Zolpidem for Insomnia: A Double-Edged Sword. A Systematic Literature Review on Zolpidem-Induced Complex Sleep Behaviors

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ABSTRACT

Background: Being a nonbenzodiazepine, zolpidem is believed to have a favorable side-effect profile and is widely prescribed for insomnia. However, in the past few years, numerous neuropsychiatric adverse reactions, particularly complex sleep behaviors (CSBs), have been reported with zolpidem.

Objective: To conduct a systematic review of zolpidem-associated CSBs.

Data Sources: An electronic search was conducted using MEDLINE, Embase, PubMed, and Cochrane database of systematic reviews to extract relevant articles till July 2020.

Study Eligibility Criteria: Any type of literature article (case report, case series, and observational or interventional study) reporting CSBs associated with zolpidem.

Results: In this review, we present aggregate summarized data from 148 patients presenting with zolpidem-induced CSBs (79 patients from 23 case reports and 5 case series; 69 patients out of 1454 taking zolpidem [4.7%] from three observational clinical studies). Various types of CSBs associated with zolpidem were reported, most common being sleepwalking/somnambulism and sleep-related eating disorder. On causality assessment, around 88% of cases were found to have a probable association with zolpidem.

Limitations: Extraction of data from observational studies and spontaneous reports, due to nonavailability of any randomized controlled trials relevant to the study objective.

Conclusion and Implication of Key Findings: Zolpidem-induced CSBs, although not very common, may develop when the drug is used at therapeutic doses for insomnia. Doctors need to be alert to monitor such adverse effects of zolpidem and exercise caution while prescribing it.

Keywords: Zolpidem, complex sleep behaviors, sleepwalking, parasomnias, somnambulism, sleep-related eating disorder

Key Messages: Zolpidem is one of the widely prescribed drugs for insomnia due to its better safety profile compared to benzodiazepines. However, various neuropsychiatric adverse events like hallucinations, sensory distortions, delirium, parasomnias or complex sleep behaviors (CSBs), amnesia, etc. associated with the use of zolpidem are a matter of serious concern. Health care professionals need to be aware of such adverse events and exercise caution while prescribing the drug.

Zolpidem, an imidazopyridine, was approved by USFDA in 1992 for the short-term treatment of insomnia. It is a rapid and short-acting sedative-hypnotic drug, with only minor anxiolytic, anticonvulsant, and muscle-relaxant properties. Being a nonbenzodiazepine, it is considered to have a favorable side-effect profile, particularly with respect to rebound insomnia, amnesia, and dependence, compared to benzodiazepines. Hence, it is nowadays widely used in clinical practice for the management of insomnia.

Numerous postmarketing studies and case reports have shown an association of zolpidem with various neuropsychiatric adverse events like hallucinations, sensory distortions, delirium, parasomnias or complex sleep behaviors (CSBs), amnesia, etc. A majority of these cases comprise CSBs like somnambulism or...
sleepwalking, sleep driving, sleep eating, sleep cooking, sleep shopping, sleep sex, etc. A literature review published in 2008 identified ten case reports of nonbenzodiazepine receptor agonists induced CSBs involving 17 patients. Out of the 17 patients, 15 had consumed zolpidem, while the other 2 had taken zaleplon and zopiclone, respectively. The incidence of somnambulism associated with zolpidem has been reported as 1% (1 in 96 patients) and 0.3% (7 in 192) in two post-marketing studies conducted in 1988 and 1995, respectively.3,4 CSBs associated with zolpidem have been a focus of attention, particularly after the USFDA requested a label change in 2007. In 2006, substantial media coverage was observed on zolpidem-associated CSBs in conjunction with a class-action lawsuit and the high-profile vehicle collision of Congressman Patrick Kennedy.6 The death of Heath Ledger, a famous Australian actor, falsely implicated to be related to zolpidem use, intensified the controversy surrounding the drug in both the United States and Australia. Furthermore, around 700 reports of impaired driving ability and roadside accidents associated with zolpidem use were received by USFDA, as a result of which the agency recommended addition to the “warnings and precautions” section of zolpidem about CSBs, including sleep driving.5,7 In January 2013, the USFDA released a safety announcement regarding the risk of next-morning cognitive impairment and residual daytime effects with zolpidem. The risk was higher with extended-release (ER) forms of the drug and in females. Later, in May 2013, another recommendation was added to the drug label to avoid driving or other activities requiring mental alertness the day after taking the drug’s ER form.8 In April 2019, based on accumulating data in FDA adverse event reporting system database and medical literature, USFDA added a boxed warning with zolpidem regarding the risk of serious injuries and deaths from CSBs, even at the lowest recommended dose and after just one dose.9 In light of the accumulating data, it was thought prudent to conduct a systematic review on the safety of zolpidem with respect to CSBs when used therapeutically for approved indications in adult patients.

