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ORIGINAL ARTICLE

Complex Behaviors Related to Zolpidem: An Analysis of Published Clinical Cases from Taiwan

Ana Isabel Wu-Chou [1], Winston W. Shen [1,2]*

[1] Department of Psychiatry, Taipei Medical University-Wan Fang Medical Center, Taipei, Taiwan
[2] Department of Psychiatry, TMU-School of Medicine, Taipei, Taiwan

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Objective: Benzodiazepines with a unique chemical structure of three-ring diabenzine can induce the benzodiazepine-gamma aminobutyric acid A receptor complex to produce sedative, anxiolytic, muscle-relaxant, and anticonvulsant effects. But they have serious side effects such as tolerance and withdrawal, memory and performance impairments, and complex behaviors associated with amnesia.
Method: We searched zolpidem-related published papers from Taiwan from 2003 to 2011. All bibliographical data of original clinical reports were studied. We focused only on complex behaviors related to zolpidem and not on the symptoms of zolpidem-related addiction, tolerance, and withdrawal.
Results: The search in PubMed with the keyword "zolpidem" yielded 729 articles published from 2003 to 2011. Of these, 20 articles were written by Taiwanese author(s). There were 15 case reports and five clinical studies. Besides the symptoms of addiction, tolerance, and withdrawal, these papers describe complex behavioral disturbances, such as performance impairments, behavioral impairment with amnesia, sleep-walking, sleep-related eating disorder, and hallucination and sensory distortion.
Conclusion: We have summarized the case reports and clinical studies of zolpidem-related adverse effects published from Taiwan and reviewed concerns about zolpidem's safety that international researchers have been voicing out in recent years. The incidence of those zolpidem-induced complex behaviors is similar to that found in Western countries. Clinicians should therefore use more antidepressants to treat the underlying diseases that present with insomnia (such as major depressive disorder or generalized anxiety disorder).

1. Introduction

Zolpidem was first introduced in France in 1988 and quickly became one of the most prescribed hypnosedatives around the world. It was later marketed in the United States under the trade name of Ambien, which literally translates to "good morning" in English, i.e., *a.m.* meaning "morning" in Latin, and *bien* "good" in French. Zolpidem is now sold worldwide using 60 different brands. From 2001 to 2002, over 1.34 million tablets of zolpidem were sold across Japan, Europe, and the United States.[1] The exact number of zolpidem prescriptions worldwide is unknown, but speculated to be over billions of tablets per year.

1.1. Complex behaviors induced by zolpidem

Zolpidem is associated with complex behavioral disturbances which are defined in the package insert: (www.ambiencr.com):

"Complex behaviors such as "sleep-driving" (i.e., driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event) have been reported with sedative-hypnotics, including zolpidem. These events can occur in sedative-hypnotic-naive as well as in sedative-hypnotic-experienced persons. Although behaviors such as "sleep-driving" may occur with Ambien CR alone at therapeutic doses, the use of alcohol and other CNS depressants with Ambien CR appears to increase the risk of such behaviors, as does the use of Ambien CR at doses exceeding the maximum recommended dose. Due to the risk to the patient and the community, discontinuation of Ambien CR should be strongly considered for patients who report a "sleep-driving" episode. Other complex behaviors (e.g., preparing and eating food, making phone calls, or having sex) have been reported in patients who are not fully awake after taking a sedative-hypnotic. As with "sleep-driving," patients usually do not remember these events. Amnesia, anxiety and other neuropsychiatric symptoms may occur unpredictably."

1.2. Magnitude and regulatory responses from various countries

In as recent as 2008, the Therapeutic Goods Administration in Australia issued a black box with the strongest warning about

* Corresponding author. Winston W. Shen, Number 111, Hsing Long Road, Section 3, Taipei 116, Taiwan.
E-mail: Winston W. Shen <Shenwinw@gmail.com>

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Table 1 Clinical case reports of zolpidem-related side effects from Taiwan ($N = 15$)

