



AN OVERVIEW OF THE RARE AND LIFE-THREATENING ADVERSE EFFECTS OF ZOLPIDEM IN THE TREATMENT OF INSOMNIA

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ABSTRACT

Background: A Common sleep disorder such as insomnia is characterized by persistent problems falling asleep, staying asleep, or experiencing nonrestorative sleep that impairs functioning during the day. Regardless of the proper conditions for sleeping every night, the sleep disruptions associated with insomnia typically manifest as difficulties falling asleep, trouble staying asleep, or waking up too early. A person's quality of life can be negatively impacted by insomnia, which can lead to frequent daytime naps, difficulty focusing, an increased risk of mistakes and accidents, and lower productivity at work. A multidisciplinary strategy is recommended for the treatment of insomnia, with an emphasis on pharmacological therapy, behavioral treatments, better sleep hygiene, psychological stress management, and hypnotic treatment. In order to limit the required dosage and any associated side effects, the most successful treatments combine medication with cognitive behavioral therapy.

The most often utilized hypnotics as supplementary therapy are non-benzodiazepine ones like zaleplon, eszopiclone, and zolpidem. Zolpidem is one of these hypnotics that is most often utilized. But zolpidem has a lot of adverse effects, and the literature has a few distinctive features to keep in mind.

Objective: To carry out a comprehensive analysis of adverse events associated with zolpidem.

Method: A variety of websites, including PubMed, Google Scholar, Science Direct, Seizure Journal, Elsevier, Medscape, WHO Pharma Newsletter, Research Gate, Springer Link, and Online Library Wiley, were reviewed in the preparation of this review study.

Observation: Owing to its superior safety profile over benzodiazepines, zolpidem is one of the most often given medications for insomnia. But zolpidem usage is associated with a number of neuropsychiatric side effects that should be taken very seriously, including hallucinations, sensory distortions, delirium, parasomnias or complex sleep behaviors (CSBs), amnesia, somnambulism, sleep-related eating disorders, suicidality, etc. When prescribing a medication, medical practitioners should be cautious and mindful of its potential harmful effects.

Study Eligibility Criteria: Scholarly articles of any kind (case reports, case series, observational or interventional studies) that detail zolpidem's neuropsychiatric side effects.

Key Words: Zolpidem, Complex sleep behavior, Parasomnias, Somnambulism, Sleep related eating disorder, and Suicidality

INTRODUCTION

In general, "insomnia" refers to chronic insomnia, which is defined as symptoms that worsen throughout the day and last longer than a month.^[1] People with chronic insomnia are those who have trouble getting to sleep and staying asleep, as per DSM-V criteria.^[2] Other often reported symptoms include weariness, focus problems, mood swings during the day, and early morning awakenings.^[3] Before a diagnosis may be made, these symptoms must be present for at least three months and significantly bother the patient.^[2] Even in cases where there are sufficient conditions for regular sleep, insomnia usually causes sleep disturbances such as difficulty falling asleep, trouble staying asleep (waking up in the middle of the night and having trouble going back to sleep), or excessive early morning wakefulness.^[4]

A person's quality of life can be negatively impacted by insomnia, which can lead to frequent daytime naps, difficulty focusing, an increased risk of mistakes and accidents, and lower productivity at work.^[4] The presentation is a little different in youngsters, and symptoms such as nightmares, resistance to going to bed, independent sleeping, and inability to fall asleep in the absence of appropriate stimulations are commonly observed.^[4] Their capacity to focus, play on a daily basis, do well in school, and behave badly can all be negatively impacted by insomnia. As much as 50% of older persons (65 years of age and older) report having trouble falling or staying asleep, and 12 to 20% of them fit the diagnostic criteria for insomnia disorder^[4], making the illness especially concerning for the elderly. About half of the patients will have a remission throughout the follow-up period, and the most prevalent complaint (50–70%) is difficulty sustaining sleep.^[5]

