Sleep Disorder Challenges, Diagnosis, and Treatments: Hypersomnolence and OSA

Written by Toni Rizzo

In a session designed to investigate various sleep orders, 2 speakers presented new theories and updates on topics related to hypersomnolence and obstructive sleep apnea (OSA).

Lynn Marie Trotti, MD, Emory University, Atlanta, Georgia, USA, discussed the diagnostic challenges and emerging treatments of disorders of daytime sleepiness that occur despite sufficient quality, quantity, and timing of nocturnal sleep, collectively referred to as *hypersomnolence*. Patients with hypersomnolence experience an excessive duration of sleep, deteriorated quality of wakefulness, and sleep inertia.

The International Classification of Sleep Disorders (ICSD) recently updated naming conventions for hypersomnolence disorders [American Academy of Sleep Medicine. *ICSD*, 3rd ed. 2014]. Narcolepsy with cataplexy and narcolepsy without cataplexy have been reclassified as narcolepsy types 1 (NT1) and 2 (NT2), respectively. Instead of basing the definition on the absence or presence of cataplexy, it is now based on the absence (NT1) or presence (NT2) of hypocretin measured in cerebrospinal fluid. The new classification of idiopathic hypersomnia (IH) now encompasses the formerly split classifications of IH with ≥ 10 hours sleep and IH with < 10 hours sleep.

An ideal diagnostic test for hypersomnolence disorders would be sensitive for problematic sleepiness, specific for pathologic sleepiness, and reproducible, and it would appropriately categorize patients based on phenotype. The Multiple Sleep Latency Test (MSLT) is heavily relied on to differentiate among hypersomnolence disorders. However, a study found that 71% of patients with IH and long sleep have a normal MSLT [Vernet C, Arnulf I. *Sleep*. 2009]. Another study reported that among 100 patients with excessive daytime sleepiness, 24-hour polysomnography results were indistinguishable between patients with IH and those with subjective excessive daytime sleepiness [Pizza F et al. *J Sleep Res*. 2013]. Two studies found that the MSLT had poor test-retest reliability [Goldbart A et al. *Sleep*. 2014; Trotti LM et al. *J Clin Sleep Med*. 2013].

The third edition of *ICSD* recommends that, in addition to a sleep log, patients should be assessed with actigraphy for 1 to 2 weeks before the MSLT [American Academy of Sleep Medicine. *ICSD,* 3rd ed. 2014]. In a study of drug-naïve patients with NT1 (n = 39) and IH (n = 24) and 30 healthy controls, actigraphy provided a reliable objective parameter to differentiate among hypersomnolence disorders, particularly NT1 cases [Filardi M et al. *Sleep Med*. 2015]. A study of the Psychomotor Vigilance Task found no correlation with the MSLT, a moderate correlation with maintenance of wakefulness tests latency ($r = 0.349$), and strong correlation with the driving simulation test ($r = -0.521$) [Thomann J et al. *J Clin Sleep Med*. 2014].

Modafinil is a first-line treatment for patients with narcolepsy and IH. A crossover trial of modafinil vs placebo in patients with narcolepsy (n = 13) and IH (n = 14) evaluated maintenance of wakefulness tests and real driving performance after 5 days of treatment [Philip P et al. *Sleep*. 2014]. When treated with modafinil vs placebo, patients made fewer inappropriate line crossings (1.1 ± 0.3 vs 2.1 ± 0.7; $P < .05$) and had lower standard deviation of lateral position (23.6 ± 0.6 vs 24.9 ± 0.9 cm; $P = .06$).

Other treatments studied for hypersomnolence include pitolisant, flumazenil, and clarithromycin (Table 1).

Dr Trotti concluded that more studies are needed on pharmacologic treatments for hypersomnolence but some exciting advances are emerging.

