

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

Niti Mittal<sup>1</sup> , Rakesh Mittal<sup>1</sup>, M. C. Gupta<sup>1</sup>

## 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 a 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

behaviours (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.<sup>1</sup>

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

<sup>1</sup>Dept. of Pharmacology, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India.

**HOW TO CITE THIS ARTICLE:** Mittal N, Mittal R, M. C. Gupta. Zolpidem for Insomnia: A Double-Edged Sword. A Systematic Literature Review on Zolpidem-Induced Complex Sleep Behaviors. *Indian J Psychol Med.* 2021;43(5):373–381.

**Address for correspondence:** Niti Mittal, Dept. of Pharmacology, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana 124001, India. E-mail: drniti.mittal@gmail.com

**Submitted:** 28 Nov. 2020  
**Accepted:** 11 Jan. 2021  
**Published Online:** 09 Mar. 2021



Copyright © The Author(s) 2021

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution- NonCommercial 4.0 License (<http://www.creativecommons.org/licenses/by-nc/4.0/>) which permits non-Commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

**ACCESS THIS ARTICLE ONLINE**  
Website: [journals.sagepub.com/home/szj](http://journals.sagepub.com/home/szj)  
DOI:10.1177/0253717621992372

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.<sup>2</sup> 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.<sup>3,4</sup>

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.<sup>5</sup> 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.<sup>6,7</sup>

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.<sup>8</sup> 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.<sup>9</sup>

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.<sup>10,11</sup> 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 ( $\leq 49\%$ ).<sup>12</sup>

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

Newcastle Ottawa Scale was used to assess the quality of observational studies.<sup>14,15</sup> 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.<sup>16</sup>

### Data Analysis

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

## Results

### Study Selection

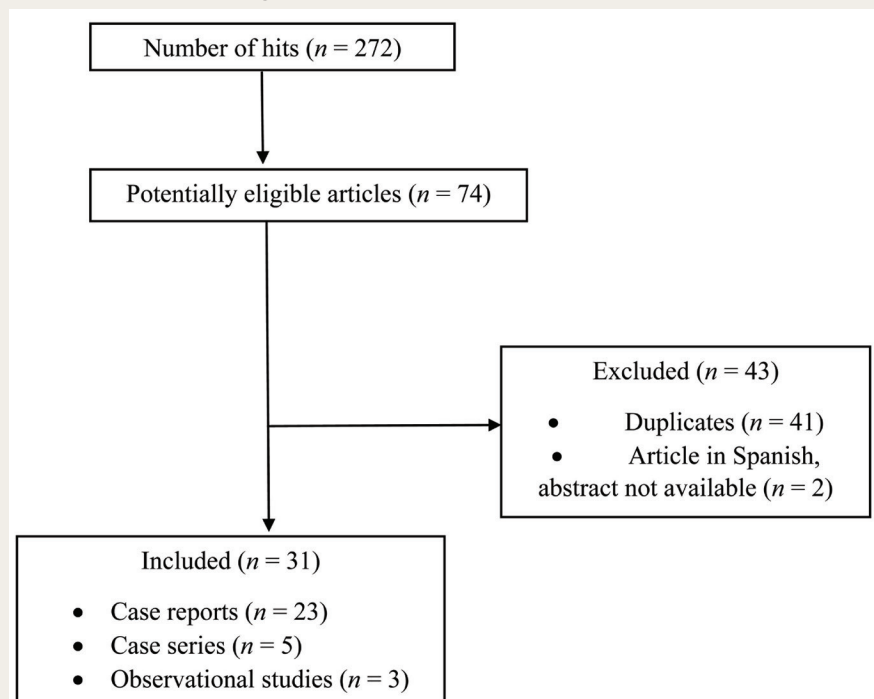
During the initial search, 272 hits were obtained using various keywords. Out of 74 articles considered to be potentially eligible, 31 were included in this systematic review (**Figure 1**). Of these, there were 23 case reports,<sup>17–39</sup> five case series,<sup>40–44</sup> and three observational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

### Study Characteristics

**Table 1** depicts the characteristics of various literature articles reporting zolpidem-associated CSBs.

FIGURE 1.