Materials and Methods

Search Strategy and Study Selection

A systematic literature search was conducted using MEDLINE, Embase, PubMed, and Cochrane database of systematic reviews, using keywords “zolpidem,” “complex sleep behaviors,” “nightmares,” “parasomnias,” “sleep eating,” “sleep talking,” “sleep walking,” “somnambulism,” “sleep terror,” and “sleep driving,” to extract all types of relevant articles until July 2020. All the searches used Boolean operators. Two investigators conducted the searches independently, which were later compiled. A manual search was also carried out by going through the reference lists of retrieved articles.

Criteria for Study Inclusion

Publications on zolpidem-associated CSBs, namely nightmares, parasomnias, sleep eating, sleep talking, sleepwalking/somnambulism, sleep terror, etc., were included in the present review. Publications of any type, including case reports, case series, conference abstracts, reviews, observational studies, and clinical trials relevant to the objective of the current review, that is zolpidem-associated CSBs, were included. Articles in languages other than English were also included, provided relevant information could be extracted from the abstract if available in English.

Data Extraction

Data extraction forms were filled to gather information on patient details, the indication for zolpidem use, dose and duration of intake of zolpidem, sleep behavior experienced, the outcome of the event, and any other relevant points.

Quality Assessment

The quality of case reports was assessed using the case report (CARE) guidelines and 13-item checklist.10,11 Each item was assigned a weighted score as 1, 0.5, or 0 for every Yes, Partly, or No recorded response, respectively, and a total score was calculated. Based on percent of the maximal total score, the quality of case reports was classified as excellent (90%–100% score), good (70%–89%), average (50%–69%), or poor (≤49%).12

The case series were assessed for quality using Joanna Briggs Institute (JBI) tool having ten criteria.13

Newcastle Ottawa Scale was used to assess the quality of observational studies.14,15 In this, quality of studies is assessed in the following three domains: (a) “selection,” that is representativeness of the exposed cohort, selection of nonexposed cohort, ascertainment of exposure, absence of outcome of interest at the start of the study; (b) “comparability,” namely comparability of cohorts based on the design or analysis; and (c) “outcome,” namely method of outcome assessment, follow-up long enough for the outcome to occur, and the adequacy of the follow-up of cohorts. A star system is used to assess study quality. Each criterion in selection and outcome domains is allotted 1 star, whereas 2 stars are assigned for comparability, making a total maximum score of 9. Depending on the overall quality score thus obtained, a study can be categorized as of good/fair/poor quality.

Study Outcome

The primary outcome was to evaluate the safety and causality of therapeutically used zolpidem with respect to CSBs in adult patients.

Causality Assessment

The causality of zolpidem with CSBs was ascertained using the WHO causality assessment scale.16

Data Analysis

Data collected were entered in Microsoft Excel and analyzed using descriptive statistics. No specific hypothesis was tested.

Results

Study Selection

During the initial search, 272 hits were obtained using various keywords. Out of 74 articles considered to be potentially eligible, 31 were included in this systematic review (Figure 1). Of these, there were 23 case reports,17–39 five case series,40–44 and three observational studies.45–47

Study Characteristics

Table 1 depicts the characteristics of various literature articles reporting zolpidem-associated CSBs.
Quality of Included Studies

Quality assessment was done for 22 case reports and three case series (full-text articles published in non-English languages in 1 case report and 2 case series). The overall quality of case reports was rated as good (59%) or average (41%). None of the reports fell in excellent or poor category. The adherence of the reports to the individual items of the CARE checklist is depicted in Figure 2; all reports showed adherence to patient information, clinical findings, timeline, therapeutic intervention, and discussion; however, none exhibited adherence for two sub-items, namely patient perspective and informed consent. All but one (appropriate statistical analysis) quality criteria on the JBI tool were adhered to in most case series (Figure 3).

