ATS core curriculum 2016: Part I. adult sleep medicine

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Overview and Pathophysiology

Parasomnias are any abnormal behaviors that occur during sleep or sleep-wake transitions and are classified as REM sleep–related parasomnias, non–REM-related parasomnias, or parasomnias without a sleep stage predilection. Non-REM parasomnias classically occur during the first third of the night, when non-REM sleep predominates relative to REM sleep. Non-REM parasomnias are varied but include confusional arousals, sleepwalking, sleep-related eating disorder, and sleep terrors. Non-REM parasomnias share a common pathophysiology and result from an incomplete transition from non-REM sleep to wakefulness during an arousal.

Non-REM parasomnias can be precipitated by (1) factors that increase sleep inertia and slow-wave sleep pressure (sleep deprivation), (2) factors that potentiate dissociative states (alcohol, sedatives, hypnotics, antidepressants, neuroleptics, stimulants, nicotine, antihistamines), and (3) factors that fragment sleep (stress, medical conditions, sleep-disordered breathing, sleep movement disorders) (1). Therefore, taking a thorough family history and medication history and screening for sleep-disordered breathing and sleep movement disorders are indicated in patients with suspected non-REM parasomnias.

Non-REM parasomnias are more common during childhood, although a significant proportion of the adult population is thought to experience them: 4.2% of adults experience confusional arousals, 1–4% of adults sleep walk, 1–2% have sleep terrors, 2% of older adults have sleep enuresis, and 1–5% of the general population is estimated to have a sleep-related eating disorder (2). Therefore, taking a thorough family history and medication history and screening for sleep-disordered breathing and sleep movement disorders are indicated in patients with suspected non-REM parasomnias.

Presentation

Non-REM parasomnias are diagnosed by the following clinical criteria: recurrent episodes of incomplete awakening from sleep,
lack of appropriate response to others, lack of associated cognition or dream imagery, partial or complete amnesia of the episode, and the event not being better explained by another cause (3). Because of the lack of episode recall, taking a history from the bed partner or a roommate is often important in making a diagnosis.

Although uncomplicated presentations can be diagnosed clinically, a polysomnogram (PSG) may be indicated for the diagnosis of non-REM parasomnias in complicated or atypical presentations, to evaluate for alternative diagnoses such as nocturnal epilepsy or to assess for triggers that fragment sleep, such as a sleep-related breathing disorder or a sleep-related movement disorder.

Features of a complicated or atypical presentation include signs or symptoms of a concomitant sleep disorder, age of onset >16 years, or a history of epilepsy (4). Confusional arousals are associated with confused behavior, such as sitting up in bed without awareness, or with thrashing movements or vocalizations. Importantly, these occur without terror or autonomic response. Sleepwalking adults may only be aware of injury that has resulted from episodes. Sleep-related eating disorder involves recurrent consumption of high-calorie foods or non-food objects during non-REM sleep. Patients may report unintentional weight gain or note open food containers without episode recall. Sleep terrors or non-REM sleep. Patients may report unintentional weight gain or note open food containers without episode recall. Sleep terrors or non-REM sleep. Patients may report unintentional weight gain or note open food containers without episode recall.

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Management
Inciting triggers, such as situational stress, insufficient sleep duration, and contributing medications and substances, should all be addressed, and contributing medical conditions or sleep disorders should be treated. Sleep hygiene, including a regular sleep–wake schedule and sufficient sleep time, should be counseled.

Most non-REM parasomnias do not require pharmacologic treatment if patient and bed-partner safety is maintained. Counseling the patient on optimizing bedroom safety (e.g., removing hazardous objects, securing windows and doors) is thus critical. Although few trials have examined pharmacologic therapy for non-REM parasomnias, benzodiazepines have demonstrated clinical efficacy for most parasomnias. For example, a 2013 case series found a 74% response rate to clonazepam therapy for these conditions (5).

For night terrors, one small case series suggested good therapeutic effect with paroxetine (6). In small trials, medications including topiramate and the selective serotonin reuptake inhibitors have been shown to be effective for patients with sleep-related eating disorder, and more recently, case reports have suggested efficacy with pramipexole and clonazepam (7). Further prospective studies are needed to determine the comparative effectiveness of these various therapies.

References

REM Sleep Parasomnias
Philippe Lachapelle and Sushmita Pandey
REM sleep parasomnias result from recurrent but temporary dissociative states between REM sleep and wakefulness. These include REM sleep behavior disorder, recurrent isolated sleep paralysis, and nightmare disorder.

