Awakening to New Therapies for Sleep Disorders

Faculty
Lance Azzo, PharmD, BCGP
Clinical Pharmacist,
AllianceRX Walgreens Prime Specialty

Patients with sleep disorders often go undiagnosed or are misdiagnosed; healthcare professionals may not understand the relatively complex diagnosis of these disorders. With moderately few existing therapeutic options, healthcare professionals should be aware of newer treatments that are available for obstructive sleep apnea, idiopathic hypersomnia, and narcolepsy. As sleep disorders are associated with comorbidities such as hypertension and psychiatric disorders, as well as a higher risk for car crashes, the stakes are higher than ever to identify these conditions, and clinicians may not understand the importance of screening patients and getting them treatment to prevent further issues. This program seeks to shed light on these often-missed conditions and give healthcare professionals the tools to treat and diagnose many sleep disorders.

Learning Objectives

**Pharmacist**
1. Identify appropriate methods for the diagnosis and testing of narcolepsy, obstructive sleep apnea, and idiopathic hypersomnia
2. Recognize data for treatment options in the management of narcolepsy, obstructive sleep apnea, and idiopathic hypersomnia
3. Specify the comorbidities and quality of life issues that are often affiliated with narcolepsy, obstructive sleep apnea, and idiopathic hypersomnia

**Pharmacy Technician**
1. Identify appropriate methods for the diagnosis and testing of narcolepsy, obstructive sleep apnea, and idiopathic hypersomnia
2. Recognize data for treatment options in the management of narcolepsy, obstructive sleep apnea, and idiopathic hypersomnia
3. Specify the comorbidities and quality of life issues that are often affiliated with narcolepsy, obstructive sleep apnea, and idiopathic hypersomnia
Awakening to New Therapies for Sleep Disorders

Accreditation

PharmCon is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

PharmCon reports CPE credits to CPE Monitor automatically after credit is earned. Your NABP ePID and birthdate must be in your online profile for successful credit submission.

PharmCon reports CPE credits to CE Broker automatically after credit is earned. Your license number must be in your online professional profile for successful credit submission.

CE hours provided by PharmCon meet the ANCC criteria for formally approved continuing education hours. The ACPE is listed by the AANP as an acceptable, accredited continuing education organization for applicants seeking renewal through continuing education credit.

Target Audience
Pharmacists, Pharmacy Technicians

Universal Activity Number

Pharmacist
0798-0000-21-150-H01-P

Pharmacy Technician
0798-0000-21-004-H01-T

Credit Hours
1.0 Hour

Activity Type
Knowledge-Based

CE Broker Tracking Number
20-761560

Activity Release Date
June 22, 2021

Activity Offline Date
December 22, 2023

ACPE Expiration Date
June 22, 2024

Educational Support Provided By
PharmCon

All opinions expressed by the author(s) are strictly their own and not necessarily approved or endorsed by PharmCon freeCE.

Consult full prescribing information on any drugs or devices discussed.

PharmCon freeCE is a division of KnowFully Learning Group.
201 N. King of Prussia Rd, Suite 370, Radnor, PA 19807

© 2021 PharmCon
All rights reserved.

None of the contents of this publication may be reproduced in any form without the written permission of the publisher.
Introduction

OSA

Obstructive sleep apnea (OSA) is a disorder that is characterized by obstructive apneas, hypopneas, and/or respiratory effort-related arousals created by repetitive collapse of the upper airway during sleep.\textsuperscript{1-4} It is most common among older males, but it can also affect women and children.\textsuperscript{5}

The estimated prevalence of OSA in North America is approximately 15 to 30\% in males and 10 to 15\% in females.\textsuperscript{6,7} The global estimate is that 936 million individuals worldwide have mild-to-moderate OSA and 425 million people have moderate-to-severe OSA.\textsuperscript{8}

The prevalence of OSA also varies by race. OSA is more prevalent in African Americans who are younger than 35 years old compared with Caucasians of the same age group, independent of body weight.\textsuperscript{9,10}

The prevalence appears to be increasing and may relate to the increasing rates of obesity. In a study, the estimated prevalence of OSA between 1990 and 2010 increased from 11\% to 14\% in adult males and from 4\% to 5\% in adult females.\textsuperscript{7} Another study from the United Kingdom also demonstrated a significant increase in the rates of OSA and obesity between 1994 and 2015.\textsuperscript{11}

Most individuals with OSA complain of daytime sleepiness, or their bed partner reports loud snoring, choking, gasping, or interruptions in breathing while sleeping.\textsuperscript{12} Additionally, morning headaches are reported by 10\% to 30\% of patients with OSA.\textsuperscript{13,14}

Narcolepsy

Narcolepsy can be conceptualized as a disorder of sleep-wake control in which elements of sleep intrude into wakefulness and elements of wakefulness intrude into sleep.\textsuperscript{15} The result is chronic daytime sleepiness with varying amounts of cataplexy, hypnagogic hallucinations, and sleep paralysis.\textsuperscript{15}