## Flowchart Depicting the Study Selection Process



## 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<sup>17</sup> and 2 case series<sup>39,41</sup>). 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 JBIs 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
Case reports						
1.	Usumoto et al. <sup>7</sup>	60/M	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.
2.	Inagaki et al. <sup>18</sup>	15/F	Insomnia	5 mg/d; 2 weeks	Sleep walking	Probable/reaction attributed to be due to interaction between Z and concurrently administered fluvoxamine
3.	Nzwalo et al. <sup>19</sup>	53/F	Situational insomnia due to husband's obstructive sleep apnea (OSA).	10 mg /d; 5 years	Sleep eating, drinking, cooking	Probable
4.	Singh et al. <sup>20</sup>	46/M	Patient took the drug without prescription	10 mg daily; few days	Sleep walking	Probable
5.	Park et al. <sup>21</sup>	71/M	Insomnia with coexisting OSA and RLS (restless legs syndrome)	–	Sleep-related eating disorder (SRED)	Probable
6.	Sharma et al. <sup>22</sup>	19/M	Insomnia	10 mg at bedtime on as needed basis; few days	Somnambulism (sleep walking)	Probable

(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. <sup>23</sup>	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 <sup>24</sup>	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. <sup>25</sup>	51/F	Insomnia	10 mg daily; few weeks	Sleep related eating, sleepwalking, and sleep talking	Probable	Good
10.	Yang et al. <sup>26</sup>	55/M	Insomnia	10 mg daily; 3 Days	Sleep walking	Probable	Good
11.	Dang et al. <sup>27</sup>	45/M	Insomnia	10 mg daily; 10 days	Sleep related eating disorder	Probable	Good
12.	Doane et al. <sup>28</sup>	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. <sup>29</sup>	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 <sup>30</sup>	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. <sup>31</sup>	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 <sup>32</sup>	13/F	Insomnia	10 mg daily; 1 day	Sleep walking	Possible/childhood and family history of sleep walking	Average
17.	Sansone <sup>33</sup>	51/F	Insomnia	10 mg daily; 2 months	Somnambulism, sleep eating	Probable	Average
18.	Siddiqui <sup>34</sup>	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 <sup>35</sup>	45/M	Insomnia and restless legs syndrome	10 mg twice a week for few weeks	SRED	Probable	Average
20.	Paulke et al. <sup>36</sup>	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. <sup>37</sup>	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. <sup>38</sup>	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

(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	
23.	Paradis et al. <sup>39</sup>	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.	Average
Case series							
S. No.	Article ID	Patient Characteristics	Indication of Zolpidem	Dose, Duration of Intake	Sleep Behavior Experienced	Causality Assessment with Zolpidem/Any Additional Remarks	
24.	Valiensi et al. <sup>40</sup>	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. <sup>41</sup>	5 patients (1M, 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.	Morgen-thaler et al. <sup>42</sup>	5 patients (3M, 2F); Age: 54–67 years	Insomnia	Data not available	Amnestic nocturnal eating episodes	Probable	
27.	Poceta <sup>43</sup>	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. <sup>44</sup>	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.	
Observational studies							
29.	Chen et al. <sup>45</sup> (Case control Study)	40 patients (37 on zolpidem, 3 on zopiclone) (17 M, 23 F); Age: 4.2±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. <sup>46</sup> (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. <sup>47</sup> (retrospective survey)	13 patients (6M, 7F); Age: 42.5±17.1 years	Insomnia	Average dose: 10 mg/day	Watching television (3), using telephone (5), 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.

FIGURE 2.

**Percentage Adherence to Individual Subitems of CARE Checklist Among the Included Case Reports**

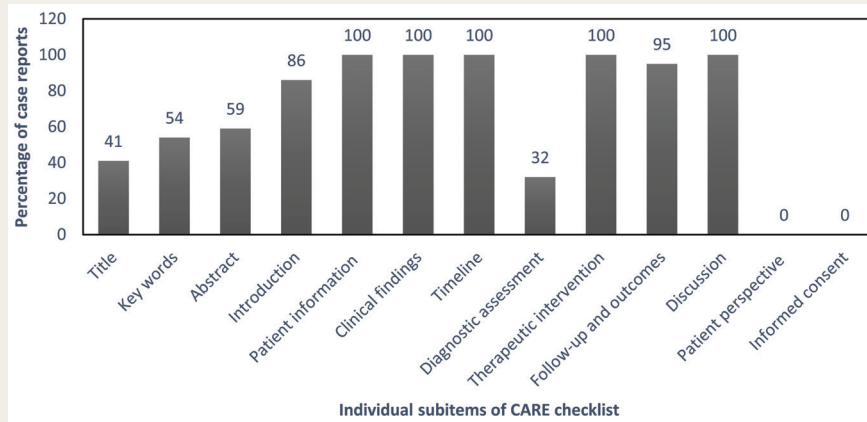


FIGURE 3.