REM Sleep Behavior Disorder
REM sleep is characterized by skeletal muscle atonia. Pathologic loss of this normal atonia may be related to dysfunction of the brainstem neuronal circuitry responsible for motor paralysis during REM sleep (1) and can give rise to REM dream enactment behaviors (2). These abnormal behaviors occur later in the night, when REM sleep increases in duration, and are typically aggressive or violent, causing injury to the patient or bed partner. When awakened, patients typically recall the associated dream content, unlike with non-REM parasomnias. The diagnosis of REM behavior disorder is made by clinical history or by video PSG documenting vocalizations or complex motor behaviors in REM sleep, in addition to the loss of REM atonia on PSG, and the exclusion of other causes of abnormal behaviors (e.g., medications or other sleep disorders). PSG is also useful in identifying mimics of REM behavior disorder, such as obstructive sleep apnea (OSA) with confusional arousals and frontal lobe epilepsy (2).

REM behavior disorder is strongly associated with α-synucleinopathy neurodegenerative disorders, namely Parkinson’s disease, multiple system atrophy, and Lewy body disease. Approximately one-half of patients with Parkinson’s disease have REM behavior disorder. Recent research suggests that 50% of patients with “idiopathic” disorder develop a synucleinopathy within 10 years of diagnosis (3). Features of early neurodegenerative disease, including anosmia (loss of sense of smell), abnormalities in color discrimination, impulsive behaviors, and autonomic dysfunction, should thus be evaluated routinely in patients with REM behavior disorder (4).

A 2013 study demonstrated that even when REM behavior disorder occurred in the setting of concomitant antidepressant therapy, neurodegenerative disease still developed, suggesting that this disorder cannot be considered to be simply a side effect of antidepressant therapy (5).

There are currently no randomized trials to guide treatment of REM behavior disorder. Safety precautions should be taken to avoid self-injury or injury to bed partners during sleep. Although
clonazepam is the recommended first-line treatment, a recent systematic review suggested similar treatment outcomes with clonazepam and with high-dose melatonin, with less frequent adverse effects reported by melatonin-treated patients (6). Prospective data on the efficacy of clonazepam and melatonin therapy are lacking.

Recurrent Isolated Sleep Paralysis
Sleep paralysis is characterized by motor paralysis on falling asleep (hypnagogic) or awakening (hypnopompic), with preserved sensorium. Auditory or visual hallucinations may accompany sleep paralysis and may be frightening to the individual. Isolated or sporadic sleep paralysis is common. Up to 7% of the general population may experience an episode, and certain subpopulations, including undergraduate and graduate students (28%) and psychiatric patients (31%), may experience an isolated sleep paralysis episode more frequently (7). Sleep deprivation and alterations in circadian rhythm can be potential triggers.

If the sleep paralysis is recurrent, a family history should be elicited for familial hypokalemic periodic paralysis, and PSG and/or multiple sleep latency testing (MSLT) should be considered to evaluate for narcolepsy. For recurrent cases of isolated sleep paralysis, treatment consists of reassurance and avoiding predisposing factors such as sleep deprivation and excess stress.

Nightmares
Nightmares are characterized by awakening with intense fear from frightening dreams in REM sleep, with recall of dream content. Unlike REM behavior disorder, there are no associated vocalizations or dream-enactment behaviors. Recurrent nightmares can lead to significant distress as well as functional and social impairment. Although nightmares typically start during childhood (ages 3–6 yr), they usually decrease in frequency with age. In a subset of individuals, nightmares can persist into adulthood and may be associated with psychiatric disorders, such as post-traumatic stress disorder, schizophrenia, and anxiety disorders (8).

Treatment should focus on controlling the underlying conditions, counseling stress management, and adjusting causative medications (e.g., β-adrenergic blockers). Psychotherapy is effective in those with recurrent nightmares (9), and a 2015 metaanalysis affirmed that prazosin is effective in nightmares related to post-traumatic stress disorder (10).

References
1 Fraigne JJ, Torontalli ZA, Snow MB, Peever JH. REM Sleep at its core - circuits, neurotransmitters, and pathophysiology. Front Neurol 2015;6:123.
which patients with OSA, and in particular, mild, asymptomatic OSA, to treat (4).

Hypopneas are characterized as obstructive if any of the following features are present: snoring during the event, increased inspiratory flattening of the nasal pressure signal or positive airway pressure device flow signal as compared with baseline breathing, or thoracoabdominal paradox during the event. Absence of these features characterizes central hypopneas. Distinguishing central from obstructive hypopneas can assume importance in conditions such as congestive heart failure, stroke, or chronic opiate use, all of which predispose to central sleep apnea.