All patients have sleepiness, but only one-third of individuals will have all of these symptoms.\textsuperscript{15} The elements of narcolepsy typically worsen during the first few months to years and then persist for life.\textsuperscript{15} It is one of the most common causes of disabling daytime sleepiness after OSA.\textsuperscript{16,17}
Narcolepsy type 1 (narcolepsy with cataplexy) is estimated to have a prevalence of 25 to 50 per 100,000 people and an incidence of 0.74 per 100,000 person-years.\textsuperscript{18-20} It is equally common in men and women.\textsuperscript{21-23} Narcolepsy typically begins in the teens and early twenties, but occasionally occurs as early as 5 years of age or as late as 40 years of age.\textsuperscript{24} The prevalence of narcolepsy type 2 (narcolepsy without cataplexy) is estimated to be 20 to 34 per 100,000 people.\textsuperscript{25}

\textbf{Idiopathic hypersomnia}

Idiopathic hypersomnia is a sleep disorder that is characterized by chronic excessive daytime sleepiness (daily periods of an uncontrollable need to sleep or daytime lapses into sleep) and often difficulty waking up from nocturnal sleep or daytime naps.\textsuperscript{26}

Based largely on sleep center referrals, idiopathic hypersomnia appears to have a prevalence of approximately 20 to 50 cases per million.\textsuperscript{27-29} The onset of this disorder typically occurs between 10 and 30 years of age.\textsuperscript{27} In a series of 77 patients, the mean age of symptom onset was 17 and the mean age of diagnosis was 30.\textsuperscript{27}

\textbf{Diagnosis}

\textbf{OSA}

Per the American Academy of Sleep Medicine (AASM), in-laboratory polysomnography is considered the gold-standard diagnostic test for OSA.\textsuperscript{30} At-home sleep apnea testing may also be used, but clinical tools, questionnaires, and prediction algorithms should not be implemented to diagnose OSA.\textsuperscript{30} Furthermore, per the AASM, polysomnography, rather than home sleep apnea testing, should be used for the diagnosis of OSA in patients with cardiorespiratory disease, respiratory muscle weakness, hypoventilation, chronic opioid medication use, history of stroke, or severe insomnia.\textsuperscript{30}

Full-night polysomnography involves monitoring the individual during the patient’s typical sleep period, which is generally nighttime. Split-night polysomnography is similar to full-night testing, except the diagnostic portion of the study is performed during the first part of the night only. According to the AASM, if clinically appropriate, split-night polysomnography is preferred over full-night polysomnography.\textsuperscript{30}
Narcolepsy

All patients with chronic daytime sleepiness should have a thorough sleep history, physical exam, and neurologic exam seeking evidence of cataplexy, hypnagogic hallucinations, or sleep paralysis. Questions that are useful in detecting possible Narcolepsy include the following:

- Are you sleepy most of the day?
- Do you feel rested upon waking in the morning?
- Do you have vivid dreams during daytime naps?
- Do you ever have muscle weakness when you tell a joke or laugh?
- Do you ever see, hear, or feel things that you know are not there as you are falling asleep?
- Are you ever unable to move when you first awake or just before falling asleep?
- Over the last 2 weeks, how often have you fallen asleep when you did not intend to?

If the answer to any of these questions is “yes,” then narcolepsy should be considered and both a polysomnogram and a multiple sleep latency test (MSLT) should be conducted.

The purpose of the polysomnogram is to exclude alternative and coexisting causes of chronic daytime sleepiness, which may warrant specific treatment. The purpose of the MSLT is to measure the mean sleep latency and identify sleep onset rapid eye movement periods (SOREMPs). Stimulants and other psychoactive medications should be stopped 1 week before testing, and antidepressants should be stopped at least 3 weeks before testing to avoid rapid eye movement (REM) sleep rebound effects.

Idiopathic hypersomnia

Idiopathic hypersomnia is a clinical diagnosis that should be considered in a teenager or adult who complains of chronic excessive daytime sleepiness with long unrefreshing daytime naps and difficulty arousing from sleep in the absence of symptoms suggestive of other common causes of excessive daytime sleepiness.
such as depression, sedating medications, insufficient sleep, and sleep-related breathing disorders. Idiopathic hypersomnia is in part a diagnosis of excursion that is achieved by a thorough history and polysomnography to ensure that other causes of excessive daytime sleepiness are not present.\textsuperscript{29}

If concern exists about the accuracy of patient-reported sleep duration, a sleep log or an activity monitor (actigraphy) should be used for confirmation.\textsuperscript{36} Actigraphy allows for multiday recording in the home environment and this can corroborate the history and provide data that supplement in-laboratory sleep testing.\textsuperscript{36} A study of 33 patients with idiopathic hypersomnia found good correlation between total sleep time as measured by actigraphy and polysomnography.\textsuperscript{36} Additionally, a medication list should be reviewed for drugs that can cause excessive daytime sleepiness and individuals should be screened for depression.\textsuperscript{37}

