JCSM
Journal of Clinical Sleep Medicine

HIGHLIGHTS from SLEEP

Advancing Circadian Rhythms Before Eastward Flight: a Strategy to Prevent or Reduce Jet Lag

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Study Objectives: To develop a practical pre-eastward flight treatment to advance circadian rhythms as much as possible but not misalign them with sleep.

Design: One group had their sleep schedule advanced by 1 hour per day and another by 2 hours per day.

Setting: Baseline at home, treatment in lab.

Participants: Young healthy adults (11 men, 15 women) between the ages of 22 and 36 years.

Interventions: Three days of a gradually advancing sleep schedule (1 or 2 hours per day) plus intermittent morning bright light (one-half hour ~5000 lux, one-half hour of 60 lux) for 3.5 hours.

Measurements and Results: The dim-light melatonin onset was assessed before and after the 3-day treatment. Subjects completed daily sleep logs and symptom questionnaires and wore wrist activity monitors.

The dim-light melatonin onset advanced more in the 2-hours-per-day group than in the 1-hour-per-day group (median phase advances of 1.9 and 1.4 hours), but the difference between the means (1.8 and 1.5 hours) was not statistically significant. By the third treatment day, circadian rhythms were misaligned relative to the sleep schedule, and subjects had difficulty falling asleep in the 2-hours-per-day group, but this was not the case in the 1-hour-per-day group. Nevertheless, the 2-hours-per-day group did slightly better on the symptom questionnaires. In general, sleep disturbance and other side effects were small.

Conclusions: A gradually advancing sleep schedule with intermittent morning bright light can be used to advance circadian rhythms before eastward flight and, thus, theoretically, prevent or reduce subsequent jet lag. Given the morning light treatment used here, advancing the sleep schedule 2 hours per day is not better than advancing it 1 hour per day because it was too fast for the advance in circadian rhythms. A diagram is provided to help the traveler plan a preflight schedule.

Key Words: Jet lag, circadian rhythms, bright light, sleep, phase shifts, melatonin, phase response curve, human, travel

Citation: Eastman CI; Gazda CJ; Burgess HJ et al. Advanced circadian rhythms before eastward flight: A strategy to prevent or reduce jet lag. *SLEEP* 2005;28(1):33-44

Low-Concentration Carbon Dioxide is an Effective Adjunct to Positive Airway Pressure in the Treatment of Refractory Mixed Central and Obstructive Sleep-Disordered Breathing

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Objectives: To assess the efficacy of added carbon dioxide as adjunctive therapy of positive airway pressure-refractory mixed obstructive and central sleep-disordered breathing, using a prototype device-the positive airway pressure gas modulator.

Design: Open-label evaluation of low concentrations of carbon dioxide added to a positive airway pressure circuit.

Setting: Physician-attended polysomnographic titration in a free-standing sleep laboratory with end-tidal and transcutaneous carbon-dioxide monitoring.

Patients: Six adult men (age 54 ± 5.7 years) with severe poorly controlled mixed sleep-disordered breathing in the absence of renal or heart failure

Interventions: Flow-independent addition of incremental concentrations of carbon dioxide during sleep.

Measurements and results: The respiratory disturbance index before treatment was 66 ± 14.5 events per hour of sleep, with a nocturnal desaturation low of 84.6% ± 10.1%. Residual respiratory disturbance index on best treatment was 43 ± 9 events per hour of sleep. There was an immediate (< 1 minute) response to the addition of 0.5% to 1% carbon dioxide, and minimal changes were required to be made across the night. There was no discomfort, shortness of breath, palpitations, headache, or significant increase in respiratory or heart rate. The residual respiratory disturbance index on carbon dioxide, scored irrespective of desaturations, was in the normal range (≤ 5 / hour of sleep). Two subjects had a second night at the concentration of carbon dioxide determined to be efficacious, with no required concentration change. No adverse effects on overall sleep architecture were noted.

Conclusions: Low concentrations of carbon dioxide added to conventional positive airway pressure effectively control severe treatment-resistant mixed obstructive and central sleep-disordered breathing.

Key words: Carbon dioxide, obstructive central sleep-disordered breathing

Citation: Thomas RJ; Daly RW; Weiss JW. Low-concentration carbon dioxide is an effective adjunct to positive airway pressure in the treatment of refactory mixed central and obstructive sleep-disordered breathing. *SLEEP* 2005;28(1):69-77

Ramelteon (TAK-375), a Selective MT_1/MT_2-Receptor Agonist, Reduces Latency to Persistent Sleep in a Model of Transient Insomnia Related to a Novel Sleep Environment

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Objective: Evaluate the efficacy of ramelteon, an MT_1/MT_2-receptor agonist, for the treatment of transient insomnia in healthy adults.