OSA is a risk factor for stroke, the fifth-leading cause of death in the United States [CDC. http://www.cdc.gov/stroke/facts.htm. Accessed May 1, 2015]. Approximately 15 million adults in the United States have OSA [Somers VK et al. *J Am Coll Cardiol*. 2008]. The link between

Peer-Reviewed Highlights From the

American Academy of Neurology 2015 Annual Meeting

April 18–25, 2015
Washington, DC, USA

Table 1. Studies of Treatments for Hypersomnolence Disorders

Treatment: Drug Class	Study Summary
Modafinil: Psychostimulant [Mayer G et al. *J Sleep Res*. 2015]	Modafinil vs placebo in IH without long sleep time (n = 33) Significantly reduced sleepiness on ESS at d 21 vs placebo ($P = .023$) Significantly reduced sleepiness from baseline to d 21 ($P < .005$) Significantly increased sleep latency on MWT at day 21 in post hoc analysis ($P < .05$)
Pitolisant: Inverse agonist of H3 histamine receptors [Dauvilliers Y et al. *Lancet Neurol*. 2013]	Pitolisant, modafinil, and placebo compared in narcolepsy with or without cataplexy (n = 95) for 8 wk Mean ESS reductions: −3.4 with placebo, −5.8 with pitolisant, −6.9 with modafinil Pitolisant superior to placebo ($P = .024$) Pitolisant not noninferior to modafinil ($P = .250$)
Pitolisant: Inverse agonist of H3 histamine receptors [Leu-Semenscu et al. *Sleep Med*. 2014]	Chart review of patients (n = 78) with refractory hypersomnolence (13 symptomatic) Pitolisant 5 to 50 mg once every morning, 5 d to 37 mo 36% response (ESS, −3)
Flumazenil: Competitive agonist at benzodiazepine binding site of GABA-A receptor [Rye DB et al. *Sci Transl Med*. 2012]	Preliminary single-blind, placebo-controlled trial of IV flumazenil (n = 7) Normalized vigilance in 7 patients Significant improvements from baseline in attentional lapses ($P = .0098$) and subjective alertness ($P < .0001$)
Clarithromycin: Macrolide antibiotic, negative allosteric modulator of the GABA-A receptor [Trotti LM et al. *J Psychopharmacol*. 2013]	Retrospective review in patients with hypersomnia with CSF that enhanced GABA-A receptor activity in vitro > controls (n = 53) Clarithromycin 500 to 1000 mg BID for 2 wk Improved daytime sleepiness in 64% AEs not tolerated in 19% Tolerable without symptomatic benefit in 17% Median reaction time was significantly improved with clarithromycin (253.6 ms on clarithromycin vs 305.8 ms without clarithromycin; $P = .014$)
Clarithromycin: Macrolide antibiotic, negative allosteric modulator of the GABA-A receptor [Trotti LM. Under review]	20 patients with untreated or refractory IH (n = 10), narcolepsy without cataplexy (n = 4), or long sleep (n = 6) Randomized to clarithromycin 500 mg BID vs placebo for 2 wk, followed by 1-wk washout, then switched to opposite treatment for 2 wk No significant difference in median reaction time ESS significantly with clarithromycin ($P < .005$) Functional outcomes of sleep significantly increased with clarithromycin ($P < .005$) Any AE, clarithromycin vs placebo: 95% vs 70% Most common AEs, clarithromycin vs placebo: unpleasant or altered taste (65% vs 0%), nausea (35% vs 25%), diarrhea (20% vs 25%) 80% preferred treatment with clarithromycin

AE, adverse event; CSF, cerebrospinal fluid; ESS, Epworth Sleepiness Scale; GABA-A, γ-aminobutyric acid type A; IH, idiopathic hypersomnia; IV, intravenous; MWT, maintenance of wakefulness tests.

OSA and stroke and the impact of treating OSA were discussed by Pablo R. Castillo, MD, Mayo Clinic, Jacksonville, Florida, USA.

Nonrapid eye movement sleep is a state of cardiovascular quiescence, with reduced sympathetic activity, heart rate, blood pressure, and arrhythmogenicity. OSA causes chronic intermittent hypoxia, nocturnal sympathetic activation, sleep loss, inflammation, and metabolic dysregulation. OSA also has been identified as a secondary cause of diurnal hypertension. The American Heart Association/American Stroke Association's guideline on preventing ischemic stroke recommends questioning patients (and their bed partners) with abdominal obesity and hypertension about symptoms of OSA and referral to a sleep specialist [Goldstein LB et al. *Circulation*. 2006]. The gold standard for diagnosis of OSA is attended overnight level 1 polysomnography. Other assessments include the subjective parameters of sleepiness, witnessed apneas, and