Respiratory effort–related arousals are defined as ≥10 seconds of increased respiratory effort or decreased airflow that does not meet the criteria for apnea or hypopnea but that results in an arousal from sleep (1). Previously, these arousals required esophageal manometry to be scored, but now, like hypopneas, they can be scored with a nasal pressure transducer.

**Periodic Limb Movements in Sleep**

The AASM defines limb movements in sleep as movements with a duration of 0.5–10 seconds, with the onset defined by a minimum of an 8 μV increase in EMG voltage above resting EMG. The end of the limb movement is defined by EMG <2 μV above resting

### Table 1. Definitions of sleep stages

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
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</table>
| Wake           | Scored when either a or b or both are seen in >50% of the epoch  
                 a.  \( \alpha \) rhythm (8–13 Hz) over the occipital region with eye closure  
                 b. Other findings consistent with wake  
                  i. Eye blinks (0.5–2 Hz)  
                  ii. Rapid eye movements with normal or high chin EMG tone  
                  iii. Reading eye movements  |
| \( \alpha \) rhythm |                                                                                                                                                                                                               |
| Stage 1 NREM   | In patients who generate \( \alpha \) rhythm, it is attenuated and replaced by LAMF activity for >50% of the epoch (4–7 Hz). In patients who do not generate \( \alpha \) rhythm, score when any of the following occur:  
                 a. LAMF with slowing of background frequencies by ≥1 Hz from that of wake  
                 b. Vertex sharp waves  
                 c. Slow eye movements  |
| LAMF           |                                                                                                                                                                                                               |
| Stage 2 NREM   | Scored when one or both of the following occur in the first half of the epoch or in the second half of a preceding epoch:  
                 a. One or more K complexes unassociated with arousals  
                 b. One or more sleep spindles  |
| K complex      |                                                                                                                                                                                                               |
| Sleep spindle  | At least 20% of the epoch consists of slow-wave activity (0.5–2 Hz, 75 μV peak-to-peak amplitude over frontal regions)  |
| Stage 3 NREM   | Scored when all of the following occur:  
                 a. LAMF without K complexes or sleep spindles  
                 b. Low chin EMG tone for the majority of the epoch and concurrent REMs  
                 c. REMs at any position within the epoch  |
| Slow wave activity |                                                                                                                                                                                                 |
| REM            |                                                                                                                                                                                                               |

*Definition of abbreviations: LAMF = low-amplitude, mixed frequency; NREM = non-REM sleep.*
Hypopnea

THERM = oronasal thermistor. PRESS = nasal pressure transducer. CHEST = thoracic movement belt. ABDMN = abdominal movement belt. ECG = electrocardiogram. SaO2 = oxyhemoglobin saturation.

A hypopnea is defined by a drop in the peak signal excursions in an airflow sensor $\geq 30\%$ of the pre-event baseline for $\geq 10$ seconds accompanied by $\geq 3\%$ oxygen desaturation or arousal (recommended) or $\geq 4\%$ oxygen desaturation (acceptable). In this example, note that the nasal pressure transducer signal (PRESS) drops significantly but the oronasal thermistor (THERM) still detects flow. This is consistent with the partially reduced airflow of a hypopnea.

Apnea

Obstructive Apnea

THERM = oronasal thermistor. PRESS = nasal pressure transducer. THO = thoracic movement belt. ABDOMEN = abdominal movement belt. SAO2 = oxyhemoglobin saturation.

An obstructive apnea is defined by a drop in the peak signal excursions in an airflow sensor $\geq 90\%$ of the pre-event baseline for $\geq 10$ seconds accompanied by continued or increased respiratory effort during the entire period of absent airflow.

Central Apnea

N/O Airflow = oronasal thermistor. PTAF = nasal pressure transducer. CHEST = thoracic movement belt. ABDOMEN = abdominal movement belt. SAO2 = oxyhemoglobin saturation.

An central apnea is defined by a drop in the peak signal excursion in an airflow sensor $\geq 90\%$ of the pre-event baseline for $\geq 10$ seconds accompanied by absent inspiratory effort during the entire period of absent airflow.

Figure 1. Scoring of respiratory events. A hypopnea is defined by a drop in the peak signal excursions in an airflow sensor of $\geq 30\%$ of the pre-event baseline for $\geq 10$ seconds accompanied by $\geq 3\%$ oxygen desaturation or arousal (recommended) or $\geq 4\%$ oxygen desaturation (acceptable). In this example, note that the PRESS signal drops significantly but the THERM still detects flow. This is consistent with the partially reduced airflow of a hypopnea.
EMG for at least 0.5 seconds. A clustering of four or more consecutive limb movements with an interval between individual limb movements of 5–90 seconds is called a periodic limb movement series (Figure 2) (3).

