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# Clinical considerations of sleep related amnestic behaviours associated with zolpidem

## *Aspekty kliniczne zachowań amnestycznych w czasie snu związanych ze stosowaniem zolpidemu*

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**ABSTRACT**

**Objective.** Zolpidem is a non-benzodiazepine agonist of GABA-A receptor indicated for the short-term insomnia treatment. Over the years, there have been reports in literature on zolpidem abuse complications and neuropsychiatric side effects involving headache, dizziness, nightmares, confusion, depression, sleepiness, memory deficits as well as hallucinations, sensory distortions, delirium and sleep-related complex behaviours with anterograde amnesia. The aim of this work is to review and highlight the most serious adverse reactions to zolpidem with emphasis on sleep-related amnestic behaviours. We also focus our attention on common traits, patterns and predisposing factors. This paper refers to zolpidem side effects or complex amnestic behaviours, or sleep related amnestic behaviours presented in literature.

**Literature review.** A comprehensive search of PubMed and Google Scholar was conducted to find relevant studies, case reports and literature reviews addressing the zolpidem use in insomniac patients.

**Conclusions.** Zolpidem may pose a risk for serious adverse reactions most common dose-dependent and associated with age, gender, concurrent use of medications and concomitant comorbidities. If severe adverse reactions occur, the drug should be immediately discontinued or switched to another hypnotic. This review indicates an association between psychotic reactions and complex sleep related behavioural abnormalities in patients using zolpidem alone or in combination with other psychotropic medications. Clinicians should adopt a cautious approach prescribing zolpidem and be alert to possible unusual adverse effects of the drug.

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KEYWORDS

- adverse drug reaction
- zolpidem
- complex amnestic behavior
- sleep related amnestic behavior
- pharmacoepidemiology

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**STRESZCZENIE**

**Cel.** Zolpidem jest niebenzodiazepinowym agonistą receptora GABA-A i ma zastosowanie w leczeniu krótkotrwałej bezsenności. Na przestrzeni lat w literaturze pojawiły się doniesienia o powikłaniach związanych z nadużywaniem zolpidemu oraz o neuropsychiatrycznych działaniach niepożądanych obejmujących bóle i zawroty głowy, koszmary senne, dezorientację, depresję, senność, deficyty pamięci, a także halucynacje, złudzenia, majaczenie oraz złożone zachowania amnestyczne związane ze snem. Celem niniejszej pracy jest przedstawienie i wyróżnienie najistotniejszych reakcji niepożądanych zolpidemu, szczególnie zachowań amnestycznych związanych ze snem, z uwzględnieniem wspólnych cech tych reakcji i czynników predysponujących do ich powstania. Autorzy odnoszą się w swojej pracy do efektów niepożądanych związanych z zolpidemem, złożonych zachowań amnestycznych oraz zachowań amnestycznych związanych ze snem opisywanych w literaturze.

**Przegląd piśmiennictwa.** Autorzy dokonali obszernego przeglądu piśmiennictwa w oparciu o PubMed i Google Scholar pod kątem istotnych badań, opisów przypadków i prac poglądowych obejmujących stosowanie zolpidemu u pacjentów z bezsennością.

**Wnioski.** Zolpidem może wiązać się z ryzykiem wystąpienia poważnych reakcji niepożądanych, najczęściej zależnych od dawki, związanych z wiekiem, płcią, równoczesnym stosowaniem innych leków i schorzeniami towarzyszącymi. W przypadku pojawienia się poważnych działań niepożądanych należy natychmiast odstawić lek lub zastosować inny o działaniu nasennym. W naszej pracy podkreślamy zależność między występowaniem objawów psychotycznych i zaburzeń zachowania związanych ze snem a używaniem zolpidemu, zarówno w połączeniu z innymi lekami psychotropowymi jak i bez nich. Klinicyści powinni z rozwagą zalecać zolpidem i zachować czujność w przypadku wystąpienia nietypowych działań niepożądanych leku.

