Abundance of Insomnia Therapies in the Pipeline

BY BRUCE JANCIN Denver Bureau

DENVER — The pharmaceutical industry envisions the insomnia market as a field of dreams, judging by the sizable array of agents moving through the developmen- opmental pipeline.

And these aren’t “me-too” drugs, either. They involve a wealth of new therapeu- tic targets and novel mechanisms of action.

“This is an exciting time in insomnia. There’s a lot of movement in terms of how people are conceptualizing the prob- lem clinically, there are new treatments coming up, and I think we’re really going to have some better options for our pa- tients in the near future,” Daniel J. Buysse, M.D., said at a satellite symposium held with the annual meeting of the Associat- ed Professional Sleep Societies.

The opportunity for new agents to make a big splash stems from the fact that insomnia is extremely common, with 6% of the population, by some estimates, meeting formal diagnostic criteria for the disorder.

In addition, although numerous drugs are commonly prescribed off label for in- somnia, the benzodiazepine receptor ag- onists and the newly approved melatonin receptor agonist ramelteon (Rozerem) are the only medications with Food and Drug Administration approval for this indication.

And only two agents—the benzodi- azepine receptor agonist eszopiclone (Lunesta) and ramelteon—are approved for long-term use. The rest of the benzo- diazepine receptor agonists carry an indi- cation for a maximum of 30 days of use.

But cross-tolerance has been observed.

Tiagabine (Gabitril), a selective GABA reuptake inhibitor already on the market for the treatment of partial seizures, is under evaluation for insomnia.

Also under investigation is a new for- mulation of zolpidem (Ambien). It con- sists of 5 mg of immediate-release drug and 7.5 mg of prolonged-release drug, for a total of 12.5 mg of zolpidem.

“Alpha-2 delta ligands,” Gabapentin (Neurontin) and pregabalin are ligands for the alpha-2 delta protein subunit of the voltage-sensitive calcium channel, which they modulate to inhibit release of excitable neurotransmitters such as sub- stance P and glutamate. Although gabapentin is marketed for the treatment of postherpetic neuralgia and epilepsy, these drugs are under investigation for in- somnia, anxiety, chronic pain syndromes, and neuropathic pain.

“If they do work in insomnia, it’s go- ing to be by a very different mechanism of action than other agents, essentially by inhibiting the release of excitatory neu- rotransmitters, rather than promoting the action of an inhibitory neurotrans- mitter like GABA,” the psychiatrist explained.

Melatonin receptor agonists. The re- cently approved ramelteon is a high- ly selective agonist for the melatonin ML-1 receptor, which is believed to play a more impor- tant role in sleep than the ML-2 re- ceptor. It is ap- proved at the dose of 8 mg for long-term use in adults. It is the only approved insomnia drug without a schedule IV classification, meaning it is deemed to be without abuse potential.

Serotonin 5-hydroxytryptamine-2 an- tagonists. Serotonin antagonists seem to increase slow-wave sleep and enhance sleep continuity while having little im- pact on sleep latency. Drugs with a strong 5-HT3 antagonist effect include trazodone (Desyrel), doxepin, mirtazapine (Remeron), and amitriptyline.

Dr. Buysse said he does not prescribe mirtazapine often because weight gain is a prominent side effect. But he does use trazodone and doxepin.

These drugs are often associated with some morning hangover, but there are pa- tients who do great on them. It would not be the case that trazodone is the first or second most widely prescribed agent for treatment of insomnia if it didn’t do some- thing for somebody. And I think that it does,” he said.

There is no authoritative, empirically validated treatment algorithm for in- somnia. In the absence of such guidance, Dr. Buysse offered his own suggested ap- proach. It begins with behavioral mea- sures: Restict time in bed, set a regular wake-up time, don’t go to bed until sleepy, and don’t stay in bed when unable to sleep.

“I treat a lot of patients with medica- tion, but I always spend some time on behavio- ral approaches as well,” the psychia- trist stressed.

His first-line pharmacotherapy, used in combination with behavioral mea- sures, is a short-acting benzodiazepine re- ceptor agonist. If the patient still wakes up too early, he’ll switch to one with a longer half-life.

His second-line therapy is low-dose tra- zodone, doxepin, or amitriptyline. Third- line therapy, reserved for desperate cases, is gabapentin or tiagabine.

One of the few situations where he doesn’t use a benzodiazepine receptor ag- onist as first-line therapy is in patients with a history of substance abuse. “Al- though there are very few true benzodi- azepine addicts out there, I just don’t feel that lucky. So if I know that a person has a history of alcohol abuse, I’ll start with something else,” he said.

Dr. Buysse said he prefers to treat in- somnia with comorbid depression or anxiety with separate medications—usually a benzodiazepine receptor agonist and a se- lective serotonin reuptake inhibitor—be- cause the disorders often don’t follow the same time course.

Dr. Buysse is a consultant to Sepracor Inc., sponsor of the satellite session, as well as to numerous other pharmaceutical companies.

Home Diagnosis of Obstructive Sleep Apnea: Far from Costly

BY BRUCE JANCIN Denver Bureau

DENVER — Home ambulatory peripheral arterial tonometry is an accurate, convenient, and far less costly alternative to polysomnography in the sleep labora- tory for diagnosis of obstructive sleep apnea. Donald Townsend, Ph.D., said at the annual meeting of the Associated Professional Sleep Societies.

He reported on 103 consecutive patients who presented to a sleep clinic with symptoms suggestive of obstructive sleep apnea.

The patients were randomized to re- ceive overnight home peripheral arterial tonometry (PAT) or standard polysomnography in the sleep clinic, Dr. Townsend reported.

Tests were available the next morning, and the 86% of patients who were in each study arm who were diag- nosed with obstructive sleep apnea then received continuous positive airway pres- sure.

The cost of diagnosis was $653 per pa- tient in the PAT group, compared with $2,181 in the polysomnography group, according to Dr. Townsend, who is with the Metropolitan Sleep Disorders Center.

Many insurers continue to be reluctant to reimburse for anything other than overnight polysomnography in the sleep lab, but that situation is changing.

At 8 weeks, patients in both groups showed similar significant improvements in scores on the Epworth Sleepiness Scale and Beck Depression Inventory.

PAT measures changes in peripheral ar- terial tone in response to bursts of sym- pathetic nervous system activity.

The spikes in sympathetic activ- ity are triggered by arousals from sleep as a result of apneic episodes. PAT is recorded using a device worn on the wrist.

A practical obstacle to wider di- agnostic use of PAT is that insur- ance coverage for the ambulatory test is mixed.

Many insurers continue to be reluctant to reimburse for anything other than overnight polysomnography in the sleep laboratory, although this situation is changing in light of the significant cost savings obtained with PAT, Dr. Townsend explained.

Dr. Townsend’s study received no ex- ternal funding.

However, the Metropolitan Sleep Dis- orders Clinic has an exclusive arrange- ment with Itamar Medical, maker of the PAT device, to manage the device in the Twin Cities area.

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<th>Average Cost of Sleep Apnea Diagnosis</th>
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<td>Polysomnography</td>
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Note: Based on a study of 103 consecutive patients presenting to a sleep clinic.

Source: Dr. Townsend