Figure 2. Period limb movement (PLM) series. The image depicts a 3-minute window of polysomnography recording. A PLM series which is defined as at least four consecutive limb movements with an interval between individual limb movements of 5–90 seconds. Each limb movement has a duration of 0.5–10 seconds with the onset defined by a minimum of an 8–μV increase in EMG voltage above resting EMG and the end defined by EMG < 2 μV above resting EMG for at least 0.5 seconds. Adapted by permission from Reference 11.

EMG for at least 0.5 seconds. A clustering of four or more consecutive limb movements with an interval between individual limb movements of 5–90 seconds is called a periodic limb movement series (Figure 2) (3).

References

In-Laboratory Sleep Testing Diagnostics

Ridhwan Y. Baba and Neomi Shah

Since the publication of the earliest sleep diagnostic guidelines in the 1990s, scientific literature regarding the objective assessment of sleep complaints has advanced significantly. Newer diagnostic tools include peripheral arterial tonometry, actigraphy, and
The following data should be recorded: start and stop times for each trial, sleep latency, total sleep time, stages of sleep achieved for evaluation of sleep and the majority of sleep disorders, the

Table 2. Recommendations for the MSLT protocol

<table>
<thead>
<tr>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. There should be five nap opportunities at 2-h intervals, initial nap 1.5–3 h after termination of nocturnal study.</td>
</tr>
<tr>
<td>2. MSLT should be done immediately after a non-split-night PSG, with at least a 6-h major sleep period.</td>
</tr>
<tr>
<td>3. Stimulants and REM-suppressing medications should be stopped 2 wk before MSLT.</td>
</tr>
<tr>
<td>4. Use of caffeine and exposure to unusual amounts of sunlight are discouraged.</td>
</tr>
<tr>
<td>5. Drug screening during the morning of MSLT can be considered.</td>
</tr>
<tr>
<td>6. Smoking should be stopped at least 30 min before each nap opportunity.</td>
</tr>
<tr>
<td>7. A light breakfast is recommended before the first nap, and a light lunch after the second nap.</td>
</tr>
<tr>
<td>8. The recording montage for the MSLT should include central EEG (C3-A2, C4-A1) and occipital (O1-A2, O2-A1) derivations, left and right eye EOGs, mental/submental EMG, and ECG.</td>
</tr>
<tr>
<td>9. After a standard biocalibration, the patient should be instructed to “Please lie quietly, assume a comfortable position, keep your eyes closed and try to fall asleep.”</td>
</tr>
<tr>
<td>10. Sleep onset is determined by the time from lights out to the first epoch of any stage of sleep. REM latency is taken as the time of the first epoch of sleep to the beginning of the first epoch of REM sleep regardless of the intervening stages of sleep or wakefulness.</td>
</tr>
<tr>
<td>11. A nap session is terminated after 20 min if sleep does not occur.</td>
</tr>
</tbody>
</table>

Definition of abbreviations: EOG = electrooculogram; MSLT = multiple sleep latency testing; PSG = polysomnography.

Table 3. Recommendations for the MWT protocol

<table>
<thead>
<tr>
<th>Recommendation</th>
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</thead>
<tbody>
<tr>
<td>1. There should be four nap opportunities at 2-h intervals, initial nap 1.5–3 h after termination of nocturnal study.</td>
</tr>
<tr>
<td>2. Performance of a PSG or use of sleep logs before the MWT should be based on clinical judgment.</td>
</tr>
<tr>
<td>3. After insulating the room from external light, a light source should be positioned slightly behind the subject’s head and should deliver an illuminance of 0.10–0.13 lux. The subject should be seated in bed with the back and head supported. Room temperature should be set on the basis of the patient’s comfort level.</td>
</tr>
<tr>
<td>4. The clinician should decide on the use of tobacco, caffeine, and other medications such as stimulants. Drug screening during the morning of MWT can be considered.</td>
</tr>
<tr>
<td>5. A light breakfast is recommended before the first nap, and a light lunch after the second nap.</td>
</tr>
<tr>
<td>6. The recording montage for the MSLT should include central EEG (C3-A2, C4-A1) and occipital (O1-A2, O2-A1) derivations, left and right eye EOGs, mental/submental EMG, and ECG.</td>
</tr>
<tr>
<td>7. After a standard biocalibration, the patient should be instructed to “Please sit still and remain awake for as long as possible. Look directly ahead of you, and do not look directly at the light.” Patients are not allowed to use extraordinary measures to stay awake.</td>
</tr>
<tr>
<td>8. Sleep onset is defined as the first epoch of &gt; 15 s of cumulative sleep in a 30-s epoch.</td>
</tr>
<tr>
<td>9. A nap session is terminated after 40 min if sleep does not occur or after unequivocal sleep, defined as three consecutive epochs of stage 1 sleep, or one epoch of any other stage of sleep.</td>
</tr>
<tr>
<td>10. The following data should be recorded: start and stop times for each trial, sleep latency, total sleep time, stages of sleep achieved for each trial, and mean sleep latency (arithmetic mean of the four trials).</td>
</tr>
</tbody>
</table>

