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REVIEW ARTICLE

In the Zzz Zone: The Effects of Z-Drugs on Human Performance and Driving

Naren Gunja

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Abstract Despite their improved pharmacokinetic profile, the Z-drugs, zolpidem, zopiclone, and zaleplon, have a spectrum of adverse effects comparable to benzodiazepines. This review focuses on the impairment from Z-drugs on cognition, behavior, psychomotor performance, and driving ability. Z-drugs are short-acting GABA agonists that reduce sleep latency without disturbing sleep architecture. Bizarre behavioral effects have prompted warnings on the prescription, dispensation, and use of Z-drugs. Psychomotor impairment, falls, and hip fractures are more likely to occur with Z-drugs that have longer half-lives, that are taken at higher-than-recommended doses and when mixed with other psychoactive substances including alcohol. Zopiclone and higher doses of zolpidem are more likely to cause anterograde amnesia than zaleplon. Z-drugs, especially zolpidem, are associated with complex behaviors such as sleepwalking, sleep-driving, and hallucinations. Patients taking zopiclone and zolpidem have an increased risk of motor vehicle collisions, over double that of unexposed drivers. Driving impairment occurs with zopiclone and higher doses of zolpidem but is unlikely to occur after 4 h post-zaleplon administration. The residual effect of Z-drugs on next-day cognitive and psychomotor performance has significant impact on lifestyle, safety, and occupational considerations, including motor vehicle and machine operation. The risk–benefit analysis of Z-drugs in the treatment of insomnia, particularly in the elderly, may not favor treatment due to the increased risks of falls and motor vehicle collisions. Prescribers should warn patients taking Z-drugs of minimum time thresholds before they operate machinery or drive motor vehicles.

Keywords Zolpidem · Zopiclone · Zaleplon · Automobile driving · Psychomotor performance

N. Gunja
NSW Poisons Information Centre, The Children's Hospital at Westmead, Sydney, Australia

N. Gunja (✉)
Discipline of Emergency Medicine, Sydney Medical School, University of Sydney, Sydney, New South Wales, Australia
e-mail: naren.gunja@sydney.edu.au

Introduction

The Z-drugs, zolpidem, zopiclone, and zaleplon, were developed as hypnotics with improved pharmacokinetics in comparison to benzodiazepines, the traditional treatments for insomnia. Their pharmacology and toxicology have been previously reviewed [1]. Zolpidem, zaleplon, and eszopiclone are the three Z-drugs currently approved by the US Food and Drug Administration (FDA) for the treatment of insomnia [2]. Like benzodiazepines, Z-drugs are $GABA_A$ receptor agonists; however, their clinically attractive properties include short duration of action, non-disturbance of overall sleep architecture, and diminished residual effects during daytime hours [3]. Z-drug doses and pharmacokinetic profiles are shown in Table 1 [4–10]. While they have been studied in the elderly, there is increasing interest in Z-drug effectiveness and residual effects in shift workers, pilots, and military personnel [11].

Residual effects are dose-dependent and vary between hypnotics based on their pharmacokinetic profile. Of considerable concern are falls in the elderly leading to hip fractures, head injuries, and other significant morbidity and mortality. Furthermore, the effect of Z-drugs on next-day human performance and driving impairment has held sharp focus in the public health sphere as well as in forensic and legal circles. In March 2007, the US FDA released a list of 13 drugs for which stronger labeling was recommended regarding the potential risk of complex sleep-related behaviors [12]. These behaviors, discussed further below, involved parasomnias such as sleep-eating and sleep-driving.