## Objective

Zolpidem belongs to the "Z-drugs" family and is a non-benzodiazepine agonist of GABA-A receptor indicated for the short-term insomnia treatment. Zolpidem was introduced to the market in 1988 in France and since 1992, it has also been available in the U.S. Zolpidem has been widely prescribed and considered to be safe as well as effective in insomniac patients. Over the years, there have been reports in literature on zolpidem abuse complications and neuropsychiatric side effects involving headache, dizziness, nightmares, confusion, depression, sleepiness, memory deficits and also hallucinations, sensory distortions, delirium and sleep-related complex behaviours with anterograde amnesia. The aim of this work is to review and highlight the most serious adverse reactions to zolpidem with emphasis on sleep-related amnestic behaviours. We also focus our attention on common traits, patterns and predisposing factors. This paper refers to zolpidem side effects or complex amnestic behaviours, or sleep related amnestic behaviours presented in literature.

## Literature review

### Introduction

Zolpidem is a non-benzodiazepine agonist of GABA-A receptor that produces its pharmacological effect by interacting with the GABA-A receptor complex in a fashion similar to the benzodiazepines (Dolder and Nelson 2008; Drover 2004). The drug binds allosterically to the GABA-A receptor enhancing the inhibitory effect of GABA, which results in an influx of chloride ions into neurons and leads to neuronal hyperpolarisation and decreased generation of action potentials. Activation of GABA-A α1 subunit produces sedative, amnestic and motor-impairing effects in central nervous system while activation of α2-, α3- and α5 GABA-A subunits results in anxiolytic, muscle relaxant, and ethanol-potentiating effects.

The mechanism of action of zolpidem differs from BZD in a way that zolpidem exhibits more selective binding to α1 subunit while BZD bind to each of α1-, α2-, α3- and α5subunits. This selectivity of zolpidem explains the lack of typical BZD-actions and adverse effects. The standard oral dose of zolpidem is 10 mg taken at bedtime; lower 5 mg dose is recommended in the elderly or in individuals with hepatic impairment.

Zolpidem is rapidly absorbed after ingestion, with onset of action of approximately 20–30 minutes and average blood serum peak concentration at 90 minutes post-dose (Daley, McNiel and Binder 2011; Gunja 2013). It is approximately 90% protein bound and undergoes extensive hepatic metabolism predominantly by CYP3A4 enzymes. Compared with the majority of BZD hypnosedatives, it has a short half-life, i.e. from two to three hours, shorter duration of action, does not change sleep architecture and provides less residual effects during daytime (Daley, McNiel and Binder 2011).

Since zolpidem has entered the European and U.S. market, it has been widely prescribed and gained popularity as considered to be safe, have milder side effects and lower abuse potential as compared to conventional benzodiazepines. In the American Academy of Sleep

Medicine Clinical Practice Guideline, Zolpidem is one of 8 medications recommended as a treatment for insomnia and is rated in this paper as effective and safe drug (Sateia *et al.* 2017). The number of prescriptions of zolpidem in the U.S. over the period of 2007–2017 fluctuated from over 17 million in 2007 to over 15 million in 2017, with the highest number of over 26 million in 2011 (Kane 2019). As zolpidem appears to be well-tolerated, over the past two decades, there have been reports in the literature on its serious neuropsychiatric side effects and abuse complications.

Recently, attention has been drawn to zolpidem-associated sleep-related complex behaviours. In 2007, FDA issued a strong warning for Z-drugs, including zolpidem, to cause complex behavioural disturbances, such as "sleep-driving." FDA specifically mentioned 13 medications of a high risk of complex behaviours and requested that medication manufactures change the drugs labelling to include new safety warnings (Dolder and Nelson 2008; FDA 2007).

## Adverse drug reactions to zolpidem

The most commonly reported central nervous system side effects of zolpidem involve headache, dizziness, nightmares, confusion, depression, sleepiness and cognitive deficits (Paradis, Siegel and Kleinman 2012). More serious neuropsychiatric adverse reactions include hallucinations, sensory distortions, delirium, amnesia and sleep-related complex behaviours, such as sleep driving, sleep-eating, sleep-cooking, sleep-sex, sleep-conversations and sleepwalking with object manipulation, all of these generally accompanied by anterograde amnesia for the episodes (Daley, McNiel and Binder 2011; Toner *et al.*, 2000).

Post-marketing studies of zolpidem have found the incidence of these adverse effects to be in a range of 1% (Ganzoni *et al.*, 1995) and 5% (Tsai *et al.*, 2009), although one study found it to be higher, i.e. 15.2% (Hwang *et al.*, 2010). It is speculated that various neuropsychiatric reactions, such as hallucinations, amnesia and sleepwalking, may be related to the rapid increase of serum concentrations of zolpidem and may be attributed to a possible toxic effect of the drug on the central nervous system (Inagaki *et al.*, 2010).

