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REVIEW ARTICLE

The Clinical and Forensic Toxicology of Z-drugs

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Abstract The Z-drugs zolpidem, zopiclone, and zaleplon were hailed as the innovative hypnotics of the new millennium, an improvement to traditional benzodiazepines in the management of insomnia. Increasing reports of adverse events including bizarre behavior and falls in the elderly have prompted calls for caution and regulation. Z-drugs have significant hypnotic effects by reducing sleep latency and improving sleep quality, though duration of sleep may not be significantly increased. Z-drugs exert their effects through increased γ-aminobutyric acid (GABA) transmission at the same GABA-type A receptor as benzodiazepines. Their pharmacokinetics approach those of the ideal hypnotic with rapid onset within 30 min and short half-life (1–7 h). Zopiclone with the longest duration of action has the greatest residual effect, similar to short-acting benzodiazepines. Neuropsychiatric adverse events have been reported with zolpidem including hallucinations, amnesia, and parasomnia. Poisoning with Z-drugs involves predominantly sedation and coma with supportive management being adequate in the majority. Flumazenil has been reported to reverse sedation from all three Z-drugs. Deaths from Z-drugs are rare and more likely to occur with polydrug overdose. Z-drugs can be detected in blood, urine, oral fluid, and postmortem specimens, predominantly with liquid chromatography–mass spectrometry techniques. Zolpidem and zaleplon exhibit significant postmortem redistribution. Zaleplon with its ultra-short half-life has been detected in few clinical or forensic cases possibly due to assay unavailability, low frequency of use, and short window of detection. Though Z-drugs have improved pharmacokinetic profiles, their adverse effects, neuropsychiatric sequelae, and incidence of poisoning and death may prove to be similar to older hypnotics.

Keywords Zolpidem · Zopiclone · Zaleplon · Poisoning · Analysis

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Introduction

Zolpidem, zopiclone, and zaleplon are non-benzodiazepine drugs used in the treatment of insomnia and commonly referred to as the "Z-drugs." Insomnia is an underrecognized and undertreated medical condition that leads to lifestyle impairment, loss of occupational productivity, and potential physical harm from accidents as well as exacerbation of other medical conditions. The rate of diagnosed insomnia in the UK and North America is estimated at 5–15 %, with up to 40 % of the population experiencing symptoms of daytime sleepiness [1, 2]. Some studies quote that up to a third of elderly North Americans are prescribed either a Z-drug or benzodiazepine for sleep disturbance, an alarming statistic given the risks associated with hypnotics in the elderly [3].

Traditional therapy for insomnia has predominantly involved the use of benzodiazepines for several decades. Since the 1980s, development of non-benzodiazepine drugs for the management of insomnia has been driven by the significant adverse effect profile of the former group of drugs. The Z-drugs have unique advantages over benzodiazepines both in their pharmacodynamic and pharmacokinetic properties. Z-drugs have significant hypnotic effects by reducing sleep latency and improving sleep quality, though their ability to prolong total sleep time is debatable [4]. Currently, there are three Food and Drug Administration (FDA)-approved, commercially available, non-benzodiazepine drugs in the USA for the treatment of insomnia: zaleplon, zolpidem, and eszopiclone (the active enantiomer of zopiclone) [5].

The ideal anti-insomnia drug is a potent sedative during the night without causing the same residual sedation during the daytime. Suboptimal clinical and adverse effects of traditional benzodiazepines have driven the development of alternative sedative–hypnotic drugs. While hypnosis and sedation are adequately achieved from oral benzodiazepines, they invariably alter sleep architecture, reduce deep (stage 3 and 4) sleep, and lead to dependence, tolerance, and withdrawal [6]. Furthermore, benzodiazepines carry the risk of residual daytime effects such as impairment of cognitive and psychomotor function. Like benzodiazepines, the newer Z-drugs are agonists at the same γ-aminobutyric acid-type A ($GABA_A$) receptor. However, they possess shorter duration of action and half-life, do not disturb overall sleep architecture, and cause less residual effects during daytime hours, making them more clinically attractive than benzodiazepines.

