Circadian Rhythm Disorders

1. Terman JS, Terman M, Lo E, et al. Circadian time of morning light administration and therapeutic response in winter depression. Arch Gen Psychiatry 2001; 58:69–75

Seasonal affective disorder (SAD) is a subtype of a mood disorder that is characterized by recurring episodes of major depression, the onset and remission of which seem to relate to particular seasons. This condition most commonly begins in autumn/winter and fully remits by spring. While the pathogenesis is uncertain, there appears to be a relationship to light exposure and delay in the affected individual’s circadian rhythm. Controlled clinical trials (including the author’s previous study,1 from which some patients were included here) have demonstrated the benefit of light exposure in improving mood in those patients with SAD. Terman and colleagues monitored plasma melatonin levels, a circadian phase indicator, and depression in 42 patients with SAD. Patients were exposed to 10,000 lux light for 30 min in the evening or the morning for 10 to 14 days while depressed, within a crossover design. Results revealed that there was no difference between the mean (± SD) percentage of change in depression ratings relative to morning light exposure (58.8% ± 29.2%) or evening light exposure (57.9% ± 28.8%). However, the remission rate (depression score, ≤ 0) was higher for morning light (50% vs 40%, respectively). This study, along with the previously reported work by these authors further defines the protocol of morning light exposure in the treatment of patients with SAD.

Insomnia


Insomnia is the most common sleep disorder and may be particularly disabling in the elderly. Behavioral therapies have not been used widely, probably because of perceptions of inadequate research study design, expense, and ease of use of medications. Morin and colleagues randomized 78 elderly patients with chronic and primary insomnia (who had no other clinical or psychiatric etiology) to receive one of the four following interventions: cognitive-behavior therapy (stimulus control, sleep restriction, sleep hygiene, and cognitive therapy); pharmacotherapy (temazepam); both therapies; or placebo. Results showed that the three active interventions were more effective than placebo. Patients treated with behavior therapy showed continued improvement at follow-up compared to those treated with medication alone and was preferable by the ratings of patients and others. This study and subsequent ones have demonstrated an important role for behavioral therapy for the management of chronic insomnia.

Narcolepsy


Investigators have created a colony of mice with a gene coding for the hypothalamic neurotransmitter
orexin, knocked out. They expected the mice to change their eating behaviors. Instead, they found that the animals would fall and lay lifeless (similar to cataplexy) for a period of time, only to quickly recover and resume normal eating and grooming behavior. Unknown to these investigators, a second group of investigators found two neurotransmitter peptides secreted by the hypothalamus, which they named hypocretins. They were controlled by the same gene as orexin. Its loss of protein function accounted for the observed autosomal-recessive mode of transmission of narcolepsy in dogs. Nishino and colleagues now extend this research by investigating how these molecules affect human sleep and narcolepsy. They measured the hypocretin-1 levels in the cerebrospinal fluid of nine people with narcolepsy and eight control subjects. All patients with narcolepsy were HLA-DR2/DQB1*0602-positive. All control individuals demonstrated detectable levels of hypocretin-1 (range, 250 to 285 pg/mL) with little interindividual variability, while seven of the nine patients had concentrations below the detectable limit (i.e., <40 pg/mL; p = 0.007). These results show that hypocretin neurotransmission is deficient in some people with narcolepsy. These results suggest that a deficiency of this neurotransmitter contributes to the sleep disorder. The authors speculate that an autoimmune-mediated destruction of hypocretin-containing neurons in the lateral hypothalamus may be responsible for narcolepsy.

**Obstructive Sleep Apnea**

**Oral Appliance Therapy**


As primary therapy for obstructive sleep apnea (OSA) or an alternative to continuous positive airway pressure (CPAP), oral appliances have been the subject of much recent research and clinical interest. However, well-designed and controlled studies with appropriate outcome measures are lacking. Mehta and coworkers prospectively randomized 28 patients with clinically and polysomnographically proven OSA to receive an adjustable mandibular advancement splint or a control oral plate in a three-period crossover study design. Compliance was monitored but not specifically measured, and other outcomes included sleep structure, oxygenation, snoring, and questionnaires evaluating quality of sleep and daytime sleepiness. Ninety-six percent of patients reported a subjective improvement, with a complete (n = 9) or partial (n = 6) response achieved in 62%. Other improvements were reported in the amount of rapid eye movement sleep, snoring, arousals, daytime sleepiness, quality of sleep, and oxygenation. The side effects of the treatments were reported as being mild to moderately severe by the patients and did not preclude continued use.

**Treatment Outcome**


Patients with OSA and associated excessive daytime sleepiness have been shown to have a higher rate of automobile accidents than the public in general. Treatment with nasal CPAP has been shown to decrease the self-reported rates of crashes, however, some question the accuracy of this measure of accident rates. Findley and coworkers were one of the first investigating groups to note the increased crash rate of patients with OSA, and in this article they have investigated department of motor vehicles accident reports to document improvement with nasal CPAP therapy. Fifty consecutive patients of a total of 67 with OSA could be included in the study. All patients were asked questions via telephone interview concerning CPAP use, driving habits, number of accidents, and the effect of CPAP therapy on their driving ability prior to and after receiving the diagnosis of OSA. Driving records were obtained for the 2 years before and after they received a diagnosis. Results revealed that patients with OSA in this study had a higher crash rate per driver per year than all drivers in the state of Colorado (0.07 vs 0.01, respectively; p < 0.02). Five of the 36 drivers who successfully used CPAP had an accident 2 years before receiving their diagnoses of OSA, while none had an accident following therapy (0.07 vs 0.0 crash per driver per year, respectively). This study is the first to confirm with traffic records that patients with OSA have fewer automobile accidents while being treated with nasal CPAP.