A complete history that includes details on sleep, health, mental health, and substance use is necessary to make a diagnosis. Comorbid conditions that may exacerbate treatment complications or induce sleeplessness should be evaluated in patients. Increasing age, female sex, concomitant medical issues, working shifts, low socioeconomic position, and potentially unemployment are risk factors.^[1] A multidisciplinary strategy should be used to treat insomnia, with an emphasis on pharmaceutical therapy, behavioral therapies, reducing psychological stresses, better sleep hygiene, and hypnotic treatment. The most successful treatments combine medication with cognitive behavioral therapy to reduce the amount of medication required and any negative effects that may arise.^[1]

In 1992, the USFDA authorized zolpidem, an imidazopyridine, for the short-term management of insomnia. It is a sedative-hypnotic that acts quickly and has only weak anxiolytic, anticonvulsant, and muscle relaxant effects. Compared to benzodiazepines, it is thought to have a more favorable side-effect profile because it is not a benzodiazepine, especially in terms of rebound insomnia, lack of memory, and dependence. As a result, it is now often utilized in therapeutic practice to treat insomnia.^[6]

It is available in immediate-release and extended-release formulations; the symptoms associated with delayed sleep onset are treated with the immediate-release formulations. Reduced sleep latency and delayed sleep onset are both treated by the extended-release preparation. Men and women should begin taking 5 or 10 mg of the immediate-release formulations right before sleep. Start with 6.25 mg for women and 6.25 mg or 12.5 mg for men if you're using an extended-release formulation. To reduce side effects in individuals 65 years of age or older, the minimal dose—which should not exceed 5 mg for immediate-release and 6.25 mg for prolonged release—should be utilized. When a patient obtains seven to eight hours of sleep before returning to activity, zolpidem should only be administered as a short-term therapy for insomnia. Patients on other medications should be prescribed this prescription with caution, especially those using opioids, muscle relaxants, sleep aids, seizure medications, or medications for anxiety or insomnia.^[7]

Patients with insomnia have better sleep after using zolpidem. It is intended for use with patients who have trouble falling asleep. In patients with transitory (transient) insomnia, this medication reduces sleep latency, lengthens sleep duration, and reduces the frequency of awakenings during sleep. Zolpidem has been associated with a number of neuropsychiatric side effects, including amnesia, delirium, hallucinations, sensory distortions, parasomnias, or complex sleep behaviors (CSBs), and dementia. This relationship has been demonstrated by several post-marketing studies and case reports. ^[8]