Design: Randomized, double-blind, placebo-controlled design using a model of transient insomnia related to sleeping in a novel environment.

Setting: Fourteen sleep research centers.

Participants: Healthy adults (N = 375; 228 women), aged 35 to 60 years, who had never previously slept in a sleep laboratory and had a reported usual sleep duration of 6.5 to 8.5 hours and usual bedtime between 8:30 PM and midnight.

Interventions: Single administration of ramelteon (16 or 64 mg) or placebo 30 minutes before bedtime.

Outcome Measures: Primary efficacy measure was latency to persistent sleep. Also evaluated were total sleep time, wake after sleep onset, percentage of each sleep stage, subjective estimates of sleep from postsleep questionnaire, number of awakenings, and subjective number of awakenings. Residual effects were assessed via Digit Symbol Substitution Test and postsleep questionnaire.

Results: Participants in ramelteon-treated groups had significantly shorter latency to persistent sleep relative to placebo. They also were associated with significantly longer total sleep time. Wake after sleep onset and time spent in each sleep stage were not significantly different from placebo. The use of ramelteon (16 mg) was associated with a shorter subjective sleep latency compared to placebo. Other subjective measures of sleep did not differ significantly from placebo. Digit Symbol Substitution Test scores did not differ significantly among the 3 groups, but the use of the 16-mg dose was associated with subjective reports of impairment in the morning.

Conclusions: Ramelteon significantly improved latency to persistent sleep and total sleep time in this model of transient insomnia in healthy adults. No dose-related differences in latency to persistent sleep were observed, and both doses were well tolerated.

Key Words: Melatonin, Ramelteon, transient insomnia

Citation: Roth T; Stubbs C; Walsh JK. Ramelteon (Tak-375), A selective MT_1/MT_2-receptor agonist, reduces latency to presistent sleep in a model of transient insomnia related to a novel sleep environment. *SLEEP* 2005;28(3):303-307

Variability of Periodic Leg Movements in Various Sleep Disorders: Implications for Clinical and Pathophysiologic Studies

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Study Objectives: Periodic leg movements in sleep (PLMS) are a frequent phenomenon in various sleep disorders. The pathophysiology of PLMS is still not understood, but recent studies indicate a hypoactivity of the dopaminergic system in subjects with PLMS. In the present study, we investigated the intrasubject variance of PLMS from one night to the other because a fluctuation in the number of PLMS may influence the outcome of pharmacologic and pathophysiologic studies.

Design: Retrospective observational study.

Setting: Data collection occurred in the sleep disorders unit.

Patients: Sleep electroencephalogram and PLMS data of 115 patients with PLMS monitoring over 2 consecutive nights were evaluated retrospectively. Patients were grouped into the following diagnostic categories: restless legs syndrome, insomnia secondary to a psychiatric disorder, primary insomnia, sleep apnea syndrome, and narcolepsy or idiopathic hypersomnia.

Interventions: N/A.

Results: In 27% of the entire patient population, we found a considerable variability of the PLMS index (difference between nights > 10/hour) and, in 19% of patients, variability of the PLMS arousal index (difference between nights > 5/hour) across the 2 investigated nights. The intraindividual variance occurred most frequently and to the highest extent in patients with RLS.

Conclusions: The variability of PLMS indexes should considered if the PLMS recording is performed in support of the clinical diagnosis or in the interpretation of studies investigating drug efficacy. Furthermore, the variability of PLMS may be an indicator of an instability of the dopaminergic system that should be taken into account in studies investigating central nervous system dopaminergic activity.

Key Words: Periodic leg movements, variability, sleep, restless legs syndrome

Citation: Hornyak M; Kopasz M; Feige B et al. Variability of periodic leg movements in various sleep disorders: implications for clinical and pathophysiologic studies. *SLEEP* 2005;28(3):331-335

Modafinil for Treatment of Residual Excessive Sleepiness in Nasal Continuous Positive Airway Pressure-Treated Obstructive Sleep Apnea/Hypopnea Syndrome

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Study Objectives: Nasal continuous positive airway pressure (nCPAP) usually reduces sleepiness in patients with obstructive sleep apnea/hypopnea syndrome. However, even with regular use of nCPAP, some patients experience residual excessive sleepiness. We evaluated the efficacy and safety of the wake-promoting agent modafinil for treating residual excessive sleepiness in nCPAP-treated patients.