Serious neuropsychiatric complications, such as hallucinations and amnesia, were first described in 1992 (Ansseau *et al.*, 1992). The authors reported on two patients with visual hallucinations and amnesia related to zolpidem (Ansseau *et al.*, 1992). Since that time, many patients with similar neuropsychiatric disorders have been reported in the medical literature. Zolpidem-induced hallucinations may be multimodal (Ram, Eiman and Gowdappa 2015), but most often they are of the visual kind and occur when falling asleep or waking up (Wu-Chou and Shen 2012). Common features of reported patients include female sex, prevalence of symptoms well corresponding to the dose escalation, onset of symptoms within 20–30minutes after zolpidem intake, spontaneous resolution of reactions without treatment. In most cases, the events were accompanied by anterograde amnesia (Wu-Chou and Shen 2012). Toner *et al.* (2000) summarised previously reported 17 cases of hallucinations associated with zolpidem treatment. Visual hallucinations were most common (82.4%); most cases (82.4%) occurred in female patients, and concomitant use of antidepressant was noticed in 58.8% of the cases. The underlying cause of hallucinations remains unclear, but it is suggested that they are associated with disruption in GABAergic transmission (Tsai 2003).

## Amnesia

A well-known side effect of zolpidem that is often associated with complex behaviours is transient anterograde amnesia, with prevalence of 1 %. Subsequent amnesia may be total or partial (Dolder and Nelson 2008; Pérez-Díaz, Iranzo and Santamaría 2010) and may exist due to the effect of zolpidem for shortening sleep latency. Successively, that may lead to the inhibition of the consolidation phase of memory formation from short to long term. As a consequence, all events experienced while conscious are of a memory loss. It has to be mentioned that amnesic effect of zolpidem is well corresponding to its dose (Dolder and Nelson 2008; Pérez-Díaz, Iranzo and Santamaría 2010).

Zolpidem was originally considered to have less amnesic potential than conventional BDZ because of the selectivity for α1 subunit of GABA-A receptors, which are relatively absent in the hippocampus, an area in the brain that is important for learning and memory consolidation (Dolder and Nelson 2008). However, studies on memory impairment associated with hypnosedatives have found that zolpidem was much potent to cause impairment in aspects of immediate and delayed memory (Dolder and Nelson 2008). Considering α1 subunit GABA-A receptors implication in amnesia, zolpidem may pose a significant risk for memory impairment for its high binding affinity for α1 subunit GABA-A receptors. However, it is worth to be mentioned that not only high selectivity of zolpidem for α1 subunit implies its amnesic properties, but pharmacokinetics as well.

Zolpidem is a short half-life agent; therefore, all the material that is learned and all events experienced during the peak concentrations of the drug are likely to be followed by loss of memory for the time period. Amnesic effect is reported to occur shortly after zolpidem administration, usually within 30 minutes (Inagaki et al, 2010), is dose-related with 16% frequency at the dose of 10 mg and 21% frequency at a 20 mg dose (Inagaki et al, 2010). The sedation-mediated amnestic character of sleep-related complex behaviours associated with zolpidem often

makes patient's self- reporting of zolpidem effects incomplete (Tsai et al, 2009).

### Sleepwalking

Sleepwalking, together with sleep terrors and confusional arousals, is classified as a Disorder of Arousal, as these behaviours come out of deep sleep following a sudden arousal and are not related to rapid eye movement. This parasomnia generally requires the presence of factors that predispose, prime and precipitate the episodes of sleepwalking (Pressman 2007; Pressman 2011). Sleep deprivation and stress are the most common priming factors while external stimuli, such as noise or touch, are the precipitating factors.

Onset of parasomnias is often reported to be associated with medications as the most often priming factor that depresses the CNS activity. It is speculated that medications may act like sleep deprivation; they may increase slow wave sleep and make it difficult for the sleepwalker to awaken completely when a potential trigger occurs (Pressman 2007; Pressman 2011).

Sleepwalking does not have a well understood pathophysiology and is regarded to be a result of a dissociative state of the brain, occurring in slow wave sleep (N3), in which elements of wakefulness and sleep coexist. The likelihood of sleepwalking and other NREM parasomnias is increased by factors or conditions that increase slow wave sleep (such as sleep deprivation) or cause arousals during slow wave sleep (Poceta 2011; Schenck, Boyd and Mahowald 1997). Concomitant intrinsic sleep disorders, such as Obstructive Sleep Apnea (OSA) or Periodic Limb Movement Disorder (PLMS), may cause arousals from NREM and trigger parasomnias (Schenck, Boyd and Mahowald 1997).