Individuals should undergo nocturnal polysomnography to exclude other causes of excessive daytime sleepiness and especially subtle forms of OSA.\textsuperscript{38,39} In idiopathic hypersomnia, polysomnography may show a short sleep latency, increased total sleep time, increased sleep spindles, and variable changes in sleep efficiency and sleep stage distribution; these findings are supportive of a diagnosis of idiopathic hypersomnia.\textsuperscript{40,41} On the day after the duration and quality of nocturnal sleep have been characterized by nocturnal polysomnography, the patient should undergo a MSLT.\textsuperscript{42} This is a series of 5 daytime nap opportunities that together allow objective characterization of the patient’s level of daytime sleepiness or physiological sleep tendency.\textsuperscript{42} Individuals must have had sufficient sleep on the night prior to the MSLT for results to be accurate and reliable.\textsuperscript{42} In idiopathic hypersomnia, the mean sleep latency is shortened, typically less than 8 minutes, and the number of SOREMPs is less than 2.\textsuperscript{27} This value is essential because 2 or more SOREMPs suggest a diagnosis of narcolepsy.\textsuperscript{43,44}
Per the International Classification of Sleep Disorders, a diagnosis of idiopathic hypersomnia requires all the following: 45

- Daily periods of uncontrollable need to sleep or daytime lapses into sleep for at least 3 months
- Cataplexy is absent
- An MSLT documents fewer than 2 SOREMPs
- The presence of at least one of the following:
  - MSLT shows a mean sleep latency of ≤8 minutes
  - Total 24-hour sleep time is ≥660 minutes on 24-hour polysomnography or by wrist actigraphy in association with a sleep log
- Insufficient sleep syndrome is ruled out
- No better explanation by another sleep disorder, medical or psychiatric disorder or use of drugs

**Treatment**

**OSA**

Weight loss and exercise should be recommended to all patients with OSA who are overweight or obese. 46-48 While rarely leading to complete remission of OSA, weight loss, including that from bariatric surgery, has been demonstrated to improve health and metabolic parameters, decrease the apnea-hypopnea index (AHI, the number of apneas and hypopneas per hour of sleep), reduce blood pressure, improve quality of life (QoL), and decrease daytime sleepiness. 49-58

The effects of weight loss on OSA were demonstrated by a study that enrolled 72 overweight study participants (mean BMI [body mass index] 32 kg/m²) with mild OSA (mean AHI 10 events per hour of sleep). 50 The patients were randomly assigned to receive a single session of general nutrition and exercise advice, or a more intensive program that included a low calorie diet for 3 months plus nutrition and exercise counseling for 1 year. 50 Individuals in the latter group had significantly greater weight loss (11 kg versus 2 kg), reduction in the AHI (mean change from baseline, -4 versus 0.3 events per hour), and improvement in QoL compared with the control group. 50

Per the AASM, PAP therapy is the mainstay of therapy for adults with OSA. 59 The mechanism of PAP involves maintenance of a positive pharyngeal transmural
pressure so that the intraluminal pressure exceeds the surrounding pressure.\textsuperscript{60} PAP also stabilizes the upper airway through increased end-expiratory lung volume; as a result, respiratory events due to upper airway collapses (eg, apneas, hypopneas) are prevented.\textsuperscript{61}

There is high-quality evidence from randomized trials and meta-analyses demonstrating that PAP has several beneficial effects on OSA. For example, in a meta-analysis of 35 randomized trials, PAP compared with sham resulted in a significant reduction in the AHI (mean difference -33.8 events/hour) as well as improved daytime sleepiness as assessed by the Epworth Sleepiness Scale (ESS, mean difference -2 points), systolic and diastolic pressure, and QoL.\textsuperscript{58} As another example, in a meta-analysis of 22 randomized trials (1160 study participants) that compared nocturnal PAP with a control (sham PAP, placebo tablets, or conservative management), nocturnal PAP significantly improved both subjective and objective sleepiness, QoL, cognitive function, and depression.\textsuperscript{62}

While the recent AASM guidelines do not discuss the pharmacotherapy for OSA, multiple Food and Drug Administration (FDA)-approved medications that are used to treat OSA exist. These agents include modafinil, armodafinil, and solriamfetol. All these drugs are used to improve wakefulness in adult patients with EDS associated with OSA.\textsuperscript{63-65}

Modafinil and armodafinil are central nervous system (CNS) stimulants that are used for the treatment of residual sleepiness in individuals with adequately treated OSA.\textsuperscript{63,64} These agents improve objective and subjective measures of daytime sleepiness.