Among observational studies, all the three studies had scores >6 on the Newcastle Ottawa Scale and were, therefore, categorized as of good quality.

### Table 1: Characteristics of Literature Articles Included in the Systematic Review

| S. No. | Article ID | Patient Characteristics | Indication of Zolpidem | Dose, Duration of Intake | Sleep Behavior Experienced | Causality Assessment with Zolpidem/Any Additional Remarks |
|--------|------------|--------------------------|------------------------|--------------------------|----------------------------|----------------------------------------------------------|
| 1.     | Usumoto et al.17 | Male 60 | Insomnia (post herpetic neuralgia) | Data not available (article in Japanese, information extracted from abstract in English language), Abnormal behavior (removed epidural catheter, sleep driving; found dead in a narrow storage water tank 10 km from hospital) | Possible/death as a result of drowning in water tank; thought to have experienced sleep driving to reach the place where found dead. | Not assessable due to insufficient information |
| 2.     | Inagaki et al.18 | Female 15 | Insomnia | 5 mg/d; 2 weeks | Sleep walking | Probable/reaction attributed to be due to interaction between Z and concurrently administered fluvoxamine | Good |
| 3.     | Nzwalo et al.19 | Female 53 | Situational insomnia due to husband’s obstructive sleep apnea (OSA), Sleep-related eating disorder (SRED) | 10 mg /d; 5 years | Sleep eating, drinking, cooking | Probable | Good |
| 4.     | Singh et al.20 | Male 46 | Patient took the drug without prescription | 10 mg daily; few days | Sleep walking | Probable | Good |
| 5.     | Park et al.21 | Male 71 | Insomnia with coexisting OSA and RLS (restless legs syndrome) | – | Sleep-related eating disorder (SRED) | Probable | Good |
| 6.     | Sharma et al.22 | Male 19 | Insomnia | 10 mg at bedtime on as needed basis; few days | Somnambulism (sleep walking) | Probable | Average |

