Update on Treating Sleep Disorders

New treatments hold promise of increasing efficacy with precision medicine.

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Understanding the neurobiology of sleep and its benefits on health and wellness continues to evolve, and new strategies have emerged to treat individuals with sleep disorders. Sleep medicine is poised to deliver care in a precision medicine model. For example, some sleep centers are using pharmacogenomics to identify better fits for medication use for patients with sleep disorders to maximize benefits and minimize potential adverse effects. New tools help nonsleep specialists identify patients with potential sleep disorders and some generate referrals, implement behavioral modifications (eg, patient homework), and provide customized education, including outlining next steps and risks of not being evaluated and treated (Figure 1). Every year, new options emerge to better evaluate and treat patients with sleep disorders. Many devices and treatment options are in early-stage development, and others are in clinical trials or available.

Insomnia

Chronic insomnia is generally categorized as difficulty falling asleep or maintaining a regular sleep schedule for at least 3 months. Patients often experience daytime sleepiness and/or reduced cognitive function that negatively interferes with daily life, affecting productivity and mood. Insomnia remains a clinical diagnosis based on these symptoms and does not require polysomnography. Clinicians, however, now have Food and Drug Administration (FDA)-approved home monitoring devices to help evaluate insomnia, which can provide high-value care for patients and more individualized understanding of a particular patient’s sleep patterns.

Cognitive-Behavioral Therapy

The accepted standard treatment for chronic insomnia is cognitive-behavioral therapy for insomnia (CBT-I). In CBT-I, patients are guided through a structured and personalized program, typically by a sleep behavior psychologist, to modify their cognitive processes and sleep behaviors in an effort to improve their sleep. The American Academy of Sleep Medicine and the American College of Physicians recommend CBT-I as first-line treatment for chronic insomnia. Strategies for CBT-I management options are listed in the Table. Because of the limited number of fellowship-trained sleep psychologists, alternative options (eg, supervised behavioral sleep-trained nurses, individuals with a master’s degree in psychology, or wellness coaches) are being explored. If patients can not access in-person CBT-I, it can be offered online or via video conference.

Other adjunctive techniques may also help treat insomnia. Mindfulness meditation can help patients adopt new ways to manage symptoms through meditation exercises, discussions, and daily monitoring of sleep-wake activities. A study showed that sleep efficacy improved from 30.87% to 69.87% following mindfulness meditation alone; however, this study was limited by lack of a control group. A randomized controlled trial is currently being performed to seek more evidence for efficacy of mindfulness meditation. Acupuncture, either alone or in combination with other treatments is an option. Acupuncture combined with estazolam (a sedative/hypnotic benzodiazepine) led to higher rates of improving sleep initiation, duration, and efficiency compared with estazolam alone. Although acupuncture may be effective, larger trials are still needed to assess the long-term effects. Hypnotherapy may have benefit, but there are some precautions to consider (eg, headache, drowsiness, creation of false memories, or strong emotions due to stressful events from earlier memories).

Sleep-Promoting Devices and Tools

A number of devices hold promise for insomnia resolution. Cranial electrical stimulation (CES) is increasingly being considered, but more research is needed to assess its clinical benefits. Alpha stimulation is a type of CES that is an FDA-approved, handheld, prescription medical device. Transcranial magnetic stimulation (TMS) has been used to understand the neurobiology of insomnia and proposed as a potential therapeutic tool. Currently, TMS is primarily used to alleviate symptoms of depression, anxiety, and migraine. Previous work has shown that TMS is safe and effective. Some studies of TMS have reported significant improvements in sleep quality, suggesting
it may also be an option in the future. Open-loop audio-visual stimulation (AVS), an at-home biofeedback program using light and sound patterns to induce slow brainwaves, is being investigated as treatment for insomnia.16

Medications to treat insomnia are not always warranted or recommended, but there are times when they can be considered. Hypocretin antagonists are relatively new treatments for insomnia. (See Sleep, Sleeplessness, and Neuropsychiatric Conditions in this issue). With a move toward precision medicine, clinicians are able to personalize health care to each patient’s unique variables that trigger and subsequently mitigate their insomnia symptoms. For example, individuals suffering from insomnia due to post-traumatic stress disorder or substance-use disorder may respond better to certain approaches compared with others.17,18 Pharmacogenomics is being used for patients with insomnia when medications are indicated, allowing for identification of a better medication match for the patient. In some instances, evidence for the lack of a good medication fit facilitates engagement in CBT–I.