A meta-analysis of 1479 patients with OSA and residual sleepiness on adequate CPAP adherence reported that compared with placebo, modafinil and armodafinil resulted in a decreased ESS score by 2.5 points, increased sleep latency in the maintenance of wakefulness test (MWT) by 2.7 minutes, and increased the reporting of minimal improvement on the Clinical Global Impression of Change scale (CGI-C) by 26%.\textsuperscript{66}

In another study, a double-blind crossover trial randomly assigned 157 patients with OSA who had persistent daytime sleepiness despite adequate conventional therapy to receive modafinil or placebo once daily for 4 weeks.\textsuperscript{67} EDS resolved in a greater proportion of individuals in the modafinil group than in the placebo group (51\% versus 27\%), as measured by the ESS.\textsuperscript{67}
The most common adverse effects of modafinil and armodafinil are headache, nausea, dry mouth, back pain, anxiety, anorexia, insomnia, diarrhea, and rhinitis.\textsuperscript{63,64}

Solriamfetol is an oral selective dopamine and norepinephrine reuptake inhibitor with wake-promoting effects.\textsuperscript{65} Solriamfetol has been shown to improve wakefulness in individuals with residual sleepiness in OSA despite PAP therapy.\textsuperscript{68,69}

A randomized, double-blind, placebo-controlled trial compared solriamfetol with placebo.\textsuperscript{68} Primary endpoints (MWT and ESS) were met with solriamfetol (P < .05).\textsuperscript{68}

Solriamfetol may increase blood pressure or heart rate; these parameters should be measured before beginning therapy, and hypertension should be adequately controlled during treatment with solriamfetol.\textsuperscript{65} This treatment and monitoring plan is extremely essential, as OSA is often associated with hypertension.\textsuperscript{65}

### Narcolepsy

The goals of therapy are to obtain normal alertness during conventional waking hours or to maximize alertness at important times of the day (eg, work, school, driving). All individuals with narcolepsy possess some degree of daytime sleepiness. Although a few manage this successfully with only an afternoon nap, most patients require an agent that promotes wakefulness.\textsuperscript{70}

Modafinil is a common agent used to treat narcolepsy because it provides good control of sleepiness, is typically well tolerated, and illicit use is uncommon.

In a randomized study that consisted of 283 patients, all individuals were assigned to either modafinil or placebo.\textsuperscript{71} After 9 weeks, patients treated with modafinil had significant improvements in their MWT and ESS measurements, without evidence of tolerance to the drug.\textsuperscript{71} Similar findings were found in a second trial involving 271 patients with narcolepsy.\textsuperscript{72}

Solriamfetol was approved by the FDA in 2019 for the treatment of narcolepsy.\textsuperscript{65}

Solriamfetol was analyzed in a randomized trial of 236 patients with narcolepsy who were randomly assigned to 1 of 3 doses of solriamfetol (75 mg, 150 mg, or 300 mg daily) or placebo.\textsuperscript{73} At 12 weeks, sleep latency on the MWT improved more in the 150 mg and 300 mg dose groups than in the placebo group (mean change from baseline 9.8 minutes, 12.3 minutes, and 2.1 minutes, respectively).\textsuperscript{73}
Additionally, ESS and global impression scores improved in all 3 dose groups compared with placebo.\textsuperscript{73}

Pitolisant is an oral Histamine-3 (H3) receptor antagonist/inverse agonist that improves daytime sleepiness and reduces cataplexy in patients with narcolepsy.\textsuperscript{74}

In a randomized study of 95 individuals with narcolepsy, pitolisant reduced the ESS by 5.8 points compared with a reduction of 3.4 points with placebo.\textsuperscript{75} Furthermore, MWT scores and frequency of hallucinations were also improved compared with placebo.\textsuperscript{75}

Pitolisant is generally well tolerated. The most common adverse effects are headache, insomnia, nausea, and anxiety.\textsuperscript{74}

Methylphenidate is a CNS stimulant and a potent wakefulness-promoting medication. It has been shown to be an effective agent for the treatment of narcolepsy.\textsuperscript{31}

Typical doses of methylphenidate increase systolic blood pressure about 5 mmHg, which may have long-term ramifications.\textsuperscript{76} Moreover, regulatory authorities reviewed several cases of sudden death in individuals taking methylphenidate and issued a warning regarding serious cardiovascular events in patients.\textsuperscript{77,78} Some of these deaths were affiliated with hypertrophic obstructive cardiomyopathy, while others may have been related to arrhythmias.\textsuperscript{77,78} Patients taking high doses of methylphenidate may also experience anorexia or psychosis.\textsuperscript{79}

Like methylphenidate, amphetamines are CNS stimulants.\textsuperscript{31} Amphetamines may be the most potent wakefulness-promoting drugs, although some individuals require high doses.\textsuperscript{31} Dextroamphetamine, dextroamphetamine-amphetamine, and lisdexamfetamine are among the most commonly prescribed. By increasing aminergic signaling, these medications may also reduce cataplexy, hypnagogic hallucinations, and sleep paralysis.\textsuperscript{80} Lisdexamfetamine is not approved by the FDA for the treatment of narcolepsy.