No.	References	Age (y)	Sex	Highest daily dose (mg/d)	Intake during daytime	Tolerance/withdrawal	Dependence on other substance	Neuropsychiatric complications
1	Tsai et al 2003[4]	23	F	5–10	(−)	n/a	(−)	(+)
2	Chang and Lin 2003[5]	24	F	10 (IV)	n/a	n/a	n/a	n/a
3	Chang and Wang 2011[6]	40	F	1000	(+)	(+)/(+)	(+)	(+)
4	Chen et al 2011[7]	53	F	160	(+)	(+)/(+)	(+)	+
5	Hsieh et al 2011[8]	27	F	200	(+)	(+)/(+)	(−)	(+)
6	Huang et al 2007[9]	35	F	500	(+)	(+)/(+)	n/a	(+)
7	Wang et al 2011[10]	43	F	400	(+)	(+)/(+)	n/a	(+)
8	Kao et al 2004[11]	59	F	600	(+)	(+)/(+)	(+)	n/a
9	Tsai et al 2009[12]	65	F	5–10	(+) Accidental	n/a	(−)	(+) TGA-like Sx
10	Chen et al 2009[13]	34	F	2000	(+)	(+)/(+)	(−)	n/a
11	Chu et al 2008[14]	28	F	400–500	(+)	(+)/(+)	(+)	(+)
12	Tsai et al 2007[15]	34	F	5–10	(−)	(−)	n/a	(+)
13	Tsai et al 2007[15]	40	F	10–15	(−)	(−)	n/a	(+)
14	Tsai et al 2007[15]	50	F	10	(−)	(−)	n/a	(+)
15	Tsai et al 2003[4]	23	F	5–10	(−)	n/a	n/a	(+)

References were obtained from a PubMed (www.ncbi.nlm.nih.gov/pubmed) search with the key word "zolpidem." A total of729 published articles was found. Fifteen articles were found to be clinical case reports describing zolpidem-related side effects written by authors from Taiwan.
F = female; IV = intravenous; n/a = not available; Sx = symptoms; TGA = transient global amnesia.

adverse drug events possible without withdrawing the drug from the country (www.tga.gov.au).[56] Asian countries such as Japan and Taiwan quickly followed suit with similar measures in recent years.

Zolpidem quickly became the most prescribed hypnotic drug in Taiwan; in 2006, it was one of the 10 most prescribed drugs according to the Taiwanese National Insurance Health Insurance, the single insurance payer on the island. About 100–300 millions pills are prescribed each year, and an extraordinary sum of at least NT$800 million (US$26.7 million) is paid by the Taiwanese National Insurance Health Insurance each year on zolpidem alone.[2] With its astounding popularity, news and television reports of extraordinary stories such as amnestic sex and rape related to zolpidem warrants further study of its pharmacological effects.

1.3. Objectives of this analysis

Given the magnitude of the problems that result from zolpidem use, our objective was to review published clinical reports from Taiwan, and to familiarize physicians with the behavioral and performance impairments, hallucinations, and amnesia associated with zolpidem. Then we reviewed the relevant clinical psychopharmacology in an attempt to help elucidate zolpidem-related complex behavioral problems.

2. Method

We searched zolpidem-related published papers from Taiwan from 2003 to 2011.

AIWC, the first author of this article, did a PubMed (www.ncbi.nlm.nih.gov/pubmed) search with the keyword "zolpidem." All bibliographical data of original clinical reports were studied. After the initial screening, she identified all published articles written by author(s) from Taiwan. Attention was focused on the description of complex behaviors—complex behavioral disturbances such as performance impairments, behavioral impairment with amnesia, sleepwalking, sleep-related eating disorder, and hallucination and sensory distortion.

3. Results

The search in PubMed using the keyword "zolpidem" yielded 729 articles. Of these, 20 articles were written by Taiwanese author(s). We found that many patients in Taiwan took zolpidem for longer-than-recommended periods and at higher than therapeutic doses. This inappropriate use of medications often resulted in potential adverse drug events.[3] Then, we divided zolpidem-related papers into two (15 case reports and 5 clinical studies) categories.

Table 1 lists 15 case reports[4–15] describing patients abusing and developing addiction-related tolerance/withdrawal symptoms and neuropsychiatric complications in Taiwan from 2003 to 2011. This should raise cautionary measures among all prescribing physicians since every reported patient is probably accompanied by hundreds of unreported cases in clinical practice. Table 2 summarizes five clinical drug trials[16–20] involving zolpidem's side effects conducted in Taiwan.