Table 1 Pharmacokinetic properties of Z-drugs

Z-drug	Dose range (mg)	T_{max} (h)	Elimination $t½$ (h)
Zolpidem IR	5–10	1–2	2.5–3
Zolpidem ER	6.25–12.5	1.5–2.5	2.5–3
Zopiclone	3.75–7.5	1.5–2	5–6
Eszopiclone	1–3	1–1.5	6–7
Zapleplon	5–20	0.7–1.4	~1

References: [4–10]

IR immediate-release preparation, *ER* extended/controlled-release preparation, T_{max} time to maximal concentration (hours), $t½$ half-life (hours)

Z-drugs were included in the FDA warning list, and this was soon followed by warnings from other drug regulatory agencies across the world, including the Australian Therapeutic Goods Administration [13]. Since then, several epidemiological studies have attempted to quantify the risk of bizarre behaviors from hypnotic drugs and any differential rates of incidence between them.

Following publicity from the FDA and other regulatory authorities in 2007, Z-drug adverse reaction reporting increased due to health professional and consumer awareness of a potential relationship. Since 2007, adverse drug reporting systems in Australia showed higher rates of reports associating zolpidem and various adverse events such as parasomnia, amnesia, hallucinations, and suicidality. However, retrospective analysis suggests that zolpidem was associated with an increased risk of these adverse events compared with other drugs even prior to the media publicity in 2007 [14].

This review focuses on the adverse effect profile of Z-drugs, specifically on their ability to impair human cognition, behavior, next-day performance, and driving ability. Ovid Medline (1980 to Nov. 2012), Embase (1980 to Nov. 2012), and Google Scholar were searched using the terms "zolpidem," "zopiclone," "eszopiclone," and "zaleplon" in combination with "impairment," "driving," "fall," "memory," "cognitive," "residual," "behavior," "hallucinations," "sleepwalking," OR "performance." Studies relevant to impairment from Z-drugs in humans were retrieved, and the bibliographies of the retrieved articles were searched for further relevant publications.

Effects on Cognition and Behavior

Like benzodiazepines, Z-drugs, particularly zolpidem and zopiclone, appear to have a dose-dependent effect on anterograde amnesia. Notably, there is an inability to remember the parasomnia or complex behavior; this phenomenon has been observed to a much lesser extent with zaleplon [15, 16]. In a healthy volunteer study, zolpidem was found to impair word recall and recognition 6 h after administration in a dose-dependent fashion, with greatest impairment observed at the highest studied dose of 20 mg [17]. In the same study, zaleplon had no effect at doses up to 20 mg. Several other studies have also confirmed that zaleplon has little or no residual effects the following morning, even when taken during the middle of the night for inability to go back to sleep [18–20]. Zopiclone, at a dose of 7.5 mg or higher, has been shown to impair memory and cognitive function using a battery of tests including the digit symbol substitution test, word learning test, and Sternberg memory scanning test [21]. Similar testing has failed to demonstrate residual effects after eszopiclone (3 mg) [22–24]. However, these studies have allowed 8 h of sleep following the dose, an unlikely scenario in insomniacs. A recent study directly comparing zopiclone (3.75 mg) with eszopiclone (3 mg) in a sleep restriction protocol showed significant next-day residual effects from both drugs, though to a slightly lesser extent with eszopiclone [25].

Many of these studies do not simulate real life scenarios in which patients are prescribed Z-drugs on a long-term basis, leading us to question whether chronic use may lead to tolerance of performance-impairing effects. There appears to be some tolerance to memory and psychomotor impairment from benzodiazepines, such as triazolam [26]. There is emerging evidence that this type of tolerance may not occur with Z-drugs. In a unique study where healthy volunteers took extended-release (ER) zolpidem nightly over a 3- to 4-week period, there was significant memory and performance impairment during nocturnal awakening, which did not improve with chronic dosing [27]. Similarly, Frey et al. showed that 5 mg zolpidem caused significant impairment of cognitive function (working memory and mathematical calculations) in both young adults (mean age 22 years) and older adults (mean age 67 years) during nocturnal awakening [28]. Nocturnal awakening may occur in patients with insomnia for several reasons, and middle-of-the-night impairment due to Z-drugs raises patient safety concerns with regard to falls, amnesia, and decision-making capacity.