Amphetamines are typically considered to be second-line agents for the treatment of narcolepsy because their sympathomimetic adverse effects can be consequential. They can produce adverse effects similar to those seen with methylphenidate.\textsuperscript{77,79} Patients prescribed amphetamines should be carefully informed about these risks and monitored regularly.
About 30% of patients with narcolepsy have cataplexy that is severe enough to warrant treatment. Although hypnagogic hallucinations and sleep paralysis typically do not require pharmacological treatment, these symptoms are often improved by medications that suppress cataplexy.\textsuperscript{81}

Brainstem circuits that generate REM sleep are strongly inhibited by norepinephrine and serotonin. Thus, agents that increase noradrenergic and serotonergic signaling suppress REM sleep and reduce cataplexy.\textsuperscript{82} Antidepressants that selectively inhibit the reuptake of norepinephrine or serotonin include venlafaxine, atomoxetine, and fluoxetine. (None of these agents are FDA-approved for narcolepsy.)\textsuperscript{31} Clinical experience suggests that they may substantially reduce cataplexy with relatively few adverse effects, although data from clinical trials are lacking.\textsuperscript{83}

For several years, cataplexy was treated with tricyclic antidepressants (TCAs) such as protriptyline or clomipramine that decrease the reuptake of aminergic neurotransmitters. These agents are very effective, but many patients are bothered by anticholinergic adverse effects, including dry mouth and constipation.\textsuperscript{84} TCAs are not FDA-approved for the management of narcolepsy.

Pitolisant also significantly reduces cataplexy.\textsuperscript{74} It is generally used as an alternative to sodium oxybate in patients whose cataplexy does not respond adequately to a REM sleep-suppressing drug such as venlafaxine.

In a randomized study of 106 patients with narcolepsy type 1, pitolisant was more effective than placebo at reducing weekly cataplexy rate (75% versus 35% relative reduction from baseline rates of 7 to 9 episodes per week).\textsuperscript{85}

Sodium oxybate is a metabolite of gamma amino butyric acid (GABA).\textsuperscript{86,87} The medication is given as a liquid.\textsuperscript{88} Sodium oxybate substantially reduces cataplexy and, therefore, is a good option for individuals with severe cataplexy.\textsuperscript{89-95} The reduction in cataplexy develops over several weeks of treatment; thus, doses should be adjusted slowly.\textsuperscript{96}

Evidence to support use of sodium oxybate in patients with narcolepsy includes a multicenter trial of 228 study participants with narcolepsy type 1 who had symptoms despite standard therapies.\textsuperscript{97-100} At 8 weeks, the median percent reduction in weekly cataplexy episodes from baseline was higher with sodium oxybate than placebo (85%, 65%, 57%, and 20% for sodium oxybate 9 g, 6 g, 4.5 g, and placebo, respectively).\textsuperscript{97-100}
Adverse effects of sodium oxybate are dose-dependent and are more common than with most other medications for narcolepsy.\textsuperscript{88} This agent rapidly produces deep sedation, so household safety should be discussed (eg, care for children, ability to respond to smoke alarms).\textsuperscript{101} Other adverse effects include nausea, dizziness, mood swings, urinary incontinence, weight loss, worsening of depression, psychosis, and sleepwalking.\textsuperscript{101} Furthermore, over-dosage of sodium oxybate can result in respiratory depression, coma, and death.\textsuperscript{102,103} Coadministration with alcohol and CNS depressants such as opioids and benzodiazepines increases risk for impaired consciousness and respiratory depression.\textsuperscript{102,103} Due to these risks, combined use of sodium oxybate with alcohol, sedatives, or hypnotics is contraindicated.\textsuperscript{104,105}

**Idiopathic hypersomnia**

Unfortunately, supporting data for pharmacotherapy in idiopathic hypersomnia are limited to case reports, retrospective series, and very few randomized trials.\textsuperscript{27,31,106-108}

A viable treatment option for idiopathic hypersomnia includes modafinil. The effectiveness of modafinil was shown in a small, randomized trial of 33 patients with idiopathic hypersomnia without long sleep time.\textsuperscript{108} In comparison with placebo, individuals treated with modafinil had improved ESS and clinical global impression rating scores.\textsuperscript{108} The utility of modafinil was also demonstrated by a multicenter cross-sectional study of 104 patients with idiopathic hypersomnia.\textsuperscript{107} All patients were treated with modafinil.\textsuperscript{107} In the subset of 63 idiopathic hypersomnia patients who completed the ESS before and after treatment, the mean improvement in the ESS score was 2.6 points.\textsuperscript{107}

Limited data also exist to support the use of sodium oxybate for idiopathic hypersomnia. In a retrospective study of 46 patients with idiopathic hypersomnia treated with sodium oxybate, 71% of patients reported improvement in morning sleep inertia, which is a very disabling and difficult symptom of idiopathic hypersomnia.\textsuperscript{109}

