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BEYOND THE BLUE:

What Fellows Are Reading in Other Journals

Alternative Therapies for Obstructive Sleep Apnea

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Recommended Reading from University of California, San Diego Fellows; Atul Malhotra, M.D., Supervisor

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Joosten SA, et al. A Randomized Controlled Trial of Oxygen Therapy for Patients Who Do Not Respond to Upper Airway Surgery for Obstructive Sleep Apnea. *J Clin Sleep Med* (1)

Reviewed by Brandon Nokes

The future of obstructive sleep apnea (OSA) treatment will likely be tailored on the basis of underlying patient traits (2). The gold standard therapy for OSA is continuous positive airway pressure, but adherence remains variable. Our group and others have defined multiple OSA endophenotypes with these ideas in mind (i.e., ventilatory control instability, low arousal threshold, impaired pharyngeal dilator activity, etc.) (2). It is unclear which patients may have the greatest benefit from upper airway surgery. Furthermore, upper airway surgical procedures are not standardized, and many individuals have residual sleep apnea despite surgical intervention (3, 4). One OSA endotype of note includes patients with elevated loop gain (unstable ventilatory control characterized by increased chemoreflex sensitivity to a given ventilatory disturbance). Joosten and colleagues recently prospectively assessed the impact of oxygen therapy on individuals with residual OSA despite upper airway surgery, for whom altered loop gain may be relevant. This trial was a single night, randomized double-blinded crossover trial for patients with OSA without response to upper airway surgery. They were treated on separate nights with oxygen therapy (4 L/min) or placebo (medical air) to assess effects of oxygen/air on apnea-hypopnea index (AHI), flow-based AHI, arousal index, and morning blood pressure. OSA endotypes were estimated to determine whether baseline OSA traits could be used to predict response to oxygen. There was a statistically significant reduction in AHI and flow-based AHI on oxygen versus placebo (flow-based AHI: 42.4 ± 21.5 vs. 30.5 ± 17.1 /h, $P = 0.008$). Arousal index was also reduced on oxygen versus placebo (41.1 ± 19.5 vs. 33.0 ± 15.3 /h, $P = 0.006$). There was no significant difference in morning blood pressure between oxygen and placebo. Notably, 7 of 20 individuals experienced a reduction of 50%

or more in flow-based AHI on oxygen (responders), and there was no difference in the baseline OSA endotypes. However, this responder subset was likely too small to detect an endotype-specific difference in response to oxygen, and the optimal method to detect and lower loop gain remains unclear (5). As the authors acknowledge, there are recent data indicating that upper airway surgery itself may lower loop gain, suggesting at least some of the abnormality in control of breathing may be acquired in OSA (6–8). Future studies with a nonsurgical comparator group would be welcome. Nonetheless, this paper by Joosten and colleagues reflects important progress toward tailoring OSA therapy to the individual patient. Specifically, the notion of combination OSA therapy (e.g., surgery to address anatomy and oxygen to address loop gain) deserves further study. ■

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Strollo PJ Jr, *et al.*; Tones 4 Study Investigators. Solriamfetol for the Treatment of Excessive Sleepiness in OSA: A Placebo-controlled Randomized Withdrawal Study. *Chest* (9)

Reviewed by Erica Lin

Despite successful treatment of OSA, a subset of patients report persistent excessive daytime sleepiness (10, 11). Although modafinil and armodafinil have been shown to improve wakefulness in OSA, they may have waning effects throughout the day and an unfavorable risk profile, particularly in premenopausal women (12–14). Solriamfetol, a selective dopamine and norepinephrine reuptake inhibitor, has been demonstrated to improve wakefulness in narcolepsy and OSA (15, 16).

Strollo and colleagues conducted a multicenter, phase III, double-blinded, placebo-controlled trial with a randomized withdrawal design to assess efficacy of solriamfetol in adults with OSA on current or prior OSA therapy, with baseline mean sleep latency <30 minutes on Maintenance of Wakefulness Test (MWT), Epworth Sleepiness Scale (ESS) score ≥ 10 , and sleep time ≥ 6 hours. After 2 weeks of titration and 2 weeks of stable dose administration, participants with improvements on their Patient Global Impression of Change scale, MWT, and ESS at Week 4 were randomly assigned to transition to placebo or continue solriamfetol for 2 additional weeks. Coprimary endpoints were change in MWT and ESS from weeks 4 to 6.