Definition of abbreviations: EOG = electrooculogram; MSLT = multiple sleep latency testing; MWT = maintenance of wakefulness test; PSG = polysomnography.
Diagnostic testing for sleep-disordered breathing

<table>
<thead>
<tr>
<th>Type</th>
<th>Definition and Parameters Assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Full, attended, in-laboratory polysomnography</td>
</tr>
<tr>
<td>II</td>
<td>Full, unattended polysomnography</td>
</tr>
<tr>
<td>III</td>
<td>Minimum of seven channels monitored (e.g., full attended polysomnography [seven or more channels] in a laboratory setting)</td>
</tr>
<tr>
<td>IV</td>
<td>Minimum of four channels monitored (may also have limited channel devices [usually using four to seven channels])</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type</th>
<th>Definition and Parameters Assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Minimum of seven channels monitored (e.g., EEG, EOG, EMG, ECG, airflow, respiratory effort, oximetry, video monitoring)</td>
</tr>
<tr>
<td>II</td>
<td>Portable respiratory polygraphy</td>
</tr>
<tr>
<td>III</td>
<td>Full unattended polysomnography (seven or more channels)</td>
</tr>
<tr>
<td>IV</td>
<td>Limited monitoring</td>
</tr>
</tbody>
</table>

One or two channels monitored, typically with one or two channels using oximetry as one of the parameters

Definition of abbreviation: EOG = electrooculogram.

Adapted with permission from “Clinical guidelines for the use of unattended portable monitors in the diagnosis of obstructive sleep apnea in adult patients” by Collop et al., 2007, J Clin Sleep Med.

mean sleep latency using first epoch of sleep, 30.4 ± 11.2 min) (2, 3). Importantly, use of the MWT for the purpose of assessing driving safety does not guarantee that the subject will not experience hypersonmolence in the work environment.

Findings from both the MSLT and the MWT are most valuable when integrated with the clinical history (e.g., medications, preceding sleep log) to reach a clinical diagnosis. Both the MSLT and the MWT are influenced by physiological, psychological, and test protocol variables (2, 3). Future research should focus on precisely defining normative data, identifying sensitivity and specificity of the MSLT and MWT protocols, and determining the impact of MSLT and MWT results on patient outcomes and/or clinical decision making.

Out-of-Center Sleep Diagnostic Testing

Barry G. Fields and Kathleen Sarmiento

Actigraphy

Actigraphy devices are worn like wristwatches and record movement and light to estimate sleep and wake time. A recent study revealed high sensitivity (0.965) but low specificity (0.329) in detecting sleep (1). Actigraphy is indicated for the initial evaluation of circadian rhythm disorders and for the measurement of treatment response in these disorders (2). It is also used to measure sleep patterns in infants and children and in older adults for whom more advanced sleep testing may be difficult. Using actigraphy during home sleep apnea testing (HSAT) improves total sleep time estimation, leading to a more accurate determination of OSA severity. Nevertheless, limited insurance reimbursement curtails its clinical use.

Home Sleep Apnea Testing

In-laboratory PSG is considered a type I study, whereas HSAT devices yield type II, III, or IV studies (Table 4) (3); type III devices are the focus of this discussion, given their frequent use in clinical care and research. A newer home testing device classification scheme is based on how sleep, cardiovascular, oximetry, position, effort, and respiratory (SCOPER) parameters are measured and reported (4). This SCOPER system enables device-specific functionality delineation, but remains less frequently used than the type II-IV system.

HSAT is indicated as an alternative to PSG in patients with a high pretest probability of having moderate to severe OSA (5). In this group, a 2014 metaanalysis demonstrated that most type III devices measuring respiratory effort and airflow are >92% sensitive in detecting OSA (apnea-hypopnea index \([\text{AHI}] > 5 \text{ events/h}) (6). The sensitivity declines as the pretest probability of disease lessens. Thus, home testing is not recommended for routine screening of populations at low to moderate risk of OSA. Home testing is also not appropriate for the diagnosis of nonbreathing sleep disorders.

