More than half of all patients with psychiatric disorders report disturbances of sleep and wakefulness. “Sleep disorders are associated with impaired daytime function and predict a heightened future vulnerability to psychiatric disease. They also diminish life span.” Details from an expert here.

Not only is obstructive sleep apnea (OSA) linked with coronary artery disease, heart failure, systemic hypertension, stroke, and diabetes, but it is also a significant risk factor for depression, said sleep expert Karl Doghramji, MD, Medical Director of the Jefferson Sleep Disorders Center, Thomas Jefferson University, Philadelphia.

Speaking at the recent American Psychiatric Association’s annual meeting in San Francisco, Doghramji described the bidirectional and interactive relationship between sleep-wake disorders and coexisting medical and psychiatric disorders.

“As more than half of all psychiatric patients complain of disturbances of sleep and wakefulness,” he wrote in his summary, “sleep disorders are associated with impaired daytime function and predict a heightened future vulnerability to psychiatric disease. They also diminish life span.”

As an example, Doghramji, Professor of Psychiatry and Human Behavior at Thomas Jefferson University, described a recent study by Chen and colleagues\(^1\) that examined the risk of depressive disorder within the first year following an OSA diagnosis. The nationwide, population-based study found that patients with sleep apnea had a 2.18 times increased risk of subsequent depressive disorder, compared with those without OSA.

Doghramji also described research by Schwartz and Karatinos\(^2\) that assessed the effects of continuous positive airway pressure (CPAP) therapy in patients who had both OSA and symptoms of depression. Patients who continued CPAP therapy had a statistically significant improvement in depressive symptoms as measured by the Beck Depression Inventory-Fast Screen for Medical Patients.

The odds ratio for having anxiety and mood disorders is much higher in patients with narcolepsy than in control subjects.\(^3\) Most narcolepsy cases with cataplexy are thought to be caused by a
deficiency of orexins (neuropeptides that are also known as hypocretins). In addition, growing evidence from preclinical and clinical studies suggests that orexins and their receptors may be involved in the physiopathology of depression.4
Rapid eye movement (REM) sleep behavior disorder (RBD; part of the parasomnias grouping) is present concurrently in some 30% of patients with narcolepsy and can be a prodrome of neurodegenerative disease, according to Doghramji. Such diseases include Parkinson disease, multiple system atrophy, and major or mild neurocognitive disorder with Lewy bodies. RBD, Doghramji warned, can be triggered by alcohol and the use of various antidepressants, notably TCAs and MAOIs. “If you have a patient with RBD, search for antidepressants in the list of medications,” he said.

Nosology
Much of Doghramji’s presentation updated attendees on nosological changes for sleep-wake disorders and some new developments in the management of these disorders.
In DSM-5, the classification sleep-wake disorders encompasses 10 disorders or disorder groups: insomnia disorder; hypersomnia disorder; narcolepsy; breathing-related sleep disorders (obstructive sleep apnea hypopnea, central sleep apnea, and sleep-related hypoventilation); circadian rhythm sleep-wake disorders (delayed sleep phase type, advanced sleep phase type, irregular sleep-wake type, non-24-hour sleep-wake type, and shift work type); non-REM sleep arousal disorders; nightmare disorder; RBD; restless legs syndrome; and substance/medication-induced sleep disorders.

Doghramji pointed out changes from DSM-IV-TR to DSM-5, some of which are the following:
• Removal of sleep disorders related to another mental disorder, and sleep disorders related to a general medical condition
• Use of the terminology “coexisting with” or “comorbidity” instead of “related to” or “due to”
• Greater specification of coexisting conditions for each sleep disorder
• Discussion of the bidirectional and interactive relationship between sleep disorders and coexisting medical and mental disorders
• “Primary insomnia” is referred to as “insomnia disorder”
• Specifier “jet lag type” was removed from the category of circadian rhythm sleep-wake disorders
• DSM-5 text emphasizes the use of biological validators for such sleep-wake disorders as breathing-related disorders

Management
To facilitate diagnosis of sleep-wake disorders, Doghramji singled out some procedures and resources he recommends.
“Polysomnography is the diagnostic sine qua non for sleep apnea,” he said. “You can’t make the diagnosis without a sleep study.”
Exploring how a clinician might detect patients who are at high risk for OSA, Doghramji noted that there are no inventories validated in a psychiatric population. Yet he mentioned the STOP-BANG Questionnaire validated in the perioperative setting.5 It is available at http://www.stopbang.ca/osa.php#screen. The STOP questions relate to snoring, tiredness during daytime, observed apnea, and high blood pressure, while the BANG questions relate to body mass index, age, neck circumference, and gender.
“If a patient has a STOP-BANG score of 3 out of 8 or more, then OSA should be suspected and he or she should be referred for a sleep study,” Doghramji said.
Another method is to have the patient open his mouth and stick out his tongue, so the clinician can see the back of the throat and uvula.6 Applying the Mallampati scoring of the oropharynx, Doghramji said, is a simple, noninvasive method that can be used to evaluate patients for possible OSA. On average, the odds of having OSA increase more than 2-fold for every 1-point increase in the Mallampati score.
For some patients with sleep-wake disorders, safety is particularly important. For example, patients with RBD, Doghramji warned, often exhibit disturbing behaviors during sleep. “Patients behaviorally act out their dreams,” he said. “One of my patients was dreaming that he was fighting with his brother, but he hit his wife so hard he fractured her jaw. There are reports of patients walking out of bed and into streets and getting hit by trucks.”
He emphasized the importance of implementing such safety measures as removing sharp furniture from the bedside, having the patient sleep on a mattress on the floor, securing windows and doors and having a housemate keep the door key in case of fire, and possibly installing motion-activated alarms.