JZP-258 is a novel oxybate agent that has 92% less sodium than sodium oxybate. JZP-258 has shown encouraging findings for the management of idiopathic hypersomnia. A double-blind, placebo-controlled, randomized withdrawal study assessed the efficacy of JZP-258 in adult patients with idiopathic hypersomnia. Individuals entering the study had excessive daytime sleepiness typical of the
idiopathic hypersomnia population. All patients were treated with JZP-258 during the open-label titration period. The primary endpoint of ESS and the key secondary endpoints of Patient Global Impression of Change (PGlc) and Idiopathic Hypersomnia Severity Scale (IHSS) were measured during the randomized withdrawal portion of the trial, which included 115 patients. There was a highly statistically significant worsening in individuals who were given placebo compared with JZP-258 for ESS, PGlc, and IHSS (all \( P < .001 \)).

None of these agents (modafinil, sodium oxybate, JZP-258) are approved by the FDA for the treatment of idiopathic hypersomnia.

### Comorbidities

**OSA**

Individuals with OSA are often obese and have an increased prevalence of numerous other cardiovascular risk factors, including hypertension. Additionally, studies have demonstrated a consistent association between OSA and cardiac arrhythmia, heart failure (HF), and coronary artery disease (CAD). Data suggest that successful treatment of OSA can improve hypertension and cardiovascular outcomes.

As an example, a prospective epidemiologic cohort study that followed 1889 patients for a median of 12 years identified an increased risk of hypertension among those with OSA untreated with PAP due to refusal (adjusted hazard ratio [HR] 2.0), nonadherence (HR 1.8), or ineligibility (HR 1.3), compared with controls. In contrast, patients with OSA treated with PAP had a lower risk of hypertension, compared with controls (HR 0.7).

Moreover, observational data suggest that treatment of OSA with PAP may reduce the incidence of CAD. For example, a prospective cohort study followed 1651 men with OSA for a mean of 10 years. Patients with OSA who were treated with PAP had a lower incidence of fatal and nonfatal cardiovascular events than patients with untreated, severe OSA. Cardiovascular events included myocardial infarction (MI), acute coronary syndrome (ACS), and stroke. In another prospective study, 449 individuals with mild or moderate OSA were followed for a median of 6 years. Treatment of OSA was affiliated with a reduction of the likelihood of a cardiovascular event (adjusted HR 0.36, 95% CI 0.21-0.62),
compared with no treatment. Cardiovascular events were defined as MI, stroke, or ACS requiring a revascularization procedure.

Additionally, data suggests that treatment of OSA reduces the risk of recurrent atrial fibrillation (AF). As an example, in an observational study of 130 individuals who had been electrically cardioverted from AF, the rate of recurrent AF in patients with untreated OSA, with treated OSA, and without OSA was 82%, 42%, and 53%, respectively.

In addition to cardiovascular events, OSA significantly increases the risk of car crashes. In a meta-analysis of 16 observational studies, the relative risk (RR) of crash in individuals with OSA compared with controls was 2.4 (95% CI 1.2-4.9). Furthermore, laboratory-based studies have shown impaired psychomotor vigilance and driving simulator performance in individuals with untreated OSA. In a study, performance of patients with mild-to-moderate OSA was worse than those with a blood alcohol concentration of 0.06%.

Treatment of OSA is a pivotal component of prevention in both commercial and noncommercial drivers. Meta-analyses of observational studies analyzing crash risk before and after initiation of PAP therapy have found that treatment is associated with a significant reduction in the risk of crash (risk ratio [RR] 0.28, 95% CI 0.22-0.35) as well as near-miss accidents (odds ratio [OR] 0.09, 95% CI 0.04-0.21) and crash-related events during driving simulator studies.

Narcolepsy

Narcolepsy has long been described to have a high comorbidity for psychiatric disease, which is frequently quoted as the cause for delay in diagnosis. Depression is the most commonly described psychiatric symptom in narcolepsy. Studies assessing narcoleptic patients with self-reported questionnaires have found up to 57% suffered from depression. Additionally, depression has been found to be a major independent risk factor for impaired QoL.

Moreover, individuals with narcolepsy are often overweight. It has been found that patients with narcolepsy have higher BMIs. There have been suggestions that these findings are related to a combination of the reduction in basal metabolism and physical activity due to sleepiness. Also, there is additional evidence that narcoleptic patients are at increased risk for various eating
disorders. For example, it has been shown that narcoleptic patients tend to report irresistible and persistent craving for food, specifically binge eating.\textsuperscript{132}

Furthermore, an increased prevalence of cardiovascular and cardiometabolic conditions, such as hypertension, diabetes, and hypercholesterolemia have been reported in individuals with narcolepsy.\textsuperscript{133,134} In one study, the odds of heart disease in patients with narcolepsy were twice than those of control subjects.\textsuperscript{133} Additionally, a separate study demonstrated that the prevalence of diabetes and stroke was significantly increased in individuals with narcolepsy compared with controls.\textsuperscript{134}