Comorbidities that degrade HSAT accuracy include heart failure, moderate to severe pulmonary disease, and the concomitant use of opioid medications, which can lead to central sleep apnea, nocturnal hypoxia, and nocturnal hypoventilation. Although current guidelines do not recommend HSAT in patients with these comorbidities, in practice, type III recorders can provide useful information regarding OSA, central sleep apnea, and Cheyne-Stokes respiration. For example, home testing demonstrates high specificity and sensitivity in detecting OSA among stable patients with heart failure (7) and has low failure rates among patients with neuromuscular disease (8).

Understanding the limitations of HSAT is critical. Technical failures (3–20%) and false-negative studies are common (up to 20%) (9, 10). The AHI is generally underestimated because of a larger denominator (total recording time vs. total sleep time on
PSG) and the inability to include disordered breathing events requiring EEG monitoring (alternate rule hypopneas and respiratory effort–related arousals). Home testing–determined OSA severity is also sometimes reported as a respiratory disturbance index to distinguish itself from the PSG–determined AHI. The AASM recently published HSAT scoring rules and definitions of key terms such as monitoring time (an approximation of total sleep time) and respiratory event index (total number of respiratory events divided by monitoring time) (11).

Although PSG remains the gold standard for OSA diagnosis, HSAT use has increased. Reasons include diminished wait time when access to PSG is limited, logistical convenience of home testing, noninferior clinical outcomes compared with PSG-driven paradigms (9, 10), and reduced cost for health care service payers (12). Those payers reimburse home testing at significantly lower rates than those for PSG, resulting in a negative cost margin for some laboratories. Thus, although HSAT is less costly to health care systems, its use has threatened the financial viability of some sleep centers.

References


Circadian Disorders: Overview of Biology

Matthew P. Butler and Steven A. Shea

Humans typically live in environments that cycle regularly with day and night, leading to the adoption of matching daily patterns of behavior such as wakefulness/sleep and eating/fasting cycles. These predictable behavioral patterns occur via priming of a number of physiological systems via endogenous circadian clocks. The priming manifests as physiological rhythms in core body temperature, heart rate, blood pressure, hormonal levels, and gene expression, etc. Measurable rhythms therefore are composed of an endogenous circadian clock component summed with effects caused by behavior or the environment.

Endogenous rhythms can be revealed by measuring changes that persist while under constant behavioral and environmental conditions (this research method is known as the constant routine protocol, which removes all potential rhythmic daily cues). Circadian rhythms are those endogenous rhythms with a period of close to 24 hours. In humans, the free-running period of the circadian clock is 24.1 hours (1). Slight variations in this period length occur among people, and those with the shortest periods have the earliest onset of melatonin secretion relative to their bedtime (2).

Circadian rhythms are governed by a pacemaker in the suprachiasmatic nucleus (SCN) of the hypothalamus, which is synchronized by light acting via the retinohypothalamic tract. Importantly, neurons of the SCN are autonomously rhythmic, and each cell contains a genetic oscillator, which is a transcription-translation feedback loop composed of the driving genes, Clock and Bmal1, and the negative repressors, Period and Cryptochrome (3). Although many interacting genes generate the rhythms, only the knockout of the Bmal1 gene has been shown to render an animal completely arrhythmic (Figure 3 (4).

The same core clock genes are expressed rhythmically in most cells of the body, and these genes can synchronize tissue-specific rhythms. Overall, it is estimated that 55% of all genes are rhythmically expressed somewhere in the body (5), but the subset of cycling genes and their phases of peak transcription can differ significantly among tissues. This allows each organ to be primed appropriately for anticipated behaviors. Under normal conditions, the SCN timing information is conveyed to these target tissues by a combination of neural and

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Figure 3. (A) SCN lie just dorsal to the optic chiasm where they receive photic cues from the retina via the RHT. The projection pattern is predominantly ipsilateral in primates. (B) The molecular clock involves transcription and translation loops that take ~24 hours to complete. The basic loop is illustrated. The positive regulators Clock and Bmal1 dimerize and initiate transcription at E-box (CACGTG) elements in the genome. The Per and Cry genes are negative regulators. These newly translated proteins dimerize and then inhibit Clock:Bmal1-dependent transcriptional activity. As the Per and Cry proteins degrade, the ~24-hour circadian cycle begins again. Cry = Cryptochrome; Per = transcribed Period; RHT = retinohypothalamic tract; SCN = suprachiasmatic nuclei.

endocrine pathways, as well as indirectly by acute responses to behaviors (e.g., the metabolic response to a meal). These multiple synchronizing pathways are normally “in tune,” but stressors such as shift work and jet lag can lead to dyssynchrony and can change the relative timing of tissue clocks across the body.

