

Update on the Safety Considerations in the Management of Insomnia With Hypnotics: Incorporating Modified-Release Formulations Into Primary Care

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Objective: From a safety perspective, several issues require assessment when a decision is made to prescribe a sleep medication, including next-day residual effects, the potential for abuse, tolerance, and dependence. This article aims to provide an update of the safety profile of agents commonly used in the management of insomnia, with an emphasis on newly approved hypnotics.

Data Sources: Publications relevant to the subject of this review were identified by a PubMed search (conducted without date restrictions; search terms: *insomnia* WITH *safety* OR *tolerability* OR *side effects* OR *tolerance* OR *dependence* OR *abuse* OR *residual effects* AND *benzodiazepines* OR *non-benzodiazepines* OR *zolpidem* OR *eszopiclone* OR *zaleplon* OR *ramelteon* OR *melatonin* OR *trazodone* OR *anti-histamines* OR *alcohol* OR *alternative therapies*), and additional articles (selected by the author on the basis of his experience) were included.

Study Selection and Data Extraction: Publications relevant to the objective of this article were obtained, and the key safety data relating to adverse events, next-day residual effects, tolerance, and withdrawal were summarized.

Data Synthesis: The non-benzodiazepines (eszopiclone, zolpidem, zolpidem extended-release, and zaleplon), which have largely replaced the benzodiazepines for insomnia treatment, have a lower risk of tolerance, dependence, abuse, and residual effects compared with benzodiazepines. The modified-release formulation of zolpidem demonstrates a comparable safety profile to that of original zolpidem but has an additional sleep maintenance benefit. Ramelteon, a novel melatonin receptor agonist, is indicated for sleep-onset difficulties and is not scheduled. Over-the-counter agents, alternative therapies, and the prescription of off-label drugs, such as trazodone, have a lack of controlled clinical efficacy and safety studies in the treatment of insomnia and as a result should be used with caution.

Conclusions: Overall, published studies report that the safety of insomnia treatments has improved considerably over the past 10 years with the introduction of agents that provide improved safety, particularly with regard to next-day residual effects and abuse liability.

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Even with advances in therapy for sleep disorders and the recognition that insomnia has a significant impact on patient health and quality of life, the majority of patients with insomnia remain undiagnosed or are not treated appropriately. In the 2005 Sleep in America Poll, the National Sleep Foundation found that less than one third of patients with insomnia were asked about their sleep during physician visits.¹ Furthermore, epidemiologic studies suggest that only 27% to 45% of individuals with disrupted sleep discuss their problems proactively during a physician visit,^{2,3} and many patients with insomnia visit their physician only after unsuccessful self-medication with over-the-counter (OTC) treatments. These studies highlight the need for improved physician-patient communication regarding sleep quality.

Insomnia may consist of 1 or more of the following features: difficulty in initiating sleep, difficulty in maintaining sleep, and waking up too early.⁴ DSM-IV classification also includes nonrestorative sleep and requires that the insomnia must also cause difficulty in the person's social, work, or other significant area of life.⁵ It is common for patients to experience more than one symptom of insomnia and for symptoms to change over time, often unpredictably.⁶ Insomnia may be transient (occurring a few nights a week for up to a month) or chronic (occurring most nights for a period longer than a month), both of which are associated with next-day consequences.

It has been estimated that 10% to 15% of the general population suffers from insomnia.⁷ The 2005 National Sleep Foundation poll reported that 54% of those surveyed experienced at least 1 symptom of insomnia (the definition of insomnia in that study also included snoring, restless leg syndrome, and pauses in breathing) for at least

a few nights a week within the previous year.¹ The poll also found that 33% experienced at least 1 symptom of insomnia every night, or almost every night, during the previous year.

The economic burden of insomnia remains largely unknown, and the direct and indirect medical costs and potential societal benefits from the effective treatment of insomnia also require further investigation.

The National Institutes of Health (NIH) recently released a state-of-the-science conference statement on the treatment of chronic insomnia.⁴ The statement summarized the treatment options available as of June 2005 and highlighted the need for clinical studies to support the safety and efficacy of agents currently used in the treatment of insomnia, especially those used off-label that at present have few data to support their efficacy in insomnia.