**Adherence to Various Criteria of JBLs Tool Among the Included Case Series**

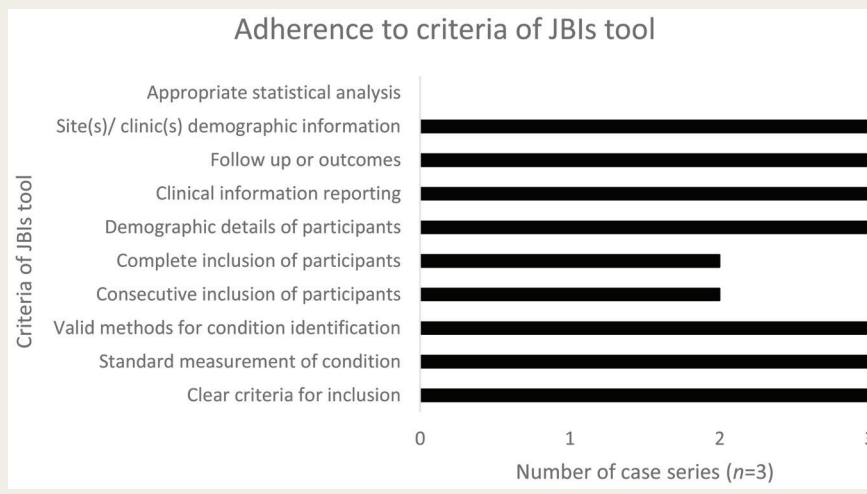


TABLE 2.

**Types of Complex Sleep Behaviors Reported with Zolpidem in Literature**

Type of CSB	Reference No. of Literature Article
Sleep driving	15, 26, 34, 41
Sleep walking/somnambulism	16, 18, 20–24, 30–32, 34, 39, 41, 43–45
Sleep eating/drinking, SRED	17, 19, 23, 25, 28, 29, 31, 33, 36, 38, 40–44
Sleep cooking	17
Sleep talking	23, 43, 39
Compulsive behavior	35
CSB related self-injury	15, 27, 34
Violent acts	37
Mixed behaviors	39, 41, 43, 45

CSBs: complex sleep behaviors, SRED: sleep-related eating disorder.

**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.<sup>45</sup> 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.<sup>46</sup> 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.<sup>47</sup> 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.<sup>48</sup>

A higher incidence of CSBs in females was reported in case reports (more than 60%) and a cross-sectional study.<sup>46</sup> 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.<sup>45</sup> 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.<sup>49</sup>

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  $\alpha_1$  subunit of GABA<sub>A</sub> receptor, which is responsible for its hypno-sedative and amnesic properties. At higher doses (>10 mg), the drug displays additional binding to  $\alpha_2$ ,  $\alpha_3$ , and  $\alpha_5$  subunits (like benzodiazepines), leading to pharmacological effects and complex behaviors as noted with benzodiazepines.<sup>45,50</sup> 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 ( $\geq 65$  years); alcohol consumption was also observed as a risk factor.<sup>51</sup> 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.<sup>48</sup> Paradis et al. reported two cases of zolpidem-associated homicide.<sup>39</sup> 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.<sup>23</sup> Valproic acid has agonistic activity at GABA<sub>A</sub> 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.<sup>5</sup> Another possible explanation is that there is a partial arousal from sleep under the influence of the drug, during which the nocturnal event occurs, with no subsequent recall due to the associated amnesia.<sup>25</sup> A mechanism hypothesized for zolpidem-induced somnambulism is the suppression of REM sleep<sup>52</sup> and increased duration of slow-wave sleep, serving as a predisposing factor for somnambulism.<sup>53</sup> It has been suggested that zolpidem produces a physiologic state during slow-wave sleep that manifests clinically as somnambulism.<sup>22</sup> An increased susceptibility for zolpidem-induced somnambulism has also been suggested in subjects with a history of sleepwalking during childhood.<sup>24</sup> 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, SRED, and sleep driving.<sup>54,55</sup>

A “serotonergic model” for hypno-sedative-induced CSBs has also been proposed.<sup>56</sup> According 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 hypno-sedatives to GABA<sub>A</sub> 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<sub>A</sub> 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 hypno-sedative 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.<sup>56</sup> In our literature search, we observed only four cases of CSBs associated with the ER formulation of zolpidem. Chiang et al.<sup>38</sup> 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 amnesic 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