Mendelson (1994) was the first to report on a man sleepwalking after taking zolpidem during a sleep laboratory research study. In the course of polysomnography, a 20-year-old research participant had a typical episode of sleepwalking during deep stage-4 sleep in response to acoustic stimuli caused by the researchers. The research subject was reported to suddenly arouse, get up from the bed and walk around. The patient had no recollection of this incident the next day (Pressman 2011; Mendelson 1994). Since then, repeatedly more reports have been described in the literature, i.e. sleepwalking and writing emails, cleaning the house, doing shopping (Daley, McNiel and Binder 2011; Tsai M, Tsai YH and Huang 2007).

Hoque and Chesson (2009) experienced a case of a 51-year-old female patient who developed sleep-related walking, eating and driving. The patient had no prior family or personal history of sleepwalking or other parasomnias. She was taking 10 mg zolpidem at bedtime, concomitant medications included paroxetine 20 mg per day, metoprolol – 25 mg twice a day, and simvastatin – 40 mg per day. A few weeks after zolpidem was administered, first episode of sleepwalking occurred. Other unusual behaviours included sleep eating, sleep driving, sleep talking, and also one episode of urination in the hallway. The patient had no recollection of the events and all sleep-related activities abruptly ceased when zolpidem was discontinued (Hoque and Chesson 2009).

### Complex amnestic behaviours

Complex behaviours associated with zolpidem include such activities as making phone calls, waxing one's legs, writing emails, cooking, cleaning and even feeding the dog (Pérez-Díaz, Iranzo and Santamaría 2010). One of the zolpidem associated complex behaviours that can be at a high risk of injuries and deaths is sleep-driving. "Sleep-driving" is a term defining bizarre behaviour, describing individuals who while still sleeping or partially awakened, arouse, get out of their beds, get into their cars and drive, often in a manner that is impaired and insecure (Pressman 2011). It is most often referred to as a variant of sleepwalking and classified as a disorder of arousal as occurring from deep sleep following a sudden arousal (Pressman 2007; Pressman 2011).

The first report of zolpidem related driving impairment in the United States was published in 1996. Six cases of impaired driving were described; the drivers had zolpidem present in their blood at therapeutic doses (Pressman 2011). The described impaired drivers' behaviour was characterised by slow, slurred speech, unsteady gait, confusion and disorientation (Pressman 2011). Pressman (2011) draws attention to the fact that sleep-driving as a variant of sleepwalking should be distinguished from impaired driving that is due to misuse or abuse of hypnosedative drugs, such as zolpidem and other z-drugs. "Sleep-driving" and "impaired driving" present different symptoms and neurophysiological basis. Sleep driving episodes present with significant cognitive impairment without equivalent severe impairments of the motor skills (Pressman 2011). In drug-impaired drivers, cognitive functions are impaired as well; however, they are preserved to some degree while physical and motor skills are severely weakened (Pressman 2011). Pressman (2011) suggested a new concept of zolpidem-induced complex behaviours, in which the onset of the episode could be parasomnia, but as the event continues, the sleep-related elements disappear, leaving the person intoxicated.

A large-scale retrospective study amongst Taiwanese patients showed that zolpidem is associated with a high risk of motor vehicle accidents the following day after zolpidem ingestion (Wu-Chou and Shen 2012). Leufkens, Lund and Vermeeren (2009) showed that zolpidem in a dose of 10 mg at bedtime significantly impairs performance in driving tests next day in the morning. At a dose of 7.5 mg, zolpidem has been reported to cause

significant impairment in learning, recall and performance that was dose- and time-dependent (Wu-Chou and Shen 2012; Leufkens, Lund and Vermeeren 2009) (see Table 1).