The most commonly used treatments for insomnia patients are OTC antihistamines, self-medication with alcohol, and prescription medications (used both on- and off-label). Other treatments include melatonin and the alternative therapies, such as valerian, kava kava, and L-tryptophan.^{1,8} Evaluation of the benefit/risk profile of insomnia treatment options reveals a number of important safety issues that require assessment, including the potential for effects on next-day performance (such as next-day cognitive and psychomotor performance) and drug-drug interactions, as well as possible abuse potential.

Here, I review safety profiles of those agents commonly used in the management of insomnia, with an emphasis on newly approved hypnotics. Publications relevant to the subject of this review were identified by a PubMed search (conducted without date restrictions; search terms: *insomnia WITH safety OR tolerability OR side effects OR tolerance OR dependence OR abuse OR residual effects AND benzodiazepines OR non-benzodiazepines OR zolpidem OR eszopiclone OR zaleplon OR ramelteon OR melatonin OR trazodone OR antihistamines OR alcohol OR alternative therapies*), and additional articles (selected by the author on the basis of his experience) were included.

BENZODIAZEPINE RECEPTOR AGONISTS

Benzodiazepine Derivatives

Benzodiazepines were the cornerstone of insomnia treatment prior to the 1990s, as supported by extensive studies and their relative safety in short-term use (in comparison to other agents available at the time). They are still prescribed for the treatment of insomnia; however, their use has significantly decreased due to concerns over abuse, dependence, cognitive and psychomotor impairments, and residual effects (“hangover”).^{9–11}

Benzodiazepines bind to and mediate the activity of the γ -aminobutyric acid-A (GABA_A) receptor complex,

which consists of 5 protein subunits (formed from the coassembly of at least 19 different subunits from at least 7 subunit families: α , β , γ , δ , ϵ , θ , ρ).¹² This diversity of subunits allows the expression of a vast number of structurally unique GABA_A receptor subtypes with distinct characteristics. There are 6 α subunit subtypes (α_{1-6}); the α_1 subunit is thought to be located predominantly in areas of the brain that are involved in sleep-wake mechanisms, sedation, and memory.^{12,13} GABA_A receptor complexes containing the α_2 , α_3 , or α_5 subunit appear to be most highly concentrated in areas responsible for cognitive and psychomotor functions, along with anticonvulsant and anxiolytic activity.¹² Benzodiazepines act at multiple GABA_A receptor subtypes (containing the α subunit subtypes 1, 2, 3, and 5), which may account for their hypnotic effects as well as undesirable effects such as impaired cognitive and psychomotor function.¹⁴

Benzodiazepines can be classified according to their pharmacokinetic profile: short half-life (e.g., triazolam), intermediate half-life (e.g., temazepam), or long half-life (e.g., flurazepam) (Table 1). The use of benzodiazepines can cause alteration of sleep architecture, in addition to tolerance to the hypnosedative effect over time, pharmacologic dependence, rebound insomnia and withdrawal reactions at discontinuation, anterograde amnesia, cognitive and psychomotor impairment, misuse episodes, and respiratory depression.^{15,16} Withdrawal symptoms occur more rapidly and more frequently with the short-acting benzodiazepines (characterized by a half-life of < 4 hours) compared with the longer-acting benzodiazepines.¹⁷ Next-day residual deficits (“hangover”) occur most frequently with long-acting benzodiazepines (characterized by a half-life > 24 hours and pharmacologically active metabolites), although they are also observed following the administration of intermediate-acting agents (characterized by a half-life of 4–24 hours and few active metabolites).^{18,19}

Non-Benzodiazepines

The next generation of sleep aids, with a more sleep-focused mechanism of action, the non-benzodiazepines, were introduced in the 1990s. These benzodiazepine receptor agonists are as effective as benzodiazepines in the promotion of sleep, but have a reduced risk of abuse and fewer side effects compared with benzodiazepines.^{20,21}

Like the benzodiazepines, non-benzodiazepines are agonists at the GABA_A receptor complex. However, non-benzodiazepines preferentially bind to the sleep-mediating α_1 subunit subtype GABA_A receptor complexes and were developed, in part, to improve on the safety profile of benzodiazepines while retaining their sleep-promoting effects.^{22,23} GABA_A receptor complexes with α_1 subunit subtype are also thought to be primarily located in areas of the brain responsible for memory; therefore, both benzodiazepines and non-benzodiazepines

Table 1. Overview of Compounds Approved in the United States for the Treatment of Insomnia

