group differed from controls ($p < .05$), reporting lower sleep efficiency (81.84% vs. 93.38%), longer latencies (43.97 vs. 17.74 minutes) and more awakenings (1.90 vs. 0.80).
Conclusion: Although both phenotypes of SWD show a nighttime phase and disrupted sleep during the day (a time outside of their circadian sleep phase), the AI phenotype shows sleep disturbances at night that are not seen in controls or the SI group. Since the AI phenotype

presents both nocturnal and diurnal sleep disturbances, its etiology may be traced to factors outside circadian misalignment.
Support (If Any): This study is supported by grant 1K01OH009996-03 from CDC/NIOSH.

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UNEXPECTED PHASE DELAYS DURING NIGHT SHIFTS IN A NATURALISTIC PILOT STUDY IN PATROL OFFICERS

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Introduction: It is believe that circadian adaptation to night work does not occur due to inappropriate light during the commute home combined with low light at night. Enriching the workplace with short wavelengths and blocking those in the morning has been proposed as a countermeasure to circadian maladaptation. This study investigated the effect of being exposed to dim blue light at night along with wearing blue-blockers during daytime on the circadian entrainment of patrol officers.
Methods: Phase shift assessment following 4 consecutive night shifts was assessed in 14 patrol officers (aged 25-32 years) submitted to 3 conditions: Blue, Red and Baseline. During Blue and Red conditions, subjects were exposed respectively to 8 uW/cm^2 of blue and 8 uW/cm^2 of red (placebo) light in their car during the night shifts and wore blue-blockers after 5 am. Baseline condition did not include any intervention. In each condition, salivary melatonin was collected hourly from 19:00-23:00 the night before and from 21:00-04:00 the night after the four night shifts. Dim-light melatonin onset (DLMO) was calculated using a 5 pg/ml threshold. The study occurred between April and October 2010 at which time sunrise ranged from 04:50-07:00.
Results: Significantly greater phase shifts were experienced in Baseline compared to Blue and Red condition (03:14 ± 01:40 h vs. 01:53 ± 01:27 h and 02:06 ± 01:14 h; $p < 0.05$). Phase shifts ranged from 1.01 to 6.60 h in Baseline, -0.64 to 4.00 h in Blue and -0.56 to 3.76 h in Red condition respectively.
Conclusion: Surprisingly, greater phase-delays were observed in Baseline in which condition natural exposure in the morning should have provoked a phase advance or at best no phase-shift albeit both large and small phase-shifts were observed in each condition. Actigraphic light and activity patterns, as well as phase-angles between sleep, DLMOs and sunrise shall provide information regarding variability and the unexpected phase-delays in Baseline.
Support (If Any): This work was supported by CIHR operating Grants (MOP 82707) to M. Hebert.

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ASSESSMENT OF CLINICAL MEASURES IN NON-24-HOUR DISORDER (NON-24) PATIENTS ENTRAINED BY TASIMELTEON

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Introduction: The majority of totally blind individuals exhibit non-24-hour circadian rhythms due to light signals not reaching the suprachiasmatic nucleus, resulting in Non-24. The central pacemaker controls circadian rhythms of hormone secretion, body temperature, sleep-wake function, and peripheral clocks that control cell cycle, cardiovascular, metabolic, and immune function. Hetlioz™ (tasimelteon) is a novel circadian regulator in development for the treatment of Non-24, a serious circadian disorder with no FDA-approved treatment.
Methods: Two phase III double-masked, placebo-controlled studies, SET and RESET, assessed the safety, efficacy and maintenance of effect of tasimelteon (20 mg/day) in blind Non-24 patients. Entrainment of circadian rhythms was assessed from urinary 6-sulfatoxymelatonin at months 1 in SET and month 7 for those continuing in RESET. Clinical assessments included duration and timing of nighttime and daytime sleep, and Clinical Global Impression of Change (CGI-C).
Results: Fourteen patients entrained by month 7 of tasimelteon treatment. Eight entrained at month 1 and six additional entrained by month 7, including 2 with treatment gaps of 32 and 47 days between studies. Tasimelteon-entrained patients experienced 82 more minutes of nighttime sleep and 74 minutes less of daytime sleep in their worst 25% of nights and days respectively (p-values < 0.01) compared to placebo. Entrained patients had 52 minutes improvement in the midpoint of their sleep timing compared to placebo (p-value < 0.01) and an average 1.2 point improvement in CGI-C scores compared to placebo (p-value < 0.01). Entrainment and the corresponding clinical response were lost upon withdrawal of tasimelteon in 80% of patients.
Conclusion: Tasimelteon treatment entrains the circadian pacemaker in blind patients with Non-24. Among Non-24 patients entrained by tasimelteon, we observed significant and clinically meaningful improvements in sleep duration, timing of sleep and global functioning. Continued tasimelteon treatment is necessary to maintain entrainment and the resulting clinical response.
Support (If Any): Vanda Pharmaceuticals Inc. ClinicalTrials.gov (NCT01163032/NCT01430754).

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GENETIC SUSCEPTIBILITY AND CIRCADIAN ACTIVITY RHYTHMS IN BLACK MOTHERS OF PRETERM INFANTS: AN EXPLORATORY STUDY

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Introduction: Postpartum depression is prevalent in mothers with a preterm labor. Depressive symptoms are known to be associated with weak circadian activity rhythms (CAR). The short allele of the serotonin transporter gene (5-HTTLPR) has also been shown to be a predictor of depression. This study is aimed to examine if the s allele of 5-HTTLPR is associated with depressive symptoms, and less synchronized CAR during early postpartum among Black mothers with a hospitalized preterm infant.
Methods: Thirty Black mothers completed a set of questionnaires, including the General Sleep Disturbance Scale, Edinburgh Postnatal Depression Scale, and Medical Outcomes Short Form-36. Wrist actigraph was used to collect total sleep time and CAR. Buccal cells from saliva were collected for identifying the short (s/l) or long (l/l) allele of 5-HTTLPR in mothers.
Results: About 38% the mothers were identified as s/l heterozygous and 62% as l/l homozygous. Among the mothers with s/l genotype, 55.5% reported clinically significant depressive symptoms as compared to 38.9% of those with l/l homozygotes. Moreover, mothers with l/l reported significantly greater sleep disturbances as compared to those with s/l. However, mothers with l/l or s/l did not differ significantly in their health-related quality of life, synchronized CAR, or actual nocturnal total sleep time in this sample.
Conclusion: Among the Black mothers with s/l genotype may be more vulnerable to depressive symptoms and poor sleep. The role of serotonin transporter gene in sleep and well-being for Black postpartum women needs to be further explored.

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