OSA Drugs No Longer Aim Only at Weight Loss

BY BRUCE JANCIN

FROM THE ANNUAL MEETING OF THE ASSOCIATED PROFESSIONAL SLEEP SOCIETIES

SAN ANTONIO — While obstructive sleep apnea is closely associated with obesity, not all the drugs being developed for the treatment of OSA are based upon weight loss as their mechanism of benefit.

For example, acetazolamide addresses ventilatory instability, which has emerged as a potential novel therapeutic target in OSA. Another early study suggests that the sedative eszopiclone (Lunesta) reduces sleep apnea severity and increases sleep duration by raising the respiratory arousal threshold, investigators reported at the meeting.

Still, weight loss is the classic source of pharmacologic improvement in OSA. The first drug shown to be of benefit in patients with OSA was sibutramine (Meridia), a serotonin and noradrenaline reuptake inhibitor, noted Dr. Ronald R. Grunstein, professor of sleep medicine at the University of Sydney.

He was lead investigator in a study that showed 6 months of sibutramine plus a 600-kcal-deficit diet and exercise not only resulted in significant weight loss, it also brought marked improvement in OSA, reduced insulin resistance, a rise in high-density lipoprotein cholesterol, and decreased visceral, subcutaneous, and hepatic fat, with no change in blood pressure (J. Clin. Sleep Med. 2009;5:416-21).

At the sleep disorders meeting, audiences learned of another weight-loss drug with evidence of efficacy for OSA: Qnexa, an investigational once-daily proprietary combination of phentermine and controlled-release topiramate.

A 45-patient OSA study showed encouraging results with Qnexa, but much larger clinical trials are needed.

DR. WINSLOW

Dr. David H. Winslow presented a double-blind, single-center trial in which 45 obese patients with OSA were randomized to once-daily Qnexa at 15-mg phentermine/92-mg topiramate CR or to placebo for 28 weeks. All participants were either noncompliant with or disinterested in continuous positive airway pressure (CPAP) therapy, and all were provided with a structured lifestyle modification program.

At week 8, the mean apnea-hypopnea index (AHI) in the Qnexa group had dropped from a baseline of 45.5 to 19.1 events per hour. By week 28, their mean AHI had fallen to 13.5, as compared with 27.2 in the placebo arm, reported Dr. Winslow, a chest physician and president of the Kentucky Research Group, Lexington.

The Qnexa group experienced a mean 11% reduction in body weight over the 28 weeks, twice that of the placebo group. Other statistically significant and clinically meaningful changes in the Qnexa group included a mean 15-mm Hg drop in systolic blood pressure from a baseline of 138 mm Hg, as compared with a 7.3-mm Hg drop in controls, along with polysomnographic improvements in arousal index and mean and minimum overnight oxygen saturation.

The most common adverse events were mild to moderate dry mouth and altered taste. There were no serious adverse events in the study.

"I think we may be looking at a new paradigm in the treatment of OSA," Dr. Winslow said in an interview.

Qnexa is under Food and Drug Administration review for a proposed indication as a treatment for obesity; a regulatory decision is expected later this year. While the results in the 45-patient OSA study are quite encouraging, getting an additional indication as a therapy for OSA will require much larger clinical trials, he noted.

Danny J. Eckert, Ph.D., of Brigham and Women's Hospital, Boston, presented a double-blind, randomized, crossover trial in which 17 untreated OSA patients received 3 mg of eszopiclone or placebo immediately prior to going to sleep during overnight polysomnography on two occasions in the sleep lab.

The patients' mean AHI was 24 events per hour on eszopiclone, compared with 31 per hour with placebo. The seven patients with a low baseline respiratory arousal threshold, defined as less than 15 cm H_2O, had a mean 42% improvement in AHI on active therapy, and all seven of them had at least a 20% improvement.

Patients on eszopiclone also had a marked increase in total sleep time, from 5.3 hours on placebo to 6.8 hours, along with fewer arousals per hour and improved sleep quality, Dr. Eckert reported.