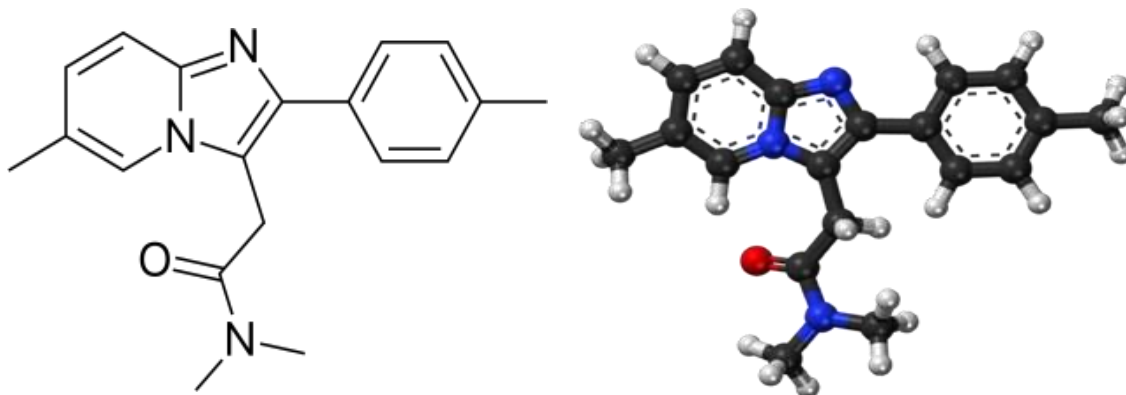


Fig. 1: Structure of Zolpidem

MECHANISM OF ACTION

A non-benzodiazepine substance called zolpidem binds to benzodiazepine receptors, especially in the cerebellum, where it has a greater affinity for BZ(ω) receptors. This results in a fast-onset, brief-duration hypnotic action. A ligand-gated ion channel including five subunits for the inhibitory neurotransmitter GABA, known as the GABA-A subtype of receptors, is linked to BZ(ω) binding sites. When zolpidem is taken at low doses, the effects of GABA are amplified, indicating that it binds better to BZ receptors containing $\alpha 1$ subunits, unlike benzodiazepines, which bind to all BZ subtypes without discrimination. On the other hand, zolpidem doses greater than those necessary to enhance GABA's actions are seen in receptors that include both $\alpha 2$ and $\alpha 3$ subunits. In receptors containing $\alpha 5$, there is minimal to no response. ^[9] The sedative, anticonvulsant, anxiolytic, and myorelaxant actions of zolpidem are facilitated by subunit binding to the GABA-A receptor. The brain sensorimotor cortical areas Lamina IV, the substantia nigra pars reticulata, the cerebellum molecular layer, the olfactory bulb, the ventral thalamic cortex, the pons, the inferior colliculus, and the globus pallidus are the main locations for the BZ(ω) receptor. ^[10]

When zolpidem is taken orally, the EEG shows slow-waves (2–4 Hz) with only brief bursts of rapid waves (12–14 Hz) at higher dosages. Compared to benzodiazepines, this effect is preferred since the former cause more intense fast-wave activity that is believed to deviate from a typical sleep pattern. EEG recordings on cats and rats have revealed that zolpidem increases slow wave sleep, often known as non-rapid eye movement sleep. These investigations showed that zolpidem improved non-rapid eye movement sleep while having minimal effect (unless at high dosages) on rapid eye movement sleep. ^[9]

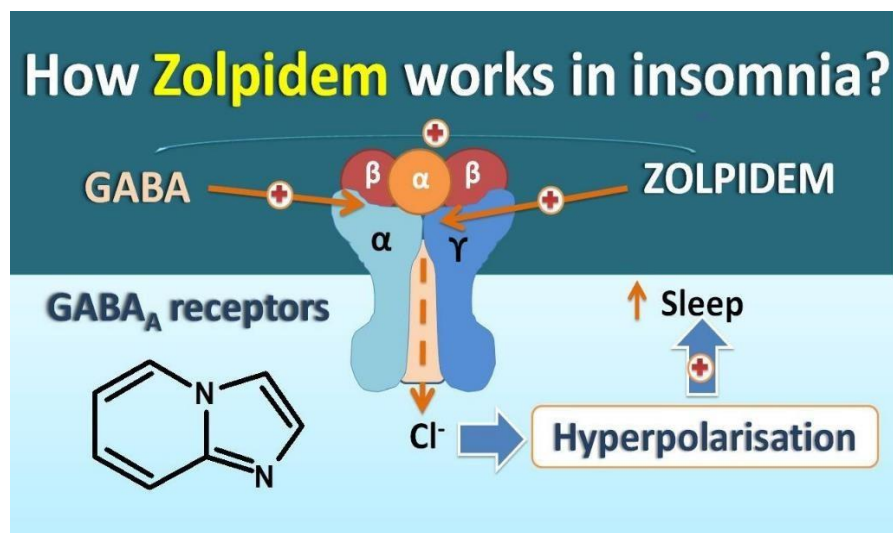


Fig. -2: Mechanism of Action of Zolpidem

PHARMACOKINETICS

When administered, zolpidem quickly enters the gastrointestinal system and continues to be absorbed for up to three hours, exhibiting biphasic absorption characteristics. The majority of CYP3A4 enzymes metabolize zolpidem, with CYP2C9, CYP1A2, CYP2D6, and CYP2C19 enzymes doing so to a lesser degree.^[11] After conversion, zolpidem is excreted mostly via the kidneys as inactive metabolites. Zolpidem's elimination half-life ranges from 1.62 to 4.05 hours, with a mean of 2.8 hours.^[12] Research on the relationship between food and sleep has indicated that taking zolpidem just after eating may hasten the beginning of sleep.^[12] Oxidation and hydroxylation are the main metabolic pathways associated with the drug.^[12] The percentage of zolpidem that is bound to plasma proteins is about 92%, and its total bioavailability is about 70%.^[12, 13]