**Table 1.** Short characteristics of parasomnias

| Short characteristics of parasomnias | |
|---|---|
| **Sleep-walking** | • Incomplete arousal from sleep is a generally accepted pathophysiology<br>• Priming factors: sleep deprivation/stress<br>• Precipitating factors: external stimuli (sound, touch)<br>• Complex behaviours occur during deep sleep, within 1–3 hours after the sleep onset, typically lasting up to 10 minutes<br>• Simple activities (sitting up in bed, walking, cleaning) and complex activities (cooking, driving, violent behaviours, grabbing at hallucinated objects)<br>• Cognitive functions impaired (planning, attention), disorientation, confusion<br>• Motor skills not highly severed<br>• Followed by anterograde amnesia |
| **Sleep-related eating disorder** | • Partial arousals from sleep to ingest food<br>• Usually within 3hours after the sleep onset<br>• Food is typically highly calorific or unusual<br>• Inability to return to sleep without eating<br>• Anterograde amnesia of the episodes<br>• Morning bloating, guilt<br>• Weight gain/poor weight control<br>• Often associated with RLS, PLMD or OSA<br>• Higher female prevalence |
| **Sleep-driving** | • Variant of sleepwalking<br>• Sudden arousal and leaving the bed is followed by driving in an impaired and unsafe manner<br>• May be associated with a high risk of vehicle accidents<br>• Significant impairment in driving tests after 10 mg zolpidem ingestion at bedtime |

## Toxicity and abuse

First large series of zolpidem poisoning cases were reported by Garnier *et al.* (1994), where the toxicity predominantly involved sedation with ingestion of zolpidem up to 1.4 g. Coma, respiratory depression, cardiovascular toxicity or death were rarely reported from zolpidem overdose. Reports of agitation, hallucinations and psychosis were described as well. Zolpidem overdose was more likely to necessitate supportive treatment in intensive care units when co-ingested with other medications, such as psychotropic drugs or over-the-counter cold and flu preparations, or ethanol (Gunja 2013).

In zolpidem overdose, onset of sedation and drowsiness is early, within the first hour of the ingestion and recovery is often complete within several hours (Gunja 2013). Flumazenil, a competitive BZD antagonist, has been shown to reverse the sedative effects of zolpidem. It is noteworthy that although zolpidem was originally marketed as a safe hypnotic with a low abuse potential and therefore not likely to cause tolerance or dependence, thereby withdrawal symptoms, several case reports in medical literature over the past 10 years provide that zolpidem may exert abuse capability, euphoric mood, tolerance and withdrawal manifestations (Cubała and Landowski 2007; Aragona 2000). If zolpidem is administered in high doses, the drug loses its selectivity for α1 GABA-A receptor and therefore produces pharmacological effects that are similar to those of BZD, including dependence and withdrawal symptoms. Rapid discontinuation of zolpidem may cause transient rebound insomnia (Pressman 2011), seizures (Cubała and Landowski 2007), and also hallucinations (Tsai, Huang and Wu 2003). Patients with history of various psychiatric diseases and prior abuse/dependence as well as those of poor compliance are at a high risk of developing zolpidem abuse and should be prescribed any hypnosedatives with a strong caution.

## Risk factors for adverse drug reactions

Recently attention has been drawn to the fact that gender plays an important role in zolpidem side effects and females are more susceptible to develop adverse reactions. Not only are women considered to suffer from insomnia more often than men do (F:M 1,5:1 ratio), but also they are of a better compliance as far as medications are concerned. That may be of a significant importance with female patients taking concomitant drugs that potentially cause pharmacokinetic and pharmacodynamic interactions with zolpidem (Cubała and Wichowicz 2008; Cubała, Landowski and Wichowicz 2008). Endocrine factors have to be mentioned as well as they are the most prominent in drugs metabolised via CYP3A4, probably due to the action of sex hormones.

In vitro studies have indicated that co-incubation of testosterone and zolpidem increases the transformation of zolpidem into its major hydroxylate metabolite; i.e. in females lower plasma concentration of free-testosterone may contribute to lower CYP 3A4 activity and slow biotransformation of CYP3A4 substrates (Cubała and Wichowicz 2008). As zolpidem is extensively metabolised via CYP3A4 mainly, thereby prolonged drug effect may be expected (Drover 2004). Salva and Costa (1995) reported that women had achieved higher zolpidem serum concentrations than men of a similar age when equivalent doses of zolpidem were administered. Serum concentration of zolpidem was 45% higher in young women and 63% higher in elderly female patients (Salva and Costa 1995).

In January 2013, FDA released a safety announcement advising lower than standard zolpidem doses particularly in women (US Food and Drug Administration 2013). Cubała and Gabrielsson (2014) reviewed 47 cases reported

with sleep-related amnestic behaviours due to zolpidem; out of them, 27 were women. In the material covered, women were reported to be having more complex behavioural side effects than men. The authors emphasise the fact that women are more vulnerable to the adverse reactions mentioned above, even at low therapeutic doses (Cubała and Gabrielsson 2014).

