



Hypnotic hazards: adverse effects of zolpidem and other z-drugs

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Summary

Zolpidem, zopiclone and zaleplon are hypnotics with similar pharmacology to benzodiazepines. In addition to the usual adverse effects of sedative drugs, there have been unusual reactions associated with the 'z-drugs', particularly zolpidem. It is unclear why there have been so many reports of bizarre behaviour in Australians taking zolpidem. Some of the cases may be the result of other conditions or drugs. As many patients with insomnia can be managed without drugs, limiting the use of hypnotics will limit any harmful effects.

Key words: benzodiazepines, insomnia, zopiclone.

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Introduction

The 'z-drugs', zolpidem, zopiclone and zaleplon, are sedatives, marketed as hypnotics. Zopiclone was marketed in Australia in 1994 with zolpidem following in 2000. Zaleplon is not currently available in Australia. The z-drugs have been promoted as being safer than benzodiazepines, and in many countries they are the most widely prescribed drugs for insomnia. As the drugs have never been listed on the Australian Pharmaceutical Benefits Scheme, there are no readily available data on how widely they have been used here.

Pharmacology

The z-drugs are sedatives which act at GABA receptors in the brain. They are not chemically related to benzodiazepines but their pharmacology is similar. (They bind to a receptor subtype known as the benzodiazepine-1 subtype.) At standard doses, in sleep laboratory tests, they do not impair memory and cognition as much as benzodiazepines. Their half-lives are relatively short (1 hour for zaleplon, 2–3 hours or so for zolpidem and about 5 hours for zopiclone). At standard doses, they are less likely to cause marked residual daytime sedation than benzodiazepines.

Unusual adverse effects

In the 1990s there were sporadic published case reports of visual hallucinations, and later of amnesia and compulsive behaviour associated with zolpidem. After the first year of marketing in Australia, the Adverse Drug Reactions Advisory

Committee (ADRAC) noted a significant number of reports of visual hallucinations and a smaller number of reports of amnesia with zolpidem. By 2007 ADRAC had received 104 reports of hallucinations, 62 of amnesia, and 16 of unusual or inappropriate behaviour of which the patient had no memory.¹ Television and newspaper reports, on the other hand, state that there have been 'more than 400' adverse event reports and 'up to 14 deaths' related to zolpidem.² Despite the numerical dominance of hallucinations in ADRAC reports, it has been inappropriate behaviour with amnesia which has created most media interest and which has dominated direct reports from consumers.³ Similar events related to zaleplon and zopiclone have rarely been reported, but media stories have often referred to problems with z-drugs as a group. There have been reports in other countries, but the rate of adverse events relating to zolpidem appears to be much higher in Australia.⁴

Although the media have been impressed with the outlandish adverse events reported with zolpidem, these events are not unprecedented. Amnesia, hallucinations and bizarre behaviour were also seen frequently in patients taking the short-acting benzodiazepine, triazolam, for insomnia.⁵

Nocturnal activity with amnesia

Complex behaviour with amnesia is a common and non-specific effect of sedative drugs. Alcohol is the prototype drug causing disinhibition, inappropriate behaviour and amnesia, but all sedative drugs can have similar effects. Z-drugs do cause sedation and amnesia, especially in higher doses.^{6,7} This effect is little different from that of the benzodiazepines – although advertisements for the z-drugs may not have conveyed this clearly. The frequency of reports of amnesia with zolpidem, with or without abnormal behaviour, may be related to a mistaken belief that it would not cause sedation and amnesia at all. Taking zolpidem with alcohol or other psychoactive drugs is common, and exaggerates the sedative and amnesic effects. Many overseas reports of bizarre behaviour with zolpidem have involved patients taking multiple psychoactive drugs as well as alcohol, but it is not clear how often this has been the case in Australia.

Sleepwalking

Many of the 'unusual behaviour with amnesia' events reported with zolpidem have been called sleepwalking, but electroencephalographic confirmation of this diagnosis is lacking, and it may not be correct. Sleepwalking occurs when

the cortex is asleep, but areas of the brain concerned with motor control are active. Z-drugs do not prevent sleepwalking in the way benzodiazepines do, but their pharmacology as it is currently understood does not suggest that they would worsen sleepwalking or cause it to start. No drug has ever been shown in laboratory studies to cause sleepwalking or even to precipitate events in known sleepwalkers. However, the reported ability of zolpidem (but not zopiclone or zaleplon) to activate the cortex in patients with anoxic brain injury does raise the possibility that it has unusual effects on the cortex.⁸ These effects could, conceivably, precipitate sleepwalking in patients predisposed to it. Since about 10% of children and 2% of adults sleepwalk there is a large pool of patients predisposed to sleepwalking, so a small effect of the drug could possibly account for what has been reported.

The spectrum of behaviour in sleepwalking is wide, from muttering and talking to getting up and walking about, but it is confined to what can be done with no cortical input: purposive or adaptive behaviour is not likely to be sleepwalking. In contrast, many reports of abnormal behaviour with zolpidem are of complex and apparently adaptive behaviour inconsistent with sleepwalking. There is a wide differential diagnosis for unusual nocturnal activity with amnesia. As well as sleepwalking, common causes are epilepsy, REM (rapid eye movement) behaviour disorder, micro-sleeps, confusional arousals and dissociative states associated with mental illness.

Normal sleep causes antegrade amnesia for the 5–10 minutes before sleep onset, and micro-sleeps (intrusions of sleep, lasting seconds, into wakefulness) also do this. Severely fatigued individuals can have frequent micro-sleeps, and thus quite long periods of amnesia, although the person is awake between the micro-sleeps and can carry out complex actions. This is relatively common in severe obstructive sleep apnoea, in parents of babies who sleep poorly, and in shift workers.

