

SEDATIVE-HYPNOTICS: SAFETY CONCERNS

Background

- Chronic insomnia is estimated to affect 10 to 15% of the US adult population, with an additional 25 to 35% suffering from transient insomnia.^{1,2}
- Traditionally, benzodiazepines (BZs) have been a primary treatment for insomnia, but recent approval of the benzodiazepine receptor agonists (zolpidem, zaleplon, & eszopiclone) and the melatonin receptor agonist, ramelteon, has led to decreased use of BZs due to lower abuse potential with these newer agents.^{3,4}
 - In 2004, the most widely prescribed sedative hypnotic was zolpidem (Ambien®) which cost Idaho Medicaid nearly \$1.4 million that year
 - Generic zolpidem will be available soon and a controlled-release version (Ambien CR®) is also becoming available.
- Significant safety concerns with sedative-hypnotics include important drug interactions and their appropriate use in special populations (the elderly, pregnant patients, and individuals with a past history of substance abuse).

Table 1: Comparison of Sedative-Hypnotics

Medication	Indication (Insomnia type)	Onset of Action (min)	Duration of Action	Half Life (hrs)	Active Metabolites	Cost (30 day supply)*
Zaleplon (Sonata)	Sleep onset	20	Ultra-short	1	No	\$85.27
Zolpidem (Ambien)	Sleep onset	30	Short	3	No	\$81.99
Triazolam (Halcion)	Sleep onset	15-30	Short	2-5	No	\$17.99
Ramelteon (Rozerem)	Sleep onset	30	Short	2-5	Yes	\$82.50
Temazepam (Restoril)	Sleep Maintenance	45-60	Intermediate	8-15	No	\$10.99
Estazolam (Prosom)	Sleep Maintenance	15-30	Intermediate	10-24	No	\$27.99
Eszopiclone (Lunesta)	Sleep maintenance	30	Intermediate	5-7	Yes	\$98.99
Quazepam (Doral)	Sleep maintenance	20-45	Long	39	Yes	\$109.68
Flurazepam (Dalmane)	Sleep Maintenance	60-120	Long (due to metabolites)	8 (~100)	Yes	\$9.33

*Per Drugstore.com October 2005 → Generic price provided if available

Drug Interactions

- The BZ hypnotics are primarily metabolized by cytochrome (CYP) P450 3A4 (except temazepam which undergoes conjugation) while the newer agents are metabolized by a combination of CYP3A4 and other cytochrome enzymes^{5,6}
- Inhibitors of CYP3A4 that may increase the effects of sedative-hypnotics include:azole antifungals (ketoconazole, itraconazole), erythromycin, clarithromycin, and cimetidine⁵
- The extent of clinically significant drug interactions appears to be less for the newer agents when compared to the BZs⁵

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Special Populations

- BZs should not be used in pregnancy due to established risk of fetal malformations⁷
 - Of the newer agents, zolpidem appears to have the best safety profile (pregnancy category B) while zaleplon, eszopiclone, and ramelteon all lack the same level of safety data (category C).
- Long-acting BZs (flurazepam & quazepam) should not be used in the elderly due to increased risk of falls and hip fractures⁸
 - The newer agents (zolpidem, zaleplon) appear to have adequate safety data supporting their use in the elderly⁹
 - Temazepam, unlike the other BZ hypnotics, is not metabolized by CYP450 oxidation and is less likely to accumulate or lead to drug interactions in the elderly^{5,6}
 - Temazepam has been found similar to zolpidem in efficacy and rebound insomnia, making it an attractive alternative, especially when considering its reduced cost^{10,11}
- BZs should be used with caution in individuals with a history of substance abuse⁴
 - The newer agents also have a higher risk of abuse in previous substance abusers but have a better risk profile than BZs⁴
 - Sedative antidepressants (i.e. trazodone, amitriptyline, doxepin) may be an alternative treatment for these patients but they have little data supporting their use in insomnia not related to depression^{7,12,13}
- Sedative hypnotic agents should generally be avoided in patients with hepatic cirrhosis or untreated sleep apnea^{6,7}

Recommendations

- BZs should be avoided and the newer agents' doses should be decreased ~50% when co-administered withazole antifungals, erythromycin, clarithromycin, or cimetidine^{5,6}
 - It is important to check if a patient takes OTC cimetidine before initiating sedative-hypnotic therapy
- It is important to treat an insomnia patient with an agent that will effectively treat their specific complaint, whether it be difficulty falling asleep or staying asleep (Table 1)
- Temazepam may be an attractive alternative to zolpidem for many patients due to similar outcomes and reduced cost of therapy
 - It is also likely the best choice of the BZs in the elderly at doses ≤ 15 mg/day⁵
- There is no rationale for the use of multiple sedative hypnotics agents to treat anxiety and insomnia⁷
 - BZs with a long elimination half life (diazepam, etc.) may be considered in these patients⁷

References

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