As shown in Table 1, the most striking finding was that all reported cases of zolpidem-induced addiction problems in Taiwan involved female patients, and that many of them took higher-than-therapeutic dose of zolpidem for a long period. Nine out of 15 patients took zolpidem in the daytime. Seven out of 15 patients took high daily doses: five patients taking daily doses in the hundreds of milligrams (160–600 mg/day), one taking 1000 mg/day, and the other one taking 20 mg/day. All high daily dose patients showed physiological symptoms and signs of drug addiction reflected by tolerance and withdrawal, whereas the development of zolpidem-related complex behavior happened both in therapeutic and high doses of zolpidem.

4. Discussion

4.1. Clinical description of zolpidem-related complex behavioral disturbances

One of the most striking findings in our review was learning the term "complex behavioral disturbances" (www.ambiencr.com).

Table 2 Clinical studies on zolpidem from Taiwan ($N = 5$)

Study name	Year	Type of study	No. of participants
Huang et al[16]	2010	Cross-sectional pilot study	125
Yang et al[17]	2010	Retrospective study	TNIHD
Wang et al[18]	2010	Retrospective study	TNIHD
Huang et al[19]	2011	Double-blind, randomized, comparative study	48
Tsai et al[20]	2009	Retrospective study	255

References were obtained from a PubMed (www.ncbi.nlm.nih.gov/pubmed) search with the key word "zolpidem." A total of729 published articles was found. Five articles were found to be clinical studies describing zolpidem-related side effects written by authors from Taiwan.
TNIHD = Taiwanese National Insurance Health Database.

Therefore, we will first discuss all those symptoms and signs to familiarize the readers with the most important types of those zolpidem-related problems.

4.1.1. Performance impairments

The effects of acute ingestion of zolpidem typically peak at 45 minutes−2.5 hours and are associated with impaired performance as measured by a battery of tests. A large-scale retrospective study using the Taiwanese National Insurance Health Database (Table 2) showed that use of zolpidem is associated with an increased risk of motor vehicle accidents in the following day (odds ratio = 1.74; 95% confidence interval = 1.25−2.43).[17] The acute performance-impairing effects of zolpidem are comparable to those of benzodiazepines (BZDs), despite using different sample populations, methods of study, and different comparison drugs.[21] At doses as low as 7.5 mg in non-elderly participants, zolpidem has shown comparable dose- and time-dependent impairment in learning, recall, and performance.[22]

Leufkens et al[23] showed that zolpidem at a middle-of-the-night dose of 10 mg significantly impairs performance in all tests of a series of highway driving tests in the morning after bedtime administration, and that increased effort did not overcome performance impairment.[23] Moreover, tolerance does not develop in acute performance impairments, including psychomotor function, attention, working memory, and episodic memory. A double-blind, placebo-controlled study showed that performance is significantly impaired during nighttime awakening even after 1 month of nightly zolpidem administration, and that these impairments could significantly affect safety during nighttime awakening.[24]

4.1.2. Behavioral impairments with amnesia

Acute ingestion of zolpidem is associated with complex behaviors that usually start during arousals from slow-wave sleep (SWS) and terminate in walking or eating within an altered state of consciousness and judgment. In descending order of frequency, these behaviors include the following: sleep eating, sleepwalking with manipulation of objects (e.g., cooking, cleaning), sleep talking (on the phone or in person), sleep driving, sleep sex, and sleep shopping.[25]

Traditional BZDs have been associated with amnesia and those with stronger gamma aminobutyric acid A ($GABA_A$)-complex binding have greater potential (e.g., triazolam). Similarly, zolpidem has been reported to have comparable memory impairments to those of triazolam and other BZDs.[26] It has also been proposed that zolpidem may have greater risks of producing amnestic complex behaviors than other Z-drugs (zopiclone and zaleplon) because of its higher affinity and selectivity to α_1-$GABA_A$ receptors which are found in lesser amounts in the hippocampus, an important structure in memory consolidation. The amnestic nature of the complex behaviors is dose-dependent and dependent on route of administration.[27] It has also been suggested that zolpidem's anterograde amnesia is related to disruption of long-term memory consolidation through the shortening of sleep latency.[28]

4.1.3. Sleepwalking

In 1994, Mendelson[29] was the first to describe the case of a man sleepwalking after taking zolpidem. The patient had gotten up and began walking around during stage 4 on polysommnography while feeling asleep subjectively. The patient had woken up the next day without memory of this event. Since then, several more reports have been described in the literature.[30,31] Although post-marketing studies reported low incidences of sleepwalking (0.3−1%),[31] they can be dangerous to patients.[32,33]

The incidence reported in Taiwan is considerably higher (5.1%)[20] as shown in one retrospective study listed in Table 2. The authors suggested that amnesia of these events appear to be dose-dependent, and that it occurred more frequently at doses higher than 15 mg. Another study by Hwang et al[19] also gave a similar conclusion (Table 2).