Wu-Chou and Shen (2012) studied 15 case reports describing patients with zolpidem induced addiction problems in Taiwan from 2003 to 2011. All reported cases involved female patients and that seems to confirm the susceptibility for zolpidem adverse reactions in women (Wu-Chou and Shen 2012).

Schenck *et al.* (1997) presented the cases of 19 patients with zolpidem-induced SRED. The authors concluded that women who suffered from depressive disorders are more likely to display SRED. In the report of 5 patients with zolpidem-associated sleep related behaviour disorders, 4 of the patients were females suffering from mood disorders; all of them developed zolpidem induced complex behaviours (Pérez-Díaz, Iranzo and Santamaría 2010).

Oral contraceptives influence zolpidem pharmacokinetics; zolpidem clearance is higher and half-life shorter. In female with zolpidem abuse, taking 160–2000 mg zolpidem-dose per day, concomitant oral contraceptives may cause withdrawal symptoms, such as seizure (Cubała and Wichowicz 2008; Salva and Costa 1995).

Somatic comorbidity is another important variable to be mentioned. Both renal insufficiency and hepatic impairment affect zolpidem plasma protein binding, which may cause higher plasma concentrations of the drug; therefore, reduction in initial dose is recommended (Drover 2004). Liver function does contribute significantly to the clearance of zolpidem, considering the large degree of first-pass metabolism of this compound, any decrease in hepatic function may be expected to decrease clearance and thereby prolong drug effect (Drover 2004).

Another fact to be considered is both pharmacokinetic and pharmacodynamic drug-drug interaction with concurrent use of antidepressants, mainly SSRI. Zolpidem is approximately 90% protein bound and a combined use of SSRI with high-protein binding properties, such as paroxetine, may elevate free zolpidem blood levels. Zolpidem may be displaced from the carrying proteins and that may result in the increased risk of zolpidem-related adverse reactions (Inagaki et al, 2010), i.e. co-administration with fluoxetine may increase half-life by 17% and co-administration with sertraline may increase peak concentrations by 43% (Sanofi-Aventis 2014).

Katz (1995) described an adolescent who presented with hallucination and delirium after concomitant use of paroxetine and zolpidem. A different report involved the case of a female who developed visual hallucinations and sensory distortion after taking paroxetine and zolpidem (Inami, Miyaoka and Horiguchi 2004). In both cases psychotic symptoms resolved when zolpidem was discontinued.

Another possible SSRI-zolpidem interaction was that described by Kito and Koga (2006). A female with no prior history of ophthalmic disease presented with visual hallucinations at a dose of fluvoxamine escalated from 50 mg per day to 150 mg per day co-administered with zolpidem at a bedtime (Kito and Koga 2006). Coleman and Ota (2004) reported a case of a 54-year-old male who developed hallucinations that might have been induced by fluoxetine-zolpidem interaction. A possible pharmacodynamic interaction of zolpidem with SSRI (such as sertraline, desipramine, fluoxetine, bupropion or venlafaxine) may lead to persistent zolpidem-related hallucinations. These phenomena were described in five case reports of patients who developed visual hallucinations lasting from 1–7 hours soon after zolpidem ingestion with concomitant antidepressants. In previously published cases, the hallucinations associated with zolpidem lasted up to 30 minutes (Elko, Burgess and Robertson 1998).

Four variables has been suggested to be considered in order to avoid severe neuropsychiatric complications when prescribing zolpidem: (1) female sex – as it is associated with higher serum concentrations of the drug; (2) zolpidem dose – as hallucinations are dose-dependent; (3) malnutrition and all the somatic conditions in which hypoalbuminemia is present; and (4) co-administration of medications that inhibit CYP3A4 hepatic isoenzyme and thereby may cause alterations in the pharmacokinetics of zolpidem (Toner *et al.* 2000).