From a clinical perspective, sleep specialists may recommend other commercially available sleep tools (eg, white-noise devices, light therapy, blue/green-light-blocking glasses, or special blankets, mattresses, or pillows). Weighted blankets, which have been found to increase sleep time and provide more secure sleep, may be of benefit for patients with insomnia but have not been subjected to any rigorous study. Although efficacy data are limited, sleep specialists are bringing such tools into their armamentarium to provide comfort and more personalized care for patients. Technology companies have also been developing consumer devices aimed at improving sleep quality (eg, Ebb Insomnia Therapy headband, Dreem Headband, SomniResonance SR1 sleep device, Dodow Sleep, and URGONight), but further study is required to assess their place in clinical practice.

Circadian Rhythm Sleep-Wake Disorders

In individuals with circadian rhythm sleep-wake disorders (CRSWD), the sleep-wake rhythm is disrupted by internal (eg, genetic predispositions or comorbid conditions) or external factors (eg, increased exposure to bright light, night-work
goal of treatment

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<th>Issue to address</th>
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<td>Improve sleep practices and behaviors</td>
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<td>Stimulus control therapy</td>
<td>Strengthen bed and bedroom as sleep stimulus</td>
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<td>Sleep restriction</td>
<td>Restrict wake time in bed to improve sleep depth and consolidation</td>
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<td>Relaxation training</td>
<td>Reduce arousal and decrease anxiety at bedtime (eg, mindfulness meditation)</td>
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<td>Cognitive therapy</td>
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<td>Observe biological signs (eg, heart rate and muscle tension)</td>
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<td>Chronotherapy</td>
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schedule, or personal life difficulties). Typically, patients with CRSWD experience insomnia or excessive sleepiness but can have both depending upon the nature of their circadian misalignment. Diagnosing CRSWD requires identifying irregular sleep-wake patterns based on a patient’s sleep log. Common CRSWD include delayed sleep-wake phase disorder, advanced sleep-wake phase disorder, irregular sleep-wake disorder, shift-work disorder, and jet lag. Actigraphy, in which the patient wears a device to measure nighttime movements to indirectly measure sleep through inactivity, may be used in the evaluation by detecting an irregular sleep-wake cycle.

In addition to CBT-I, medications may be used to help manage CRSWD. Melatonin is commonly used as a circadian rhythm anchor; however, the recommended dosages and timing remain unstandardized. Chronotherapy (gradually shifting the sleep time in accordance with a desired schedule) and bright light therapy can also be used to reset the sleep-wake rhythm and help alleviate insomnia or hypersomnia. Increased or decreased exposure to bright light at a particular time can significantly stabilize the circadian rhythm, thus improving sleep and mood. Physical exercise may also be beneficial. Exercise increases the core body temperature, reduces anxiety, promotes serotonin release, and modifies immune function, all of which may benefit sleep initiation. Exercise at different times of the 24-hour day has been shown to result in phase advances that are specific to the time of exercise, and, thus, can be strategically used to gradually shift the circadian rhythm to be parallel with the desired cycle, resulting in improved sleep quality. Whereas late nocturnal exercise can delay circadian timing, exercise in the early evening can advance the intrinsic biorhythm. It is important to speak with patients regarding their exercise routines and work with them to identify optimal exercise times that will not interfere with their sleep and may even improve sleep quality.

Sleep Apnea

Among the most common sleep-related breathing disorders, obstructive sleep apnea (OSA) affects patients of all ages. Patients with morbid obesity, type 2 diabetes, epilepsy, or cardiovascular disease are at higher risk for OSA, which occurs when upper airway obstruction leads to repetitive episodes of apnea or hypopnea during sleep. Typically associated with heart failure or neurologic disease, central sleep apnea (CSA) is less common, occurring when the central neural signal to breathe is not transmitted. Patients with OSA or CSA experience difficulty breathing during sleep, insomnia, daytime fatigue or sleepiness, and/or snoring. Sleep apnea is associated with several risks (eg, cardiac disease, stroke, hypertension, diabetes, reflux, erectile dysfunction, weight gain, memory and concentration issues, and mood disturbances) and can be listed as a cause of death on death certificates.