Of the 174 participants enrolled, 124 met inclusion criteria in the withdrawal phase and were randomized to placebo ($n = 62$) or solriamfetol ($n = 62$). In the modified intention-to-treat analysis, the mean sleep latencies improved from 12.3 to 29.0 (placebo) and 13.1 to 31.7 (solriamfetol) minutes and ESS scores from 16.0 to 5.9 (placebo) and 15.3 to 6.4 (solriamfetol) by week 4, respectively. Participants who continued solriamfetol maintained this improvement (least squares [LS] mean \pm SE changes of -1.0 ± 1.4 min on MWT and -0.1 ± 0.7 on ESS), whereas participants who were switched to placebo had worse scores (LS mean \pm SE changes of -12.1 ± 1.3 min on MWT and 4.5 ± 0.7 on ESS, with LS mean differences between treatments of 11.2 min [95% confidence interval, 7.8 to 14.6; $P < 0.0001$] and -4.6 [95% confidence interval, -6.4 to -2.8 ; $P < 0.0001$] on MWT and ESS, respectively). Neither score returned to baseline.

Overall, this trial showed that initial responders to solriamfetol maintained improvements in sleepiness with therapy continuation compared with worsened measures among participants randomly assigned to withdraw. This finding further supports the efficacy of solriamfetol, making it an important addition to the pharmacologic management for residual excessive daytime sleepiness in OSA. Conclusions are limited to initial responders. Further studies are needed to evaluate the impact on sleep-related quality of life, long-term effects, and its comparison to other pharmacologic therapies. ■

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Eastwood PR, *et al.* Bilateral Hypoglossal Nerve Stimulation for Treatment of Adult Obstructive Sleep Apnoea. *Eur Respir J* (17)

Reviewed by W. Cameron McGuire

When positive airway pressure therapy fails in OSA treatment, alternatives include hypoglossal nerve stimulation (HNS). HNS (18) has been U.S. Food and Drug Administration approved after the publication of the STAR (Stimulation Therapy for Apnea Reduction) Trial using the Inspire device (19) and has shown durable results (20). However, HNS has seen relatively low uptake owing to unilateral stimulation, need for respiratory sensing leads, expense, and requisite time-consuming surgery. Given these limitations, ongoing efforts have been made to identify alternative HNS therapies, such as the Genio device.

After a small incision above the hyoid bone, the Genio is implanted above the genioglossus muscle between the right and left hypoglossal nerves. A rechargeable, external activation unit is affixed under the chin with a disposable adhesive patch, and transdermal stimulation is provided without indwelling wires or battery packs. Optimization of stimulation frequency is titrated over time to obviate the need for respiratory sensing leads.

Eastwood and colleagues studied the Genio HNS in a single-arm, uncontrolled feasibility study (17). Adults (age 21–75 yr) with a body mass index $\leq 32 \text{ kg} \cdot \text{m}^{-2}$ and an obstructive AHI of 20–60 events $\cdot \text{h}^{-1}$ were eligible for enrollment if there was no positional OSA, low rates of central/mixed AHI, and no evidence of complete concentric collapse on drug-induced sleep endoscopy ($n = 22$).

Baseline polysomnogram values were obtained before implantation, the device was activated 4–6 weeks later, and titrations were performed during Months 2 through 4. Outcome measurements on fixed therapeutic settings were obtained at Month 6 on a full-night polysomnogram. Primary outcomes included change in AHI and incidence of device-related serious adverse events (SAEs).

The AHI decreased from 23.7 ± 12.2 to 12.9 ± 10.1 events \cdot h⁻¹ ($P < 0.0001$). Statistically significant improvements were observed in secondary outcomes, including ESS, oxygen desaturation index, and time at oxygen saturation as measured by pulse oximetry $< 90\%$. Patient-reported use was 91% for > 5 days/week and 77% for > 5 hours/night. There were no device-related SAEs, although there were four surgery-related SAEs, including explantation of two units because of surgical site infection.

Lack of a control group combined with a limited duration of therapy and a modest sample size limit any definitive conclusions. However, we are aware of a multicenter trial to investigate this technology further in a more rigorous manner (21). Moreover, response to HNS may be endotype specific (22). ■

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

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