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 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.

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.

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DR. WINSLOW

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, he 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. ■

Disclosures: *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.*

Gabapentin Enacarbil Promising for Restless Legs Syndrome

BY BRUCE JANCIN

FROM THE ANNUAL MEETING OF THE ASSOCIATED PROFESSIONAL SLEEP SOCIETIES

SAN ANTONIO — Long-term use of gabapentin enacarbil for treatment of restless leg syndrome does not lead to the symptom augmentation that commonly occurs with dopaminergic agents, a study shows.

The symptom augmentation study was but one of a flurry of clinical trials of the investigational drug for restless legs syndrome (RLS) presented at the meeting.

Gabapentin enacarbil is a once-daily oral prodrug of gabapentin with pharmacokinetics superior to the parent drug.

The RLS augmentation that occurs as an unwanted side effect of dopaminergic therapy consists of increased symptom severity, extension of symptoms to previously unaffected parts of the body, or onset of symptoms at least 2 hours earlier in the evening than before treatment.

Dr. Richard K. Bogan reported on 427 patients with a mean 14-year history of RLS who were randomized double-blind to 12 weeks of gabapentin enacarbil at 1,200 mg or placebo once daily at 5 p.m. taken with food.

Mean scores on the International Restless Legs Scale (IRLS) in the gabapentin enacarbil group improved by 13.1 points from a baseline of 23, which was significantly better than the 9.3-point drop with placebo.

The average duration of RLS symptoms per evening in the gabapentin enacarbil group decreased by 52 minutes from a baseline of 102 minutes, and by 37 minutes from a baseline of 112 minutes in placebo-treated patients.

Gabapentin enacarbil was not associated with any increase in daytime sleepiness, a common side effect with pramipexole and ropinirole.

There was no suggestion of RLS symptom augmentation with the investigational drug based on time to onset or duration of symptoms, according to Dr. Bogan, chairman and chief medical officer of SleepMed Inc. in Columbia, S.C.

Dr. Aaron L. Ellenbogen presented an open-label, 52-week extension study of 386 patients who were treated with gabapentin enacarbil.

Mean IRLS scores improved from 23.2 at baseline to 8. The investigators rated 85% of the subjects as "responders" on the Clinical Global Impression-Improvement scale.

Gabapentin enacarbil was not associated with any increase in daytime sleepiness, a common side effect with pramipexole (Mirapex) and ropinirole (Requip), the dopamine agonists approved for treatment of RLS.

Mean scores on the Epworth Sleepiness Scale in the open-label study went from 6.7 at enrollment to 5.7 after a year.

Eleven percent of patients withdrew because of adverse effects, the most common of which were somnolence and dizziness, reported Dr. Ellenbogen of the Michigan Institute for Neurological Disorders, Farmington Hills, Mich.

Roughly 60% of patients report pain in association with their RLS, and one-third of them describe this as their most troublesome symptom.

Gabapentin enacarbil effectively relieves this pain, according to Dr. Daniel O. Lee.

He reported on 321 patients with moderate to severe RLS who were randomized to gabapentin enacarbil at 1,200 or 600 mg or placebo once daily for 12 weeks.

Sixty-nine percent of those on gabapentin enacarbil at 1,200 mg and 68% on 600 mg reported at least a 30% reduction from baseline in pain scores, compared with 52% on placebo.

Moreover, 60% of patients on 1,200 mg/day and 56% on 600 mg/day reported at least a 50% reduction in pain, compared with 44% on placebo, said Dr. Lee of East Carolina Neurology in Greenville, N.C. ■

Disclosures: *XenoPort Inc., which is collaborating with GlaxoSmithKline Inc. in developing gabapentin enacarbil, supported the studies. Dr. Lee, Dr. Ellenbogen, and Dr. Bogan disclosed serving as consultants to numerous pharmaceutical companies, including GlaxoSmithKline.*