Moreover, patients with narcolepsy have a 3- to 4-fold increased risk of having a car crash, and over one-third have had an accident due to sleepiness\textsuperscript{135-139}. A case-control study assessed 70 control drivers and 424 drivers who had untreated sleep disorders including OSA, narcolepsy, another sleep disorder with excessive sleepiness, or a sleep disorder without excessive sleepiness.\textsuperscript{116} Patients with narcolepsy were most likely to be involved in a sleep-related crash.\textsuperscript{135}

Clinicians should have an open and honest discussion with patients regarding their driving ability. As sleepiness can be difficult for the patient to recognize, feedback from family and friends may be helpful. If an individual reports persistent sleepiness or has had an accident due to sleepiness, the MWT may be appropriate to determine whether the patient can stay awake even under monotonous conditions (such as driving for lengthy time periods on the highway).\textsuperscript{140} This test cannot guarantee that a patient will remain alert while driving, but the results of the test can be useful for optimizing medications.

Small studies suggest that modafinil improves driving performance in patients with narcolepsy, but overall, there is little research on whether narcolepsy medications improve driving safety and how to determine whether a patient is safe to drive.\textsuperscript{141,142}

**Idiopathic hypersomnia**

Data suggests that many patients with idiopathic hypersomnia also have cognitive dysfunction. Memory problems are reported by 79\% of idiopathic hypersomnia patients and attention problems by 55\%. Furthermore, a feeling of one’s mind going blank (58\%) or making a mistake in a habitual activity (61\%) are also commonly reported in idiopathic hypersomnia patients.\textsuperscript{143}
The Role of the Pharmacist

Pharmacists play a pivotal role in managing sleep disorders.

A pharmacist encountering a patient with common symptoms of sleep disorders should review the individual’s medical profile to determine whether other disorders or medications could be responsible for the disorder. The pharmacist can help identify risk factors for sleep disorders and counsel individuals about good sleep hygiene. Pharmacists can also make recommendations concerning nonpharmacological and nonprescription remedies and counsel patients about prescription medications once they have begun therapy. By counseling patients about proper dosing and administration, potential drug interactions, and common adverse effects, the pharmacist can be instrumental in optimizing these therapies.

The Role of the Pharmacy Technician

Pharmacy technicians also play a huge role when encountering patients with sleep disorders.

Stimulant medications (eg, methylphenidate, dextroamphetamine-amphetamine) are commonly prescribed for various sleep disorders. Regionally-specific, stimulant-induced elevations in brain dopamine appear to be integral for potential of abuse. Pharmacy technicians can help decrease the amount of abuse caused by stimulants by examining the prescription for its validity, assessing the patient’s medication history to determine whether there is drug diversion, performing outreach to the prescriber’s office to verify that the prescription is legitimate, and conducting prescription drug monitoring programs (PDMPs) when appropriate.

Conclusion

OSA is a disorder that is characterized by obstructive apneas, hypopneas, and/or respiratory effort-related arousals created by repetitive collapse of the upper airway during sleep. It is most common among older males, but it can also affect women and children. Most individuals with OSA complain of daytime sleepiness, or their bed partner reports loud snoring, choking, gasping, or interruptions in breathing while sleeping. Additionally, morning headaches are reported by 10% to 30% of patients with OSA.
Narcolepsy can be conceptualized as a disorder of sleep-wake control in which elements of sleep intrude into wakefulness and elements of wakefulness intrude into sleep.\textsuperscript{15} The result is chronic daytime sleepiness with varying amounts of cataplexy, hypnagogic hallucinations, and sleep paralysis.\textsuperscript{15} All patients have sleepiness, but only one-third of individuals will have all of these symptoms.\textsuperscript{15} The elements of narcolepsy typically worsen during the first few months to years and then persist for life.\textsuperscript{15} It is one of the most common causes of disabling daytime sleepiness after OSA.\textsuperscript{16,17}

Idiopathic hypersomnia is a sleep disorder that is characterized by chronic excessive daytime sleepiness (daily periods of an uncontrollable need to sleep or daytime lapses into sleep) and often difficulty waking up from nocturnal sleep or daytime naps.\textsuperscript{26}

Sleep disorders affect a moderate proportion of the population and are underdiagnosed. The National Sleep Foundation estimates that more than 18 million US adults have sleep apnea.\textsuperscript{145} An analysis demonstrated that the prevalence ranges from 9\% to 38\% of the population across 24 studies globally and is higher in men than women.\textsuperscript{146} It is estimated that 135 000 to 200 000 people in the United States have narcolepsy, with males and females affected equally.\textsuperscript{147}