Children have a three-fold higher clearance of zolpidem than young adults, and the elderly have a lower clearance.^[14] Therefore, zolpidem dosages for elderly individuals should be reduced. Since older people are more likely to exhibit signs of persistent insomnia, zolpidem dosage reductions are beneficial for them. Most significantly, individuals have a higher likelihood of experiencing negative side effects from drugs that affect the central nervous system.^[14] It has also been suggested that when zolpidem is stopped, the possibility of rebound insomnia is reduced.^[14]

PHARMACODYNAMICS

The structure of zolpidem differs from that of benzodiazepines.^[13] By selectively binding to the benzodiazepine-1 (BZ1) receptor, zolpidem increases the action of the inhibitory neurotransmitter γ -aminobutyric acid (GABA). This leads to hyperpolarization of neurons, increased conductance of chloride, and suppression of the action potential, all of which together reduce neuronal excitability and provide the sedative and hypnotic effects associated with this drug.^[12, 13] Zolpidem is selective for the $\alpha 1$ and $\alpha 5$ subunits of the BZ1 receptor rather than the BZ2 receptor site. Its minor side effects related to agonism at the BZ2 receptor site include myorelaxant, anticonvulsant, and anxiolytic actions.^[12] Zolpidem is necessary for maintaining deep sleep stages 3 and 4 because the BZ1 receptor is highly expressed in structures that are important for controlling sleep, such as the globus pallidus, substantia nigra (pars reticulata), olfactory bulb, ventral thalamic complex, pons, inferior colliculus, and Lamina IV of the sensorimotor cortical regions.^[13]

ADVERSE EFFECTS OF ZOLPIDEM

NEUROPSYCHOLOGICAL ADVERSE EFFECTS:

➤ COMPLEX SLEEP BEHAVIOURS

The zolpidem drug has been associated with complex behaviors carried out in a "sleep-like" condition, which is characterized by impaired motor function, decreased awareness of one's surroundings, difficulties thinking, memory loss, and illogical speech. ^[15] 10% of zolpidem adverse effects, according to the Therapeutic Drugs Association (TGA), included "sleep-driving." ^[16] Therapeutic and supratherapeutic zolpidem dosages were used in these patients. When someone consumes zolpidem and commits a crime they don't recall, the legal situation is complicated by the unclear awareness or decision of the patient during this sleep-like condition. The level of behavioral complexity that an individual may achieve in this condition is even more remarkable. This is a crucial factor in any case involving homicide or vehicular homicide. ^[15]

➤ SLEEP WALKING

A comprehensive analysis of 24 prior studies on the topic of zolpidem-induced sleepwalking showed that the connection was independent of age, dosage, medical history, or even a prior history of sleepwalking at any point in time. ^[17] Patients should be advised of this, as the product information included with the medicine only lists sleepwalking as a danger in conjunction with another CNS depressant or at dosages higher than 10 mg. Among all the prescription drugs included in the study, zolpidem was shown to have the greatest relationship with sleepwalking throughout the literature in this analysis. ^[17]

➤ SUICIDALITY

Zolpidem usage has been successfully associated with both attempted and completed suicide (OR 2.08; 95% CI 1.83-2.63) in individuals, regardless of the existence of concomitant mental disorders. ^[18, 19] The International Journal of Neuropsychopharmacology reviewed 23,420 cases of ADRs related to dependence and withdrawal, of which 102 cases (0.5%) included intentional "self-injurious behavior," 44 cases (0.2%) included suicidal behavior, and 3,101 cases (13.2%) were classified as "suicidal attempts." ^[20] Zolpidem had the greatest risk of fatal result (20.3%) with these forms of ADRs when compared to zaleplon and zopiclone. ^[20]