Postulated mechanisms for Z-drug-induced amnesia include dose-dependent agonist activity at $GABA_A$ receptors that is also proportional to binding affinity. Pharmacokinetic drug interactions with CYP3A4 enzyme substrates may explain why zolpidem and zopiclone have higher incidence of these adverse effects than zaleplon, which has a different metabolic pathway. Another potential explanation for amnestic effects from all hypnotics is their ability to reduce sleep latency and block memory consolidation, that is, the transfer of short-term memory into long-term storage [15, 29]. In this regard, zolpidem has been shown to impair memory consolidation in mice similar to midazolam [30].

Adverse effects of parasomnia, amnesia, and hallucinations associated with zolpidem have been reported in the last decade over and above all other drugs in a health professional and self-reporting system [14]. The odds ratios (OR) for these adverse events were around 14.0–26.3 (95 % CI 9.9–35.2), compared with other hypnotics. Furthermore, the OR increased up to tenfold for parasomnia events following media publicity in 2007. Confirmatory electroencephalographic (EEG) evidence of sleep during these parasomnia events is lacking, hence the uncertainty regarding their differentiation from a confusional arousal state in which amnesia and automatisms may occur. There is also concern that Z-drugs are being prescribed in patients with prior histories of parasomnia or hallucinations. These patients may already have lower thresholds for such adverse events, which are being exacerbated by Z-drug use [31].

Parasomnia includes abnormal behavior or events during sleep, such as nightmares and terrors, sleepwalking (somnambulism), sleep-eating, sleep-talking, sleep-sex, and sleep-driving. Among the Z-drugs, these phenomena have been mainly associated with zolpidem use. Sleep-driving is considered separately below. Tsai et al. reported three female patients with repetitive behaviors (eating and cleaning) associated with anterograde amnesia after commencing zolpidem at doses of 10–15 mg [32]. Anecdotal reports of neuropsychiatric adverse effects from zolpidem have been higher for women, though this may reflect higher milligram-per-kilogram dosing rather than a gender-based sensitivity to zolpidem. Parasomnia cases have also had a female preponderance, though suicidality from zolpidem has a greater association with the male sex [14]. Somnambulism and amnesia from zolpidem appeared to be rare events with isolated case reports and low prevalence in initial post-marketing surveillance. However, a retrospective Taiwanese study in a cohort of psychiatric outpatients found that over 5 % of zolpidem-treated patients had amnesia or somnambulism [33].

Sleep-Driving

Sleep-driving is the act of driving a vehicle in a semi-awake state after getting out of bed during sleep, in which the individual has no memory of the act afterward. Sleep-driving has been characterized as a variant of sleep-walking (somnambulism), a type of parasomnia in which automated behavior may be performed in a partial arousal from sleep, usually in the first few hours. Some have advocated that sleep-driving should be differentiated from Z-drug-related driving impairment, as it is likely a separate phenomenon with a different etiology and pathophysiology; the latter phenomenon is due to the residual effects of Z-drugs impairing driving ability in an awake individual [34]. Prior to 2006, 14 post-marketing cases of sleep-driving were reported to the FDA, 13 of which were associated with zolpidem therapy and one with zaleplon [35]. As for other parasomnias, reports of sleep-driving associated with Z-drugs increased following media speculation about a causal link.

The main contention with Z-drug-related sleep-driving is the lack of detailed clinical case reports with objective polysomnographic evidence of a parasomnia occurring during sleep. The few case reports in the medical literature relate to zolpidem therapy at doses between 10 and 12.5 mg [36–38]. In these reports, sleep-driving occurred anywhere from a few weeks to 2 years after initiation of zolpidem. From these few cases, it appears that risk factors for the development of sleep-driving associated with zolpidem include concomitant alcohol, or other sedative intake, and pre-existing or co-existing parasomnia, such as sleepwalking. Further research into the pathophysiology of this parasomnia as well as case series with confirmatory objective evidence of sleep-driving are required before a causal link can be ascribed to Z-drugs.

