# Light and Melatonin Can Reset Circadian Rhythm

BY JANE SALODOF MACNEIL
*Senior Editor*

SCOTTSDALE, ARIZ. — Before traveling from California to South Africa, Dr. Alon Y. Avidan prepared for the time change by spending afternoons in his office, out of the sun. After he arrived in South Africa, he awoke between 5 a.m. and 7 a.m. every morning and took a walk for an hour or more in bright sunlight.

"In a few days, I was on South African time," he told those attending a meeting on sleep medicine sponsored by the American College of Chest Physicians.

Light therapy can be highly effective in correcting jet lag and other circadian rhythm disorders, according to Dr. Avidan, medical director of the University of California, Los Angeles, neurology clinic and associate director of UCLA's sleep disorders center.

Melatonin, a dietary supplement with no approved medical indications, is another useful treatment when delayed sleep is a problem, he said, and ramelteon (Rozerem) shows promise. Although ramelteon is approved only for insomnia, Dr. Avidan said he prescribes it off label to patients with the type of circadian rhythm disorder that causes night owls to complain they can't fall asleep at normal bedtimes or wake up early in the morning.

Often they are tired all day, but not at night, with detriment to their quality of life. "Circadian-related disruption leads to insomnia, hypersomnia, or both," he said, and it can cause impairment of social, occupational, or other areas of functioning.

Sunlight is the most powerful external time cue for regulating and synchronizing the body's circadian rhythms with the environment, Dr. Avidan said. It promotes wakefulness as input from the retina goes to the suprachiasmatic nucleus (SCN) of the hypothalamus, which contains a circadian pacemaker.

To opposite ends, the pineal gland releases melatonin in response to darkness. Melatonin promotes sleep, but levels of it decrease with aging. Compensating with the dietary supplement has been shown to help advance the circadian clock, according to Dr. Avidan.

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For patients with delayed sleep phase, he recommended exposure to bright light—as much as 10,000 amps—in the early morning and taking 0.5 mg of melatonin 5-7 hours before the patient's habitual sleep time, or 12-14 hours before the time a person wishes to awake.

In response to an audience question, Dr. Avidan said several small studies not yet published suggest ramelteon also can advance sleep time. It acts on the melatonin receptors MT1 and MT2, he noted, and described ramelteon as "a true drug." When using ramelteon off label for a circadian sleep disorder, he prescribes a 4-mg dose (which is half the 8-mg dose approved for insomnia).

Advanced sleep-phase disorder is often seen in poorly lit nursing homes, according to Dr. Avidan. People become sleepy very early in the evening, which causes them to go to bed before 8 p.m. and wake, still sleepy, as early as 3 a.m. or 4 a.m. To delay sleep time and wake time, he recommended exposure to bright lights from 7 p.m. to 9 p.m., but not melatonin because—in addition to promoting sleep—it can exacerbate coronary artery disease in some patients.

Irregular sleep-wake patterns also are seen in nursing homes, he noted. In these cases, although residents accumulate normal sleep time for their age, they do so in three or more irregular periods of sleep. Low doses of melatonin did not help in a multicenter study with Alzheimer's disease patients, according to Dr. Avidan, but 10-mg doses produced a trend toward improvement.

For patients whose weariness is related to working night shifts, Dr. Avidan suggested having the patients align circadian rhythms by wearing dark glasses in the morning, keeping the bedroom dark, going to bed soon after the night shift, and seeking exposure to bright light while working. Other possible interventions include stimulants such as caffeine and modafinil (approved for excessive sleepiness caused by shift work), short-acting hypnotics for insomnia, and melatonin to improve duration of daytime sleep, although it has shown little impact on alertness during night shifts.

Finally, the direction of travel can affect the presentation and treatment of jet lag. People traveling east across two or more time zones will have difficulty falling asleep, whereas those traveling west may struggle to maintain sleep.

In both cases, he said, exposure to and avoidance of light at appropriate times can be "very, very effective." People traveling west should seek morning light at the new location and avoid exposure to light in the evening. When traveling east, they should do the opposite. "Avoid light in the early morning, and get as much light as possible in the afternoon/early evening," Dr. Avidan said.

He said it would be advisable to avoid excessive use of caffeine and alcohol in either direction and added that slow-release caffeine has been shown to improve daytime alertness, and melatonin has been shown to foster sleep after an eastbound flight. For specific recommendations geared to time zones of departure and arrival, he recommended using the jet lag calculator in the travel clinic section of www.fleetstreet-clinic.com, a British Web site.

