

# Tolerance Not Seen With Sublingual Zolpidem

BY CAROLINE HELWICK

FROM THE ANNUAL CONGRESS OF THE EUROPEAN COLLEGE OF NEUROPSYCHOPHARMACOLOGY

AMSTERDAM – A sublingual 3.5-mg formulation of zolpidem tartrate is effective for middle-of-the-night insomnia, producing no tolerance, rebound, or increase in use over a 4-week period, a study has shown.

“Awakening during the night with difficulty falling back to sleep is a prevalent condition, and a PRN treatment for this is needed as it may decrease overall drug exposure,” said the study’s coinvestigator, Thomas Roth, Ph.D., of Henry Ford Hospital, Detroit.

Zolpidem sublingual tablets 3.5 mg and 1.75 mg were developed for the treatment of insomnia that is characterized by difficulty returning to sleep after middle-of-the-night (MOTN) awakening.

**VITALS Major Finding:** Persons who received a new formulation of low-dose sublingual zolpidem for middle-of-the-night insomnia showed no potential for abuse of the drug in the form of dependency, tolerance, or rebound potential, compared with placebo recipients.

**Data Source:** A 4-week outpatient study of 146 subjects.

**Disclosures:** Dr. Roth has served as a consultant to Transept Pharmaceuticals Inc., the manufacturer of the sublingual formulation of zolpidem tartrate. He has also received research support from and had other relationships with numerous pharmaceutical companies.

The compound is formulated with binary buffers to promote buccal absorption of a portion of the drug. This facilitates bioavailability, resulting in a rapid return to sleep.

Previous studies have found that sublingual zolpidem significantly reduces sleep latency after MOTN dosing.

In a sleep laboratory study, sleep latency time was approximately 28 minutes with placebo but just 10 minutes with zolpidem 3.5 mg (*Sleep* 2008;31:1277-84).

“This is a reduced dose of zolpidem, and importantly it is a sublingual formulation so you achieve much faster blood levels to help you fall back asleep but you reduce the total blood level as compared to taking it prophylactically. The concern is that over time, people take more and more of the medication,” Dr. Roth said at the meeting.

The drug is currently under review by the Food and Drug Administration for MOTN awakening.

In a study designed to address possible abuse liability associated with PRN use of the drug, 75 outpatients received zolpidem and 71 patients received placebo; all were assessed for latency to sleep onset after MOTN dosing across a 4-week treatment period.

To address rebound potential, outcomes also were observed on the first night of nondosing after 1 or more nights of medication use. Dependence and tolerance also were examined.

The study found no evidence of residual sleepiness after MOTN dosing with zolpidem. Patients who received the drug actually reported greater alertness, compared with baseline. On a scale of 1-9 (with 9 being most alert), the mean score was 4.9 at baseline, increasing to 5.7 after zolpidem dosing. Scores in the placebo arm were 4.7 and 5.2, respectively.

Sleep quality also improved significantly. Mean scores were 4.7 at baseline and 5.8 after treatment with zolpidem, compared with 4.5 and 5.2, respectively, with placebo.

The study found no evidence for the development of tolerance to zolpidem’s efficacy.

Latency to sleep onset improved over the first 2 weeks, and apparently stabilized by week 3, for both the active-treatment and placebo groups, suggesting a non-specific trend toward improvement in outcome over time.

The response to the medication did not change across the entire treatment period, and drug use was not different between treatment and placebo groups, Dr. Roth reported.

In fact, weekly medication use showed a decline for both the active and placebo groups, with medication use during week 4 being significantly lower than during week 1 in both arms.

The mean number of tablets taken during weeks 1



Middle-of-the-night awakening with difficulty falling back to sleep is a prevalent condition.

and 4 were 4.9 and 4.0, respectively, for the zolpidem group and 4.9 and 4.3, respectively, for the placebo group. There was no evidence of rebound effects on sleep initiation or total sleep time on nondosing nights, regardless of the number of nights of continuous use.

On average, for nights during which zolpidem was not dosed, total sleep time was similar for the active and placebo groups.

Dr. Roth noted that the improvement over placebo of about 20 minutes is clinically meaningful.

“It doesn’t sound impressive, but try sleeping 20 minutes less every night for 3 months – you’ll be in a coma. The effect is cumulative. It’s about 2 hours a week.”

## Children With Sleep Apnea Had Lower Grades in School

*Sleep-disordered breathing may be linked to a higher risk of learning and behavioral problems.*

BY BRUCE JANCIN

FROM THE ANNUAL MEETING OF THE ASSOCIATED PROFESSIONAL SLEEP SOCIETIES

SAN ANTONIO – Children with obstructive sleep apnea get worse grades in school than do their classmates without sleep-disordered breathing, a study shows.

These 10- to 16-year-olds with even mild obstructive sleep apnea (OSA) were also independently rated both by parents and by teachers as more likely to have attention and learning problems, Dean W. Beebe, Ph.D., reported at the annual meeting of the Associated Professional Sleep Societies.

“There was an impressive impact of sleep-disordered breathing on academic grades. That leaves the subjects with moderate to severe sleep apnea at a serious disadvantage,” said Dr. Beebe of Cincinnati

Children’s Hospital Medical Center.

The study included 163 overweight youths aged 10-16 years, who were recruited from sleep or weight management clinics. Investigators rated 42 of them as having moderate to severe OSA based on an apnea-hypopnea index in excess of 5 events/hr. Another 58 had mild OSA, defined by an apnea-hypopnea index of 1-5 events/hr. Twenty-six participants were classified as snorers, while 37 were free of sleep-disordered breathing (SDB).

Subjects without SDB maintained a collective B average at school. Snorers trended toward lower grades, although the difference was not significant. But participants with OSA, whether mild or more severe, averaged half a grade point lower than did those without SDB. The difference—a B-/C+ average rather than a solid B—

could have implications down the road in terms of college and career opportunities, Dr. Beebe noted.

Thirty percent of students with moderate to severe OSA had a C average or less, compared with just 15% of those without SDB. And while 15% of subjects with no SDB had an A average academically, that was the case for only a single student with moderate to severe OSA.

**Subjects without sleep-disordered breathing maintained a collective B average at school. Participants with obstructive sleep apnea, whether mild or more severe, averaged half a grade point lower.**

On the validated Behavior Assessment System for Children (BASC), teachers rated the students with mild or more severe OSA as having significantly more attention and learning problems than those without

SDB. Teachers also rated the non-SDB youths significantly higher in terms of the BASC adaptive functioning domains of leadership, social skills, and study skills.

Parents of students with SDB rated them on the BASC as having more attention, anxiety, depression, aggression, and hyperactivity problems.

Given the worsening obesity epidemic and the fact that obesity is a major risk factor for SDB in middle childhood, the evidence that SDB has adverse academic, behavioral, and cognitive consequences suggests a major public health concern, according to Dr. Beebe.

He said the next stage of his research will be to see whether the academic and learning deficits associated with SDB in middle childhood and adolescence are remediable when the respiratory condition is treated.

The study was funded by the American Sleep Medicine Foundation and the National Institutes of Health. Dr. Beebe reported having no financial conflicts.