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

## ORCID iD

Niti Mittal  <https://orcid.org/0000-0001-7209-098X>

## References

- 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.
- Dolder CR and Nelson MH. Hypnosedative-induced complex behaviours: incidence, mechanisms and management. *CNS Drugs* 2008; 22: 1021–1036.
- Sauvanet JP. Imidazopyridines in sleep disorders. In: Sauvanet JP, Lager SZ, and Morselli PL (eds) *Imidazopyridines in sleep disorders: a novel experimental and therapeutic approach*. New York: Raven Pr, 1988, pp. 219–230.
- 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.
- 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.
- 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.
- US Food and Drug Administration. FDA requests label change for sleep disorder drug products. 2013. [www.fda.gov/bbs/topics/NEWS/2007/NEW01587.html](http://www.fda.gov/bbs/topics/NEWS/2007/NEW01587.html). Accessed May 17, 2020.
- 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/drug-safety-and-availability/questions-and-answers-risk-next-morning-impairment-after-use-insomnia-drugs-fda-requires-lower>. Accessed May 17, 2020.
- 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/drug-safety-and-availability/fda-adds-boxed-warning-risk-serious-injuries-caused-sleepwalking-certain-prescription-insomnia>. Accessed May 20, 2020.
- 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.
- CARE Case Report Guidelines Checklist [Internet]. CARE Group (IMI LLC); 2018. <http://www.care-statement.org/resources/checklist>. Accessed November 26, 2020.
- 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.
- Munn 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.
- Newcastle–Ottawa quality assessment scale case control studies. [http://www.ohri.ca/programs/clinical\\_epidemiology/nosgen.pdf](http://www.ohri.ca/programs/clinical_epidemiology/nosgen.pdf). Accessed November 26, 2020.
- The modified Newcastle Ottawa scale for cross sectional studies. <https://journals.plos.org/plosone/article/file?type=supplementary&id=info:doi/10.1371/journal.pone.0136065.s004>. Accessed November 26, 2020.
- The use of the WHO-UMC system for standardised case causality assessment. [https://www.who.int/medicines/areas/quality\\_safety/safety\\_efficacy/WHOCausality\\_assessment.pdf](https://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOCausality_assessment.pdf). Accessed November 26, 2020.
- Usamoto Y, Kudo K, Sameshima N, et al. An autopsy case of abnormal behaviour induced by zolpidem. *Fukuoka Igaku Zasshi* 2015; 106(6): 202–205.
- Inagaki T, Miyaoka T, Tsuji S, et al. Adverse reactions to Zolpidem: case reports and a review of the literature. *Prim Care Companion J Clin Psychiatry* 2010; 12(6): PCC.09r00849.
- Nzwalo H, Ferreira L, Peralta R, et al. Sleep-related eating disorder secondary to zolpidem. *BMJ Case Rep* 2013.
- Singh H, Thangaraju P, and Natt NK. Sleepwalking a rarest side effect of zolpidem. *Indian J Psychol Med* 2015; 37(1): 105–106.
- Park Y M and Shin H W. Zolpidem induced sleep-related eating and complex behaviors in a patient with obstructive sleep apnea and restless legs syndrome. *Clin Psychopharmacol Neurosci* 2016; 14(3): 299–301.
- Sharma A and Dewan V K. A case report of zolpidem induced somnambulism. *Prim Care Companion J Clin Psychiatry* 2005; 7(2): 74.
- Sattar SP, Ramaswamy S, Bhatia SC, et al. Somnambulism due to probable interaction of valproic acid and zolpidem. *Ann Pharmacother* 2003; 37(10): 1429–1433.
- Mendelson WB. Sleepwalking associated with zolpidem. *J Clin Psychopharmacol* 1994; 14(2): 150.
- Hoque R and Chesson AL. Zolpidem-induced sleepwalking, sleep related eating disorder, and sleep-driving: fluorine-18-fluorodeoxyglucose positron emission tomography analysis, and a literature review of other unexpected clinical effects of zolpidem. *J Clin Sleep Med* 2009; 5(5): 471–476.
- Yang W, Dollear M, and Muthukrishnan SR. One rare side effect of zolpidem—sleepwalking: a case report. *Arch Phys Med Rehabil* 2005; 86: 1265–1266.
- Dang A, Garg G, and Rataboli P V. Zolpidem induced Nocturnal Sleep-Related Eating Disorder (NSRED) in a male patient. *Int J Eat Disord* 2009; 42: 385–386.
- Doane J A and Dalpiaz A S. Zolpidem induced sleep driving. *Am J Med* 2008; doi: 10.1016/j.amjmed.2008.04.035.
- Gibson CE and Caplan JP. Zolpidem-associated parasomnia with serious



- self-injury: a shot in the dark. *Psychosomatics* 2011; 52: 88–91.
30. Najjar M. Zolpidem and amnesic 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 Neuropharm* 2013; 36: 173–174.
  32. Lange C L. Medication associated somnambulism. *J Am Acad Child Adolesc Psychiatry* 2005; 44 (3): 211–212.
  33. Sonsane 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.12bro1363.
  40. Valiensi 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. *Neurologia* 2010; 25(8): 491–497.
  42. Morgenthaler TI and Silber MH. Amnesic 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): 632–638.
  44. Schenck C, Conroy D, Castellanos M, et al. zolpidem induced amnesic 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-hypnotic drugs in nonpsychotic patients. *Neuropsychiatr Dis Treat* 2013; 9: 1159–1162.
  46. Hwang T, Ni H, Chen H, et al. Risk predictors for hypnotic-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* 2019; 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.