Dr. Avidan disclosed receiving a consultant fee and serving on the speakers bureau and advisory committee of Takeda Pharmaceuticals, which sells ramelteon in North America. He also listed relationships with Sepracor Inc., GlaxoSmithKline, and Boehringer Ingelheim. ■

# Polysomnography Study: Migraine Linked to Disturbed Sleep in Children

BY PATRICE WENDLING
*Chicago Bureau*

CHICAGO — Sleep apnea was observed in more than half of children with migraine in a study presented at the annual meeting of the American Academy of Neurology.

Polysomnography revealed sleep apnea in 56% of children with migraine, compared with 30% of those with nonmigraine headache in a study of 90 children aged 5-19 years with headache and sleep complaints.

The association between sleep apnea and migraine was significant, with an odds ratio of 2.1, Dr. Martina Vendrame, chief resident, Temple University Hospital, Philadelphia, and colleagues reported.

Two-thirds of the children with migraine also had frequent arousal during sleep.

Children with chronic migraine, defined as 15 days or more of migraine per month, took longer to fall asleep, had a shorter total sleep time, woke more frequently during the night, and had shorter REM and slow-wave sleep.

"Clinicians should ask all children with headaches and their parents about sleep problems," including snoring, awakenings during sleep, and day-time sleepiness, Dr. Vendrame told reporters during a press briefing at the meeting. If concerns are raised, patients should be referred to ENT specialists for evaluation and treatment of sleep apnea.

Two-thirds of children in the study identified with sleep apnea were evaluated by ENT specialists, and half underwent tonsillectomy. Of these, 80% had some benefit, including reduced migraine frequency, she said.

Dr. Vendrame acknowledged that the presence of headache could contribute to sleep disturbances, as children suffering from headache will often take daytime naps. In addition, it is widely accepted that headache and sleep disorders share common pathophysiologic mechanisms. Previous studies have evaluated the relationship between headache and sleep disturbances, but this is the first to use polysomnography in children, she said.

The study comprised 60 children with migraine, 11 with chronic daily headaches, 6 with tension headaches, and 13 with nonspecific headaches.

Sleep apnea was also noted among 54% of patients with nonspecific headache, and was observed more frequently in those with a higher body mass index.

Children with chronic daily headache had shorter total sleep time, longer sleep latency, shorter REM sleep, and a higher arousal index.

Among the six children with tension headaches, 50% suffered from teeth grinding, versus 2.4% of children with nontension headaches (OR 1.95).

When asked if the study was biased by having a population of children who already had reported headaches and sleep disturbances, Dr. Vendrame said she hopes to repeat the study in a general population of children, in children without headache, and over an extended period of time to minimize the "first night" effect experienced when children are away from home.

The study was conducted at St. Christopher Hospital for Children, Drexel University, Philadelphia; and the authors had no conflicts of interest to disclose. ■

# *Altered Brain Response Seen in IBS Patients*

Patients with irritable bowel syndrome have altered brain responses to the anticipation of pain and to pain itself, which might make them more sensitive to painful stimuli, reported Dr. Steven M. Berman and his colleagues from the Center for the Neurobiology of Stress at the University of California, Los Angeles.

During expectation of pain, irritable bowel syndrome patients generate higher levels of tonic noradrenergic activity, producing a bias toward interpretation of network activity as pain, and are inefficient at reducing such activity when discrimination of nonpainful stimulation should be maximized, they said (J. Neurosci. 2008;28:349-59).

Functional magnetic resonance imaging (fMRI) was used to measure the blood oxygen level-dependent response to anticipated and delivered rectal distention in 14 female IBS patients and 12 healthy controls (mean age 36 years). When controls were anticipating a painful stimulus, brain activity decreased in several regions, but there was less of this anticipatory deactivation in the IBS patients.

Visceral distention of the rectum was then performed using a computer-driven pump and rectal balloon. Four to six sessions of 16 inflations were performed. Each inflation was preceded by an anticipatory cue. During rectal distention, increases in activity in the insula, dorsal anterior cingulate cortex, and dorsal brainstem were more extensive in IBS patients than in controls.

The results show that during expectation of experimental abdominal/pelvic discomfort, female IBS patients are more anxious and less able than healthy controls to downregulate activity within the CNS network activated by potentially aversive stimuli, the authors noted.

**—Kate Johnson**

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