Taking Care of Persistent Sleepiness in Patients with Sleep Apnea

Excessive sleepiness, a common manifestation of obstructive sleep apnea (OSA), is present in 52–58% of sleep clinic patients with moderate or more OSA (1). Continuous positive airway pressure (CPAP) therapy reduces sleepiness with improvement dependent on the level of CPAP adherence (2). Despite high levels of adherence, it is clear that some individuals have persistent sleepiness. Persistent sleepiness (defined by an Epworth sleepiness score >10) in the context of at least 3 hours of nightly CPAP use occurs in approximately 12–18% of patients, whereas 9% of patients have sleepiness despite more than 6 hours per night of use (3, 4).

Persistent sleepiness has been used to justify the use of wake-promoting agents in patients with treated OSA. Modafinil, a weak inhibitor of dopamine reuptake, was the first alerting agent approved by the U.S. Food and Drug Administration, in 2004, followed by the approval of its longer-acting R-enantiomer armodafinil in 2007. In this issue of the *Journal*, Schweitzer and colleagues (pp. 1421–1431) report findings from a double-blind, randomized, placebo-controlled, parallel-group 12-week trial of a novel alerting medication, solriamfetol, in sleepy individuals with OSA (5). Solriamfetol is a wake-promoting agent that inhibits reuptake of dopamine and norepinephrine. Solriamfetol improved maintenance of wakefulness test outcomes and Epworth sleepiness score in a dose–response fashion. Effect sizes for maintenance of wakefulness test change were large and were maintained up to 9 hours at doses of 75 mg and above. Epworth sleepiness scores were reduced by more than 4 U at the higher doses evaluated (150 mg and higher), and by 1.5–2 U at the lower doses (37.5–70 mg). It was reassuring that solriamfetol use did not reduce CPAP adherence.

The investigators addressed potential concerns regarding medication use. Adverse events were common (68% vs. 48% for placebo) but overwhelmingly mild to moderate in severity (95%). At lower doses, few adverse events led to drug discontinuation ($<6\%$), whereas at the highest dose, more participants were affected (14%). Of some concern, the highest dose caused a 2.5-mg increase in systolic and 1.5-mg increase in diastolic blood pressure. Further, heart rate increased by 2–3 beats per minute at doses above 75 mg. To put the potential effect of these small changes into perspective, it has been estimated that a 2 mm Hg decrease in average blood pressure in the general population would reduce all-cause mortality annually by 3%, whereas a 2–3 beats per minute increase in heart rate in healthy middle-aged men has been estimated to increase mortality over the course of 16 years by 3.2–4.8% (6, 7).

This study has notable strengths. The investigators used a double-blind placebo control design, assessed a variety of doses, incorporated both objective and subjective measures of sleepiness, and monitored for a reasonable range of adverse effects over the course of 12 weeks. There is little doubt that solriamfetol has robust clinically important effects on alertness at doses of 75 mg and higher and is reasonably tolerated by many patients in the short term. The authors note two limitations: the study's duration limits an assessment of potential long-term cardiovascular consequences, and the lack of an active comparator such as modafinil prevents a firm understanding of relative efficacy.

An important issue that cannot be addressed in the context of an efficacy study is whether the medication will eventually be used in an appropriate population. Specifically, will primary and reversible causes of persistent hypersomnia be addressed before patients are prescribed the medication? This concern is heightened by some of the trial's inclusion criteria: patients not currently using effective OSA therapy and those with as few as 6 hours of sleep per night. Although there are valid scientific reasons to retain these patients, their inclusion may encourage the use of this medication in cases in which reversible causes of sleepiness are not adequately addressed. This would unnecessarily expose patients not only to the unknown long-term adverse consequences of the medication but also to the potential adverse effects of untreated OSA and sleep deprivation.

Persistent sleepiness in treated OSA can arise from a variety of factors: discomfort associated with CPAP use, depression, and restless legs are known contributors to persistent sleepiness (3, 4). When subjects with these factors are excluded, only 6% of treated patients with OSA have persistent sleepiness (4). Additional patient factors that can cause sleepiness include insufficient sleep, concomitant sleep disorders, sedating medications including nonprescribed substance use, and undiagnosed medical disorders (e.g., hypothyroidism, iron deficiency) (8). One postulated irreversible cause is hypoxemia-related brain damage. This mechanism remains to be adequately evaluated, but is supported by studies that demonstrate neuronal loss after exposure to intermittent hypoxia in mice and structural brain changes including gray matter loss in patients with OSA (9–11). The prevalence and identification of patients affected by this last mechanism is of interest, as this may represent an ideal group in which to use alerting agents.