Economical burdens are acknowledged as well. The estimated cost for diagnosing and treating OSA in the United States in 2015 was $12.4 billion.\textsuperscript{148} Based on costs for medical devices, treatments, and surgeries, the average cost per OSA patient is estimated to be $2105.\textsuperscript{148} Narcolepsy is associated with approximately 1.5-fold higher mortality versus healthy cohorts and almost double the annual direct medical costs.\textsuperscript{149,150}

While the recent AASM guidelines do not discuss the pharmacotherapy for OSA, multiple FDA-approved medications that are used to treat OSA exist. These agents include modafinil, armodafinil, and solriamfetol. All these drugs are used to improve wakefulness in adult patients with EDS associated with OSA.\textsuperscript{63-65} Furthermore, per the AASM, PAP therapy is the mainstay of therapy for adults with OSA.\textsuperscript{59}

The goals of therapy for narcolepsy treatment are to obtain normal alertness during conventional waking hours or to maximize alertness at important times of the day (eg, work, school, driving). All individuals with narcolepsy possess some degree of daytime sleepiness. Although a few manage this successfully with only
an afternoon nap, most patients require an agent that promotes wakefulness. Treatment options for narcolepsy include solriamfetol, pitolisant, methylphenidate, amphetamines, antidepressants, and sodium oxybate.

Unfortunately, supporting data for pharmacotherapy in idiopathic hypersomnia are limited to case reports, retrospective series, and very few randomized trials. Modafinil, sodium oxybate, and JZP-258 are viable treatment options for the management of idiopathic hypersomnia.

Although sleep disorders such as OSA, narcolepsy, and idiopathic hypersomnia are not extremely common in the United States, they are often underdiagnosed or misdiagnosed. Their diagnosis and management can be complex. Clinicians may lack the knowledge or ability to screen patients for and manage these issues appropriately. Research has shown that sleep problems can be associated with comorbidities and poor QoL for patients. In addition, they are linked to a higher rate of motor vehicle accidents, especially for commercial drivers. Moreover, clinicians may be unaware of optimal treatment strategies for patients with sleep disorders. Thus, education to help healthcare professionals recognize and treat these disease states is of critical importance.
References

2. Leppänen T, Kulka A, Mervaala E, Töyräs J. Increase in Body Mass Index Decreases Duration of Apneas and Hypopneas in Obstructive Sleep Apnea. Respir Care. 2019;64(1):77-84. doi:10.4187/respcare.06297
11. Lechner M, Breeze CE, Ohayon MM, Kotecha B. Snoring and breathing pauses during sleep: interview survey of a United Kingdom population sample reveals a significant increase in the rates of sleep apnoea and obesity over the last 20 years - data from the UK sleep survey. Sleep Med. 2019;54:250-256. doi:10.1016/j.sleep.2018.08.029

Awakening to New Therapies for Sleep Disorders
© 2021 PharmCon


105. FDA Drug Safety Communication: Warning against use of Xyrem (sodium oxybate) with alcohol or drugs causing respiratory depression


Activity Test
Awakening to New Therapies for Sleep Disorders

Activity tests must be completed online at www.freeCE.com. A passing grade of 70 or higher and completion of an online activity evaluation are required to earn credit.

1. Per the American Academy of Sleep Medicine (AASM), what is considered the gold-standard diagnostic test for obstructive sleep apnea (OSA)?
   a. At-home sleep apnea testing
   b. In-laboratory polysomnography
   c. Multiple sleep latency test (MSLT)
   d. Sleep log

2. Per the AASM, what is considered the mainstay of therapy for adults with OSA?
   a. Solriamfetol
   b. Pitolisant
   c. Methylphenidate
   d. PAP therapy

3. Which of the following agents is not approved by the Food and Drug Administration (FDA) for the management of OSA?
   a. Modafinil
   b. Armodafinil
   c. Solriamfetol
   d. Pitolisant

4. Which of the following is not a common adverse effect of modafinil?
   a. Constipation
   b. Headache
   c. Nausea
   d. Dry mouth
5. Pitolisant is an oral _________.
   a. Histamine-2 (H2) receptor antagonist
   b. Selective dopamine and norepinephrine reuptake inhibitor
   c. Histamine-3 (H3) receptor antagonist/inverse agonist
   d. Metabolite of gamma amino butyric acid (GABA).

6. Which of the following is not a common adverse effect of pitolisant?
   a. Headache
   b. Nausea
   c. Blurred vision
   d. Anxiety

7. Combined use of sodium oxybate with _________ is contraindicated.
   a. Hypnotics
   b. Clarithromycin
   c. Colchicine
   d. Verapamil

8. Which of the following comorbidities is not typically associated with OSA?
   a. Hypertension
   b. Urinary tract infection
   c. Heart failure
   d. Coronary artery disease

9. Which of the following comorbidities is not typically affiliated with narcolepsy?
   a. Depression
   b. Diabetes
   c. Car crashes
   d. Seizure

10. Data suggest that many patients with idiopathic hypersomnia also have _________.
    a. Gout
    b. Psoriasis
    c. Cognitive dysfunction
    d. Asthma