Reviews/Evaluations

Literature Review of Nonbenzodiazepine Hypnotics

Indication: Short-term treatment of primary insomnia

Advantage: An advantage of these agents over typical benzodiazepines is their quick onset of action and short elimination half-life. Zaleplon, with an average onset of activity of 15 to 20 minutes, can be dosed during the middle of the night with little risk of daytime sedation.

Data: According to the manufacturer of both zolpidem (Ambien®) and zaleplon (Sonata®), duration of therapy should be limited to 7-10 days.(1, 2) There is no published data available that supports the chronic use of either agent. In fact, in two unpublished controlled trials, it was determined that chronic standard zolpidem therapy (5-10mg qhs) was no better than placebo for a number of sleep characteristics.(1)

Table 1. Data From Two Controlled Long-Term Zolpidem Trials.

Sleep Characteristic	Week One	Week Two	Week Three	Week Four	Week Five
Study #1-10mg qhs for 5 weeks (arrow indicates when efficacy is greater than placebo)					
Sleep Latency	←				
Sleep Efficiency	←				
Number of Awakenings	no better than placebo during entire study duration				
Study #2-10mg qhs for 4 weeks (arrow indicates when efficacy is greater than placebo)					
Sleep Latency	←				
Total Sleep Time	←				
Number of Awakenings	←				
Sleep Quality	←				

Two 4-week zaleplon clinical trials were performed in chronic insomniacs. Results of these studies showed that while zaleplon significantly decreases time to sleep onset (by approximately 10-20 minutes) compared to placebo, it does not have any affect on sleep duration or number of awakenings.(2) Other sleep laboratory studies

performed in outpatient chronic insomniacs have had a maximum duration of 28 days. A summary of these findings demonstrated that zaleplon significantly reduced latency to persistent sleep compared to placebo during the first two nights of therapy only.(2) Zaleplon comparative efficacy trials have failed to clearly demonstrate an advantage over the short-acting benzodiazepine triazolam.(3)

Regulation of the Sleep-Wake Cycle in Bipolar Affective Disorder: There is some evidence to suggest that the disruption of sleep in bipolar patients may precipitate a manic episode.(4, 5) Disrupted sleep schedules may occur as a result of psychosocial stressors such as jet lag, school examinations, or rotating work shifts. Sleep is typically considered a priority in the clinical treatment of manic patients, thus necessitating the use of a short-term sedative/hypnotic. There is no data regarding the need, efficacy or adverse effects of chronic sedative administration in this patient population. It is therefore recommended that sedative/hypnotics be prescribed on an acute basis only.

Agent selection is based on empirical judgement. There are no studies to confirm that the use of one sedative is superior to another in bipolar patients. It is therefore recommended that practitioners utilize the most cost-effective and best tolerated agents, such as low-dose trazodone or short-acting benzodiazepines. Research is also underway to determine the efficacy of supplemental melatonin administration. Atypical antipsychotics, used for the treatment of psychotic symptoms in bipolar disorder, have sedative side effects. The coadministration of a sedative and an atypical antipsychotic is unnecessary.

Summary of Findings: Nonbenzodiazepines should only be used in patients with primary sleep latency disorders. All agents within this class have failed to demonstrate consistent improvements in sleep duration, number of awakenings, and overall sleep quality. There are no distinct advantages of these agents over conventional benzodiazepines. Their use long-term has not been fully evaluated and should not be recommended at this time.

References

1. Ambien® package insert. Searle, 1999.
2. Sonata® package insert. Wyeth-Ayerst, 1999.
3. Micromedex Inc. Healthseries 2000. "Zaleplon."
4. Leibenluft E, Suppes T. Treating Bipolar Illness: Focus on Treatment Algorithms and Management of the Sleep-Wake Cycle. *American Journal of Psychiatry*. 1999; 156:1976-1981.
5. Malkoff-Schwartz S, et al. Stressful Life Events and Social Rhythm Disruption in the Onset of Manic and Depressive Bipolar Episodes. *Archives of General Psychiatry*. 1998; 702-707.