Sleepwalking is a disorder of arousal that often initiates during SWS and is purposeless in nature.[34] Zolpidem increases SWS especially in young adults, and this effect is not seen with other BZDs. In fact, conventional BZDs (e.g., clonazepam) have, in turn, been useful in treating these parasomnias.[34] Thus, zolpidem-medicated patients have a predominance of non-REM sleep, so when the drug action is weaning down, the patient is still in non-REM sleep.

Several authors have suggested an interesting theory on the cause of somnambulism involving theoretical cerebral pattern generators (CPGs).[34] CPGs are neuronal collections in the brain, brainstem, and spinal cord that are thought to control innate motor behaviors that are crucial for living, such as feeding and locomotion. Diffuse binding of zolpidem in the central nervous system (CNS) elicits CPGs-associated evolutionarily preserved actions such as walking and eating, leading to sleepwalking and sleep-related eating disorders. CPGs that reside in cortical areas release overlearned behaviors such as driving.

4.1.4. Sleep-related eating disorder

Strunkard et al first described the syndrome of night eating in obese patients back in 1955.[35] Since then, many more detailed cases of patients presenting with partial or full amnesia of nocturnal eating behavior have been reported in the literature.[35−37] Collectively known as sleep-related eating syndrome (SRED), the spectrum encompasses many abnormal behaviors that are characterized by nocturnal eating episodes in a partially aroused state and consequent morning anorexia/bloating, feelings of guilt, and weight gain. Patients often describe these experiences as "automatic" penchants to eat and suffering from the inability to return to sleep unless they have completed this act. Patients may exhibit nocturnal eating only after initiation of zolpidem, while other patients may continue their preexisting nocturnal eating problem but with increased frequency and newly onset amnesia of events.

Once the medication was discontinued, the unusual behavior stopped in most of the reported cases. Najjar[38] in 2007 observed two types of patients with preexisting eating disorders: (1) patients who experience nocturnal eating as a symptom of a diurnal eating disorder, and (2) those who exhibit nocturnal eating as a result of an eating disorder that presents predominantly during sleep. The second group often complains of insomnia, and the patients are fully awake during their nocturnal eating episode. An association exists between somnambulism and SRED.[39,40] The ingested substances can be either ordinary or unusual and are typically of high-calorie content.

The precise pathological mechanism of SRED is unclear, but is thought to be related to dysregulation of the dopaminergic system in the CNS. This is supported by evidence of increased prevalence of SRED in patients with restless legs syndrome, periodic limb movement disorder, and the improvement of SRED to dopamine agonists. Other conditions that cause fragmented sleep (e.g., obstructive apnea, withdrawal from nicotine, alcohol, opiates, and cocaine) are also known to be associated with SRED.[41]

Although zolpidem was marketed as weight-neutral, most conventional BZDs have been shown to induce hyperphagia in mammals.[42] Given the recent reports about zolpidem-related SRED, the effect of zolpidem on appetite and weight control in humans warrants further reassessment.

4.1.5. Hallucinations/sensory distortion

Since Ansseau et al[43] in 1992 first reported two patients with zolpidem-induced visual hallucinations and amnesia, stories of

patients with similar neuropsychiatric conditions (Table 1) have repeatedly been reported in Taiwan[4,12] and around the world. Zolpidem-induced hallucinations are mostly of the visual kind and often occur when patients are falling asleep or waking up. Although the mechanism is unclear, hallucinations are thought of result from GABAergic abnormalities.[4]

Zolpidem-related hallucinations should raise awareness in clinicians since even at therapeutic levels, it can be associated with transient cognitive and behavioral complications[43,44] that can result in patients self-harm.[45] Common characteristics among the described patients include: female sex, a dose-dependent reaction, the symptoms appearing around 20–30 minutes after zolpidem ingestion, and the spontaneous clearance of the cognitive/behavioral symptoms without need of treatment several hours later or after discontinuation of zolpidem use. In most severe cases, patients even develop delirium.[44,46]