Given the pervasive nature of the circadian rhythm, it is not surprising that disrupting it can be harmful. In patients, jet lag and shift work increase the risk of obesity, diabetes, heart disease, cancer, and major mood disorders (6–8). Jet lag or genetic disruptions of the clock also cause glucose intolerance, insulin resistance, increased susceptibility to myocardial injury, and heart failure (8, 9). Circadian disruptions are not limited to shift workers, and a variety of genetic disorders can advance or delay the circadian clock (e.g., familial advanced or delayed sleep disorders).

An individual’s biological rhythm therefore reflects the function of clocks across many cells and tissues. Recognition of this fact has led to an increase in interest in chronopharmacology, a field aimed at increasing a drug’s efficacy and reducing its toxicity by identifying the best times of administration. Many top-selling medications in the United States act on gene targets that are rhythmically expressed, at least at the messenger RNA level (5). Thus, the time a drug is administered may be able to improve its therapeutic potential, and future research is expected in this area.

References


Management of Circadian Disorders

Janelle V. Baptiste and Katherine M. Sharkey

Circadian rhythm sleep-wake disorders encompass syndromes in which the patient’s sleep-wake behavior is not synchronized to customary clock times and/or the 24-hour day. Epidemiologic
phase disorder. Shifting and entraining circadian rhythms in delayed sleep-wake times. Patients report sleep-onset insomnia and excessive daytime sleepiness when attempting to keep to a prescribed sleep-wake schedule. Delayed sleep-wake disorder should thus be considered in patients who report sleep-onset insomnia, particularly in adolescents and young adults, who have an increased propensity for this condition.

Recommended treatments include strategically timed melatonin administration, morning bright-light exposure, and prescribed sleep-wake schedules (2). Light therapy should be sufficiently bright (5,000–10,000 lux) to elicit a clinically significant response but also short enough in duration to ensure patient compliance. Morning bright-light exposure produces the largest phase advances, and although the circadian system is most responsive to short wavelength (blue) light of 460 nm, appropriately timed broad-spectrum white light is also effective at shifting and entraining circadian rhythms in delayed sleep-wake phase disorder.

Patients with advanced sleep-wake phase disorder have earlier sleep-wake times with respect to their desired/required times. Consequently, these patients have difficulty staying awake in the evening and wake up at an earlier-than-desired time and this may be misinterpreted as sleep-maintenance insomnia. Evening bright-light exposure is the recommended therapy, because light at this time produces phase delays of endogenous circadian rhythms.

Irregular sleep-wake rhythm disorder is characterized by the lack of a clear circadian pattern of sleep-wake behavior. Patients experience periods of wakefulness during conventional sleep hours, with fragmented, insufficient sleep leading to excessive sleepiness and daytime napping. There is typically no major sleep period. This condition is more common among patients with neurodevelopmental or neurodegenerative disorders and can pose challenges for caregivers. Timed bright-light therapy and prescribed sleep-wake schedules are recommended for all patients. Strategically timed melatonin is also recommended for developmentally delayed children/adolescents with irregular sleep phase disorder (2) but not for elderly patients because of a lack of efficacy and an increased risk of depressive mood symptoms (3).

Most individuals’ endogenous circadian periods are not exactly 24 hours and therefore require daily resetting by exposure to the light-dark cycle to stay synchronized to the 24-hour day. Non–24-hour sleep-wake disorder occurs when patients fail to entrain to the 24-hour light-dark cycle. Patients exhibit sleep-wake patterns that show a progressive delay or advance, depending on the period length of their endogenous circadian clock. They often cycle in and out of typical alignment with conventional sleep-wake times. During a symptomatic period, sleep times gradually shift into daytime hours, and patients experience insomnia at night and daytime sleepiness.

Most patients with non—24-hour sleep-wake disorder are totally blind, but this disorder also occurs in sighted individuals who fail to maintain entrainment despite exposure to environmental light-dark cues. Strategically timed melatonin is recommended (4), and a 2015 study found the melatonin agonist, tasimelteon, to be effective for the treatment of this condition (5). Figure 4 summarizes the typical sleep periods

