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Continuing Education Activity

Insomnia is a highly prevalent disorder in the US and worldwide. Insomnia is defined as the presence of long sleep latency, frequent nocturnal awakenings, or prolonged periods of wakefulness during the sleep period, or even frequent transient arousals. Zaleplon is a medication used in the management and treatment of insomnia. It is in the hypnotic class of drugs but is unrelated to benzodiazepines, barbiturates. This activity reviews the indications, actions, and contraindications for zaleplon when using it as a valuable agent in managing insomnia.

Objectives:

- Describe the mechanism of action of zaleplon.
- Review the appropriate dosing of zaleplon.
- Summarize the potential adverse effects for patients using zaleplon.
- Explain the importance of using zaleplon and how improving care coordination among the interprofessional team will lead to better outcomes.

Access free multiple choice questions on this topic.

Indications

Insomnia is a highly prevalent disorder in the US and worldwide. The definition of insomnia is the presence of "long sleep latency, frequent nocturnal awakenings, or prolonged periods of wakefulness during the sleep period or even frequent transient arousals." Another definition describes insomnia disorder as the 'subjective report of difficulty with sleep initiation, duration, consolidation, or quality which occurs despite having an adequate opportunity for sleep and resulting in some form of daytime impairment. According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association 2013) and the third edition of the International Classification of Sleep Disorders (ICSD-3) (American Academy of Sleep Medicine 2014), dissatisfaction with sleep quantity or quality has to occur at least three nights per week over at least three months to merit a diagnosis of chronic insomnia. These criteria differ from the previous classification by considering the frequency criterion and the increase in the duration of symptoms from one to three months.

The criterion used to distinguish individuals with insomniacs from good sleepers are self-reported sleep symptoms, such as sleep latency (time to fall asleep) or wakefulness after sleep onset (WASO) greater than 30 minutes.

The actual prevalence of insomnia varies according to the stringency of the definition used. Insomnia symptoms are seen in approximately 33% to 50% of the adult population, insomnia symptoms with distress or impairment in 10% to 15%, and specific insomnia disorders in 5% to 10%.

This result of insomnia has far-reaching adverse consequences on the physical, social, mental, and emotional health and wellbeing of the patient, including increased risk of accidents, decreased work productivity, increased risk of comorbid psychiatric disorder, decreased quality of life, and increased usage of healthcare resources. Various pharmacologic and non-pharmacologic modalities have been tried to help patients with this condition. Regardless of the chosen modality, therapy aims to improve the quality and quantity of sleep while minimizing daytime impairments as well as improving the overall quality of life.

Mechanism of Action

There has been a proposal that insomnia is a hyperarousal disorder that could reflect a deficit in sleep homeostasis. Hence, it is imperative to understand the changes occurring at the neurotransmitter level for planning the optimum pharmacology.

In the central nervous system (CNS), there is a balance between the excitatory effects of the Glutamate receptors and the inhibitory effects of the GABA receptors. In the central nervous system, GABA exerts its influence via ionotropic GABAA and GABAC receptors and metabotropic GABAB receptors. Most sedative-hypnotics used in the treatment of insomnia target the GABAA receptors. The GABAA receptors contain alpha, beta, and gamma receptors in the vast majority in the 2:2:1 stoichiometry. GABA released from the presynaptic neuron activates the ligand-gated ion channel to increase chloride ion permeability, leading to hyperpolarization of the membrane and a decrease in the excitability of the neuron.

BZs and Z-drugs act via the so-called BZ-binding site located at the interface between a- and c-subunits and thereby specifically bind to gamma-containing receptors. BZs and Z-drugs are positive allosteric modulators, i.e., they enhance the GABA-induced chloride current, herby mediating phasic inhibition. The classical benzodiazepines were introduced in 1960, and the so-called Z drugs came onto the scene in the 1980s. These classes of drugs contain imidazopyridines like zolpidem, cyclopyrrolones like zopiclone, and pyrazolopyrimidine like zaleplon.

Zaleplon, a pyrazolopyrimidine hypnotic, binds to the benzodiazepine type 1 site on the gamma-aminobutyric acid subtype A (GABA-A) receptor/chloride-ion channel complex. The chemical name of zaleplon, is N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethylacetamide.

Zaleplon has selectivity for specific BZ receptor subtypes and does not have the neuromuscular relaxation or anticonvulsant effects of the standard benzodiazepines. Zaleplon has a quick onset of action and a peak plasma concentration and elimination half-life of approximately 1 hour each. The better action on sleep induction rather than maintenance could be explained by its short half-life and quick onset of action. The American Academy of Sleep Medicine, in its 2017 Clinical guidelines, suggests that practitioners use zaleplon as a medication for sleep-onset insomnia (versus no treatment) in adults.