Toner et al[40] suggested four variables that should be considered when prescribing zolpidem in order to avoid these neuropsychiatric complications: (1) female sex is associated with higher serum drug levels; (2) zolpidem dose, hallucinations occurred at higher doses and were dose-dependent; (3) zolpidem-related hallucinations are more severe in patients suffering from malnutrition or hypoalbuminemia, because zolpidem has high protein binding affinity. Some antidepressants with high-protein binding properties may also displace zolpidem from carrying proteins and increasing the amount of zolpidem; and (4) medications that inhibit CYP3A4 hepatic izoenzyme may interfere with the metabolism of zolpidem. Besides taking into account these four factors, individual variations in pharmacodynamics sensitivity and neuroanatomical differences need also to be considered when prescribing zolpidem.[46]

4.2. Why zolpidem is more likely to elicit complex behavior compared to other BZDs and other Z-drugs

The Food and Drug Administration issued a warning about hypnosedative-related complex behaviors on 13 types of hypnosedatives in as recent as March 2007 (www.fda.gov). Besides being the most prescribed hypnotic in Taiwan, the focus on zolpidem was chosen because side effects such as amnesia, confusion, and even psychosis have already been well documented in the literature for many decades, whereas zolpidem-induced complex behaviors are still relatively understudied despite its popularity as a prescription drug. Even though the remaining Z-drugs (zopiclone and zaleplon) have also been linked to complex behaviors, zolpidem is the drug most frequently reported.[24] It is unclear whether this phenomenon is because of an increased risk for complex behaviors in zolpidem or simply because it is more frequently prescribed. After documenting zolpidem-related pharmacoepidemiology in Taiwan, clinical descriptions, and magnitude of its use and associated side effects, we have made an attempt to explain why zolpidem-induced side effects are better known compared to other BZDs or BZD-receptor agonists.

4.2.1. Mechanisms of action of BZDs and Z-drugs

Figure 1 summarizes BZD and BZD-receptor agonists (Z-drugs). All of them exert similar pharmacologic properties that include anxiolytic, hypnotic, anticonvulsant, and muscle relaxant effects, but they have several side effects—amnesia, hyperphagia, and parasomnia—as described previously. GABA exerts inhibitory effects in the CNS by binding to $GABA_A$ receptors and causing an influx of chloride ions into neurons. BZDs and Z-drugs bind to $GABA_A$ receptors at a site near the GABA binding site and enhance the effects of GABA. In the absence of GABA, hypnotics cannot exert their effects.[47]

The BZD–$GABA_A$–chloride ion channel complex has a transmembrane pentameric structure with subunits chosen from eight polypeptide classes: α, β, γ, δ, ε, π, ρ, and τ. The α subunits dictate the pharmacology of the BZD receptor site. Activation of the α_1 subunit results in sedative, amnesic, and motor impairments but not in anxiolytic, myorelaxant, or alcohol-potentiating effects. The latter effects are due to actions on the α_2, α_3, and α_5 subunits.[42] Cooper[42] suggested that hyperphagia is medicated by the α_2 and α_3 subunits. Variations in $GABA_A$ receptor subunits among patients may partly explain the differences in the pharmacodynamic effects of zolpidem.[44]

4.2.2. Hypothesized pathological mechanisms of complex behavior and amnesia

4.2.2.1. α_1-Agonist activity. BZDs with higher affinity to alpha subunits, such as triazolam, tend to produce more amnesia and complex behaviors.[48,49] According to this theory, zolpidem may have greater risks for these side effects because it has the strongest binding affinity for alpha and greater *in vitro* intrinsic activity than the rest of the Z-drugs.[50,51] Originally, zolpidem was thought to have less amnesia than the other BZDs because of its selectivity to α-$GABA_A$ receptors and the relative lack of these receptors in the hippocampus. However, memory impairments of zolpidem are comparable to those of triazolam.[52] Theoretically, zolpidem loses its selectivity for α_1 subunits at higher concentrations and shows similar pharmacological effects to those of traditional BZDs. It is therefore not surprising that zolpidem has been associated with complex behaviors previously reported with BZDs. This phenomenon results in amnesia of events experienced while a person is conscious.