Continuous positive airway pressure (CPAP) therapy remains the first-line therapy, especially in moderate or severe OSA. Positive airway pressure is used to maintain airway patency. There are challenges with adherence to CPAP because some patients may have claustrophobia or anxiety and can experience difficulty tolerating the mask or treatment pressures. Optimizing mask comfort in a single session by refitting a patient’s mask can result in improved adherence and thus represents a simple and cost-effective approach to improving outcomes. Personalized 3D-printed CPAP masks may be a new potential method to treat patients with OSA because they could improve comfort and effectiveness in a more personalized manner. Although available for children with OSA and craniofacial anomalies, these 3D-printed CPAP masks for adults with OSA are not yet available clinically.

Oral dental appliances are approved therapy for mild and mild-to-moderate OSA. The oral appliance pushes the lower jaw and tongue slightly forward, preventing throat muscles from collapsing back into the airway and allowing for normal breathing during sleep. Positional therapy may be an option for patients with positional OSA, particularly given the efficacy of a new generation of objective monitoring/stimulating devices, which may improve upon the limited efficacy of prior methods (such as the “tennis ball method” or any variety of positioning devices that can be strapped on).

Although surgical intervention is not first-line treatment for OSA, patients may benefit from a formal evaluation based on their specific combination of anatomic risk factors. The recent approval of hypoglossal nerve stimulators that activate upper airway breathing may be another option, particularly for indi-
vinduals with moderate-to-severe OSA who fail CPAP therapy.26 An implantable neurostimulation device may be another new treatment method for CSA in patients with comorbid heart failure but long-term use, safety, tolerability, efficacy, and battery shelf life are currently under clinical investigation.27,28

Although there are no approved medications for OSA, cannabinoids have gained attention. Dronabinol has been shown effective for patients with moderate or severe OSA based on a blinded parallel, placebo-controlled, randomized trial. Specifically, dronabinol was associated with lower apnea-hypopnea index (AHI) and overall treatment satisfaction compared with placebo. The best approach to cannabinoid therapy for OSA remains unclear; large trials are needed to assess treatment approaches.29 Dimethyl fumarate, an immunomodulatory agent approved for treatment of multiple sclerosis is being studied as a potential treatment of OSA.30

### Hypersomnias

Central hypersomnias, including idiopathic hypersomnia (IH) and narcolepsy, result in profound hypersomnia or excessive daytime sleepiness.31 Narcolepsy, often un- or under-diagnosed, can affect almost all aspects of life with sudden episodes of somnolence. Type 1 narcolepsy is the combination of hypersomnia and either cataplexy—sudden loss of muscle tone triggered by strong emotions—or a deficiency of hypocretin (orexin), a chemical that promotes wakefulness, arousal, and appetite. Type 2 narcolepsy does not include cataplexy or a hypocretin deficiency.

Sodium oxybate is the first-line and only approved treatment for cataplexy32,33 and was recently approved for pediatric patients with narcolepsy. Tricyclic antidepressants (TCAs) have been used to treat cataplexy, despite not being thoroughly evaluated in randomized controlled trials and having undesirable anticholinergic effects. Serotonin-norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs) are another option to treat cataplexy, with venlafaxine being the preferred choice. Additionally, TCAs, SSRIs, and SNRIs may help with other symptoms common in narcolepsy: sleep paralysis and hypnagogic/hypnopompic hallucinations. Pitolisant, an inverse agonist of the H1 histamine receptor, is the newest medication, hoped to be approved soon for narcolepsy, targeting cataplexy and excessive daytime sleepiness.34

Modafinil, a nonamphetamine, wakefulness-promoting agent, is used to treat excessive daytime sleepiness in narcolepsy, followed by various other stimulant medications. There are a host of additional therapies being developed to address the excessive daytime sleepiness of the primary central nervous system hypersomnias. The H3 histamine receptor inverse agonists and a novel dopamine-norepinephrine reuptake inhibitor, solriamfetol, have both demonstrated efficacy for excessive daytime sleepiness associated with narcolepsy and other primary and secondary hypersomnias, but are not yet approved.34-36 Other drugs under investigation for hypersomnia include hypocretin/orexin peptides, cell replacement therapies, GABA	extsubscript{B} agonist baclofen, and immunomodulation.37

There are no approved medications for treatment of IH. Modafinil, various stimulants (eg, methylphenidate), and sodium oxybate are generally used off-label for hypersomnia in IH. Other treatments such as BTD-001, a GABA	extsubscript{A} antagonist, are currently in development.38 Finally, referral to the sleep behavioral psychologist can also be helpful in improving behaviors and practices for better sleep quality.