Zaleplon improves sleep without producing rebound effects in outpatients with insomnia. The effect on improvement on sleep latency is evident through multiple studies. Elie and et al. showed during their studies in 1999 that the Sleep Latency gets shortened during four weeks of treatment with zaleplon. James Walsh and et al. found that sleep latency (SL) was significantly shortened with zaleplon 10 mg for all five weeks of treatment as assessed by polysomnography and subjective sleep measures.[17] Studies have not shown any clinical benefit between using zaleplon versus placebo in the total sleep time (TST). No clinical significance was apparent in the wake after sleep onset [WASO] between zaleplon and placebo. Data from studies also showed no significant differences in the number of awakenings (NOA) for either zaleplon 10 mg or zaleplon 5 mg at any study week.

Administration

Zaleplon is a Schedule IV prescription medication. It is available as 5 mg and 10 mg oral capsules. It comes in a capsulated form with an opaque green cap and an opaque pale green body with 5 mg and 10 mg written with black ink on the body. The recommendation is to start with 5 mg by mouth, to be taken immediately before bedtime. The usual dose is 10 mg by mouth immediately before bedtime. It is given 7 hours before the planned awakening. The maximum dose can go up to 20 mg by mouth to be taken directly before bedtime. The maximum dose in elderly or debilitated patients should be 10 mg by mouth taken immediately before bedtime. If the provider plans to stop the medication, they should taper it down slowly.

Zaleplon is metabolized mainly by the liver, and correspondingly the dose of zaleplon requires a reduction in patients with mild to moderate hepatic impairment. The oral clearance of zaleplon decreases by 70% and 87% in compensated and decompensated cirrhotic patients compared to healthy subjects. In cases of hepatic impairment, the dose should be lowered to 5 mg by mouth, taken immediately before bedtime. Its use is not recommended for use in patients with severe hepatic impairment.

The kidneys minimally metabolize zaleplon, and hence the pharmacokinetics of zaleplon is not altered in patients with renal insufficiency. Doses do not require modification for patients with mild to moderate renal impairment. The medication has not had adequate research in patients with severe renal impairment.

Currently, there is a lack of randomized controlled trials and the availability of evidence regarding the safety and appropriateness of usage of hypnotics in the pregnant population. One of the studies from Wikner and colleagues in 2011 reported that there did not seem to be an increased risk of malformations with these medications, and the tentative association with some intestinal malformation may be due to chance alone. Similarly, studies by Okun et al. reported no correlation of increased risk of congenital defects with these medications but did show an increased risk of preterm birth, low birth weight, and small-for-gestational-age infants in the pregnant cohort. This small number of studies with a small number of subjects restricts the ability of providers to make prescription decisions about their use during pregnancy. Therefore it is considered a Category C medication and not recommended for usage during pregnancy, labor, and delivery.

A small amount of the medication is secreted in breast milk, especially about 1 hour after its use. Even these small amounts of the drug from breast milk may result in potentially significant concentrations in infants. Because its effects on a nursing infant are unknown, it is not recommended for lactating mothers.

There is also currently a lack of data regarding the safety and effectiveness of zaleplon in the pediatric population.

Adverse Effects

More common adverse effects include drowsiness, dizziness, diarrhea, grogginess, and decreased ability to concentrate. Other less common adverse severe events include abnormal thoughts and behavior, including aggressive behavior, confusion, agitation, hallucinations, worsening of mood issues including worsening depression, suicidal thoughts, memory loss, and severe allergic reactions, including anaphylaxis.

Most Z-drugs appear to have a dose-dependent effect on anterograde amnesia, supposedly explained by the agonistic action on the GABAA receptors. Zaleplon is less likely than zolpidem and zopiclone to cause anterograde amnesia. The amnestic effects are also explainable by the ability of the hypnotics to reduce sleep latency and block memory storage.] Zaleplon also has less ability to affect word recall and recognition six hours after administration. It did not show this effect even at higher doses. Several studies have shown little or no residual effects the following morning, even when taken in the middle of the night.

Patients have reported adverse effects of parasomnia, amnesia, and hallucinations associated with Z-drugs. Parasomnia is a phenomenon where patients can experience abnormal events or behaviors or events while asleep. These can range from nightmares, night terrors, somnambulism), sleep-eating, and even sleep-driving. Sleep-driving is a variant of somnambulism, characterized by driving a vehicle in a half-asleep state with no recollection of it afterward. Such events have been reported in both sedative-hypnotic-naive as well as in sedative-hypnotic-experienced persons. The FDA has recently added a Boxed Warning on zaleplon to warn about the possibility of having these problems while on the Z drugs. Such complex sleep

behaviors may occur with zaleplon alone at therapeutic doses but increase with the use of alcohol and other CNS depressants, as well as by exceeding the maximum recommended dose. The concern is also about the risk of suffering a severe injury or even death during these episodes.