Table 2. Trend Analysis for Relationship Between Increased OSA Severity and Composite of Stroke or Death From any Cause

Severity of Syndrome	Stroke or Death		Mean Follow-up Period *yr*	Hazard Ratio (95% CI)
	No. of Events	No. of Patients		
AHI ≤3 (reference score)	13	271	3.08	1.00
AHI 4–12	21	258	3.06	1.75 (0.88–3.49)
AHI 13–36	20	243	3.09	1.74 (0.87–3.51)
AHI >36	34	250	2.78	3.30 (1.74–6.26)

n = 1022; *P* = .005 by the Chi-squared test for linear trend.

AHI, apnea-hypopnea index; OSA, obstructive sleep apnea.

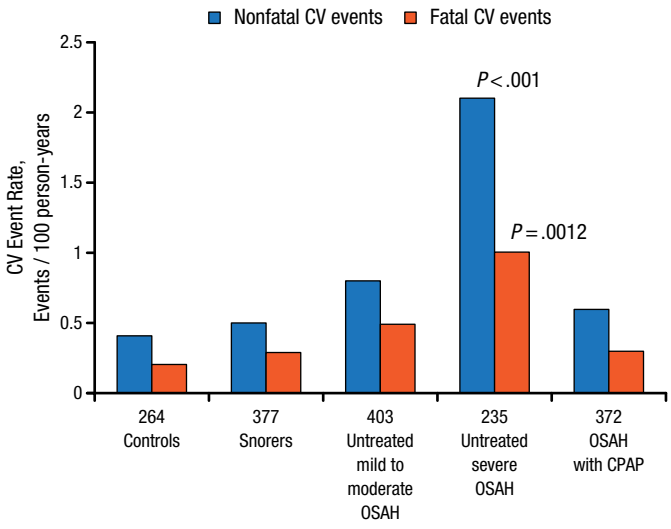
From *N Engl J Med*, Yaggi HK et al., Obstructive Sleep Apnea as a Risk Factor for Stroke and Death, Volume No. 353, 2034-2041. Copyright © (2005) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

snoring; morphometric data, including body mass index, neck size, and cephalometric measures; associated hypertension; and oximetry data.

About 25% of strokes occur during sleep, while wake-up stroke occurs close to awakening [Rimmele DL, Thomalla G. *Front Neurol.* 2014]. OSA has been shown to increase the risk of stroke independent of traditional risk factors, such as hypertension and diabetes [Mohsenin V. *Am J Med*. 2015]. In a 2005 study of 1022 consecutive patients with no previous stroke, 68% had OSA. The probability of event-free survival was significantly lower for patients with OSA compared with controls (log-rank *P* = .003). Trend analysis showed a stepwise increase in the risk of stroke or death with increasing OSA severity (*P* = .005; Table 2). A significant association was found between OSA and stroke or death from any cause in unadjusted (HR, 2.24; 95% CI, 1.30 to 3.86; *P* = .004) and adjusted analyses (HR, 1.97; 95% CI, 1.12 to 3.48; *P* = .01).

Treatment of OSA was associated with better cardiovascular outcomes before treatment with continuous positive airway pressure (CPAP) became available. In a 2005 study, the potential protective effect of CPAP was studied in a male population of 264 healthy men, 377 simple snorers, 403 with untreated mild to moderate OSA, 235 with untreated severe OSA, and 372 with CPAP-treated OSA. Patients with untreated severe OSA had a significantly higher incidence of fatal (1.06/100 person-years) and nonfatal (2.13/100 person-years) cardiovascular events compared with the other groups (Figure 1).

Figure 1. Incidence of Fatal and Nonfatal CV Events



CV, cardiovascular; CPAP, continuous positive airway pressure; OSAH, obstructive sleep apnea-hypopnea syndrome.

Source: Marin JM et al. *Lancet*. 2005.

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OSA is a valid syndrome that increases cardiovascular risk. The long-term ongoing randomized SAVE trial [NCT00738179] is examining whether CPAP treatment of OSA reduces the risk of cardiovascular events. The trial has a global recruitment target of 5000 patients, and results are expected in early 2016.