➤ PARASOMNIAS

Retrospective case-control study: after adjusting for patient demographics and concurrent medication use, zolpidem was significantly associated with parasomnias (OR 4.34; $P < 0.0001$), amnesia (OR 2.78; $P < 0.0001$), hallucinations (OR 1.69; $P < 0.0001$), and suicidality (OR 1.70; $P < 0.0001$). The largest link was seen for movement-based parasomnias, with an odds ratio (OR) of 35.20 (CI 31.65-39.14) when drug-exposure variables were taken into account and a 95% confidence interval (CI) of 31.39-37.68 when adjusted for patient demographics. Significant increases in parasomnias (OR 7.65; $P < 0.05$), movement-based parasomnias (OR 64.92; $P < 0.05$), and amnesias (OR 4.29; $P < 0.05$) were linked to intense public scrutiny of zolpidem between 2006 and 2009. It is important to take notoriety bias into account subsequent to media attention, even though there was a substantial correlation with these adverse medication responses before the media storm. ^[21]

ABUSE, DEPENDENCE, AND WITHDRAWAL

Even when a patient takes the recommended dosage of zolpidem, abruptly quitting the prescription might cause rebound insomnia and withdrawal symptoms. This risk is increased in patients who also have concomitant alcohol or drug dependence. ^[20, 22] It has been demonstrated that ADRs associated with misuse, abuse, dependence, and withdrawal account for 11.35% (95% CI 11.21-11.49%) of all ADRs seen while using zolpidem. The Centre for Evaluation and Information on Pharmaco-dependence (CEIP) provided data on zolpidem abuse and dependence for the post-marketing period in France from 2003 to 2010, which showed a steadily rising rate of "suspect prescriptions possibly indicating abuse" during this time. In 2009, zolpidem was the medication most frequently linked to these kinds of forged prescriptions. In this study, 30 cases of zolpidem misuse and dependency were studied. The average age of the users was found to be

38 years old, with an average daily dosage ranging from 50 to 2000 mg (616.61 mg). More than half of the patients had concurrent disorders of drug misuse (40.0%) and mental illnesses (13.3%).^[23]

Many incidences of seizures that occurred after zolpidem cessation have been documented.^[22, 24] The majority of instances show that patients receiving daily doses of about 450–600 mg had withdrawal symptoms; however, some patients reported experiencing them at dosages as low as 160 mg. Diazepam is a long-acting benzodiazepine that may be used to successfully treat all cases of zolpidem withdrawal seizures. It allows for a gradual reduction of neural inhibition.^[24]

Zolpidem prescribers have expressed fear about rebound insomnia. Studies show that there was a nonsignificant difference in total sleep time (2-4 minutes; 95% CI -11.4 to 6.6) on the initial night after stopping zolpidem. But it has been shown that on the initial night following discontinuing zolpidem, sleep begin latency is considerably higher (13.0 minutes; 95% CI 4.3-21.7; $P < 0.01$). There was no evidence of rebound insomnia for more than six months, starting to appear two to four weeks after the medication was stopped.^[25]

OBSTRUCTIVE SLEEP APNEA

The effect of hypnotics on obstructive sleep apnea (OSA) mechanisms, including upper airway function and breathing during sleep, was investigated in double-blind, placebo-controlled, cross-over research. Electroencephalograms (EEGs), electrooculograms (EOGs), and sub-mentalis electromyograms (EMGs) were employed for measurements after participants were randomized to receive temazepam 10 mg, zolpidem 10 mg, zopiclone 7.5 mg, or placebo. The epiglottic pressure at the base of the tongue was measured with a pressure-tipped catheter, and the genioglossus EMG was recorded using intramuscular electrodes. When compared to placebo, minute breathing, inspiratory and expiratory times, peak inspiratory flow, and upper airway resistance characteristics did not vary statistically ($P > 0.05$) in those using temazepam, zolpidem, or zopiclone. In comparison to the placebo, all three medication groups had more breaths per minute ($P < 0.03$). When compared to the placebo group, zolpidem (27%; $P = 0.02$) and zopiclone (37%; $P < 0.001$) both markedly raised the respiratory arousal threshold; temazepam did not ($P = 0.17$). When compared to a placebo, none of the three medications had an adverse effect on passive upper airway collapsibility. Remarkably, in contrast to temazepam ($P = 0.54$) and zopiclone ($P = 0.98$), zolpidem paradoxically enhanced the genioglossus muscle response to airway closure ($P = 0.03$).^[26] Since hypnotics are typically not recommended in cases of OSA, this is a crucial consideration. The hypothesis states that a reduction in reflex sensitivity should result from neuronal inhibition at the hypoglossal ganglion following GABA activation.^[26]