<table>
<thead>
<tr>
<th>Type</th>
<th>Bedtime</th>
<th>Wake Time</th>
<th>Typical Patient Population</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed sleep-wake phase disorder</td>
<td>&gt;2 h later than desired</td>
<td>Later than desired</td>
<td>Adolescents and young adults</td>
<td>Timed melatonin, morning bright light, prescribed sleep-wake schedules</td>
</tr>
<tr>
<td>Advanced sleep-wake phase disorder</td>
<td>Earlier than desired</td>
<td>Earlier than desired</td>
<td>Elderly</td>
<td>Evening bright light</td>
</tr>
<tr>
<td>Irregular sleep-wake rhythm disorder</td>
<td>Variable, without clear circadian pattern</td>
<td>Variable, without clear circadian pattern</td>
<td>Patients with neurodevelopmental or neurodegenerative disorders</td>
<td>Timed bright-light therapy, prescribed sleep-wake schedules, timed melatonin for children/adolescents</td>
</tr>
<tr>
<td>Non–24-hour sleep-wake disorder</td>
<td>Progressively delayed or advanced</td>
<td>Progressively delayed or advanced</td>
<td>Blind patients</td>
<td>Timed light exposure, prescribed melatonin, alteration of sleep schedules, modafinil/armodafinil</td>
</tr>
<tr>
<td>Shift-work disorder</td>
<td>Circadian misaligned</td>
<td>Circadian misaligned</td>
<td>Night-shift workers</td>
<td>Prescribed sleep-wake and light-dark schedules, timed melatonin, zolpidem</td>
</tr>
<tr>
<td>Jet-lag disorder</td>
<td>Disrupted and variable</td>
<td>Disrupted and variable</td>
<td>People who travel across more than two time zones</td>
<td>Prescribed sleep-wake and light-dark schedules, timed melatonin, zolpidem</td>
</tr>
</tbody>
</table>

Table 5. Circadian rhythm sleep disorders

Studies show that adults in Western cultures typically have a single sleep bout at night with reported bedtimes between 22:00 and 24:00 and wake times between 6:00 and 8:00, with sleep onset occurring about 2 hours after the onset of melatonin secretion.

The International Classification of Sleep Disorders, Third Edition (1) defines six major circadian rhythm sleep-wake disorders. These are characterized by significant deviations from typical patterns, as summarized in Table 5. Circadian disorders are diagnosed via history and a documentation of sleep patterns with sleep diaries and/or actigraphy for 7–14 days (which should include both workdays and work-free days). An abnormal pattern of the endogenous melatonin rhythm may also be helpful in diagnosing circadian disorders.

Delayed sleep-wake phase disorder is characterized by a delay (usually >2 h) of sleep onset with respect to the patient’s desired sleep-wake times. Patients report sleep-onset insomnia and excessive daytime sleepiness when attempting to keep to a conventional schedule. Delayed sleep-wake disorder should thus be considered in patients who report sleep-onset insomnia, particularly in adolescents and young adults, who have an increased propensity for this condition.

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Most patients with non–24-hour sleep-wake disorder are totally blind, but this disorder also occurs in sighted individuals who fail to maintain entrainment despite exposure to environmental light-dark cues. Strategically timed melatonin is recommended (4), and a 2015 study found the melatonin agonist, tasimelteon, to be effective for the treatment of this condition (5). Figure 4 summarizes the typical sleep periods...
of the major circadian rhythm sleep disorders caused by intrinsic alterations of the circadian timing system.

Shift-work sleep disorder is diagnosed in patients who experience insomnia or sleepiness in association with work hours that occur, at least in part, during usual sleep times. The circadian clocks of most night-shift workers do not align with daytime sleep, in part because the light-dark cycle opposes adaptation and because most night-shift workers revert to daytime wakefulness and nighttime sleep on days off.

The alertness-promoting medications modafinil and armodafinil are Food and Drug Administration approved for use during the night shift to treat shift-work sleep disorder. Often, however, neither alertness medications nor hypnotic medications to facilitate daytime sleep can overcome the effects of circadian misalignment (6). Countermeasures that control light and dark using timed light exposure, sunglasses, eye/window shades for daytime sleep, and light during night work can facilitate adaptation and help with insomnia and sleepiness. Timed melatonin administration and adopting a sleep schedule on days off that overlaps with sleep times on workdays can also ease the transitions between workdays and days off (7).

Jet lag disorder refers to sleep difficulties leading to a reduction of sleep time and/or daytime functional impairment associated with travel across at least two time zones. Symptoms include malaise, cognitive impairment and performance deficits, and/or somatic symptoms after travel. Although jet lag disorder is usually self-limited, prescribed sleep-wake and light-dark schedules and appropriately timed melatonin can be helpful in preventing and/or treating jet lag. Zolpidem taken before east-bound transatlantic nighttime flights and/or at bedtime in the new time zone has also been shown to improve subjective sleep quality in individuals traveling eastward across five to nine time zones (8, 9).

In conclusion, circadian rhythm sleep disorders are chronic conditions that cause significant sleep difficulties and daytime impairment and require therapies to adjust and set the circadian rhythm and to ameliorate symptoms. Further research is needed to identify biomarkers for a more precise diagnosis and also to devise more effective personalized treatment regimens for these disorders (10).

Author disclosures are available with the text of this article at www.atsjournals.org.

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