Given this, the FDA has further issued a contraindication for the use of Z-drugs in patients who have previously experienced these kinds of behaviors while on these medications. There is also a concern since most of the patients on these medications already have a lower threshold, and these Z- drugs can exacerbate those symptoms. Because of the risk to the patient and the community, clinicians should plan to discontinue zaleplon should a patient report such episodes.

Psychomotor effects of the Z-drugs are a significant concern in the elderly as their impact becomes exaggerated secondary to altered pharmacokinetics. They are listed in the Beers List for medications to avoid in the elderly. Nocturnal awakening, which is common in the elderly, also predisposes them to balance issues, and an increased risk of falls may get pronounced when they are on these drugs. The residual psychomotor effects from Z-drug use include dizziness, postural instability, ataxia, and falls. Falls can occur at higher than usual dosages or when mixed with other psychoactive substances. These falls in the elderly can be associated with an increased risk of head injuries, hip fractures, and even death. The risk-benefit analysis of these drugs in the geriatric population is not favorable. Hypnotics have shown minimal benefit with significant adverse effects in this population.

Psychomotor impairment during midnight awakening is more pronounced with Z-drugs with a longer half-life like zopiclone and zolpidem, rather than with zaleplon. Zaleplon has not shown this impairment with doses up to 10 mg at bedtime. However, at doses of 20 mg, psychomotor impairment from zaleplon occurred, around one 1 hour after administration, but showed no residual effects at 6 hours. A study done in the aviation industry found showed performance impairment from a 10-mg dose of zaleplon for up to 1 to 2 hours only. Zaleplon does not seem to cause impairments in driving 4 hours after administration. Several other studies have also confirmed that zaleplon has little or no residual effects the following morning, even when taken during the middle of the night for the inability to go back to sleep. Doses exceeding therapeutic concentrations have the potential to cause impairments of psychomotor functions as well as the level of consciousness and ability to drive.

Contraindications

Contraindications include hypersensitivity to zaleplon or any ingredients in the formulation of the medication. There have been reports of symptoms such as throat closing, shortness of breath, nausea, and vomiting after taking the medication, suggesting anaphylaxis. Rare reports of angioedema exist in patients after taking the first or subsequent doses of sedative-hypnotics, including zaleplon. Patients with a history of angioedema with zaleplon should not receive this drug. As mentioned earlier, zaleplon is not recommended in patients with severe hepatic impairment.

Recently FDA has added Boxed Warning to certain prescription insomnia medication after reports of injury and death resulting from complex sleep-related behaviors like sleepwalking, sleep-driving, and engaging in other activities while in a sleep-like state after taking these medicines. These new warnings will be necessary for the Z group of drugs, including eszopiclone, zaleplon, and zolpidem. Contraindications to using these Z drugs, including zaleplon, include patients who have had a history of such complex sleep-related behaviors. CNS depression causing impaired mental and physical impairment, primarily if used concomitantly with other drugs that cause CNS depression.

Toxicity

Toxicity in a milder form can cause lethargy, drowsiness, and confusion. Severe toxicity can lead to respiratory depression, ataxia, hypotension, hypotonia, loss of consciousness, coma, and rarely death. Rare cases of fatalities have following overdose with zaleplon have been reported, most of which correlate with the use of other CNS depressants.

Management aims at providing supportive treatment, including gastric lavage and IV fluids. Researchers have conducted animal studies that show flumazenil is useful as an antagonist to zaleplon, but there are no clinical trials regarding the use of flumazenil as an antidote to zaleplon overdose.

Enhancing Healthcare Team Outcomes

The interprofessional healthcare team, including clinicians, PAs and NPs, nursing staff, and pharmacists, must work together to understand the type of patient's sleep problems. Taking a good history is paramount because many times, there could be extraneous factors like infants, pets, loud neighbors, erratic work schedules, medications causing or confounding sleep problems. If the clinician decides on prescribing a pharmacological treatment for the patient, they must account for the demographics of the patient and comorbid issues. The interprofessional team needs to be upfront in cautioning the patient and their families about minimizing any other central nervous system depressants with the medication.

Teams should also be good at communicating with the patients about the potential side effects of the drug while at the same time keeping a watch for the rare ones if they occur; this is where a nurse who is familiar with the drug can counsel the patient and answer any questions. The nurse can also be alert for any "red flags" to prescribing the medication and alert the prescriber should they be present. The pharmacist will verify that dosing is patient-appropriate and verify the patient's medication record to check for drug interactions, and consult with the prescriber should they see any issues. These examples of interprofessional team dynamics can make zaleplon therapy more effective while minimizing adverse events. [Level 5]

Review Questions

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