(Table 1 continued)
| S. No. | Article ID | Patient Characteristics | Indication of Zolpidem | Dose, Duration of Intake | Sleep Behavior Experienced | Causality Assessment with Zolpidem/Any Additional Remarks |
|--------|------------|-------------------------|------------------------|--------------------------|---------------------------|----------------------------------------------------------|
| 7.     | Sattar et al. | 47/M Bipolar disorder | 5 mg daily | Somnambulism (condition appeared within 2 days of starting adjunctive valproic acid) | Unlikely/Patient did not experience somnambulism while on zolpidem monotherapy; both dechallenge and rechallenge were positive with valproic acid; case described as a probable interaction between zolpidem and valproic acid leading to somnambulism | Good |
| 8.     | Mendelson | 20/M Participant in a study on sedatives induced alterations in sleep perception and wakefulness | 10 mg; single dose | Sleep walking | Possible | Average |
| 9.     | Hoque et al. | 53/F Insomnia | 10 mg daily; few weeks | Sleep related eating, sleepwalking, and sleep talking | Probable | Good |
| 10.    | Yang et al. | 55/M Insomnia | 10 mg daily; 3 Days | Sleep walking | Probable | Good |
| 11.    | Dang et al. | 45/M Insomnia | 10 mg daily; 10 days | Sleep related eating disorder | Probable | Good |
| 12.    | Doane et al. | 48/M Insomnia | 10 mg 2–3 times/week; 2 years | Sleep driving | Certain/history of similar episode 1 year back after taking 30 mg of zolpidem | Average |
| 13.    | Gibson et al. | 49/M Insomnia | Dose (?) few Weeks | Self-inflicted gunshot wound related to CSBs | Possible/previous history of multiple episodes of sleep walking and sleep eating; no information on management | Average |
| 14.    | Najjar | 46/F Depression and insomnia | 6.25 mg controlled-release; 1 year | Multiple episodes of SRED after 3 weeks of drug intake | Probable | Good |
| 15.    | Kim et al. | 57/F Insomnia | 10 mg daily; 6 months | Compulsive evening eating behavior/SRED | Probable/concomitant intake of diazepam, lorazepam, quetiapine and escitalopram | Good |
| 16.    | Lange | 13/F Insomnia | 10 mg daily; 1 day | Sleep walking | Possible/childhood and family history of sleep walking | Average |
| 17.    | Sansone | 51/F Insomnia | 10 mg daily; 2 months | Somnambulism, sleep eating | Probable | Average |
| 18.    | Siddiqui | 44/F Insomnia | 10 mg daily for 4 years; 15 mg daily at the time of presentation | Sleep walking associated with writing mails | Probable/resolution of symptoms after dose reduction to 10 mg daily | Average |
| 19.    | Yun | 45/M Insomnia and restless legs syndrome | 10 mg twice a week for few weeks | SRED | Probable | Average |
| 20.    | Paulke et al. | 2 patients; (31/M, 43/F) Self-administration | 10 mg tablet single dose | Somnambulism, involuntary self-intoxication, sleep driving and amnesia | Possible/both patients suffered from psychiatric disorders and one patient had depression; possibility of increased risk of CSBs due to concomitant illnesses | Good |
| 21.    | Tsai et al. | 3 patients (all females); age: 34–50 years | Insomnia | 10–15 mg daily | Compulsive behavior (cleaning, uncontrolled eating) with anterograde amnesia | Probable in all patients. | Good |
| 22.    | Chiang et al. | 2 patients; 70–75 years old females | Sleep maintenance difficulty | 12.5 mg zolpidem ER | SRED | Probable/complete recovery after switching to IR formulation of zolpidem | Good |
| S. No. | Article ID | Patient Characteristics | Indication of Zolpidem | Dose, Duration of Intake | Sleep Behavior Experienced | Causality Assessment with Zolpidem/Any Additional Remarks |
|--------|------------|-------------------------|------------------------|--------------------------|--------------------------|--------------------------------------------------------|
| 23.    | Paradis et al.39 | 2 patients; 45/M, 62/F | Insomnia | > 10 mg daily | Noncharacteristic, complex acts of violence associated with total amnesia, both patients killed their spouses. | Possible/No history of aggression prior to killing; concomitant intake of paroxetine in both cases. |
| 24.    | Valiensi et al.40 | 8 patients (6 F, 2M); 32–72 years old | Sleeping disorders | 10 mg daily (7 patients); 12.5 mg daily (1 patient) | Sleep related eating disorder; symptom onset at mean 39.8 days after starting the medication; 1–8 nocturnal eating episodes per night | Probable (Article in Spanish; information extracted from abstract in English language) |
| 25.    | Pérez-Díaz et al. | 5 patients (M, 4F); Age: 27-79 years | Insomnia | Data not available | Sleep walking (telephoning, house cleaning, feeding the dog or waxing their legs); Inappropriate feeding behavior with excessive food intake during the night and weight gain in all | Probable (Article in Spanish; information extracted from abstract in English language) |
| 26.    | Morgenthaler et al.42 | 5 patients (3M, 2F); Age: 54–67 years | Insomnia | Data not available | Amnestic nocturnal eating episodes | Probable |
| 27.    | Poceta43 | 8 clinical patients (4M, 4F); 28–65 years old; 6 legal cases (4M, 2F); 33–54 years old | Insomnia (3), daytime ingestion for headache (1), accidental daytime ingestion (4), Insomnia (6 legal cases) | 5–20 mg daily 10–31.25 mg daily | Automatism, confusion, amnesia, inebriation, sleep driving, sleep walking, sleep Eating | Probable in all cases |
| 28.    | Schenck et al.44 | 19 patients (3M, 16 F); Age: 17–78 years | Persistent insomnia | 10–20 mg daily | Amnestic sleep related eating disorder (SRED) | Probable in all patients/concomitant intake of antidepressants and other drugs for psychiatric or medical disorders in most patients; family history of zolpidem induced SRED in 1 patient; history of "nocturnal eating syndrome" in 1 patient. |
| 29.    | Chen et al.45 (Case control Study) | 40 patients (37 on zolpidem, 3 on zopiclone) (17 M, 23 F); Age: 42±13.86 years | Insomnia | Average dose: 10 mg/day | Antegrade amnesia (20), eating (11), somnambulism (4), excitement/talkativeness (2), others like dizziness (3) | Patients reporting CSBs were younger compared to those not having CSBs (34.2 versus 39.3 years) |
| 30.    | Hwang et al.46 (retrospective cross-sectional pilot study) | 19 patients | Insomnia | – | Somnambulism with object manipulation, sleep-related eating, and other amnestic sleep-related behaviors | Patients with CSBs as compared to those without CSBs were significantly more likely to be younger, females, taking a higher dose of zolpidem (> 10 mg/d) and not going to sleep immediately after taking zolpidem |
| 31.    | Tsai et al.47 (retrospective survey) | 13 patients (6M, 7F); Age: 42.5±17.1 years | Insomnia | Average dose: 10 mg/day | Watching television (3), using telephone (3), sleep walking (1), mixed behaviors (4) | Patients with CSBs had intake of lower doses of zolpidem compared to those without CSBs. |