We propose that a more systematic and robust approach to addressing reversible causes of persistent hypersomnia may yield more benefit than the liberal use of alerting agents. In this regard, the development of a standardized approach to evaluate and address persistent hypersomnia would be helpful. As with insomnia, structured delivery of behavioral sleep medicine interventions may have value to patients with central hypersomnias (12). It is time to consider the development of a behavioral program to address reversible causes of persistent sleepiness in patients with OSA. Within this framework, patients with OSA who have significant sleepiness after comprehensive clinical evaluation and intervention would be well suited to receive alerting therapy. Among these patients, solriamfetol may provide particular value for those not adequately addressed by less expensive and more extensively evaluated alerting agents. ■

Originally Published in Press as DOI: 10.1164/rccm.201812-2291ED on December 27, 2018

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

Vishesh K. Kapur, M.D., M.P.H.
University of Washington School of Medicine
Seattle, Washington

Lucas M. Donovan, M.D., M.S.
University of Washington School of Medicine
Seattle, Washington
and
Veterans Affairs Puget Sound Health Care System
Seattle, Washington

ORCID IDs: 0000-0002-5417-1097 (V.K.K.); 0000-0001-8187-2641 (L.M.D.).

References

1. Bjorvatn B, Lehmann S, Gulati S, Aurlien H, Pallesen S, Saxvig IW. Prevalence of excessive sleepiness is higher whereas insomnia is lower with greater severity of obstructive sleep apnea. *Sleep Breath* 2015;19:1387–1393.
2. Weaver TE, Maislin G, Dinges DF, Bloxham T, George CF, Greenberg H, *et al*. Relationship between hours of CPAP use and achieving normal levels of sleepiness and daily functioning. *Sleep* 2007;30:711–719.
3. Gasa M, Tamisier R, Launois SH, Sapene M, Martin F, Stach B, *et al*.; Scientific Council of the Sleep Registry of the French Federation of Pneumology-FFP. Residual sleepiness in sleep apnea patients treated by continuous positive airway pressure. *J Sleep Res* 2013;22:389–397.
4. Pépin JL, Viot-Blanc V, Escourrou P, Racineux JL, Sapene M, Lévy P, *et al*. Prevalence of residual excessive sleepiness in CPAP-treated sleep apnoea patients: the French multicentre study. *Eur Respir J* 2009;33:1062–1067.
5. Schweitzer PK, Rosenberg R, Zammit GK, Gotfried M, Chen D, Carter LP, *et al*. Solriamfetol for excessive sleepiness in obstructive sleep apnea (TONES 3): a randomized controlled trial. *Am J Respir Crit Care Med* 2019;199:1421–1431.
6. Whelton PK. Epidemiology of hypertension. *Lancet* 1994;344: 101–106.
7. Jensen MT, Suadicani P, Hein HO, Gyntelberg F. Elevated resting heart rate, physical fitness and all-cause mortality: a 16-year follow-up in the Copenhagen Male Study. *Heart* 2013;99:882–887.
8. Chapman JL, Serinel Y, Marshall NS, Grunstein RR. Residual daytime sleepiness in obstructive sleep apnea after continuous positive airway pressure optimization: causes and management. *Sleep Med Clin* 2016;11:353–363.
9. Veasey SC, Davis CW, Fenik P, Zhan G, Hsu YJ, Pratico D, *et al*. Long-term intermittent hypoxia in mice: protracted hypersomnolence with oxidative injury to sleep-wake brain regions. *Sleep* 2004;27:194–201.
10. Canessa N, Castronovo V, Cappa SF, Aloia MS, Marelli S, Falini A, *et al*. Obstructive sleep apnea: brain structural changes and neurocognitive function before and after treatment. *Am J Respir Crit Care Med* 2011;183:1419–1426.
11. Owen JE, Benediktsdottir B, Gislason T, Robinson SR. Neuropathological investigation of cell layer thickness and myelination in the hippocampus of obstructive sleep apnea patients. *Sleep* [online ahead of print] 20 Oct 2018; DOI: 10.1093/sleep/zsy199.
12. Neikrug AB, Crawford MR, Ong JC. Behavioral sleep medicine services for hypersomnia disorders: a survey study. *Behav Sleep Med* 2017; 15:158–171.