Initial trials and experience with the Z-drugs were promising with respect to lower incidence of adverse effects and reduced potential for dependence and abuse. Over the last 15 years, increasing reports of bizarre and complex behavioral effects from Z-drugs have prompted drug regulatory agencies to issue warnings and restrictions on the prescribing, dispensing, and use of Z-drugs [7]. This review focuses on the pharmacology and toxicology of Z-drugs with respect to their adverse effect profile, toxicity, and forensic considerations of detection and analysis. Ovid MEDLINE (1980–Nov 2012), Embase (1980–Nov 2012), and Google Scholar were searched using the terms: "zolpidem," "zopiclone," "eszopiclone," "zaleplon" in combination with "mechanism," "pharmacokinetics," "detection," "analysis," "level," "interaction," "poisoning," "toxicity," or "death". Articles relevant to human pharmacology, toxicology, and analysis of Z-drugs were retrieved. Furthermore, the bibliographies of the retrieved articles as well as textbooks, FDA, and other drug agency reports were searched for additional relevant publications. The hypnotic effects of Z-drugs and their clinical efficacy in treating insomnia are not reviewed here. Neither does this review examine the purported benefits of Z-drugs over traditional benzodiazepines in the management of insomnia.

Pharmacology

Benzodiazepines primarily cause their sedative–hypnotic effect by binding non-selectively to the ω_1 (BZ_1) and ω_2 (BZ_2) receptor subtypes of the $GABA_A$ receptor complex. This leads to increased binding of GABA, a major inhibitory neurotransmitter in the central nervous system (CNS), to its own separate binding site and thereby increases the frequency of chloride channel opening [8]. Type 1 (BZ_1) benzodiazepine receptors contain $\alpha_1\beta_{1\text{-}3}\gamma_2$ subunits while BZ_2 subtypes contain $\alpha_{2,3,5}\beta_{1\text{-}3}\gamma_2$ subunits [9]. Sedation and amnesia are mediated through the α_1 subunit, the most commonly distributed subunit throughout the brain, while those mediated via the α_2 and α_3 subunits appear to be involved in sleep regulation and anxiolysis [10]. Z-drugs bind to the same binding site as benzodiazepines, both of which rely on the presence of GABA to exert their effects—hence the term "GABAergic." There appears to be differential binding of Z-drugs to the various $GABA_A$ receptor isoforms.

Zolpidem, an imidazopyridine agent, mediates its effects largely through activation of the α_1-containing $GABA_A$ (BZ_1) receptor, though it has some agonist activity at α_2 and α_3 subunits, and very little at the α_5 subunit. Hence, zolpidem is considered a potent sedative and hypnotic with minimal anxiolytic efficacy. The standard oral dose is 10 mg taken at bedtime, though a lower 5 mg dose is recommended in the elderly or in patients with hepatic impairment. Zolpidem is also available as an extended-release preparation (12.5 and 6.25 mg) intended for better management of sleep maintenance [11, 12]. Treatment duration is commonly for 1 to 6 months depending on patient age, comorbidities, and type of pharmacokinetic preparation (immediate- or extended-release). Clinical efficacy of zolpidem for insomnia has been shown in multiple trials to be comparable to both short-acting and long-acting benzodiazepines, with regard to time to sleep onset, duration, and quality of sleep [13].

Zopiclone is a cyclopyrrolone drug with a chemical structure unrelated to zolpidem, benzodiazepines, or other CNS depressants; it has similar pharmacodynamic and pharmacokinetic properties to zolpidem. It is available as a racemic mixture of two enantiomers one of which is marketed in the USA, the (S)-enantiomer, eszopiclone. Zopiclone shows preferential agonist activity at the α_1 subunit of the $GABA_A$ receptor and its duration of action is the longest of the Z-drugs, comparable with some short-acting benzodiazepines. Hence, zopiclone is useful in both induction and maintenance of sleep. Eszopiclone differs from its racemic mixture in that it has greater efficacy at the α_2 and α_3 subunits. The addition of the R-enantiomer in racemic zopiclone may augment efficacy at the α_1 subunit and potentially lead to increased sedation and residual effects [14].