Generic Name	Brand Name	Mechanism of Action	Half-Life (hr)	T _{max} (hr)	Recommended Adult Dose (mg)
Benzodiazepines					
Triazolam ⁷⁰	Halcion ^a	Benzodiazepines bind to the benzodiazepine recognition site located between the α and γ subunits of the GABA _A receptor complex and interact with 4 of the 6 α subunit variations (α_1 [believed to modulate sedation and memory], α_2 , α_3 , and α_5 [believed to mediate anxiolytic, muscle relaxant, and anticonvulsant activity]). Interaction with the GABA _A receptor complex facilitates an enhancement of chloride ion influx through the GABA _A receptor, thus altering the inhibitory properties of that neuron ^{12,71}	1.5–5.5	2.0	0.25
Temazepam ⁷²	Restoril ^a		8.8	1.5	7.5–30
Estazolam ⁷³	ProSom ^a		10–24	0.5–6.0	1.0–2.0
Quazepam ⁷⁴	Doral ^a		39–73 ^b	2.0	7.5–15
Flurazepam ⁷⁵	Dalmane ^a		47–100 ^b	0.5–1.0	15–30
Non-benzodiazepines					
Zolpidem ⁷⁶	Ambien ^a	Chemical structure unrelated to benzodiazepines. Mechanism of action is similar to benzodiazepines, but these agents interact with the α_1 subunit of the benzodiazepine recognition site only, which is believed to modulate sedation	2.5 (2.9 in elderly)	1.6	10 (5.0 in elderly)
Zolpidem extended-release ²⁵	Ambien CR ^a		2.8 (2.9 in elderly)	1.5	12.5 (6.25 in elderly)
Eszopiclone ⁴⁴	Lunesta ^a	Chemical structure unrelated to the benzodiazepines. Eszopiclone binds to benzodiazepine receptor on GABA _A receptor complex, although subunit binding properties are not presently known ⁴⁴	6.0 (9.0 in elderly)	~1.0	2.0, 3.0 (1.0 in elderly)
Zaleplon ⁴⁹	Sonata ^a	Chemical structure unrelated to the benzodiazepines. Similar mechanism of action as benzodiazepines, although zaleplon has a low affinity for both the α_1 and α_2 subunits—with preferential binding to α_1	~1.0	~1.0	10, 20 (5.0 in elderly)
Melatonin agonists					
Ramelteon ⁵⁶	Rozerem	Melatonin receptor agonists have high-affinity binding to melatonin MT ₁ and MT ₂ receptors, and selectivity over the MT ₃ receptor ⁵⁶	1.0–2.6	0.75	8.0

^aClassified as a schedule IV controlled substance (C_{IV}).

^bIncluding active metabolite.

Abbreviations: GABA = γ -aminobutyric acid, T_{max} = time to maximum plasma concentration.

have the potential to adversely affect this area of functioning.²⁴ Additionally, compared with the majority of benzodiazepines, non-benzodiazepines are relatively short-acting, with half-lives ranging from ultra-short (zaleplon, 1 hour) to intermediate (eszopiclone, 6–9 hours).

Zolpidem extended-release and zolpidem. Zolpidem extended-release,²⁵ a modified-release formulation of original zolpidem, has recently been approved by the U.S. Food and Drug Administration (FDA) and was developed to improve on the efficacy profile of original zolpidem while retaining the low risk for next-day functional impairments. Zolpidem extended-release is a 2-layer tablet with a biphasic absorption property; approximately 60% is released immediately while the remainder is released at a slower rate. Zolpidem extended-release has a rapid onset of action and a short half-life, similar to original zolpidem; however, zolpidem plasma levels are maintained beyond 3 hours with zolpidem extended-release.

Zolpidem is a member of the imidazopyridine class of hypnotics, with selective affinity for the α_1 subunit GABA_A receptor subtype, and does not have anticonvulsant or myorelaxant properties at recommended doses. Unlike original zolpidem, zolpidem extended-release is indicated for both sleep onset and sleep maintenance

insomnia and can be prescribed as long as medically necessary.²⁵

In healthy volunteers, zolpidem extended-release had a longer duration of sedation compared with zolpidem (measured by a biomarker of sedation: relative electroencephalogram beta frequency band amplitude).²⁶ In 2 additional studies in healthy volunteers, zolpidem extended-release in adults (12.5 mg) and the elderly (6.25 mg and 12.5 mg [double the recommended dose in the elderly]) did not impair objective and subjective measurements of psychomotor and cognitive performance measured 8 hours postdose.^{27,28} This is similar to findings that zolpidem did not have an adverse effect on memory or cognitive function the morning after nighttime administration in healthy volunteers^{29–32} or in patients with insomnia.³³

