Sleep disorders such as insomnia affect many people and their ability to sleep effectively throughout the night. As a result, a new class of medications known as “Z-drugs” has been developed to decrease the frequency of sleep disruptions among such individuals. These drugs produce an inhibitory effect on certain receptors in the brain and make it easier for individuals to fall and stay asleep. However, these drugs can have a negative impact on various aspects of cognitive and behavioral function, warranting further research on the benefits and consequences of such medications.

History of Zolpidem and Related Hypnotic Drugs

Hypnotic or soporific drugs ("sleeping pills") are among the most frequently prescribed medications in the United States (Mihic & Harris, 2011). In the last two decades, a new class of prescription hypnotic drugs has entered clinical practice and become the most commonly prescribed medication of its kind. The most widely used of these is Zolpidem (Ambien®), with prescriptions in the United States increasing from 16.4 million in 2007 to more than 40 million in 2012 (IMS Health, 2015). Two related drugs are Zaleplon (Sonata®) and Zopiclone (marketed in the United States as eszopiclone, Lunesta®). The colloquial term for this group of drugs is “Z-drugs,” due to their generic names starting with the letter Z. The following discussion in this article focuses on Zolpidem, but it should be noted that the other Z-drugs are very similar to Zolpidem in terms of pharmacology and toxicology.
Zolpidem has pharmacologic similarities to benzodiazepines, a drug class commonly used to induce sedative effects and treat anxiety, seizures, and sleep disorders (Dang, Garg, & Rataboli, 2011). The four most commonly prescribed benzodiazepines are Alprazolam (Xanax®), Clonazepam (Klonopin®), Lorazepam (Ativan®), and Diazepam (Valium®). Benzodiazepines are only recommended for short-term treatment of insomnia and can be helpful in shortening the time to fall asleep while also prolonging sleep time. However, continued use beyond two to four weeks is not recommended due to the risk of subsequent drug tolerance (Mihic & Harris, 2011).

How Does Zolpidem Help People Sleep?

Zolpidem has a similar mechanism of action to benzodiazepines in that it increases the actions of the neurotransmitter gamma-aminobutyric acid (GABA) at GABAA receptors in the brain (Nutt & Stahl, 2010). GABAA receptors have an inhibitory effect on neural transmission within the brain. Extra stimulation of these receptors can lead to the onset of sleep. Zolpidem is a relatively short-acting medication, with half of the drug cleared from the body in about 2.5 hours (Dang, Garg, & Rataboli, 2011).

Side Effects of Zolpidem

Zolpidem is generally well-tolerated (Terzano, Rossi, Palomba, Smerieri, & Parrino, 2003). Common side effects include drowsiness, headache, dizziness, nausea, amnesia, and anxiety. In addition to the more frequent side effects discussed above, patients taking Zolpidem have reported visual and auditory hallucinations, agitation, bizarre behavior, and depersonalization. In rare cases, Zolpidem has been associated with parasomnias, a type of sleep disorder that involves abnormal movements, behaviors, emotions, and perceptions. Parasomnias can occur throughout the sleep cycle and may induce sleepwalking, night terrors, sleep eating, teeth grinding, and somniloquy (talking or yelling during sleep) (Pressman, 2011).

Impact of Zolpidem on Cognition and Motor Skills

Medication effects that may linger after awakening can interfere with cognitive function and tasks such as driving or operating machinery (Farkas, Unger, & Temple, 2013). These side effects are similar to those seen with the benzodiazepines. Despite a half-life of approximately 2.5 hours, there may still be detectable amounts of Zolpidem in the bloodstream even after seven to eight hours of sleep. The residual Zolpidem that may be present after sleep can potentially cause problems with alertness and cognitive function. Multiple studies have demonstrated that Zolpidem and the other Z-drugs can impair driving performance after bedtime use (Bocca et al., 1999; Leufkens, Lund, & Vermeeren, 2009; Vermeeren et al., 2014). These impairments worsened if the medications were used during the night. Higher blood concentrations of Zolpidem have been found in cases of death related to motor vehicle accidents compared to other causes of death. A decade-long retrospective study in Taiwan found that Zolpidem use was associated with increased risk of head injury in the adult population (Lai, Lin, Liu, Li, & Kao, 2014).
Toxicology of Zolpidem

Compared to other central nervous system (CNS) depressants such as benzodiazepines and barbiturates, Zolpidem is safer during overdoses. Fatalities due to Zolpidem overdose are very rare. However, concurrent use of Zolpidem with other CNS depressants increases toxicity and the risk of sustaining injuries resulting from cognitive impairment. Thus, it is not recommended to consume ethanol, benzodiazepines, or other sedative-hypnotics together with Zolpidem (Terzano, Rossi, Palomba, Smerieri, & Parrino, 2003).

Zolpidem Use in Children, Elderly, and Pregnant Women

Zolpidem use among children is uncommon. Preliminary studies indicate limited effectiveness of Zolpidem in treating sleep deprivation in pediatric burn patients (Cronin, Gottschlich, Gose, & Kagan, 2015). There are also concerns about the safety of Zolpidem in the geriatric population, although no large-scale studies have been reported (Dolder, Nelson, & McKinsey, 2007; Wong & Nguyen, 2014). It seems prudent to advise elderly patients taking Zolpidem of the potential risks of falls or other injuries, especially since this population is already at an elevated risk for such injuries. There is also some preliminary data that suggests that Zolpidem use in pregnancy increases the risk of unfavorable obstetric outcomes (Wang, Lin, Lin, & Chen, 2010). Further research is needed in this area.

Zolpidem Abuse

Zolpidem and the other Z-drugs are currently classified by the Drug Enforcement Agency (DEA) as schedule IV substances, a category of drugs with low potential for abuse and a low risk of dependence. Several benzodiazepines (Alprazolam, Diazepam, Lorazepam) also fall under this DEA category. Abuse of Zolpidem is relatively uncommon, although there are some patients who use Zolpidem chronically and may even escalate dosages to increase the effects (Victorri-Vigneau et al., 2014). The clinical trials for Zolpidem only followed patients’ medication use for up to 35 days. Any chronic use of Zolpidem for longer than this has not been carefully studied.

Summary

Zolpidem and other Z-drugs are widely used for sleep disorders. The overall safety record of these medications has shown promise; however, these drugs do have side effects that can potentially impair alertness and coordination with tasks such as driving. Health providers and pharmacists should take a proactive role in alerting patients to the potential dangers of hypnotic medications, especially hazards associated with next-morning impairment. Research is specifically needed on the risks of Zolpidem in the elderly, in pregnant women, and in those using the drug long term.
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References