Zaleplon, a pyrazolopyrimidine drug, has unique properties in its receptor affinity as well as pharmacokinetics, potentially increasing its utility in select sleep disorders. Zaleplon exerts its effects through selective binding at BZ_1 receptors (α_1 subunit); it has low affinity and potency at α_2 and α_3 subunits [10]. It is an ultra-short-acting Z-drug that has the benefit of reducing sleep latency and can be taken after trying but failing to fall asleep. Zaleplon, though not appropriate for sleep maintenance therapy, may be taken for middle-of-the-night awakening [15].

Pharmacokinetics

The pharmacokinetics of the three Z-drugs are similar in that they are all rapidly absorbed and have short half-lives. These characteristics emulate the ideal hypnotic agent, one with rapid peak levels to reduce sleep latency and fast clearance to minimize undesirable residual effects. This is in comparison with short-acting benzodiazepines that have elimination half-lives around 8–10 h. However, too short a half-life may be a problem for patients that require sleep maintenance therapy. Pharmacokinetic properties of Z-drugs are shown in Table 1; major metabolic pathways are in italics [10, 12, 15–19].

Zolpidem is approximately 90 % protein-bound and is extensively metabolized to inactive metabolites by cytochrome P450 enzymes in the liver, predominantly CYP3A4. Elderly patients and those with hepatic impairment are known to have higher area under curve (AUC), time to maximal concentration (T_{max}), and half-life, necessitating dosage reduction in these patient groups. A newer sublingual formulation appears to further reduce sleep latency compared with the oral tablet in a subset of insomniacs [20]. In January 2013, The FDA released a safety announcement advising lower than standard zolpidem doses, particularly in women, due to delayed elimination and residual daytime effects [21].

Zopiclone has the longest latency and half-life of all the Z-drugs with potential for residual effects. Although the pharmacokinetics of eszopiclone is less well characterized, they appear to be more advantageous than the racemic mixture. Eszopiclone's onset is shorter and its offset more rapid than when the racemic mixture is administered to healthy volunteers [22, 23]. This may be explained by the reduced AUC and half-life of the active metabolite, (S)-desmethylzopiclone, following eszopiclone administration as compared to racemic zopiclone [22]. Metabolism of zopiclone involves oxidation, methylation, and decarboxylation with active metabolites that are renally excreted. It is the only Z-drug where dosage reduction in patients with renal impairment is recommended, though accumulation of metabolites has not been shown in studies; no such reduction is recommended for eszopiclone.

Zaleplon has the shortest T_{max} and half-life providing it with a rapid onset and offset profile. Its low bioavailability is due to significant first-pass effect and dosage should be reduced in patients with hepatic impairment. Hepatic metabolism is primarily through the enzyme aldehyde oxidase, with a minor pathway through CYP3A4, to inactive metabolites.

Drug interactions are predictable for Z-drugs metabolized by CYP3A4, especially zolpidem and zopiclone. Flumazenil has been reported to antagonize the sedative effects of all three Z-drugs [24–27]. Zaleplon has few significant interactions due to its main metabolic pathway being aldehyde oxidase. Smoking and oral contraceptive use have been studied in young women, with little effect on zolpidem kinetics [28]. The combination of zolpidem and benzodiazepines has been shown to significantly increase the risk of hospitalization and hip fractures in the elderly [29]. Clinically significant drug interactions of Z-drugs are shown in Table 2 [8, 18, 30–34].

