Indiana Medicaid Drug Utilization Review Board Newsletter

November 2005

Volume 8 Issue 5

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Indiana Medicaid DUR Board
Room W382
Indiana State Gvmt Center, South
402 West Washington Street
Indianapolis, Indiana 46204

Non-Benzodiazepine Agents for the Treatment of Insomnia

Insomnia is a relatively nonspecific term used to describe conditions characterized by a patient's perception of poor or inadequate sleep. Common complaints include difficulty falling asleep, frequent awakenings, and tiredness during the day. Insomnia is often secondary to physical illness or psychological disorders. Many cases of insomnia will resolve spontaneously with effective management of the underlying disorder or by the use of stress-relieving techniques. However, pharmacotherapy may be required for some patients to overcome insomnia. The ideal agent for the treatment of insomnia would rapidly induce sleep without causing residual side effects or abuse potential.

Benzodiazepines are commonly prescribed for the short-term treatment of insomnia. Five benzodiazepines are FDA-approved for this indication: estazolam (Prosom), flurazepam (Dalmane), quazepam (Doral), temazepam (Restoril) and triazolam (Halcion). All but estazolam are available generically. Benzodiazepines enhance the effects of the inhibitory neurotransmitter, gamma-aminobutyric acid (GABA) by non-selectively binding to benzodiazepine receptors in the CNS. Through their effects on GABA, benzodiazepines decrease sleep latency and increase sleep continuity and total sleep time. All benzodiazepines are schedule IV controlled substances with potential for dependence and/or abuse. Additionally, tolerance to the sedative effects may develop, and they are often associated with dose-dependent cognitive and psychomotor impairment, anterograde amnesia, withdrawal symptoms, and rebound insomnia after abrupt discontinuation.[4]

The adverse effects and misuse/abuse potential associated with benzodiazepines has lead to efforts to develop alternative therapy. Currently, there are four non-benzodiazepine sedative hypnotics approved by the FDA for the treatment of insomnia. They include zolpidem (Ambien), zaleplon (Sonata), eszopiclone (Lunesta), and ramelteon (Rozerem).

Zolpidem

Zolpidem (Ambien) is indicated for the short-term treatment of insomnia. In controlled clinical trials, it decreased sleep latency and increased duration of sleep for up to 35 days. Although zolpidem is not a benzodiazepine, it exerts its effect by interacting with the GABA-benzodiazepine receptor complex. However, unlike benzodiazepines, which bind to all three known omega-receptor subtypes, zolpidem preferentially binds to the omega-1 receptor. Zolpidem has a rapid onset of action and a reduced occurrence of residual effects compared to benzodiazepines. Zolpidem is a schedule IV controlled substance. The most common adverse effects are drowsiness, dizziness, and diarrhea. The recommended dose for non-elderly adults is 10mg immediately before bedtime. The recommended dose in elderly, debilitated, or

hepatically impaired patients is 5mg. Therapy should generally be restricted to 7-10 days. Extended-release zolpidem (Ambien CR) received final approval on September 2, 2005.[4-6]

Zaleplon

Zaleplon (Sonata) is indicated for the short-term treatment of insomnia. In controlled clinical trials, it decreased sleep latency for up to 30 days. It has not been shown to increase total sleep time or decrease the number of awakenings. No development of tolerance to zaleplon's effect on sleep latency was observed during a four-week study. Zaleplon is an agonist at the omega-1 receptors on the GABA-benzodiazepine receptor complex. Zaleplon has a rapid onset of action and may be taken immediately before retiring or after having gone to bed and experiencing difficulty falling asleep. Zaleplon is the only sedative-hypnotic that can be taken after attempting to fall asleep. In large clinical trials, zaleplon exhibited a dose-dependent risk of next-day memory impairment. Data suggest that rebound insomnia the first night after treatment discontinuation may be dose-dependent as well. The most common adverse effects are headache, dizziness, nausea, and somnolence. Zaleplon is a schedule IV controlled substance. The recommended dose for non-elderly adults is 10mg immediately before bedtime or after having gone to bed and experiencing difficulty falling asleep. The recommended dose in elderly, debilitated, or hepatically impaired patients is 5mg. Therapy should generally be restricted to 7-10 days. Zaleplon is the agent of choice when a patient has fewer than eight hours to sleep.