CARE: case report. SRED: sleep related eating disorder, ER: extended release, CSBs: complex sleep behaviors.
Study Outcomes

Table 2 enlists various types of CSBs reported with zolpidem in the literature.

Case Reports and Case Series. Out of a total of 79 cases, 49 (61%) were females. The majority of the cases occurred in the age group of 36–64 years, with a relatively lesser incidence in the extremes of age. The most common types of CSBs reported were sleep-related eating disorder (SRED) and somnambulism/sleepwalking.

Observational Studies. In a case-control study, Chen et al. reported an incidence of 3.27% (37/1132 patients) of CSBs with zolpidem in nonpsychotic patients. No significant association with older age or sex was observed; the incidence of CSBs was, in fact, higher in younger patients.45 Hwang et al. reported 28.3% incidence of CSBs with zolpidem (19/67 patients), with the more affected groups being younger patients, females, patients taking a higher dose of zolpidem, and patients not sleeping immediately after the drug intake. A higher dose of zolpidem (>10 mg/day) was concluded as a key risk predictor for CSBs.46 Tsai et al. reported a 5.1% incidence (13 out of 255 patients) of CSBs associated with zolpidem use in Taiwanese patients. No significant association was observed with age, gender, or concomitant diseases.47 Combining the data from the three observational studies, we obtained a 4.7% (69/1454) incidence of zolpidem-associated CSBs.

Causality Assessment

Among the included case reports and case series, the causality association of zolpidem with CSBs was ascertained as mainly probable (69/79, 88%) and possible (8, 10%). Very few reports had certain (1, 1%) and unlikely (1, 1%) causal association with zolpidem intake.

Discussion

Various types of CSBs have been reported with zolpidem. Major variables identified as risk factors for zolpidem-induced CSBs are female sex, advanced age, and >10 mg daily dose.48 A higher incidence of CSBs in females was reported in case reports (more than 60%) and a cross-sectional study.46 One possible explanation is the slower elimination of the drug in females, based on
which USFDA has recommended a 50% dose reduction in females. Chen et al., however, did not observe a similar pattern of occurrence of CSBs. In another study, Greenblatt et al. concluded that the lesser dose recommendation in women needs scientific evidence and may, in fact, lead to underdosing and inadequate treatment of insomnia in women.

This review found very few cases of CSBs reported in the elderly. Hence, there is a lack of evidence on advanced age as a risk factor for zolpidem-induced CSBs.

Dose relatedness of zolpidem-associated CSBs has been hypothesized. At low doses, zolpidem exhibits selective binding to the α1-subunit of GABA_A receptor, which is responsible for its hypnosedative and amnesic properties. At higher doses (>10 mg), the drug displays additional binding to α2, α3, and δ5 subunits (like benzodiazepines), leading to pharmacological effects and complex behaviors as noted with benzodiazepines. Chen et al. reported that a higher dose of zolpidem (>10 mg daily) was associated with CSBs in only adult patients (20–55 years) and not in older adults (>65 years); alcohol consumption was also observed as a risk factor. Nevertheless, there is an imminent demand for evidence-based medicine to ascertain the association of such neuropsychiatric adverse events with dose and blood concentration levels of zolpidem.

Some role of drug interactions has also been implicated in increasing the risk of CSBs with zolpidem. Since zolpidem is mainly metabolized by CYP3A4, concomitant administration of CYP3A4 inhibitors may increase the risk of CSBs with zolpidem. Paradis et al. reported two cases of zolpidem-associated homicide. Both the patients were concomitantly taking paroxetine, and it was hypothesized that, being highly protein-bound, SSRIs like paroxetine might cause displacement reactions and elevate blood levels of free zolpidem. Apart from pharmacokinetic interactions, pharmacodynamic drug interactions (concomitant administration of two or more GABAergic agents) may also increase the risk of CSBs with zolpidem. Sattar et al. reported somnambulism in a 47-year-old male taking valproate and zolpidem. Valproic acid has agonistic activity at GABA_A receptor, and the additive GABAergic effect of zolpidem and valproate was postulated to be the cause of somnambulism. Valproate, in addition, has pharmacokinetic interaction with zolpidem by virtue of its CYP-inhibiting property.