Adverse Effects

In general, Z-drugs are well tolerated and the most common adverse effects include headache, gastrointestinal upset, and dizziness [4, 6]. For a given dose, adverse reactions appear to be worse in elderly patients; hence, lower doses are recommended in this group [4, 16]. A bitter or unpleasant taste has been reported in a dose-dependent fashion in 10–35 % of patients taking zopiclone or eszopiclone, enough to cause cessation of the drug; less common adverse effects include pruritus, visual disturbance, and xerostomia [19]. The daytime residual effects of hypnotic drugs on cognitive and psychomotor performance are a major concern in patients regularly taking these medications.

In March 2007, the US FDA released a list of 13 drugs, including all three Z-drugs, for which stronger labeling was required regarding potential risk from complex sleep-related behaviors, such as sleep-eating and sleep-driving [35]. Of the

Table 1 Pharmacokinetic properties of Z-drugs

Z-drug	T_{max} (h)	Oral bioavailability	Elimination $t_{½}$ (h)	Dose range	Metabolism
Zolpidem IR	1–2	65–70 %	2.5–3	5–10 mg	*CYP 3A4, 2C9*, 1A2
Zolpidem ER	1.5–2.5	65–70 %	2.5–3	6.25–12.5 mg	
Zopiclone	1.5–2	75–80 %	5–6	3.75–7.5 mg	*CYP 3A4*, 2C8
Eszopiclone	1–1.5	75–80 %	6–7	1–3 mg	*CYP 3A4*, 2E1
Zaleplon	0.7–1.4	30 %	~1	5–20 mg	*Aldehyde oxidase*, CYP 3A4

Major metabolic pathways are in italics. References include [10, 12, 15–19]

IR immediate-release preparation, *ER* extended/controlled-release preparation, T_{max} time to maximal concentration (hours), $t_{½}$ half-life (hours), *CYP* cytochrome P450 enzyme

Table 2 Z-drug interactions

Z-drug	Pharmacodynamic	Pharmacokinetic	
		Increased Z-drug effect	Decreased Z-drug effect
Zolpidem	CNS depressants (including benzodiazepines and ethanol)	Azole antifungals	Rifampicin
		Cimetidine	St. John's wort
		Ciprofloxacin	Carbamazepine
	Chlorpromazine	Fluvoxamine	
	Flumazenil	Protease inhibitors	
	SSRIs		
Zopiclone	CNS depressants	Azole antifungals	Rifampicin
	Chlorpromazine	Erythromycin	
	Flumazenil		
Zaleplon	CNS depressants	Cimetidine	Rifampicin
	Flumazenil		
	Thioridazine		

References include [8, 18, 30–34]

Z-drugs, the majority of these events appear to relate to zolpidem though this may merely reflect its higher usage rates or higher doses [7]. Z-drugs have the potential to cause residual effects post-awakening that relate to cognition, memory, parasomnia, and bizarre behavior. They have a profound effect on nocturnal and next-day psychomotor performance including body balance, reaction times, and the ability to multi-task. Z-drug-induced neuropsychiatric adverse effects such as hallucinations and psychosis have been described for over 15 years, particularly with zolpidem [36–38]. The mechanism does not appear to be entirely dose-related or due to elevated plasma concentrations of zolpidem. Drug interactions between zolpidem and various serotonergic and noradrenergic agents including SSRIs, venlafaxine, and tricyclic antidepressants have been reported to induce hallucinations [39].

Tolerance, dependence, and withdrawal are all reported with Z-drugs, though this appears to be less severe and with lower incidence than for traditional benzodiazepines in the treatment of insomnia [5, 13, 40, 41]. Withdrawal symptomatology resembles that from benzodiazepines, including insomnia, delirium, craving, anxiety, tremor, palpitations, and rarely, seizures and psychosis [42]. Rebound insomnia, upon immediate cessation of the hypnotic drug, has been reported with higher doses of zolpidem [43]. This phenomenon has not been reported with therapeutic doses of zopiclone and zaleplon [1, 8]. The potential for zolpidem abuse and dependence in insomniacs is being increasingly recognized with warnings on product labels appearing since 2004 [44]. Though abuse potential exists for all Z-drugs, it is more commonly reported for zolpidem and zopiclone [43, 45].