4.2.2.2. Inhibition of memory consolidation. The risk of zolpidem-induced complex behaviors may not be completely explained by actions on the α_1 subunit. Decreasing sleep latency may increase the risk of complex behaviors because it interferes with the transferring of memory from short-term memory to long-term storage, otherwise known as memory consolidation. This phenomenon results in amnesia of events experienced while a person is conscious.

Zolpidem decreases sleep latency more than other BZDs because of its faster onset of action.

4.2.2.3. Other considerations. Another noteworthy factor is zolpidem's potential for abuse and dependence. Zolpidem was first marketed as a safe hypnotic and free of abuse and dependence liability,[53,54] but the number of case reports in the literature that proves otherwise is overwhelming.[8,55] These case reports describe patients developing long-term dependence and withdrawal symptoms, and rebound insomnia may develop even within therapeutic doses.[53] To the best of our knowledge, there is only one randomized, double-blind, comparative study conducted in Taiwan that evaluated zolpidem's safety in the treatment of insomnia.[15] This study showed that zolpidem is more significantly effective in reducing sleep latency, from a baseline of 61.9 ± 44.7 to 30.0 ± 31.1 minutes ($p < 0.05$), and observed no rebound insomnia. However, the participants in the study were treated with zolpidem for only 2 weeks, a significantly shorter period than the several months and even years seen in clinical practice.

4.2.2.4. Summary of the hypothesis. Several hypotheses have been proposed to explain the occurrence of zolpidem-induced complex behavior. While no single postulate complete explains the phenomenon, the combined data suggest that the risks are higher with high doses of zolpidem. To note, the conclusion of this review is hypothetical as there is a lack of head-to-head trials comparing complex behavior elicited by zolpidem compared to that of BZDs and other Z-drugs.