The pathophysiology of zolpidem-induced CSBs remains unclear. A postulated hypothesis is that after taking zolpidem, a patient may inadvertently or intentionally remain awake and experience disinhibited behaviors or hallucinations, with associated amnesia. Another possible explanation is that there is a partial arousal of sleep under the influence of the drug, during which the nocturnal event occurs, with no subsequent recall due to the associated amnesia. A mechanism hypothesized for zolpidem-induced somnambulism is the suppression of REM sleep and increased duration of slow-wave sleep, serving as a predisposing factor for somnambulism. It has been suggested that zolpidem produces a physiologic state during slow-wave sleep that manifests clinically as somnambulism. An increased susceptibility for zolpidem-induced somnambulism has also been suggested in subjects with a history of sleepwalking during childhood. There is also the “theory of cerebral pattern generators (CPGs),” which are postulated to be neuronal collections in the central nervous system and have a role in controlling innate motor behaviors like walking, driving, eating, etc. It is hypothesized that diffuse binding of zolpidem in the cortex releases CPGs, leading to disorders of arousal such as sleepwalking, driving, and sleep episodes.

A "serotonergic model" for hypnosisedative-induced CSBs has also been proposed. Accordingly to this, increased activity of serotonergic neurons in the dorsal raphe nuclei is associated with short periods of microarousals during slow-wave sleep. The binding of hypnosedatives to GABA_A causes an initial activation of the receptors, followed by their desensitization. As a result of the desensitization, the spontaneously firing serotonergic neurons display a postinhibitory rebound phenomenon, causing a transient increase in serotonergic activity, which in turn manifests as an overt behavioral reaction. Later, autoregulatory mechanisms lead to a compensatory decrease in the serotonin release, which is responsible for the termination of the serotonin-dependent behavior. Hence, the time window for CSBs comprises the delay between the GABA_A receptors’ desensitization and the compensatory decrease in the serotonin levels. Factors like individual variability in receptor desensitization, serotonin autoregulatory mechanism, and drug pharmacokinetics may determine the risk of developing CSBs. For example, if the concentration of a hypnosedative drug is very low during the time window for CSBs, there is an increased serotonergic activity due to persistent receptor desensitization, leading to CSBs. On the other hand, higher drug concentration during this period may surpass the receptor desensitization and suppress serotonergic neurons, preventing CSBs. Hence, the ER formulation of zolpidem, producing a higher drug concentration during the 3–6 hours postadministration period, is assumed to be associated with a lower incidence of CSBs. In our literature search, we observed only four cases of CSBs associated with the ER formulation of zolpidem. Chiang et al. reported SRED associated with ER preparations of zolpidem in two elderly females. Both the patients had been taking the immediate-release (IR) form of the drug (10 mg daily) for a few years; due to inadequate sleep maintenance, they were shifted to the ER form of zolpidem (12.5 mg daily), after which they developed amnestic SRED. In both patients, the condition totally resolved after switching back to the IR form of the drug. A possible explanation for such behavior, as given by the authors, is the higher peak blood levels and greater blood levels achieved later in the night with the ER formulation. This, however, contradicts the hypothesis explained by the serotonergic model. The evidence for an association of zolpidem-induced CSBs with the formulation of the drug, hence, needs to be substantiated by a systematic comparison between ER and IR forms of the drug.

Limitations

A major limitation of our review is the extraction of data from observational studies and spontaneous reports, due to the nonavailability of any randomized controlled trials relevant to the study objective. Due to the lack of any data on the number of patients exposed, the
exact incidence of zolpidem-associated CSBs could not be commented upon. Also, there is a paucity of clinical information on concomitant disorders, such as epilepsy, restless legs syndrome, depression, and dementia, which may also be associated with such neuropsychiatric adverse events. Information on concurrent consumption of alcohol and other recreational or illicit substances, too, is especially crucial because of their potential interference with sleep architecture.