Analysis and Detection of Z-drugs

The Z-drugs can be analyzed and detected in all common biological matrices, both clinical and forensic samples. The principal mode of analysis remains gas or liquid chromatography with the detection method of choice being mass spectrometry, due to its rapid turnaround time and low limits of quantification [46]. These techniques are also useful in screening for CNS depressants, including benzodiazepines and Z-drugs, such as in cases of unknown drug exposure. With increasing frequency of Z-drug prescriptions and abuse in Europe and North America, benzodiazepine screening tests that employ highly sensitive mass spectrometers are recommended to routinely include Z-drugs. Techniques used in the analysis and detection of Z-drugs in various biological matrices are shown in Table 3 [46–52].

Blood and urine are the commonest matrices for detection of Z-drugs. Urine is most likely to be useful in cases of drug-facilitated crimes where the detection window is longer than in blood or plasma. The detection window in plasma for therapeutic doses of Z-drugs is projected to be around 6–20 h, in urine, roughly 24–48 h [16, 53]. This window is likely to be increased with supratherapeutic ingestions and Z-drug poisoning, though more definitive data are lacking. In drug-facilitated crimes, where higher doses may have been administered, maximum recommended time intervals for Z-drug detection is 48 h in blood and 72 h in urine [54]. Therapeutic maximal concentrations (C_{max}) and those found in fatalities are shown in Table 4 [47, 51, 53, 55–62].

Oral fluid testing provides a simple and noninvasive method for roadside and workplace-based testing. Risk of transmissible infection is much less than blood testing and there is evidence that oral fluid is more likely to show recent drug exposure [63]. With increasing incidence of driving under the influence of drugs, there is an incentive for improving oral fluid testing technique and methodology. Disadvantages of oral fluid as a reliable matrix include significant operator variability, inadequate saliva volumes, interference from food and beverages including deliberate adulteration, and lower drug concentrations than in urine.

Table 3 Detection of Z-drugs

Z-drug	Clinical specimens	Analytical techniques	Postmortem considerations
Zolpidem	Plasma Urine	HPLC, LC-MS/MS LC-MS/MS with electrospray ionization (ESI)	Exhibits postmortem redistribution (PMR)
	Hair	LC-MS/MS (ESI), GC-MS	
	Oral fluid	LC-MS/MS (ESI), GC-MS	
	PM specimens	GC-MS	
Zopiclone	Plasma Urine	LC-fluorescence or UV detection Non-chiral: LC-MS/MS, GC-MS	Low PMR. Unstable in vitro, in methanol and alkaline solvents
		Chiral: capillary electrophoresis (LIF detection) and LC-fluorescence detection	
Zaleplon	Plasma	LC-MS (ESI or chemical ionization)	Exhibits PMR
	Urine PM specimens	Capillary electrophoresis (LIF detection) and LC-MS GC-electron capture detection (LLE and SPE)	Positive in very few postmortem cases

References include [46–52]

ESI electrospray ionization, *GC* gas chromatography, *HPLC* high-performance liquid chromatography, *LC* liquid chromatography, *LIF* laser-induced fluorescence, *LLE* liquid–liquid extraction, *MS* mass spectroscopy, *SPE* solid-phase extraction, *UV* ultraviolet, *PM* postmortem, *PMR* postmortem redistribution

Oral fluid samples are usually tested for benzodiazepines and Z-drugs using gas chromatography–mass spectrometry or liquid chromatography–mass spectrometry techniques.

Hair analysis may be useful in confirming prior exposure to Z-drugs, such as in cases of chronic use or drug-facilitated sexual assault. It can potentially complement tests done on blood and urine, though in some scenarios hair may be the only matrix available. Hair as a biological matrix has several advantages including ease of sampling, storage, and transportation [64]. In general, detection of Z-drugs in hair is difficult due to the low level of uptake into hair. The most developed and sensitive method to detect Z-drugs in hair is liquid chromatography coupled with tandem mass spectroscopy [52]. Depending upon the dose and frequency of Z-drug use, length of hair sampling, and analytical technique utilized, exposure may be confirmed by hair testing weeks, if not months, later. Hair testing must be interpreted appropriately based on limits of detection, inability to determine dose ingested, and potential for poor drug uptake into hair at very low doses [65].

