

Drug Improves Sleep Induction Without Sedation

BY BRUCE JANCIN
Denver Bureau

DENVER — The novel melatonin receptor agonist ramelteon was associated with significant reductions in the time it took to fall asleep in two phase III clinical trials totaling 1,234 adults with primary insomnia, investigators reported at the annual meeting of the Associated Professional Sleep Societies.

The recently approved drug accomplished this while maintaining a reassuring safety profile. Testing revealed no next-day effects on residual memory or psychomotor function, and no rebound insomnia upon discontinuation of ramelteon.

Results Mixed On Tiagabine For Insomnia

DENVER — The anticonvulsant tiagabine (Gabitril) increased slow wave sleep in dose-dependent fashion in a 30-center randomized trial involving 232 adults with primary insomnia, James K. Walsh, Ph.D., reported at the annual meeting of the Associated Professional Sleep Societies.

But whether this drug-induced alteration in sleep architecture will translate into clinical utility for the treatment of insomnia remains an unanswered question. Of note, patients given tiagabine didn't report their sleep as being any deeper, more refreshing, or of better quality than patients on placebo, said Dr. Walsh, director of the sleep medicine and research center at St. Luke's Hospital, St. Louis.

Tiagabine is a selective γ -aminobutyric acid (GABA) reuptake inhibitor that boosts synaptic GABA availability through selective inhibition of the GABA transporter-1 receptor.

The randomized trial compared four doses of tiagabine—4, 6, 8, and 10 mg at bedtime—and a placebo in a two-night polysomnographic study. Slow wave sleep increased from baseline by a mean of 19 minutes with 4 mg of tiagabine, 32 minutes with 6 mg, 40 minutes with 8 mg, and 53 minutes with 10 mg, compared with an 11-minute increase with placebo. A corresponding dose-related decrease in stage 1 sleep with tiagabine was also noted.

The 4- and 6-mg doses of tiagabine had a side effect profile similar to placebo, while dizziness and nausea were the most prominent adverse events noted in patients on 8- and 10-mg doses of the drug.

Patients on the 10-mg dose scored significantly worse than the placebo group on the assessment of daily functioning questionnaire in terms of ability to concentrate and think clearly, sense of physical well-being, and alertness. They also reported notable psychomotor impairment. For these reasons, doses of less than 10 mg will be utilized in further trials evaluating tiagabine efficacy in primary insomnia.

The trial was sponsored by Cephalon Inc.
—Bruce Jancin

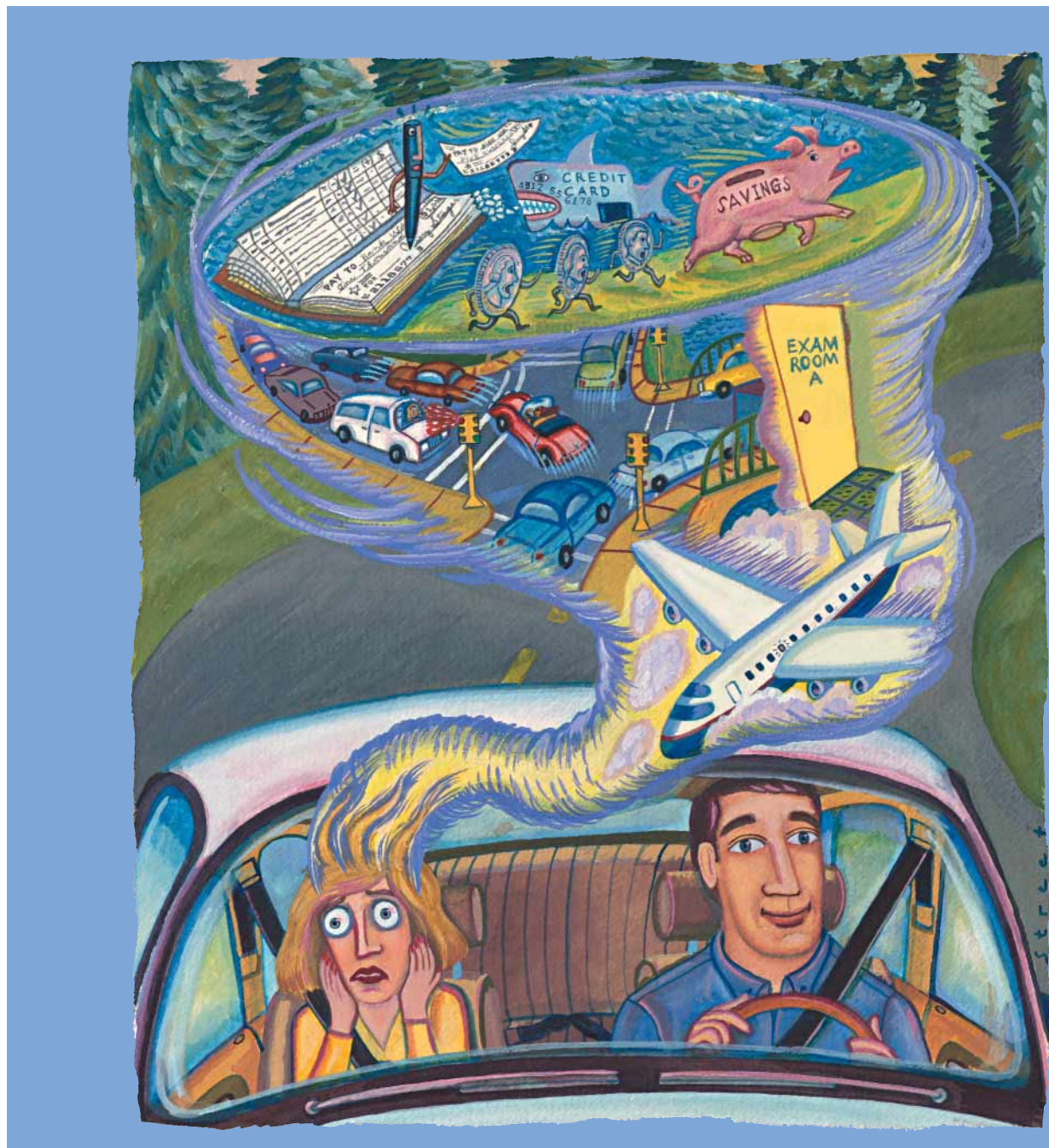
Moreover, unlike most sedative-hypnotics, which are classified as schedule IV controlled substances, ramelteon appears to lack abuse potential. It also lacks the generalized CNS depressant effects characteristic of traditional sedative-hypnotics, making it an attractive agent for treating insomnia in patients with chronic obstructive pulmonary disease (COPD), according to studies presented at the meeting.