Zolpidem extended-release was well tolerated in clinical studies, with the most commonly occurring adverse events being headache, somnolence, and dizziness.²⁵

There is an abundance of information regarding the safety of zolpidem in the treatment of insomnia. In a large postmarketing surveillance database involving 16,944 patients, only 182 patients (1.1%) reported an adverse event after zolpidem treatment.³⁴ The risk of abuse and tolerance with zolpidem is low when used as directed.^{20,31,35} No

significant withdrawal effects have been reported following discontinuation of zolpidem.^{20,34,36}

As with other non-benzodiazepines, a brief (first-night) rebound effect, in which insomnia symptoms are worse than the initially presented insomnia, has been reported following discontinuation of zolpidem extended-release^{37,38} or zolpidem.³⁹⁻⁴¹

Eszopiclone. Eszopiclone is a non-benzodiazepine recently approved for the treatment of insomnia. Eszopiclone is an S(+)-enantiomer of zopiclone, a cyclopyrrolone hypnotic that binds to a site close to the benzodiazepine receptor on the GABA_A receptor complex.⁴² Eszopiclone has a half-life of 5 to 6 hours in adults and has shown minimal evidence of residual drug effects 9.5 and 12 hours after drug administration.^{43,44} However, in elderly patients, the half-life increases to 9 hours.⁴⁵ A 2-week safety and efficacy study in elderly patients showed that eszopiclone did not affect morning sleepiness, daytime alertness, or daily ability to function compared with placebo when measured by a questionnaire completed by patients upon waking.⁴⁶

The safety and tolerability of eszopiclone (1–3.5 mg) have been shown to be similar to placebo, with an unpleasant taste being the most frequent dose-related adverse event,⁴⁵ reported more often in eszopiclone-treated patients than in the placebo-treated group. Other adverse events included somnolence, headache, dizziness, and unpleasant dreams.^{45,47,48} Dependence on eszopiclone has not been reported, although it is classified as a schedule IV medication by federal regulation, and no evidence of serious withdrawal syndrome was reported. Tolerance, as assessed over 6 and 12 months, was not observed.^{47,48} As described before with other non-benzodiazepines, rebound insomnia was observed with eszopiclone 2 mg on the first night after discontinuation.⁴⁴

Zaleplon. Zaleplon⁴⁹ has a pyrazolopyrimidine structure that binds to both the α_1 and α_2 subunit GABA_A receptor subtypes, but with preferentiality for the α_1 subtype.⁴⁹ Zaleplon is a very short acting drug with a half-life of 1 hour that has demonstrated efficacy for sleep induction but does not improve sleep maintenance nor total sleep time. The ultra-short half-life contributes to the low propensity toward next-day effects on memory in healthy individuals^{50,51} and in those with insomnia.⁵²

Compared with placebo, zaleplon did not impair performance in various psychometric tests 8 to 12 hours after dosing.⁵³ No significant evidence of rebound insomnia or serious withdrawal reactions has been documented.⁴¹ Zaleplon has a favorable safety profile and is well tolerated. The incidence of adverse events is comparable with placebo in most studies, with headache being the most commonly reported adverse event, which appears to be dose-dependent. Other commonly reported adverse events include dizziness, nausea, abdominal pain, and somnolence.⁴¹ After 4 weeks of

zaleplon treatment, withdrawal effects are not evident upon discontinuation.⁴¹

MELATONIN RECEPTOR AGONISTS

Ramelteon belongs to a new class of drugs with a novel mechanism of action that specifically targets the melatonin type-1 and type-2 (MT₁ and MT₂) receptors in the brain, which are believed to be involved in the regulation of the body's sleep-wake cycle.⁵⁴ Ramelteon is the first prescription hypnotic approved by the FDA that is not classified as a controlled substance. While ramelteon has demonstrated efficacy for sleep induction, it does not improve sleep maintenance.