Table 4 Z-drug blood concentrations (in nanogram per milliliter)

Z-drug	Therapeutic C_{max} (dose)	Postmortem levels in poisoning fatalities
Zolpidem	100–200 (10 mg)	>4,000 (zolpidem only)
		1,100–4,500 (co-ingestants)
Zopiclone	60–90 (7.5 mg)	>600 (zopiclone only)
		250–4,000 (co-ingestants)
Zaleplon	20–30 (10 mg)	>1,000 (none solely attributed to zaleplon)

Therapeutic maximal concentrations are in plasma and shown with corresponding administered doses (in parentheses). Postmortem levels are in whole blood; blood/plasma ratio for zopiclone and zaleplon is 1. References include [47, 51, 53, 55–62]

C_{max} maximal concentration

Z-drugs are becoming increasingly part of forensic toxicology testing in postmortem cases. Z-drugs can be quantified in a variety of postmortem specimens including blood, urine, bile, liver, kidney, spleen, vitreous humor, and gastric contents. Central and peripheral postmortem blood specimens show differential concentration for some Z-drugs. This postmortem redistribution (PMR) is observed for many drugs, including benzodiazepines [50]. With PMR, drugs diffuse rapidly across membranes and tissues after death causing differential concentrations between central and peripheral blood compartments. Both zolpidem and zaleplon exhibit significant PMR, though this seems to be low or negligible for zopiclone [48, 66–68]. Zolpidem has been reported to have a central to peripheral blood concentration ratio of 3.74 in postmortem specimens, though previous studies have had lower values [48]. The extent of PMR for zaleplon has yet to be quantified as it is detected in few postmortem cases; this may be related to its lower frequency of use or its very short half-life and antemortem elimination.

Clinical Toxicology of Z-drugs

Overdose, chronic abuse, poisoning, and death have been reported from all Z-drugs. The relative frequency of toxicity appears to be related more to availability and prescription numbers rather than the inherent toxicity of the agents themselves. Comparative toxicity between the Z-drugs has been difficult to quantify due to the fact that the denominator is unknown. However, for zaleplon, the improved

pharmacokinetic profile may contribute to its apparent lower rate of toxicity and fatalities; a confounder to this postulate is that the detection window is more limited and zaleplon ingestion may be missed. In an American Poison Control Center study, zolpidem overdose was more likely to lead to intensive care admission when co-ingested with over-the-counter cold and flu preparations, other psychotropic medication, or ethanol [69].

Garnier et al. reported the first large series of zolpidem poisoning cases in 1994, where the toxicity predominantly involved sedation with ingestions up to 1.4 g [56]. Rarely did zolpidem cause coma, respiratory depression, cardiovascular toxicity, or death. Since then, reports of agitation, hallucinations, psychosis, and coma from Z-drug overdose have been published [70–73]. Other unusual reports include hemolytic anemia and methemoglobinemia from zopiclone, suggesting oxidative stress from either the parent drug or its metabolites, one of which is an *N*-oxide derivative [74–76].

Onset of drowsiness from Z-drug overdose is early, and recovery is often complete within several hours. Pediatric cases of Z-drug ingestion have similarly demonstrated minimal toxicity in accidental poisoning [77]. Onset of drowsiness was invariably within the first hour of ingestion and few cases required any intervention. Manufacturers have altered some zaleplon products by adding a blue colorant, in order to minimize covert drug administration into liquids and drinks. The blue colorant, indigo carmine, has been observed in overdose patients' gastric contents and urine (chromaturia) [27].