FALLS AND FRACTURES

Short-term treatments of zolpidem for insomnia have been linked to a higher incidence of falls in hospitalized patients, with an OR of 4.28 ($P < 0.001$).^[18,27] In individuals using zolpidem, the relative risk (RR) for hip fractures was 1.92 (95% CI 1.65-2.24; $P < 0.001$), with hip fractures being the most prevalent kind of fracture.^[18, 28] A recently published meta-analysis that included eight case-controls (OR = 1.53; 95% CI 1.31-1.77) and two cohort studies (OR = 2.10; 95% CI 1.76-2.49) showed a significant correlation between zolpidem and fracture risk, both alone and in combination (OR = 1.63; 95% CI 1.42-1.87). The study's subgroup analysis showed that using z-drugs increased the incidence of fractures when compared to a control group with insomnia (OR = 1.28; 95% CI 1.08-1.53) and even when the group's age was limited to those over 65 (OR = 1.70; 95% CI 1.36-2.12). Furthermore, zolpidem usage was associated with a higher risk of non-specific injury (OR = 2.05; 95% CI 1.95-2.15).^[29, 30]

PREGNANCY OUTCOMES

Zolpidem has been categorized by the FDA as a category C medication due to unfavourable effects on animal fetuses. In population-based research conducted across the country, the frequency of unfavorable pregnancy outcomes was compared between women who used zolpidem during their pregnancy and those who did not. The infant's gender, parity, mother's educational attainment, gestational hypertension, gestational diabetes, pre-eclampsia/eclampsia, and anemia were all corrected for in the control group. Low birth weight (OR = 1.39; $P < 0.001$), preterm delivery (OR 1.49; $P < 0.001$), small for gestational age (SGA)

infants (OR = 1.34; $P < 0.001$), and caesarean births (OR = 1.74; $P < 0.001$) were all more common in the mothers who were exposed to zolpidem. Zolpidem did not substantially raise the risk of congenital malformations (0.48 vs. 0.65%; $P = 0.329$).^[31]

CONCLUSION

The symptoms of insomnia include weariness, being easily distracted, mood swings, low contentment, and a general decline in quality of life. Patients' quality of life can be improved and their return to baseline can be facilitated with optimal treatment. To treat insomnia, a range of modifications to lifestyle and medications are available. These include cognitive behavioral therapy, hypnosis, sleep restriction, benzodiazepines, non-benzodiazepine hypnotics, and patient education about minimizing coffee intake and daytime naps. In addition to cognitive-behavioral therapy, zolpidem is a useful medication for the treatment of insomnia. It does have some negative effects, like any medication, but patients typically find that they are worth it in exchange for an improved quality of life. Due to their slower medication metabolism, elderly people should have their prescription doses reduced.

However, zolpidem is seen as a suitable therapeutic option since, in comparison to other medications, it has a reduced incidence of residual daytime drowsiness and falls. The potential negative effects of using the drug should be addressed to all patients. These effects include fractures and falls, an increased risk of suicide attempts regardless of co-occurring psychiatric conditions, complex behaviors performed in a sleep-like state, dependence and rebound insomnia, obstructive sleep apnea, reductions in attention and verbal memory, and impairment the day afterward. Complex behaviors such as dozing, hallucinations, increased suicidality, driving vehicles while asleep, and even murdering in a few cases have been observed in zolpidem-using individuals. These side effects are frequently the most alarming and widely reported. Doctors should carefully consider the possible advantages and disadvantages of prescribing zolpidem to patients. They should decide whether to prescribe it and how much to prescribe on an individual basis, considering the psychological and psychiatric risks associated with managing insomnia in patients versus those who would benefit from taking zolpidem for the same condition.

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DECLARATION OF CONFLICT OF INTEREST

In response to being an author, doing research, or having the work published, the author(s) showed that they had no conflicts of interest.

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