Effects on Psychomotor Performance

Psychomotor adverse effects from the use of hypnotics are a major concern in the elderly. A risk–benefit analysis of hypnotic drug use in elderly insomniacs may not favor treatment. This is primarily due to a higher incidence of falls and motor vehicle collisions in elderly patients on hypnotic drugs. Hypnotics have a small beneficial effect with a number needed to treat of 13 for improved sleep versus a number need to harm of 6 for any adverse event [39].

Residual psychomotor effects from Z-drug use include dizziness, postural instability, ataxia, and falls. In the geriatric population, falls are associated with significant morbidity including fractures, head injuries, and potentially death. The increased risk of psychomotor disturbance from benzodiazepine use has been well reported [40, 41], and the associated costs to the community have been estimated in billions of dollars [42]. In a Korean insurance registry study, zolpidem use increased the risk of hip fractures nearly twofold (OR 1.72, 95 % CI 1.37–2.16) [43]. In this study, zolpidem use was associated with a higher risk than benzodiazepine use. A similar odds ratio for zolpidem use was found in an aged and disabled program database from New Jersey [44].

Balance tests in healthy young volunteers suggest that both zolpidem and zopiclone have a profound dose-dependent effect on postural sway and body balance in the first few hours after intake [17, 18, 45]. This effect correlates with peak plasma levels of these Z-drugs but may persist into the morning. Psychomotor effects are

exacerbated in elderly Z-drug users due to altered pharmacokinetics and increased sensitivity to peak drug action [46]. Although most people will be asleep in the first few hours after Z-drug ingestion, many elderly users may awaken and mobilize, predisposing them to imbalance and falls. Zolpidem, at a dose of 5 mg, induced middle-of-the-night tandem walk failures on a 10-cm-wide beam in older subjects compared with younger ones and controls; in this study, subjects were awakened 2 h after zolpidem administration [28]. The failure of tandem walking occurred in 3 out of 13 younger subjects only in the first few minutes after awakening. However, persistent impairment was seen in older subjects with 2 out of 12 failing the tandem walk 30 min after awakening. This is of considerable concern as zolpidem induces imbalance and ataxia at the reduced dose of 5 mg, recommended for elderly patients.

Psychomotor impairment during middle-of-the-night awakening has not been demonstrated for zaleplon at doses up to 10 mg in laboratory studies [47, 48]. At 20 mg, impairment in psychomotor testing from zaleplon occurs at peak levels, around 1 h post-administration. However by 6 h, no residual psychomotor impairment was observed for these doses of zaleplon [17]. A study in aviation personnel found short-lived (1–2 h) performance impairment from a 10-mg dose of zaleplon [49]. In the same study, zopiclone at a dose of 7.5 mg had significant impact on performance, more than zaleplon or temazepam, up to 6 h post-dose. Another study of 13 military personnel found significant psychomotor and task performance impairment when subjects were woken up 2 h after a 20-mg dose of zolpidem [50]. This was greater than the impairment observed with 10 mg of zolpidem.

Psychomotor impairment, falls, and hip fractures are more likely to occur with zopiclone, with its longer half-life, and with higher-than-recommended doses of zolpidem. Zaleplon impairs psychomotor performance in correlation with its T_{max} but has negligible residual effect in the morning.

Effects on Driving

With the advent of a 24-h society, shift work, and ever-increasing use of prescription medication, driving while intoxicated with drugs is being encountered with higher frequency than ever before. Cases of suspected driving under the influence of drugs (DUID) increased 18-fold over a 30-year period to 2007 in Finland, with males comprising nearly 90 % of the suspects [51]. Z-drugs and benzodiazepines were implicated in over three quarters of cases, as was poly-drug use. Benzodiazepines were detected in 15.6 % of injured drivers presenting to a trauma center emergency department in Melbourne, Australia [52].

Various jurisdictions around the globe have instituted roadside drug testing and field sobriety tests in a campaign to increase awareness of the problem, improve road safety, and prevent road deaths. Over the last 10 years, Z-drugs have made their way into screening tests for drugs of impairment in injured or deceased drivers. In addition to their ability to impair cognition, memory, and psychomotor performance, Z-drugs produce residual effects on driving performance the day after nocturnal hypnotic administration.