At doses up to 20 times the recommended dose, no differences in subjective responses indicative of abuse potential were seen between ramelteon and placebo in preclinical studies.⁵⁵ No next-day residual effects were seen after 2 nights of ramelteon administration. In a 35-night double-blind study that measured next-day residual effects at 3 timepoints, small differences were observed between the ramelteon (8 mg) and placebo groups at weeks 1 and 3, but not at week 5.⁵⁶

In a crossover study, ramelteon (5 treatment periods consisting of 2 nights of ramelteon treatment at doses of 4, 8 [recommended dose], 16, and 32 mg, separated by a 5- to 12-day washout period) was found to have similar withdrawal effects to placebo, and there was also no evidence of rebound insomnia.⁵⁷ The most commonly reported adverse events were headache, somnolence, and sore throat. In an evaluation of the effect of ramelteon on endocrine function, no significant abnormalities were reported in either the thyroid or adrenal axis; however, abnormalities were noted within the reproductive axis. Decreased testosterone levels and increased prolactin levels (32% of ramelteon-treated patients reported increased prolactin levels, compared with 19% of placebo patients) have been associated with the use of ramelteon.⁵⁶ As a result, patients are advised to seek medical attention if they experience cessation of menses or galactorrhea (females), decreased libido, or problems with fertility.

Ramelteon has a highly variable intersubject pharmacokinetic profile. The major cytochrome P450 (CYP) isoenzyme involved in the metabolism of ramelteon is CYP1A2, and, to a lesser degree, the CYP2C subfamily and CYP3A4 isoenzymes are also involved. Therefore, the use of alcohol and strong inhibitors of these isoenzymes, in particular fluvoxamine (CYP1A2 inhibitor), rifampin, ketoconazole, and fluconazole, should be avoided with ramelteon.⁵⁶

OFF-LABEL PRESCRIPTION DRUGS

In the United States, the antidepressant trazodone is one of the most commonly prescribed medications for the

treatment of insomnia.⁴ Although there are no long-term studies on the use of trazodone in the treatment of insomnia, reports of sedation, dizziness, psychomotor impairment, and tolerance related to its use are of concern. The efficacy of trazodone use in the treatment of insomnia beyond 2 weeks is also unknown, and this lack of controlled clinical studies regarding efficacy and safety in the treatment of insomnia is seen across a range of antidepressants (e.g., amitriptyline, doxepin, mirtazapine). Two studies on the safety of sedating antidepressants in patients with primary insomnia found that these medications used in this context had more frequent and more serious safety concerns compared with benzodiazepines.^{58,59} In 1 investigation, 2 of 4 patients with primary insomnia in the doxepin-treatment group who withdrew from the study cited significant adverse events as the reason for discontinuation (leukopenia, thrombopenia, and increased levels of liver enzymes).⁵⁸

Most information on the sedative properties of antidepressants comes from experience in patients with depression⁶⁰; therefore, a dose-response relationship needs to be established for safe prescription of these drugs in the treatment of insomnia in nondepressed patients.

Other prescription medications have been used off-label in the treatment of insomnia, including antipsychotics (e.g., quetiapine, olanzapine). There are, however, limited studies to demonstrate the usefulness of these medications for either short- or long-term treatment of insomnia. In addition, these agents have significant risks, and, therefore, their use in the treatment of chronic insomnia was not recommended by the NIH State of the Science Conference Panel.⁴

NONPRESCRIPTION DRUGS

Over-the-Counter Drugs

Antihistamines are well known for their sedative effects. Patients may, however, also experience adverse events such as urinary retention, confusion, and delirium and side effects including daytime sleepiness, dizziness, drunken movements, blurred vision, and dry mouth and throat.⁶¹

Diphenhydramine is the most commonly used antihistamine OTC product for sleep. It has an elimination half-life of approximately 9 hours in adults.^{62,63} Commonly used drugs may simply contain diphenhydramine alone (Nytol, Sleep-Eez, Sominex) or combinations of diphenhydramine with pain relievers (Anacin P.M., Excedrin PM, Tylenol PM). Sedating antihistamines can have next-day residual effects⁶⁴ and may not be very effective in providing restful sleep. There is also the potential for drug-drug interaction, often increasing the sedative effects of other medications, which is especially common in the elderly who are often taking a number of prescription medications simultaneously.⁶⁵