Treatment of Z-drug overdose is largely supportive, as for benzodiazepine poisoning, with complete recovery expected within 6 h. Attention to airway patency and supportive management of ventilation and hemodynamics are usually sufficient. With rapid absorption, potential for early sedation and short duration of effect, decontamination methods are rarely warranted. The administration of activated charcoal is likely to be more harmful than beneficial in pure Z-drug overdose. Flumazenil, a competitive benzodiazepine antagonist, has been shown to reverse the sedative effects of all three Z-drugs [24–27]. Flumazenil has also been reported to reverse sedation within minutes in pediatric ingestions of zolpidem [78]. In pure Z-drug poisoning, where sedation is of short duration and flumazenil may be indicated, bolus doses are likely to be sufficient, with infusions being unnecessary. Caution is advised when administering flumazenil in unknown or polydrug overdose, as unmasking of ingested pro-convulsant drugs may lead to seizure activity.

Z-drug Deaths

Early clinical trials failed to show major morbidity or mortality from Z-drugs either used therapeutically or in overdose. Over the past 15 years, increasing red flags from forensic cases, drug-facilitated crimes, and motor vehicle crash statistics indicate that mortality from Z-drugs may be similar to benzodiazepines. Bizarre behavior, falls, accidents, and other injuries may also lead to death.

In the study by Garnier et al., 6 % of zolpidem overdose cases died; however, none were directly attributable to zolpidem [56]. A 10-year audit of coronial deaths in New South Wales, Australia identified over 90 cases where zolpidem was detected in postmortem blood or liver [79]. A quarter of these cases had femoral blood zolpidem levels above 1,000 ng/mL (therapeutic C_{max} 100–200 ng/mL). Of note, the majority of cases in which zolpidem was thought to contribute to death were mixed drug overdoses, with the most common co-ingestants being alcohol, antidepressants, benzodiazepines, and opioids.

Z-drugs had a significantly lower fatal toxicity index (FTI) than benzodiazepines and barbiturates in a UK review of deaths from 1983 to 1999 [80]. Zolpidem and zopiclone caused ~2 deaths per million prescriptions in England and Scotland, compared with ~7 for benzodiazepines and ~150 for barbiturates. In this study, cumulative data on zopiclone-related deaths suggest that it may have the lowest FTI of anti-insomnia drugs. However, a New Zealand study contradicted these findings showing that zopiclone had a similar FTI to commonly prescribed benzodiazepines [81]. Caution should be used in interpreting FTI as a reliable marker of inherent drug toxicity, as it may merely represent frequency of drug abuse or prescribing patterns in patients with higher suicidality.

Z-drug concentrations in forensic cases are shown in Table 4 with comparison plasma levels from therapeutic dosing. Their short half-lives make them seldom found substances in forensic cases, both in drug-related deaths as well as in drug-facilitated crimes. Interpretation is complicated by considerable individual variation, small sample sizes, and the presence of co-ingestants. Polydrug overdose is a major confounder in deciding whether the fatalities are attributable to detected Z-drugs. Although there have been several reported fatalities where zaleplon has been ingested along with other drugs, none have been solely attributable to zaleplon [66, 82]. This may represent lower zaleplon use or difficulties in measuring zaleplon levels due to its ultra-short half-life and rapid antemortem metabolism.

Summary

Z-drugs have few distinct advantages over their predecessors, the benzodiazepines, and in many ways they have similar adverse and toxic effects, especially zopiclone. The effects of Z-drugs largely derive from their GABAergic action and pharmacokinetic profiles, which decide the

extent of efficacy and toxicity. Adverse Z-drug effects and toxicity are more likely with polydrug use in therapeutics and co-ingested psychoactive substances in overdose. Z-drug poisoning is clinically similar to benzodiazepine overdose with supportive care sufficient in managing the majority of cases. The increasing ability to detect Z-drugs in various biological matrices is promising for future forensic endeavors. Postmortem redistribution appears to be significant for zolpidem and likely also for zaleplon. It is recommended that public health and drug regulatory authorities maintain a high level of toxicovigilance with regard to Z-drugs and their adverse outcomes.

Conflict of Interest None

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