Epidemiology

Use of benzodiazepines has been known to increase the risk of motor vehicle collisions (MVC) since the 1990s. It has also been shown that long-acting benzodiazepines, such as diazepam, clonazepam, and nitrazepam, are more likely to cause MVC than short-acting ones [53]. Hypnotic medication doubled the risk of MVC in a large national population health survey held in Canada [54]. Pharmaco-epidemiological studies suggest that there may be an increased risk of MVC with Z-drugs. In a UK study of drivers involved in a first-time MVC, the odds ratio for an accident associated with benzodiazepines (including zopiclone) was 1.62 (95 % CI 1.24–2.12), greater than for any other psychoactive drug [55]. In this study, zopiclone was the only short-acting hypnotic associated with an increased risk of MVC. A Norwegian study found increased risk of MVC with all four hypnotics studied—zolpidem, zopiclone, nitrazepam, and flunitrazepam [56]. Greatest risk was associated with users of flunitrazepam, who had four times the risk of MVC compared with non-users; zolpidem and zopiclone use increased the risk by a factor of 2.2 and 2.3, respectively.

Zopiclone is one of the most prescribed hypnotics in Scandinavia. In a Norwegian study, zopiclone was detected in 1.4 % of randomly tested drivers, a greater prevalence than for any other detected hypnotic [57]. Similarly, in deceased drivers, zopiclone was the most frequently encountered hypnotic drug in post-mortem samples [58]. A French study confirmed the increased risk of MVC for benzodiazepines but failed to demonstrate any increased risk for zopiclone [59]. They did, however, show that MVC risk was associated with inappropriate use of zolpidem, such as taking more than one tablet a day. A meta-analysis of all driving risk studies showed mixed results for zopiclone-related fatality or injury, but a high risk of property damage [60].

As insomnia affects women more than men and hypnotic medication is more likely to be prescribed for women, it may be expected that there is a gender difference in driving effects after Z-drugs. This has only been demonstrated for zolpidem in one study, that is, women drive significantly worse than men after zolpidem at a dose of 10 mg [61].

Driving Impairment

Driving a motor vehicle is a complex task encompassing psychomotor capability, physical space awareness, reaction times, and other areas of human physiology. The psychopharmacological mechanisms that underlie driving impairment from Z-drugs clearly involve GABA-ergic effects, though other neurotransmitter pathways are important in wakefulness and attention [62]. The impairment of driving ability from medications has been studied for over 30 years with the "on-the-road driving test" being validated as the gold standard for such a purpose [62, 63]. Other tests of driving ability include driving simulators, subjective driving assessments, and laboratory tests of psychomotor performance. The on-the-road driving test typically involves a 100-km supervised and video-recorded drive in which deviation from a standard lateral position within the slow lane of a highway is measured. As the car weaves within the lane, a mean lateral position may be calculated over the 100 km, from which the degree of weaving (standard deviation of lateral position (SDLP)) is derived [64]. Depending on the study, the SDLP (measured in centimeters) is around 17–22 cm in drivers administered the placebo treatment.

Measures of driving performance the morning after nocturnal hypnotic use have been studied for all three Z-drugs. The most consistent findings relate to zopiclone-induced driving impairment at a dose of 7.5 mg [21, 64]. Zopiclone, the Z-drug with the longest half-life, impairs driving the morning after middle-of-the-night dosing, or even if taken before sleep as a nocturnal dose. The driving impairment from zopiclone is reliable to the extent that 7.5 mg has been used in various studies as a positive control and benchmark for comparison with other hypnotics [65, 66]. Impaired driving, measured by mean (±SEM) SDLP, increased from 18.2 (±0.5) cm in placebo controls to 21.6 (±0.8) cm in subjects dosed with zopiclone 7.5 mg, 10–11 h earlier; this effect was double that of alcohol in subjects with an average blood alcohol concentration (BAC) of 0.03 % [67]. In the same study, zaleplon 10 mg had no effect on mean SDLP scores. A 15-mg dose of zopiclone (twice the recommended dose) may cause persistent driving impairment through to the afternoon, 16 h after nocturnal administration [64]. Next-day driving impairment was not observed 10 h after a nocturnal 3-mg dose of eszopiclone [24].