Conclusion

The presence of a clear causal association of zolpidem with CSBs, when used therapeutically, demands the need for physicians and healthcare professionals to be vigilant while prescribing this drug. Certain risk factors, including female sex, advanced age, a higher dose of the drug, and the possibility of drug interactions, need to be duly considered to reduce the incidence of such adverse behaviors. Also, well-designed prospective randomized clinical trials need to be planned to provide quality evidence in this direction.

Declaration of Conflicting Interests

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References

1. Holm KJ and Goa KL. Zolpidem: an update of its pharmacology, therapeutic efficacy and tolerability in the treatment of insomnia. Drugs 2000; 59(4): 865–889.
2. Dolder CR and Nelson MH. Hypnosedative-induced complex behaviours: incidence, mechanisms and management. CNS Drugs 2008; 22: 1021–1036.
3. Sauvanet JP. Imidazopyridines in sleep disorders. In: Sauvanet JP, Lager SZ, and Morossi PL (eds) Imidazopyridines in sleep disorders: a novel experimental and therapeutic approach. New York: Raven Pr, 1988, pp. 219–230.
4. Ganzoni E, Santoni J P, Chevillard V, et al. Zolpidem in insomnia: a 3-year post-marketing surveillance study in Switzerland. J Int Med Res 1995; 23: 61–73.
5. Ben-Hamou M, Marshall N S, Grunstein R R, et al. Spontaneous adverse event reports associated with zolpidem in Australia 2001–2008. J Sleep Res 2011; 20: 559–568.
6. Wong C K, Marshall N S, Grunstein R R, et al. Spontaneous adverse event reports associated with zolpidem in the United States 2003–2012. J Clin Sleep Med 2017; 13(2): 223–234.
7. US Food and Drug Administration. FDA requests label change for sleep disorder drug products. 2013. https://www.fda.gov/bbs/topics/NEWS/2007/NEW01587.html. Accessed May 17, 2020.
8. FDA Questions and Answers. Risk of next-morning impairment after use of insomnia drugs: FDA requires lower recommended doses for certain drugs containing zolpidem (Ambien, Ambien CR, Edluar, and Zolpimist). 2018. https://www.fda.gov/drugs/drugsafety-and-availability/questions-and-answers-risk-next-morning-impairment-after-use-insomnia-drugs-fda-requires-lower. Accessed May 17, 2020.
9. FDA Drug Safety Communication. FDA adds boxed warning for risk of serious injuries caused by sleepwalking with certain prescription insomnia medicines. 2019. https://www.fda.gov/drugs/drugsafety-and-availability/fda-adds-boxed-warning-risk-serious-injuries-caused-sleepwalking-certain-prescription-insomnia. Accessed May 20, 2020.
10. Gagnier JJ, Kienle G, Altman DG, et al. The CARE guidelines: consensus-based clinical case report guideline development. J Diet Suppl 2013; 10(4): 381–390.
11. CARE Case Report Guidelines Checklist [Internet]. CARE Group (IMI LLC); 2018. http://www.care-statement.org/resources/checklist. Accessed November 26, 2020.
12. Ravi R, Mulkalwar A, Thatte UM, and Gogtay NJ. Medical case reports published in PubMed-indexed Indian journals in 2015: adherence to 2013 CARE guidelines. Ind J Med Ethics 2018; 3(3): 192–195.
13. Munns Z, Barker TH, Moola S, et al. Methodological quality of case series studies: an introduction to the JBI critical appraisal tool. JBI Database System Rev Implement Rep 2019; 17(0): 1–7.
14. Newcastle–Ottawa quality assessment scale case control studies. http://www.ohri.ca/programs/clinical_epidemiology/ nosgen.pdf. Accessed November 26, 2020.
15. The modified Newcastle Ottawa scale for cross sectional studies. https://journals.
self-injury: a shot in the dark. Psychosomatics 2011; 52: 88–91.

30. Najjar M. Zolpidem and amnestic sleep related eating disorder. J Clin Sleep Med 2007; 3(6): 637–638.

31. Kim HK, Kwon JT, Baek J, et al. Zolpidem-induced compulsive evening eating behavior. Clin Neuropharmac 2013; 36: 173–174.

32. Lange C L. Medication associated somnambulism. J Am Acad Child Adolesc Psychiatry 2005; 44 (3): 211–212.

33. Sonsante L A. Zolpidem, somnambulism, and nocturnal eating. Gen Hosp Psychiatry 2008; 30: 90–91.

34. Siddiqui F, Osuna E, and Chokroverty S. Writing emails as part of sleepwalking after increase in zolpidem. Sleep Med 2009; 10: 262–264.