Thomas Roth, Ph.D., explained that ramelteon differs from the endogenous

hormone melatonin in that ramelteon is highly specific for the melatonin receptors MT1 and MT2 involved in the sleep-wake cycle; indeed, ramelteon has up to a 16-fold greater affinity for those sites than melatonin itself. And unlike melatonin, it has no serotonergic metabolites. Ramelteon has low affinity for the MT3 receptor and other CNS binding sites, including the benzodiazepine, opioid, muscarinic, dopamine, and γ -aminobutyric acid receptors.

Dr. Roth presented a randomized, double-blind, placebo-controlled trial of ramelteon in 829 elderly patients with chronic insomnia. The results were similar to those seen in a separate phase III double-blind trial presented by Gary Zammit, Ph.D., involving 405 younger adults—mean age 39 years—with chronic insomnia. Both trials lasted for 5 weeks.

From the very beginning of both trials, the time it took for subjects to fall asleep was significantly less with ramelteon than



NIRAVAM is contraindicated in patients with known sensitivity to this drug or other benzodiazepines, in patients with acute narrow-angle glaucoma, and in patients taking potent CYP3A inhibitors, such as ketoconazole and itraconazole.

At doses greater than 4 mg per day (often required for panic disorder), the risk of dependence may be higher than in those taking smaller doses.

Since NIRAVAM has a CNS depressant effect, patients should be cautioned about mental alertness, impaired performance and taking alcohol or other CNS depressant drugs during treatment with alprazolam. If alprazolam is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Adverse events ($\geq 5\%$ and at least 50% greater than placebo) in clinical trials include drowsiness, impaired coordination, memory impairment, dysarthria, increased or decreased libido, and constipation.

Certain adverse clinical events are a direct consequence of physical dependence to alprazolam. These include a spectrum of withdrawal symptoms, the most important being seizure.

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with placebo, according to Dr. Zammit, director of the Sleep Disorders Institute at St. Luke's-Roosevelt Hospital, New York.

Headache, somnolence, and fatigue were roughly twice as common with ramelteon.

Takeda Pharmaceutical Co. filed for marketing approval of ramelteon with an insomnia indication last fall; in July it was approved by the Food and Drug Administration. But physicians will need a bit of experience with the drug to learn how to effectively use an agent with such subtle effects, according to Dr. Roth of Wayne State University, Detroit.

"Ramelteon has a significant effect upon

sleep induction, yet it is not sedative. That's a unique thing in the sleep arena. It's going to be a clinical challenge, much like physicians faced when non-sedating antianxiety agents became available. People had treated anxiety for many, many years with sedating drugs, and one of the early clues an antianxiety agent was working was that the patient felt sleepy. The same issue arose when the nonsedat-



ing antihistamines came along," he noted.

In another randomized double-blind study, Stephen Sainati, M.D., Ph.D., reported on 26 patients with mild to moderate COPD. They received 16 mg of ramelteon or placebo 1/2 hour before bedtime and were monitored overnight using pulse oximetry and respiratory inductance plethysmography. Patients crossed over to the other study arm

after a 5- to 12-day washout.

The primary end point was mean arterial oxygen saturation. It was unchanged throughout the night with ramelteon. That's welcome news, since traditional sedative-hypnotics have a respiratory-depressant effect. The clinical relevance of the absence of such an effect with ramelteon lies in the fact that insomnia is roughly threefold more prevalent in COPD patients than the general population, according to Dr. Sainati of the Takeda Global Research and Development Center, Lincolnshire, Ill.

All of these studies were sponsored by Takeda. ■

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