Zaleplon, when taken at the recommended dose of 10 mg or doubled to 20 mg, has not been shown to impair driving in the morning. Middle-of-the-night doses of zaleplon up to 20 mg also appear to be safe, as long as at least 4 h has passed before getting behind the wheel of a car, a reflection of its ultra-short half-life [17, 18]. Similarly, zolpidem produces little residual driving impairment the morning after a nocturnal dose of 10 mg in healthy adults. However, at a dose of 20 mg, or when taken in the middle of the night, zolpidem has the ability to significantly impair daytime driving [17, 68]. Two studies of older drivers, aged 55–65 years, revealed residual impairment from zolpidem that persisted 10 h after a 10-mg dose [69, 70]. Overall, driving impairment occurs with zopiclone and higher doses of zolpidem but is unlikely to occur after 4 h post-zaleplon administration.

Forensic and Legal Considerations

While driving impairment from alcohol use has been well established, the effect of psychoactive medication on driving performance has much less epidemiological data. Obtaining drug levels for psychoactive substances from drivers in MVC and injured or deceased drivers may be a method of differentiating prevalence among drugs. While there may be legislation in some countries mandating drug testing of drivers in MVC, obtaining blood for the measurement of drug concentrations in random drivers is difficult due to a high refusal rate [71]. Data collection is improved in some studies by offering monetary incentives and collecting urine or oral fluid samples instead of blood. Oral fluid testing has significant intra- and inter-individual variation, and ratios of oral-to-blood concentrations can be misleading in individual cases. At a population level, oral fluid testing can be a rapid, non-invasive, and acceptable form of collecting drug data in drivers. Another advantage of oral fluid is that it may be a better marker of recent drug use and impairment at the time of oral fluid testing [72]. Oral fluid appears to be reliable for detecting zopiclone in DUID cases, showing good correlation with blood concentrations [73].

A Swedish study examined zolpidem and zopiclone levels in impaired drivers and in post-mortem blood samples from deceased drivers; it showed elevated levels of both Z-drugs, suggestive of supratherapeutic use [74]. Caution should be used when interpreting these levels, as there were considerable variation, overlap with therapeutic concentrations, and potential for drug interactions. Gustavsen et al. demonstrated a clear dose relationship between increasing zopiclone levels and the degree of driving impairment, similar to that for alcohol [75]. The proportion of impaired drivers was roughly equal when the BAC exceeded 0.1 % and zopiclone concentrations were greater than 130 ng/mL. No such relationship was demonstrated for zolpidem in the same study. There are little data on zaleplon levels and driving impairment likely due to low prescription rates and a short detection window.

While many jurisdictions around the world have implemented traffic laws based on legal limits for BAC, such systems are generally not in place for drug concentrations of other CNS depressants or psychoactive medication.

There is strong evidence to link reductions in MVC, traffic injuries, and deaths to decreasing BAC limits [76]. Such studies for benzodiazepines fail to demonstrate a reliable correlation between drug level and extent of driving impairment. While higher benzodiazepine levels correlate with higher risk of MVC and greater driving impairment, significant intra- and inter-individual differences prevent the setting of legal limits as for alcohol [55, 77].

In Norway, legislators have sought to set impairment limits for illicit substances and prescription medications comparable to those set for alcohol. Norway is the first country in the world to set legally binding limits for drugs other than alcohol [78]. Since February 2012, 13 substances including benzodiazepines and 2 Z-drugs have legal limits with graded sanctions; the set limits are not intended to apply to drivers with a valid prescription for the detected medication [79]. Driving impairment thresholds for zolpidem and zopiclone in Norway are shown in Table 2 [58, 73, 74, 80]. Some authors have suggested that per se limits for illicit substances and psychoactive medications are impractical and likely to be ineffective due to inter-individual differences in drug tolerance, poly-drug use, and poor correlation between drug concentration and impairment [81]. It is suggested that field sobriety testing and confirmation of impairment, coupled with valid prescriptions for medication, would be more reliable and objective grounds for a legislative framework.