**Auto-CPAP**


Nocturnal nasal CPAP is the treatment of choice for patients with OSA. However, patient compliance...
with use each night has limited the effectiveness of therapy in certain patients. Hudgel and Fung evaluated 60 newly diagnosed patients with OSA (n = 53) and upper airway resistance syndrome (n = 7) in a 12-week randomized, crossover, single-blind comparison of standard CPAP therapy vs therapy using an autotitrating, self-adjusting CPAP device (APAP). The latter device has the advantage of being able to sense and adjust to the airway turbulence and thus reduce the amount of pressure needed to overcome the obstruction. Patients were randomly assigned to receive either of the two treatments for the first 12 weeks followed by an alternate treatment for the remaining 12 weeks. The average (± SD) pressure for APAP was significantly lower than that for CPAP (6.4 ± 0.4 vs 10.6 ± 0.4 cm H₂O, respectively) with a greater average daily machine use (6.0 ± 0.3 vs 5.5 ± 0.3 h, respectively) with a similar number of nights used. This study offers a longer follow-up than many studies of autotitrating devices. Furthermore, the results suggest that APAP may be better tolerated than CPAP by patients with both OSA and upper airway resistance syndrome, and that they may be more likely to continue therapy with this device.

Hypertension


The association between OSA and chronic hypertension remains controversial, despite more than 2 decades of research. Early studies used small numbers of patients as well as self-reported history of snoring as being indicative of sleep apnea. In addition, confounding variables such as age, sex, and obesity have caused many to question whether there is truly any relationship. Nieto and colleagues describe the largest cohort of persons with sleep apnea studied to date. They performed home sleep studies in 6,841 participants enrolled in the National Institutes of Health-sponsored Sleep Heart Health Study. Results revealed a linear association between BP and the respiratory disturbance index, which persisted after adjustments for age, sex, and body mass index. The sleep time spent at < 90% oxygen saturation also showed a relationship to hypertension, while self-reported snoring did not. While the causal relationship between sleep apnea and hypertension was not addressed by this study, mechanisms were proposed.

Parasomnias

Restless Legs Syndrome/Periodic Limb Movements in Sleep


The International Restless Legs Syndrome (RLS) Study Group has developed minimal criteria for this disabling disorder to include the following: (1) an intense, irresistible urge to move the legs, usually associated with sensory complaints (paresthesias or dysesthesia); (2) motor restlessness; (3) worsening of symptoms at rest and relief with motor activation; and (4) increased severity in the evening or at night. Periodic limb movements in sleep (PLMS), detected by an overnight sleep study and present in at least 80% of patients with RLS, is the only laboratory abnormality typically associated with RLS. Traditional therapy has included the administration of opioids, benzodiazepines, levodopa, and D2-receptor agonists. They provide some relief, but effectiveness may be limited by the persistence of mild symptoms or side effects. Montplaisir and coworkers report on the safety and efficacy of pramipexole, a full D3-receptor agonist, in 10 patients that met the criteria described above for RLS. Pramipexole treatment resulted in a 72 to 84% improvement in questionnaire ratings for subjective restlessness in the daytime, evening, at bedtime, or during the night, compared to placebo. Furthermore, there was a 98% decrease in both the number and index of PLMS as well as improvement in the number of associated arousals, compared with placebo during polysomnography. The number of leg movements while awake also improved. This study supports the hypothesis that the D3 receptors play a significant role in RLS/PLMS and provide a significant advance in the treatment of these disabling disorders.

Pediatric Sleep Disorders

Sudden Infant Death Syndrome


Sudden infant death syndrome is defined as the sudden death of an infant < 1 year of age that remains unexplained after a thorough case investigation, which includes a complete autopsy, examination of the death scene, and clinical history review. Sudden infant death syndrome is the third leading cause of infant mortality (8.9%), accounting for 2,529 deaths in 1998 in the
United States. Facedown sleeping occasionally occurs in healthy full-term infants who are sleeping prone and can result in transient episodes of airway obstruction and asphyxia. Willinger et al examined socioeconomic characteristics, motivation, and message exposure to ascertain which factors influenced a caregiver’s choice of infant sleeping position after the implementation of the program. Approximately 1,000 telephone interviews were conducted during each year of the study between 1994 and 1998, within the 48 contiguous United States. Results showed that prone positioning declined 44 to 17% among white infants and from 53 to 32% among black infants. During this period, reports of supine recommendations from all four sources including the physician, neonatal nurse, reading materials, and radio/television advertisements further increased the probability of supine placement (odds ratio, 6.01; 95% confidence interval). Thus, the authors concluded that recommendations from the physician at well-baby check-ups, from neonatal nursery staff, as well as from the media increased the proportion of infants who were placed in the supine position for sleep.

Sleep-Disordered Breathing


Sleep-disordered breathing (SDB) affects between 1% and 3% of the pediatric population. Adverse health effects can include growth impairment, increased BP, and neurocognitive and behavioral dysfunction. Adenotonsillectomy is the primary therapy in children compared to adults, in whom nasal CPAP therapy is preferred. Previously recognized risk factors for SBD include the following: a high preoperative respiratory disturbance index; underlying comorbidity; and an anatomically small airway. Morton and coworkers performed an observational study of 577 children (< 18 years of age) as part of the Cleveland Family Study, an ongoing longitudinal genetic-epidemiologic study of SDB. These findings indicate that adenotonsillectomy does not eliminate the risk of SDB in children, especially black children, obese children, and children with a family member who has SDB.

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REFERENCES
