in patients taking antidepressants, and in some, these medications may unmask this early indicator of neurodegeneration. Synucleinopathies probably cause neuronal loss in brainstem regions that regulate muscle atonia during REM sleep, and loss of these neurons permits movements to break through during REM sleep. RBD also occurs in about 30% of patients with narcolepsy, but the underlying cause is probably different, as they seem to be at no increased risk of a neurodegenerative disorder.

Many patients with RBD have sustained improvement with clonazepam (0.5–2.0 mg qhs).[3] Melatonin at doses up to 9 mg nightly may also prevent attacks.

CIRCADIAN RHYTHM SLEEP DISORDERS

A subset of patients presenting with either insomnia or hypersomnia may have a disorder of sleep *timing* rather than sleep *generation*. Disorders of sleep timing can be either organic (i.e., due to an abnormality of circadian pacemaker[s]) or environmental/behavioral (i.e., due to a disruption of environmental synchronizers). Effective therapies aim to entrain the circadian rhythm of sleep propensity to an appropriate phase.

Delayed Sleep-Wake Phase Disorder Delayed sleep-wake phase disorder (DSWPD) is characterized by: (1) reported sleep onset and wake times intractably later than desired; (2) actual sleep times at nearly the same clock hours daily; and (3) if conducted at the habitual delayed sleep time, essentially normal sleep on polysomnography (except for delayed sleep onset). Patients with DSWPD exhibit an abnormally delayed endogenous circadian phase, which can be assessed by measuring, in a dimly lit environment, the onset of secretion of the endogenous circadian rhythm of pineal melatonin in either the blood or saliva, as light suppresses melatonin secretion. Dim-light melatonin onset (DLMO) in DSWPD patients typically occurs later in the evening than normal, which is about 8:00–9:00 PM (i.e., about 1–2 h before habitual bedtime). Patients tend to be young adults. The delayed circadian phase could be due to: (1) an abnormally long, genetically determined intrinsic period of the endogenous circadian pacemaker; (2) reduced phase-advancing capacity of the pacemaker; (3) slower rate of buildup of homeostatic sleep drive during wakefulness; or (4) an irregular prior sleep-wake schedule, characterized by frequent nights when the patient chooses to remain awake while exposed to artificial light well past midnight (for personal, social, school, or work reasons). In most cases, it is difficult to distinguish among these factors, as patients with either a behaviorally induced or biologically driven circadian phase delay may both exhibit a similar circadian phase delay in DLMO, making it difficult for both to fall asleep at the desired hour. DSWPD is a self-perpetuating condition that can persist for years and may not respond to attempts to reestablish normal bedtime hours. Treatment methods involving phototherapy with blue-enriched light during the morning hours and/or melatonin administration in the evening hours show promise in these patients, although the relapse rate is high. Patients with this circadian rhythm sleep disorder can be distinguished from those who have sleep-onset insomnia because DSWPD patients show late onset of dim-light melatonin secretion.

Advanced Sleep-Wake Phase Disorder Advanced sleep-wake phase disorder (ASWPD) is the converse of DSWPD. Most commonly, this syndrome occurs in older people, 15% of whom report that they cannot sleep past 5:00 AM, with twice that number complaining that they wake up too early at least several times per week. Patients with ASWPD are sleepy during the evening hours, even in social settings. Sleep-wake timing in ASWPD patients can interfere with a normal social life. Patients with this circadian rhythm sleep disorder can be distinguished from those who have early wakening due to insomnia because ASWPD patients show early onset of dim-light melatonin secretion.

In addition to age-related ASWPD, an early-onset familial variant of this condition has also been reported. In two families in which ASWPD was inherited in an autosomal dominant pattern, the syndrome was due to missense mutations in a circadian clock component (in the casein kinase binding domain of *PER2* in one family, and in casein kinase I delta in the other) that altered the circadian period. Patients with ASWPD may benefit from bright-light and/or blue enriched phototherapy during the evening hours to reset the circadian pacemaker to a later hour.

Non-24-h Sleep-Wake Rhythm Disorder Non-24-h sleep-wake rhythm disorder (N24SWRD) can occur when the primary synchronizing input (i.e., the light-dark cycle) from the environment to the circadian pacemaker is compromised (as occurs in many blind people with no light perception) or when the maximal phase-advancing capacity of the circadian pacemaker cannot accommodate the difference between the 24-h geophysical day and the intrinsic period of the patient's circadian pacemaker, resulting in loss of entrainment to the 24-h day. Rarely, self-selected exposure to artificial light may, in some sighted patients, inadvertently entrain the circadian pacemaker to a >24-h schedule. Affected patients with N24SWRD have difficulty maintaining a stable phase relationship between the output of the pacemaker and the 24-h day. Such patients typically present with an incremental pattern of successive delays in sleep propensity, progressing in and out of phase with local time. When the N24SWRD patient's endogenous circadian rhythms are out of phase with the local environment, nighttime insomnia coexists with excessive daytime sleepiness. Conversely, when the endogenous circadian rhythms are in phase with the local environment, symptoms remit. The interval between symptomatic phases may last several weeks to several months in N24SWRD, depending on the period of the underlying nonentrained rhythm and the 24-h day. Nightly low-dose (0.5 mg) melatonin administration may improve sleep and, in some cases, induce synchronization of the circadian pacemaker.

Shift-Work Disorder More than 7 million workers in the United States regularly work at night, either on a permanent or rotating schedule. Many more begin the commute to work or school between 4:00 AM and 7:00 AM, requiring them to commute and then work during the time of day that they would otherwise be asleep. In addition, each week, millions of "day" workers and students elect to remain awake at night or awaken very early in the morning to work or study to meet work or school deadlines, drive long distances, compete in sporting events, or participate in recreational activities. Such schedules can result in both sleep loss and misalignment of circadian rhythms with respect to the sleep-wake cycle.

The circadian timing system usually fails to adapt successfully to the inverted schedules required by overnight work or the phase advance required by early morning (4:00 AM to 7:00 AM) start times. This leads to a misalignment between the desired work-rest schedule and the output of the pacemaker and to disturbed daytime sleep in most individuals. Excessive work hours (per day or per week), insufficient time off between consecutive days of work or school, and transmeridian travel may be contributing factors. Sleep deficiency, increased length of time awake prior to work, and misalignment of circadian phase produce decreased alertness and performance, increased reaction time, and increased risk of performance lapses, thereby resulting in greater safety hazards among night workers and other sleep-deprived individuals. Sleep disturbance nearly doubles the risk of a fatal work accident. Long-term night shift workers have higher rates of breast, colorectal, and prostate cancer and of cardiac, gastrointestinal, and reproductive disorders. The World Health Organization has added night-shift work to its list of probable carcinogens.

Sleep onset begins in local brain regions before gradually sweeping over the entire brain as sensory thresholds rise and consciousness is lost. A sleepy individual struggling to remain awake may attempt to continue performing routine and familiar motor tasks during the transition state between wakefulness and stage N1 sleep, while unable to adequately process sensory input from the environment. Motor vehicle operators who fail to heed the warning signs of sleepiness are especially vulnerable to sleep-related accidents, as sleep processes can intrude involuntarily upon the waking brain, causing catastrophic consequences. Such sleep-related attentional failures typically last only seconds but are known on occasion to persist for longer durations.

[3]No medications have been approved by the FDA for the treatment of RBD.