### Rapid-Eye-Movement Sleep Behavior Disorder

Involving loss of atonia associated with rapid-eye-movement (REM) sleep, REM sleep behavior disorder (RBD) causes physical dream enactment that can result in harm to the patient or bed partner. Securing the sleep environment for safety and optimizing sleep practices are key. Relaxation techniques and the use of weighted blankets, sleeping bags, or bed/door alarms, can also help. Imaging rescripting (IR) and imaginal exposure (IE) as part of CBT can also be helpful. In IE, patients are encouraged to imagine the feared images, thoughts, or situations and repetitively confront those until their nightmares are no longer frightening.39 Melatonin and clonazepam are the common medications used to treat RBD, but their efficacy and safety are limited. Although only a small body of literature exists to support its use in RBD, clonazepam is noted to be more than 80% efficacious.40 However, because of the multiple risks of using benzodiazepines in individuals over age 65, melatonin may be a better first choice. As a result of the limited options for treating this potentially devastating disorder, studies are underway to explore other medications that may help prevent RBD episodes, based on case reports in patients with RBD refractory to current therapies.41-43

### Restless Legs Syndrome

Characterized by a strong, irresistible urge to move the limbs, restless legs syndrome (RLS) is diagnosed when this urge gets worse during rest or periods of inactivity. Patients often find sensations in their legs uncomfortable and describe them as aching, pulling, itching, crawling, or creeping.44 The neurobiology of RLS remains complex (Figure 2). It is theorized that iron deficiency leads to downregulation of adenosine A1 receptors (A1R) that cause hypersensitive striatal glutamatergic terminals and an increase in striatal dopamine release. The increased dopaminergic and glutamatergic activity gives rise to the commonly associated phenomenon of periodic limb movements of sleep (PLMS) as well as hyperarousal.45

Iron therapy is a mainstay of treatment for patients with RLS who have low iron; iron status should always be part of the
evaluation in RLS.\(^{46}\) Subsequently, δ\(^{-}\) ligands (eg, gabapentin, enacarbil, or pregabalin) are preferred first-line agents over dopaminergic therapy because of their short-term efficacy with the lower risk of augmentation of RLS.\(^{47}\) Nonetheless, the non-ergoline dopamine agonists, such as pramipexole, ropinirole, and rotigotine, often used in standard RLS treatment might be helpful for personalizing treatment in patients with RLS and comorbid Parkinson’s disease. Moreover, although age has not been shown to affect ropinirole and rotigotine metabolism, pramipexole plasma concentration can be as much as 68% higher in individuals over age 65 compared to those under age 65 may require about one-third the daily dose of pramipexole.\(^{49}\)

Finally, although low-dose opioid therapy is a viable practice-parameter–approved option for patients with RLS, both patients and clinicians face the challenges of using opioids or any narcotic in the current opioid-abuse epidemic. Opioids can also exacerbate sleep problems, such as sleep apnea. Other strategies should be tried before considering opioids.\(^{49}\)

Long-term treatment of RLS can be challenging and pharmacogenomics may be helpful. The development of new drugs acting on adenosinergic (including recent report of the use of dipyridamole) and glutamatergic neurotransmission hold promise, but require further investigation.\(^{50}\) As the genetic underpinnings and central and peripheral pathophysiology of this disorder are being revealed, more targeted therapies can be developed to address the specific mechanism of disease.

**Conclusion**

Several new and promising avenues to treat sleep disorders have arisen in recent years. Time will tell which of several novel agents currently at various stages of clinical trials are safe and effective. Longitudinal outcome studies are required for newly approved management options to assess their long-term safety and efficacy. Regardless, the outlook is promising that providers will have a greater armamentarium of treatment options as we are just beginning to reveal and target the underlying mechanisms of sleep and wake.