Likewise interaction of zolpidem with valproic acid had already been described. The authors reported on a 47-year-old male who experienced sleepwalking after taking valproic acid along with zolpidem (Sattar 2003). As both drugs have agonist activity at GABA-A receptor, the additive GABAergic effect of these two agents was hypothesised to cause somnambulism (Sattar 2003). A risk factor to be highlighted and taken into consideration when prescribing zolpidem is a psychosocial determinant. Patients with comorbid psychiatric illnesses, including mental and behavioural disorders of multiple-substance use are more likely to develop deliberate misuse or abuse and dependence after zolpidem intake. Recreational use of high doses of zolpidem, often in combination with alcohol or psychotropic drugs, may cause euphoric mood, hallucinations and decreased anxiety. Concomitant ingestion of zolpidem and other medication, as well as ethanol, often required admission to Intensive Care Units.

From a drug interaction viewpoint, zolpidem may pose a threat of pharmacokinetic and pharmacodynamic drug interaction, inducing psychotic symptoms or complex behaviours, especially when inappropriate use of zolpidem is concerned (see Table 2).

**Table 2.** Risk factors for adverse effects

| Risk factors for adverse effects |
|---|
| 1. Gender: females more susceptible for adverse effects |
| • endocrine factors |
| • oral contraceptives |
| • prevalence of insomnia, mood disorders and addiction to zolpidem in females |
| 2. Somatic comorbidity |
| • renal and/or liver impairment |
| • malnutrition and other conditions with hypoalbuminemia |
| 3. Concomitant use of SSRI, alcohol or other sedating medications, including CYP 3A4 inhibitors (pharmacokinetic and pharmacodynamic interactions) |
| 4. History of prior dependence/abuse of sedating medications (BZD, Z-drugs), alcohol and other psychoactive substances |
| 5. Dose of zolpidem |
| 6. Misuse of zolpidem (dose higher than recommended, time of ingestion) |
| 7. History of various psychiatric disorders |
| 8. History of parasomnia |
| 9. Concomitant sleep disorder (RLS, PLMD, OSA) |
| 10. History of poor-compliance |
| 11. Living alone |

## Conclusions

Zolpidem is very effective in treating short-term insomnia; however, it may carry a risk similar to that presented by conventional BZD.

Sleep-related complex behaviours due to zolpidem have been repeatedly reported in the literature and should be taken into consideration before drug prescription. It is worth mentioning that not only zolpidem has a potential to cause severe adverse effects as mentioned above in the paper. Other hypnotics that belong to the "Z-drug" family or BDZ hypnotics, which may pose a risk for adverse reactions; however, this may be less recognised as they are not frequently and commonly prescribed.

Physicians should be aware of zolpidem-induced potential side effects and undertake certain management strategies to prevent or minimise adverse reactions. This includes evaluation of the cause of insomnia, individual patients' risk factors and clear instructions on proper use of medications (see Table 3). Physicians should raise cautionary measures in patients with parasomnia predisposing factors and comorbid somatic diseases as well as prior history of abuse or dependence, with previous poor compliance.

**Table 3.** Indication for best clinical practice

| Indication for best clinical practice |
|---|
| • Patient's psychoeducation |
| • Proper dosage and proper timing of the dose |
| • Allowing sufficient time in bed (7–8 hours) after zolpidem ingestion |
| • Proper sleep hygiene |
| • Sleep patterns assessment |
| • Risk factors identification (including prior episodes of parasomnias) |
| • Possible interactions assessment (alcohol, nicotine, other chemicals and medications, CYP 3A4 and CYP 2D6 inhibitors) |
| • Regular follow-up and family members questioning about unusual patient's behaviours |
| • Management strategies for zolpidem-associated adverse effects |

To minimise the risk of adverse effects, the medication should be started with a low dose, taken at usual bedtime only and ingested immediately prior to going to bed. Zolpidem should be used at the lowest effective dose and for the shortest duration possible, together with non-pharmacological treatments such as good sleep hygiene and behavioural techniques. If severe adverse reactions occur, the drug should be immediately discontinued or switched to another hypnotic. Clinicians should adopt a cautious approach prescribing zolpidem and be alert to possible unusual adverse effects of the drug. ■

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Authors' contributions / Wkład autorów: AMG – literature search, data analysis and interpretation, information systematizing, conceptual work / zebranie piśmiennictwa, analiza i interpretacja danych, usystematyzowanie informacji, wkład w koncepcję i projekt pracy; JJL – critical review, conceptual work / krytyczne zrecenzowanie pod kątem istotnej zawartości intelektualnej, wkład w koncepcję i projekt pracy; WJC – conceptual work, acceptance of the final manuscript version / wkład w koncepcję i projekt pracy, akceptacja ostatecznej wersji do opublikowania

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