Eszopiclone

Eszopiclone (Lunesta) is indicated for the treatment of insomnia. In controlled outpatient and sleep laboratory studies, eszopiclone decreased sleep latency and improved sleep maintenance. No development of tolerance was observed over six months. The eszopiclone labeling allows for the chronic treatment of insomnia, and it is the first agent to be approved for sleep maintenance. Eszopiclone is believed to interact with GABA-receptor complexes at binding sites close to or coupled with the benzodiazepine receptors. Eszopiclone has a rapid onset of action and two primary metabolites with little or no activity at therapeutic doses. The longer half-life of this product most likely contributes to the mild residual effects of impaired memory and confusion. Rebound insomnia occurred during clinical trials on the first night after treatment discontinuation. The most common adverse effects with eszopiclone are unpleasant taste, headache, somnolence, dizziness, and dry mouth. Eszopiclone is a schedule IV controlled substance. The recommended dose for most non-elderly adults is 2mg immediately before bedtime. The dose may be increased to or initiated at 3mg if clinically necessary, since the 3mg dose is more effective for sleep maintenance. In elderly patients whose primary complaint is difficulty falling asleep, patients with severe hepatic impairment, and patients receiving concurrent therapy with potent CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, nefazodone, ritonavir), the recommended starting dose is 1mg. If clinically indicated, the dose may be increased to 2 mg. In elderly patients whose primary complaint is difficulty staying asleep, the recommended dose is 2mg.

Ramelteon

Ramelteon (Rozerem) is indicated for the treatment of insomnia where there is difficulty in falling asleep. In clinical studies, ramelteon reduced the length of time to persistent sleep compared to placebo. The FDA-approval allows for long-term use in adults. Ramelteon is the first prescription sleep medication that is not a controlled substance. It is also the first in a new class of agents termed melatonin-receptor agonists. Three subtypes of melatonin receptors have been identified: MT1, MT2 and MT3. The MT1 receptor is believed to regulate sleep. The MT2 receptor is thought to help the body shift between day and night. The importance of the MT3 receptor is not well defined. Ramelteon selectively targets the MT1 and MT2 receptors with greater affinity and selectivity than melatonin, resulting in a better ability to induce sleep. Ramelteon undergoes extensive first-pass metabolism. The major metabolite, M-II, has approximately one-tenth and one-fifth the binding affinity of the parent molecule for the MT1 and MT2 receptors, respectively. There was evidence of mild next-day residual effects during a 35-night, placebo-controlled study in adults with chronic insomnia. At week 1, the ramelteon 8mg group indicated more fatigue. At week 3, the ramelteon 8mg group had a lower mean score for immediate recall, and also at week 3, all ramelteon-treated patients indicated more sluggishness. At week 5 there were no differences from placebo in next-day residual effects. The abuse potential for ramelteon was equivalent to placebo at doses up to 20 times the recommended dose. The most common adverse effects seen with ramelteon during clinical trials were somnolence, dizziness and fatigue. The recommended dose of ramelteon is 8mg taken within 30 minutes of going to bed. Ramelteon should not be used in patients with severe liver impairment. The product is expected to be available in US pharmacies in late September 2005.

Conclusion

The non-benzodiazepine sedative-hypnotics offer unique advantages. Zolpidem has proven efficacy whether the patient's major complaint is with falling asleep, staying asleep, or waking too early.

Zaleplon offers treatment for patients who have unsuccessfully tried to fall asleep and for patients who need to be awake and alert on less than a full night's sleep. Eszopiclone can be used in the treatment of chronic insomnia. However, all of these agents are schedule IV controlled substances and have residual effects and rebound insomnia. Ramelteon is not a controlled substance and can be used chronically. However, ramelteon is indicated only for patients who have difficulty falling asleep. There are other agents being investigated for the treatment of insomnia. With each new agent developed, the management of insomnia comes closer to the ideal.

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Program Assistance

All prior authorization requests or questions regarding the PDL should be directed to the ACS Clinical Call Center at 1-866-879-0106.

PDL Listing

The fee-for-service PDL listing may be found at the following website:
http://www.indianapbm.com/

Prior Authorization

Requests for Prior Authorization (PA) may be initiated by calling ACS at 866-879-0106 between the hours of 8AM to 8PM. All PA requests (with the exception of Early Refill) must be initiated by the Prescriber's office. Early Refill requests may be initiated by the patient's pharmacy. Many PA requests can be handled over the phone, but in some instances a faxed request may be required. Copies of the PA forms may be obtained by calling the above number, or by downloading a copy of the form at www.indianapbm.com under the "Forms" section.

In instances where a PA cannot be immediately obtained, a pharmacist may dispense up to a 96-hour supply of a covered outpatient drug. All emergency claims should be processed with the Level of Service = 03 (Emergency Indicator) and the actual "days supply" being dispensed up to but not exceeding "4".