The International Council on Alcohol, Drugs and Traffic Safety (ICADTS) has classified prescription medications, including Z-drugs, into three categories based on their likelihood of impairing driving performance [82]. These three categories loosely correspond to BAC as follows: category I (unlikely to impair driving or no effect, BAC<0.05 %), category II (likely to produce minor–moderate effects, BAC 0.05–0.08 %), and category III (likely to produce severe or dangerous effects, BAC>0.08 %). ICADTS has categorized zopiclone as category III, while zolpidem and zaleplon are assigned to category II [83, 84]. Both zolpidem and zaleplon may be considered category I if taken at 10 mg and driving occurs after 10 and 5 h post-dose, respectively.

There have been several media stories and reports in case law of defendants claiming diminished liability due to Z-drug use prior to committing a criminal or civil offense. Nearly all of these cases have involved alleged parasomnia associated with zolpidem use. Examples include assault or murder during a sleepwalking episode, property damage or personal injury during sleep-driving, and periods of amnesia during which criminal actions were carried out [85]. Courts are unlikely to look favorably on co-ingested alcohol or illicit substances as they are presumed to have been ingested intentionally with knowledge of their adverse effects. The defendant must demonstrate that the Z-drug was ingested unknowingly and that during the time of the offense he or she was intoxicated involuntarily [86]. The defendant will likely need to show that they had no prior knowledge of the adverse effects of zolpidem. This may be more difficult to prove since the FDA warning in 2007 and strengthened package labeling by manufacturers [87].

In past decades, criminal acts during somnambulism and parasomnia have been given leniency, since the requirements of *actus reus* (guilty act) and *mens rea* (guilty mind) were not entirely fulfilled [88]. These two common law elements substantiating a voluntary act are part of the burden of proof beyond reasonable doubt in many jurisdictions including the USA, UK, and Australia. The American legal system has dealt with the defense of somnambulism inconsistently and connected it with automatisms, unconsciousness, and insanity [89]. The emerging field of sleep physiology and increasing knowledge of sleep disorders, coupled with objective EEG and polysomnographic evidence, may better inform expert discrimination between sleep automatisms and intentional acts.

Summary

Z-drugs, in particular zopiclone, appear to have similar adverse effects to their predecessors, the benzodiazepines. The residual effects on human performance and driving impairment of Z-drugs are derived from their GABA-ergic

Table 2 Z-drug blood concentration (ng/mL) in driving impairment

Z-drug	Therapeutic C_{max} (dose)	Legal limit[a]	Driving impairment[b]	Driving impairment[c]
Zolpidem	100–200 (10 mg)	31	77	184
Zopiclone	60–90 (7.5 mg)	12	23	58

Blood/plasma ratio for zopiclone is 1.0. References: [58, 73, 74, 80]

C_{max} maximal plasma concentration at therapeutic doses (in brackets)

[a] Legal limit in Norway

[b] Driving impairment lower threshold (whole blood concentration) for graded sanctions in Norway, comparable to BAC 0.05 %

[c] Driving impairment higher threshold (whole blood concentration) for graded sanctions in Norway, comparable to BAC 0.12 %

action and pharmacokinetic profiles. Z-drugs, especially zolpidem, are associated with complex behaviors, hallucinations, and memory impairment. The increased risk of falls and motor vehicle collisions is notably significant for elderly insomniacs on Z-drugs. The risk–benefit analysis of Z-drugs for the management of insomnia in the elderly may not favor treatment. Prescribers should warn patients taking Z-drugs of minimum time thresholds before they operate machinery or drive motor vehicles.

Conflict of Interest None

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