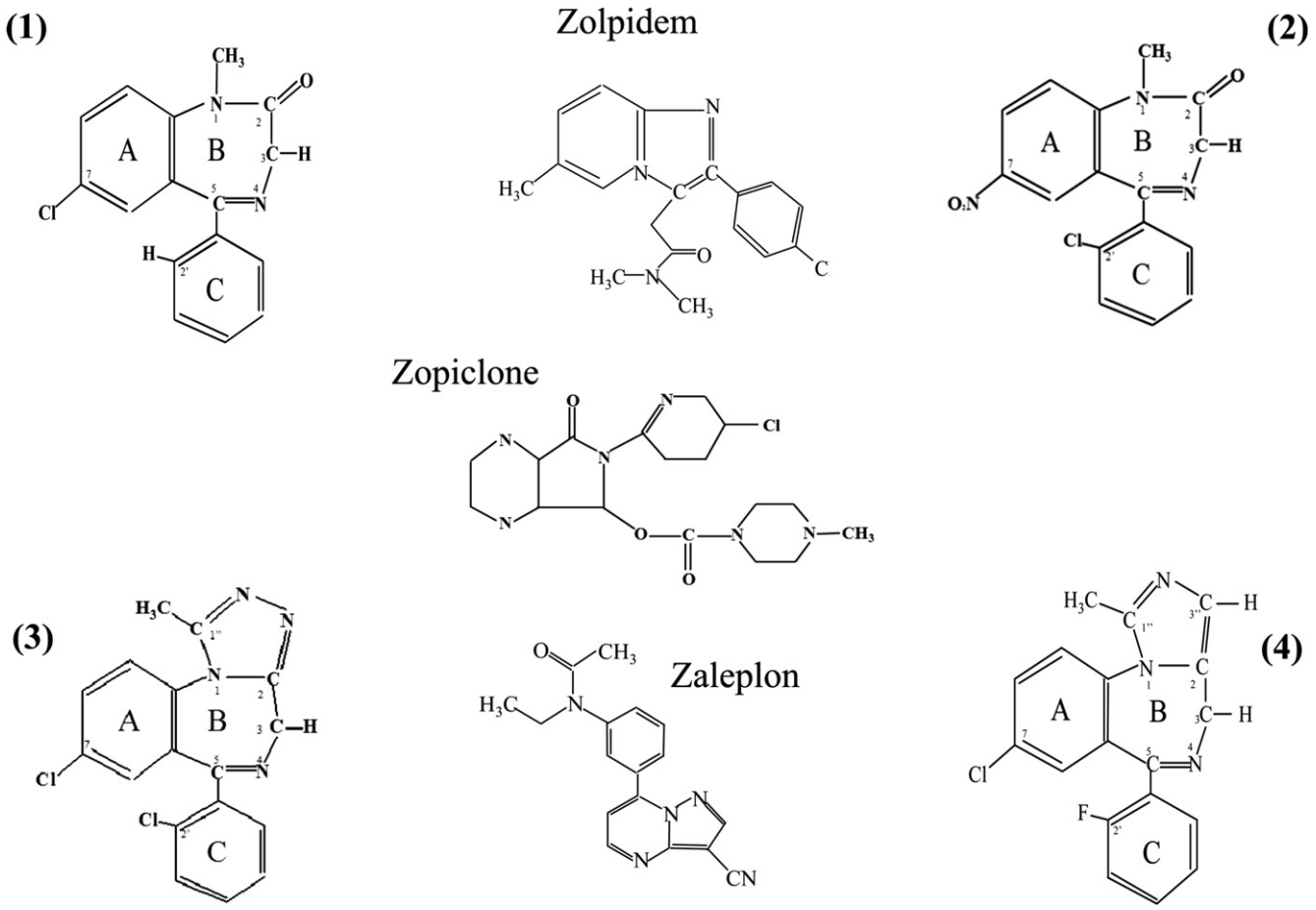

Figure 1 Benzodiazepines (BZDs) and BZD receptor agonists. Samples of BZD groups are shown in structures (**1**), (**2**), (**3**), and (**4**). (**1**) Chemical structure of diazepam. Its related BZDs are nordazepam, temazepam, oxazepam, chlordiazepoxide, etc. (**2**) Clonazepam. Its related compounds are flunitrazepam and nitrazepam. (**3**) Triazolam. Its related BZD is alprazolam. (**4**) Midazolam. Z-drugs include zolpidem, zopiclone, and zaleplon. All Z-drugs do not have the structure of benzodiadepine—i.e., A ring and B ring as well as C ring as shown in (**1**), (**2**), (**3**), and (**4**). All chemicals in this figure with or without BZD structure, bind the BZD receptor site of the BZD–$GABA_A$–chloride ion channel protein.

4.3. Clinical suggestion for zolpidem use in clinical practice

While zolpidem is clinically effective in treating insomnia, it carries the same risks as conventional BZDs. Besides its addictive potential, zolpidem was reported to have higher odds for parasomnia, amnesia, hallucinations, and perhaps suicidality compared to other hypnotics.[57] Table 1 shows that development of zolpidem-withdrawal symptoms and tolerance tended to occur in patients taking zolpidem at the dose level higher than therapeutic dose levels (>100 mg daily), while neuropsychiatric complications occurred at doses of as low as 5 mg daily. Patients taking large daily doses corresponded to those diagnosed with zolpidem dependence, whereas patients who developed neuropsychiatric complications did not necessarily have addiction problems. To note, all reported cases in Table 1 were female patients and confirmed previous suggestions that female patients are more susceptible to the side effects of zolpidem.[18] Although they are small in number, there have been clinical studies conducted in Taiwan (see Table 2) that challenges the previously assumed safety of zolpidem. Management strategies for zolpidem-related side effects include discontinuing the use of this drug, switching to another hypnotic, or using nonpharmacological treatments such as relaxation techniques and encouraging sleep hygiene. Interestingly, patients should be advised against using excessive caffeinated beverages to counteract the acute ingestion effects of zolpidem as a recent studied has shown that up to four cups of coffee can only partially reverse the performance-impairing effects of zolpidem.[57]

The constellation of zolpidem-related adverse drug events can often be overlooked in clinical practice when physicians let their guard down while prescribing this drug in the hopes that the latest introduced hypnotic in the 21st century is the best and the safest. We advocate that zolpidem be used judiciously by following the Taiwan and U.S. Food and Drug Administration warnings, and with the same caution usually reserved for all traditional BZDs: at the lowest possible effective dose and for the shortest duration possible. The clinicians should prescribe more antidepressants to treat the underlying diseases with clinical presentation with insomnia (such as major depressive disorder or generalized anxiety disorder).[58]

Conflict of interest

The authors declare no conflict of interest in all the drugs mentioned in this article.

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