35. Yun CH and Ji KH. Zolpidem-induced sleep-related eating disorder. J Neurol Sci 2010; 288: 200–201.

36. Paulke A, Wunder C, and Toennes SW. Sleep self-intoxication and sleep driving as rare zolpidem-induced complex behaviour. Int J Legal Med 2015; 129(1): 85–88.

37. Tsai MJ, Tsai YH, and Huang YB. Compulsive activity and antero-grade amnesia after zolpidem use. Clin Toxicol 2007; 45: 179–181.

38. Chiang A and Krystal A. Report of two cases where sleep related eating behavior occurred with the extended-release formulation but not the immediate-release formulation of a sedative-hypnotic agent. J Clin Sleep Med 2008; 4(2): 155–156.

39. Paradis CM, Siegel LA, and Kleinman SB. Two cases of zolpidem-associated homicide. Prim Care Companion CNS Disord 2012; 14(4): PCC.12br01361.

40. Valensi SM, Cristiano E, Martínez OA, et al. Sleep related eating disorders as a side effect of zolpidem. Medicina (B Aires) 2010; 70(3): 223–226.

41. Pérez-Díaz H, Iranzo A, and Santamaría J. Zolpidem-induced sleep-related behavioural disorders. Neurology 2010; 25(8): 491–497.

42. Morgenthaler TI and Silber MH. Amnestic sleep-related eating disorder associated with zolpidem. Sleep Med 2002; 3(4): 323–327.

43. Poceta JS. Zolpidem ingestion, automatisms, and sleep driving: a clinical and legal case series. J Clin Sleep Med 2011; 7(6): 652–658.

44. Schenck C, Connoy D, Castellanos M, et al. Zolpidem induced amnestic sleep-related eating disorder in 19 patients. Sleep 2005; 28: A259 Abstract supplement.

45. Chen L, Lin C, Chou Y, et al. A comparison of complex sleep behaviors with two short-acting Z-hypnosedative drugs in nonpsychotic patients. Neuropsychiatr Dis Treat 2013; 9: 1159–1162.

46. Hwang T, Ni H, Chen H, et al. Risk predictors for hypnosedative-related complex sleep behaviors: a retrospective, cross-sectional pilot study. J Clin Psychiatry 2010; 71(10): 1331–1335.

47. Tsai J, Yang P, Chen C, et al. Zolpidem-induced amnesia and somnambulism: rare occurrences? Eur Neuropsychopharmacol 2009; 19(1): 74–76.

48. Salva P and Costa J. Clinical pharmacokinetics and pharmacodynamics of zolpidem: therapeutic implications. Clin Pharmacokinet 1995; 29: 142–153.

49. Greenblatt DJ, Harmatz JS, and Roth T. Zolpidem and gender: are women really at risk? J Clin Psychopharmacol 2015; 39(3): 189–199.

50. Huang MC, Lin HY, and Chen CH. Dependence on zolpidem. Psychiatry Clin Neurosci 2007; 61: 207–208.

51. Chen CS, Huang MF, Hwang TJ, et al. Clinical correlates of zolpidem-associated complex sleep-related behaviors: age effect. J Clin Psychiatry 2014; 75(11): e1314–1318.

52. Feinberg I, Maloney T, and Campbell IG. Effects of hypnotics on the sleep EEG of healthy young adults: new data and psycho-pharmacologic implications. J Psychiatr Res 2000; 34: 423–438.

53. Nicholson AN and Pascoe PA. Hypnotic activity of an imidazo-pyridine (zolpidem). Br J Clin Pharmacol 1986; 21: 205–211.

54. Tassinari C A, Rubboli G, Gardella E, et al. Central pattern generators for a common semiology in fronto-limbic seizures and in parasomnias: a neuroethologic approach. Neurol Sci 2005; 26 (Suppl 3): s225–s232.

55. Yuste R, MacLean JN, Smith J, et al. The cortex as a central pattern generator. Nature Rev 2005; 6: 477–483.

56. Juszczak G. R. Desensitization of GABAergic receptors as a mechanism of zolpidem-induced somnambulism. Med Hypotheses 2011; 77: 230–233.