Treatment approaches
Pharmacological agents that are available or are being developed for sleep-wake disorders, Doghramji said, include hypnotic and sedative medications that work by increasing the activity of γ-aminobutyric acid (GABA), such as zolpidem, zaleplon, and eszopiclone; melatonin receptor agonists, such as ramelteon; and antagonists of the histamine system, such as low-dose doxepin. “Something that was not part of our basic training as psychiatrists are hypocretins (orexins),” Doghramji said.

These peptides are localized in the dorsolateral hypothalamus. They have wide projections throughout the brain and projections in the spinal column. Involved in locomotion, metabolism, and possibly mood and arousal, the hypocretin system seems to be important in controlling transitions between sleep and wakefulness, Doghramji said, adding that the system impinges on other neurotransmitter systems.

“So medications are being developed that are orexin receptor antagonists for treating insomnia,” he said. “Almorexant, an orexin OX1 and OX2 antagonist, was abandoned in 2011, but Suvorexant, an orexin OX1 and OX2 antagonist, is being developed by Merck and has completed some phase 3 trials.” The FDA’s Peripheral and Central Nervous System Drugs Advisory Committee recently expressed its support for FDA approval of a low-dose form of the drug for insomnia. Committee members concluded that the safety profile of 15 mg for elderly patients and 20 mg for nonelderly patients is acceptable.

In discussing zolpidem, Doghramji said the benzodiazepine receptor agonist is now available in several formulations, including sublingual (Edluar), oral spray (ZolpiMist), and a lower-dose sublingual tablet (Intermezzo).

“These are all agents that put people to sleep, but they are each slightly different,” Doghramji said. “For example, the oral spray taken at the beginning of night seems to put people to sleep more rapidly, while the low-dose sublingual tablet is indicated for people who wake up in the middle of the night and can’t get back to sleep, so they take it at 2 or 3 if they have at least 4 hours of bedtime remaining.”

Studies have shown that sublingual zolpidem has a faster sleepinduction effect but does not differ from the oral formulation in terms of sleep maintenance. Doghramji also discussed the FDA’s recommendation of reduced doses and a study of the risk factors for zolpidem-induced parasomnias.

Earlier this year, the FDA recommended reducing doses of zolpidem formulations. New data, according to the FDA, show that blood levels in some patients, particularly women, may be high enough the morning after use to impair activities that require alertness, including driving. Women appear to be more susceptible, because they eliminate zolpidem from their bodies more slowly than men do.

For the immediate-release forms of zolpidem (Ambien, Edluar, and ZolpiMist), the FDA recommended that the dose for women be lowered to half of the maximum approved dose (lowered from 10 mg to 5 mg, immediately before bedtime) and for extended-release (Ambien CR), from 12.5 mg to 6.25 mg. For men, the FDA recommended that health care professionals consider prescribing lower doses—5 mg for immediate-release products and 6.25 mg for extended-release products.

With regard to zolpidem-linked parasomnias, Doghramji cautioned that researchers do not know yet whether such effects are limited to zolpidem or whether they are effects shared with other GABA receptor agonists. He urged clinicians to be careful in prescribing zolpidem if a patient has a history of parasomnias or a concomitant sleep disorder, such as OSA.

Other risk factors cited in a review by Poceta include concomitant ingestion of alcohol or sedating medications; hypnotic sedative ingestion at times other than habitual bedtime, during an agitated state with decreased likelihood of sleep, and when sleep-deprived; poor management of pill bottles; and living alone.

Doghramji noted that the most important advance in the behavioral treatment of insomnia over the past few years has been the introduction of Internet-based cognitive-behavioral therapies. He also emphasized the importance of sleep hygiene principles, such as adherence to a regular morning out-of-bed time; setting aside a worry time; exercising regularly in the morning or afternoon; and avoiding exposure to light, particularly from electronic devices, before bedtime. He recommended the use of sunglasses at night for patients with sleep-wake disorders and the use of the f.lux application to make the color spectrum and brightness of a computer’s display adapt to the time of day. He also emphasized the importance of morning light exposure.

“Emergence of novel pharmacological and cognitive-behavioral techniques,” Doghramji concluded, “provides for greater specificity in the treatment of sleep-wake disorders.”
References:


3. Ohayon MM. Narcolepsy is complicated by high medical and psychiatric comorbidities: a comparison with the general population. Sleep Med. 2013;14:488-492.


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