Design: 12-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled trial.

Patients: Patients aged 18 to 70 years diagnosed with obstructive sleep apnea/hypopnea syndrome and having residual excessive sleepiness during nCPAP therapy were eligible.

Interventions: Once-daily modafinil, 200 mg or 400 mg, or placebo.

Measurements and Results: Assessments included the Maintenance of Wakefulness Test, Epworth Sleepiness Scale, Clinical Global Impression of Change, and Functional Outcomes of Sleep Questionnaire. Both doses of modafinil significantly improved mean (SD) results of Maintenance of Wakefulness Test at weeks 4, 8, and 12 compared with placebo (week 12: modafinil 400 mg, 15.0 [5.3] minutes; 200 mg, 14.8 [5.3] minutes; placebo, 12.6 [5.8] minutes; $P < .0001$). The Epworth Sleepiness Scale score decreased more in patients taking modafinil compared with those in the placebo group (week 12: modafinil 400 mg, -4.5 [4.3]; 200 mg, -4.5 [4.7]; placebo, -1.8 [3.5]; $P < .0001$). At week 12, overall clinical condition improved for 61% and 68% of patients treated with modafinil 200 mg and 400 mg, respectively, versus 37% of placebo-treated patients ($P < .001$). Modafinil was generally well tolerated and did not adversely affect nighttime sleep or nCPAP use.

Conclusions: These results confirm previous shorter-term controlled trials, indicating modafinil is a useful adjunct therapy for improving wakefulness in patients with residual excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome who were treated with nCPAP.

Key Words: Modafinil, obstructive sleep apnea/hypopnea syndrome, sleepiness, wakefulness

Citation: Black JE; Hirshkowitz M. Modafinil for treatment of residual excessive sleepiness in nasal continuous positive airway pressure-treated obstructive sleep apnea/hypopnea syndrome. *SLEEP* 2005;28(4):464-471

Individual Differences in Adult Human Sleep and Wakefulness: Leitmotif for a Research Agenda

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Abstract: This paper reviews the literature on interindividual variability in human sleep parameters, sleepiness, responses to sleep deprivation, and manifestations of sleep disorders. Variability among individuals in sleep/wake biology and behavior is pervasive. The magnitude of such individual differences is often considerable and comparable to the effect sizes of many experimental and clinical interventions. Evidence is accumulating that certain aspects of sleep/wake-related variability-such as sleep duration, daytime sleepiness, and vulnerability to the effects of sleep loss-involve trait characteristics in healthy populations and among sleep-disordered patients. Establishing the trait-specific nature of variability in sleep/wake parameters is a prerequisite for elucidating the corresponding neurophysiologic and/or genetic mechanisms. At present, it remains largely unknown what underlies or predicts sleep/wake-related traits, what relationships these traits may have to each other, and what functional significance may be associated with specific traits. Scientific studies addressing these issues are warranted, as understanding the basis of trait variability may yield new insights into sleep/wake regulation and sleep pathology. Understanding individual differences in sleep and wakefulness may also have provocative but important implications for health economics and clinical care, as well as for safety, productivity, and general well-being. This paper gives suggestions for a research agenda focusing on individual differences in sleep research and sleep medicine.

Keywords: Individual differences, trait variability, genetics, sleep behavior, sleep architecture, sleepiness, waking neurobehavioral functions, sleep deprivation, differential vulnerability, sleep disorders, adult humans

Citation: Van Dongen HPA; Vitellaro KM; Dinges DF. Individual differences in adult human sleep and wakefulness: Leitmotif for a research agenda. *SLEEP* 2005;28(4):479-496

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According to our previous work,[1,3-8,19]

The patients were studied as follows[3,4]:

Sample references

Article:

1. Meier-Ewert K, Matsubayashi K, Benter L. Propranolol: long-term treatment in narcolepsy-cataplexy. Sleep 1985;8:95-104.

2. Carskadon MA, Dement WC. Sleep loss in elderly volunteers. Sleep 1985;8:207-21.

Book:

3. Guilleminault C, Lugaresi E, eds. Sleep/wake disorders: natural history, epidemiology, and long-term evolution. New York: Raven Press, 1983.

Chapter of a book:

4. Coleman RM, Bliwise DL, Sajben N, et al. Epidemiology of periodic movements during sleep. In: Guilleminault C, Lugaresi E, eds. Sleep/wake disorders: natural history, epidemiology, and long-term evolution. New York: Raven Press, 1983:217-30.

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