Alternative Therapies

A number of herbal and alternative therapies, including melatonin, valerian, camomile, kava kava, and 5-hydroxytryptophan, are used for the treatment of insomnia,⁸ although available clinical data suggest minimal to no efficacy for these agents, and there are few data on safety to warrant recommendation of use.⁴ The FDA does not regulate these agents, and thus preparations vary in content and purity. While some alternatives, such as melatonin, may be safe for short-term use,⁶⁶ others may have significant risks.⁴ For example, there have been case reports of hepatotoxicity with the use of valerian-based remedies.⁸

Alcohol is well known for its sedative properties and is a common form of self-medication for insomnia.⁶⁷ However, in addition to serious side effects, including dependence and tolerance, and despite the initial sedative effect, alcohol is associated with an increased number of awakenings and sleep-stage changes.⁶⁸ Use of alcohol in combination with hypnotics is contraindicated and can significantly increase the risk of serious drug interactions.

DISCUSSION

It is the role of the physician to ensure that all sleep medications are taken appropriately. Patients should be informed that all sleep medications should be taken strictly as prescribed, never with alcohol, and always immediately before the patient intends to get into bed, with the exception of ramelteon, which should be taken 30 minutes prior to going to bed, after which patients should confine their activities to those necessary to prepare for bed. Drug-drug interactions should be considered prior to the prescription of sleep medications, especially with the use of cough and cold medications and sedating antihistamines used for an alternative indication.

It is also advisable that sleep medications, in particular those with a longer duration of action, should only be taken when the patient has enough time for a full night's sleep (7–8 hours). With regard to this point, half-life is an important consideration, as drugs with longer half-lives may impair next-day performance and some agents (like eszopiclone) have significant pharmacokinetic changes in older patients. The newer non-benzodiazepines and melatonin agonists have the best data to support lack of residual effects, but not all clinical trials measured next-day functioning during the time when patients are likely to be starting their day. For example, the zolpidem extended-release efficacy studies^{37,38} measured morning performance within 30 minutes of awakening (8.5 hours postdose), whereas eszopiclone studies measured performance 9.5 hours postdose or when the patient naturally awoke.^{43,44}

The NIH has emphasized the move toward thinking of insomnia as a chronic disorder that needs to be treated over the long term, rather than a short-term condition with

a short-term solution, making safety an even more important consideration. This certainly corroborates the findings from the 2002 National Sleep Foundation poll that reported 15% of respondents continually used (at least a few nights per month) either a prescription sleep medication (8%) and/or an OTC sleep aid (10%) to help them sleep over the past year.⁶⁹ This shift in thinking has also led the FDA to approve 3 new drugs in 2005 without recommended limitations on duration of use: eszopiclone, ramelteon, and zolpidem extended-release. This is a significant change from previous FDA decisions, when hypnotics were approved only for short-term treatment of insomnia. Now, with over a decade of clinical experience in the United States with non-benzodiazepines such as zolpidem and the recognition of insomnia as a chronic condition, the approval for the short-term use of previously approved insomnia drugs is being revisited.

CONCLUSIONS

The safety of insomnia treatments has improved considerably over the past 10 years with the introduction and development of new treatment options that provide improved safety, especially with regard to next-day effects and abuse liability. Despite a lack of demonstrated efficacy and safety, use of OTC agents, alternative therapies, and off-label prescription medications in patients with insomnia remains high. A recent statement produced by an independent panel assembled by the NIH to advise physicians recommends the use of only those treatments studied in clinical trials that have been shown to be safe and effective for the treatment of insomnia.⁴ According to the NIH findings, the non-benzodiazepine hypnotics have a superior safety profile compared to the older benzodiazepines.

In 2005, 3 new agents were approved for the treatment of insomnia without any recommendations for limiting the duration of use. These were zolpidem extended-release (a modified-release formulation of zolpidem), eszopiclone (a novel non-benzodiazepine), and ramelteon (a melatonin receptor agonist). Zolpidem extended-release was designed to extend the duration of action through the middle-of-the-night, thus improving sleep maintenance while retaining the sleep initiation benefits and the established safety profile of original zolpidem.

Drug names: estazolam (ProSom and others), eszopiclone (Lunesta), fluconazole (Diflucan and others), flurazepam (Dalmane and others), ketoconazole (Ketozole and others), mirtazapine (Remeron and others), olanzapine (Zyprexa), quazepam (Doral), quetiapine (Seroquel), ramelteon (Rozerem), rifampin (Rimactane and others), temazepam (Restoril and others), triazolam (Halcion and others), zaleplon (Sonata), zolpidem (Ambien).

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