Abundance of Insomnia Therapies in the Pipeline

BY BRUCE JANCIN
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DENVER — The pharmaceutical industry envisions the insomnia market as a field of dreams, judging by the sizable array of agents moving through the developmental pipeline.

And these aren't "me-too" drugs, either. They involve a wealth of new therapeutic 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 problem clinically, there are new treatments coming up, and I think we're really going to have some better options for our patients in the near future," Daniel J. Buysse, M.D., said at a satellite symposium held with the annual meeting of the Associated 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 insomnia, the benzodiazepine receptor agonists 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 benzodiazepine receptor agonist eszopiclone (Lunesta) and ramelteon—are approved for long-term use. The rest of the benzodiazepine receptor agonists carry an indication for a maximum of 30 days of use or less, a restriction frequently ignored in clinical practice.

It's worth noting that little supporting evidence of efficacy exists for off-label use of agents for insomnia. Moreover, surveys show that many patients with chronic insomnia self-medicate with alcohol, which is obviously problematic, and with diphenhydramine, which causes cognitive and anticholinergic adverse effects, particularly in the elderly, added Dr. Buysse, professor of psychiatry at the University of Pittsburgh.

Here are highlights of the new pharmacologic developments emerging for insomnia:

► **GABA receptor agents.** Gaboxadol is a nonselective γ-aminobutyric acid-A agonist. Unlike all of the other γ-aminobutyric acid (GABA) receptor agents, which are directed at synaptic receptors, gaboxadol interacts primarily with extrasynaptic GABA receptors. It appears to have an additive rather than synergistic effect with benzodiazepine receptor agonists. No 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.

► **New benzodiazepine receptor agonists.** Indiplon is well along in clinical trials. It is a nonbenzodiazepine benzodiazepine receptor agonist selective for receptors having the alpha-1 subunit. Both immediate-release and modified-release formulations are being developed.

Also under investigation is a new formulation of zolpidem (Ambien). It consists 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 excitatory neurotransmitters such as substance P and glutamate. Although gabapentin is marketed for the treatment of postherpetic neuralgia and epilepsy, these drugs are under investigation for insomnia, anxiety, chronic pain syndromes, and neuropathic pain.

"If they do work in insomnia, it's going to be by a very different mechanism of action than other agents, essentially by inhibiting the release of excitatory neurotransmitters, rather than promoting the action of an inhibitory neurotransmitter like GABA," the psychiatrist explained.

► **Melatonin receptor agents.** The recently approved ramelteon is a highly selective agonist for the melatonin ML-1 receptor, which is believed to play a more important role in sleep than the ML-2 receptor. It is approved 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.

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DR. BUYSSE

► **Serotonin 5-hydroxytryptamine-2 antagonists.** Serotonin antagonists seem to increase slow-wave sleep and enhance sleep continuity while having little impact on sleep latency. Drugs with a strong 5-HT_2 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 patients 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 something for somebody. And I think that it does," he said.

There is no authoritative, empirically validated treatment algorithm for insomnia. In the absence of such guidance, Dr. Buysse offered his own suggested approach. It begins with behavioral measures: Restrict 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 medication, but I always spend some time on behavioral approaches as well," the psychiatrist stressed.

His first-line pharmacotherapy, used in combination with behavioral measures, is a short-acting benzodiazepine receptor 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 trazodone, 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 agonist as first-line therapy is in patients with a history of substance abuse. "Although there are very few true benzodiazepine addicts out there, I just don't feel that lucky. So if I know that a person has a history of, say, alcohol abuse, I'll start with something else," he said.

Dr. Buysse said he prefers to treat insomnia with comorbid depression or anxiety with separate medications—usually a benzodiazepine receptor agonist and a selective serotonin reuptake inhibitor—because 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 Less Costly

BY BRUCE JANCIN
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DENVER — Home ambulatory peripheral arterial tonometry is an accurate, convenient, and far less costly alternative to polysomnography in the sleep laboratory 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 receive overnight home peripheral arterial tonometry (PAT) or standard polysomnography in the sleep clinic, Dr. Townsend reported.

Test results were available the next morning, and the 86% of patients who were in each study arm who were diagnosed with obstructive sleep apnea then received continuous positive airway pressure.

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

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

Obstructive sleep apnea was deemed sufficiently severe in eight patients based upon PAT results that they required confirmatory testing via polysomnography, which is considered the standard for diagnosis of the disorder.

In a follow-up survey, patients in both study groups indicated a high degree of satisfaction with the testing procedures. 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 arterial tone in response to bursts of sympathetic nervous system activity.

The spikes in sympathetic activity 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 diagnostic use of PAT is that insurance 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 external funding.

However, the Metropolitan Sleep Disorders Clinic has an exclusive arrangement with Itamar Medical, maker of the PAT device, to manage the device in the Twin Cities area. ■