Dr. Bradley A. Edwards, also of Brigham and Women's Hospital, presented a preliminary physiologic study in which six CPAP-treated patients with OSA underwent 2 nights of baseline polysomnography, and then took acetazolamide SR 500 mg twice daily for a week. This was followed by another 2 nights of polysomnography in which CPAP was intermittently turned down to subtherapeutic levels in order to see whether acetazolamide reduced ventilatory control instability. This indeed proved to be the case in all six patients.

Moreover, five of the six patients experienced an associated reduction in AHI.

Dr. Grunstein said other drugs being explored as possible OSA therapies include lorcaserin, now under FDA review as a potential antiobesity drug, and testosterone.

Dr. Winslow disclosed that he serves as a consultant to Vivus Inc., which is developing Qnexa. Dr. Eckert's study was partially funded by a research grant from Sepracor Inc. Dr. Grunstein's sibutramine study was supported by Abbott Laboratories. Dr. Edwards reported no financial conflicts. ■

CPAP Reverses Left Ventricular Remodeling in Severe Apnea

BY BRUCE JANCIN

FROM THE ANNUAL MEETING OF THE ASSOCIATED PROFESSIONAL SLEEP SOCIETIES

SAN ANTONIO — Six months of continuous positive airway pressure therapy markedly improved adverse left ventricular and atrial remodeling in patients with moderate to severe obstructive sleep apnea in a prospective study.

Diastolic as well as systolic abnormalities were reversed, raising the welcome prospect that CPAP is likely to prevent the development of one of the most dreaded complications of severe obstructive sleep apnea (OSA)—chronic heart failure—although this point remains speculative, Dr. Saleh Al-Mutairi said.

He recruited 32 patients with newly diagnosed moderate to severe OSA for the study, which involved serial follow-up by cardiac magnetic resonance (CMR), echocardiography, and cardiac biomarkers through 6 months of individually titrated CPAP therapy.

The subjects averaged 51 years of age, with a mean baseline apnea-hypopnea index of 53 events/hour and a mean body mass index of 34.5 kg/m^2. None of the participants had known cardiac disease. Adherence to CPAP was good. The patients' weight didn't change significantly during the study, and those being treated for hypertension remained on the same doses of medication throughout the follow-up period.

This is the first study with follow-up as long as 6 months using cardiac magnetic resonance and echocardiography.

DR. AL-MUTAIRI

Other studies have shown improvement in left ventricular dysfunction with CPAP, but they were short-term trials. This is the first study with follow-up as long as 6 months using both CMR and echocardiography, according to Dr. Al-Mutairi of the University of Manitoba, Winnipeg.

He focused on the CMR results because he considers that technology more reliable than echocardiography for assessing ventricular size and function. The echo findings, however, corroborated the CMR results.

Most of the left ventricular measurements followed during the study were abnormal at baseline. The 6-month results included a 25% reduction from baseline in left ventricular end-diastolic volume and a 19% decrease in left ventricular mass. (See chart.)

Dr. Al-Mutairi drew particular attention to the 30% reduction in left atrial volume index. "The treatment of OSA with CPAP may prevent the left atrial remodeling measured by CMR and echo as the left atrial volume index. This is a very important point, given the association between the left atrial volume and cardiovascular events," he observed.

There was no significant change in C-reactive protein, brain natriuretic peptide, or other cardiac biomarkers during the 6 months of CPAP use.

The mechanism by which OSA is thought to predispose to heart failure involves an exaggerated negative thoracic pressure in response to the apneic episodes. This presumably leads to increased left ventricular systolic transmural pressure, which the left atrium resists, with resultant increased compliance and atrial overstretching, explained Dr. Al-Mutairi, who reported having no relevant conflicts of interest.

He and his colleagues are in the midst of expanding their study to 50 patients in order to strengthen the conclusions. ■

Key Cardiac Magnetic Resonance Changes Within 6 Months of CPAP

	Baseline	Follow-up
Left ventricular end-systolic volume	68 mL	53 mL
Left ventricular end-diastolic volume	199 mL	150 mL
Left ventricular mass	184 g	149 g
Left atrial volume index	49 mL/m^2	34 mL/m^2

Notes: Based on a study of 32 patients with moderate to severe obstructive sleep apnea. All reductions are statistically significant.
Source: Dr. Al-Mutairi