Confusional arousals are arousals from sleep with disorientation, amnesia and sometimes automatism, which can involve inappropriate or aggressive behaviour. Mild events are common in fatigued individuals, such as long distance travellers (waking up in hotel rooms with no idea where they are) and shift workers. Sedatives of all kinds can also cause these events, and the combination of fatigue and sedative drugs makes them more frequent and worse.

Bizarre and compulsive behaviour

Many reports of behaviour with amnesia related to zolpidem have emphasised its bizarre or inappropriate character. Sleep-eating, sleep-sex and sleep-driving have been reported. However, in no case is there electroencephalographic evidence that the patient was asleep at the time, that is, evidence to distinguish sleepwalking from, for example, confusional arousal. Often, it is said that the behaviour was compulsive or irresistible, but it is unclear what is meant by this when

amnesia is reported as well.⁹ For example, the ADRAC Bulletin has spoken of patients with 'uncontrollable urges to eat while asleep'¹, but if the patients were asleep, how did they know they had uncontrollable urges?

While these forms of behaviour seem outlandish, there are case series of sleep-eating and sleep-sex in patients who have not taken z-drugs which are larger than those in patients who have. Nocturnal eating is common, and although it can occur during sleepwalking, when there are feelings of compulsion the eating occurs during wakefulness.^{10,11}

Reports, or claims, of having sex while asleep are also common.¹² The difficulty is to distinguish sex during sleep from (what is far more likely) sex with amnesia for the event caused by subsequent sleep (assisted, perhaps, by alcohol or another drug). The great majority of carefully studied cases of sex with amnesia have been found to represent sex after partial or confusional arousal rather than sex during sleep.^{13,14}

Sleep-driving is a more difficult problem because it cannot be studied in the sleep laboratory in the way that sleep-sex and sleep-eating can. Carefully studied cases of sleep-driving are rare, and are actually cases of patients who have histories of driving with amnesia and well-documented sleepwalking.¹⁵ Wakeful driving with amnesia caused by drugs is a far more likely cause of reports of sleep-driving, and is certainly the cause of the great majority of cases of sleep-driving reported with zolpidem in the USA.

Zolpidem has been linked to suicide, although in one widely publicised Australian case zolpidem had been withdrawn and replaced by zopiclone a week before death.² Database evidence shows clearly that z-drugs are not associated with a higher risk of suicide from poisoning^{16,17}, and although an effect on other means of suicide is not excluded it must be unlikely.

Hallucinations and psychosis

The most frequent unusual adverse effect of zolpidem reported in Australia has been visual hallucinations. In published reports the hallucinations usually last 30 minutes or so, although there are reports of hallucinations lasting several hours in patients taking both zolpidem and serotonin reuptake inhibitors.¹⁸ In most reported cases the hallucinations have been an isolated phenomenon, but there are reports of psychotic reactions to zolpidem.¹⁹

Comparative incidence of adverse effects

Whether abnormal behaviour with amnesia and hallucinations are commoner with z-drugs than with other sedatives cannot be determined from the available data. Systematic reviews of controlled trials of z-drugs have not revealed the adverse effects reported by patients in Australia. However, adverse events occurring in less than 1% of patients would not be expected to be revealed in trials.²⁰ Systematic reviews do show that in

older people adverse cognitive and psychomotor effects are common with all sedatives, but they are not obviously more common with z-drugs.²¹ Motor vehicle accidents are increased by use of z-drugs (relative risk 2.3), but somewhat less than by use of benzodiazepines (relative risk for nitrazepam 2.7 and for flunitrazepam 4.0).²²

Postmarketing surveillance outside Australia has not revealed a high prevalence of behavioural adverse events with z-drugs. For example, a survey of 14 029 patients treated with zolpidem for four weeks found 20 patients who reported nightmares, 19 who reported agitation, and one who developed paranoid ideation during treatment.²³ A French regional study of prescriptions for hypnotics, anxiolytics and antidepressants given to adolescents found that of 3286 prescriptions issued in one year, 2724 were for zolpidem, but there were only three reports of adverse drug reactions.²⁴

Available data also do not answer the question of whether the frequency or severity of adverse effects of z-drugs may relate to particular patient characteristics. Psychiatric illnesses, particularly anxiety and depression, are common in patients with insomnia, but it is not clear that this plays a role in the adverse event reports.

Recommendations

Z-drugs are effective for insomnia – in a manner of speaking. 'In a manner of speaking' because the effect on the deficits complained of by patients with insomnia is small. Across all hypnotic drugs there is a mean increase in total sleep time of 25 minutes.²¹ Only for zopiclone is there evidence from randomised controlled trials of sustained improvements in self-reported work performance and quality of life. These effects were small and there is, obviously, a problem with blinding in placebo-controlled trials of a drug with zopiclone's action.²⁵

Z-drugs are no better for insomnia than benzodiazepines. They cause sedation and increase the risk of motor vehicle accidents, and are not a safe alternative to benzodiazepines in patients who need to drive. Z-drugs do cause dependency²⁰, and are not a safe alternative for patients who have had problems with dependence on benzodiazepines.

It is possible to manage insomnia without ever using hypnotic drugs and this approach should be the rule rather than the exception. Insomnia is commonly caused by delayed sleep phase syndrome*, constitutional short sleep need†, or the effects of caffeine or alcohol, and sedative drugs should not be used for these patients. Some patients with depression and others with significant psychiatric illness may need drug treatment specifically for poor sleep, but most patients seen in general practice do not.

At present, there is no good evidence that z-drugs should be prescribed with unique precautions. On the other hand, it is seldom a good idea to prescribe any sedative drug for insomnia

in patients over 60 years of age, for patients who may need or choose to drive or make important decisions within eight hours of taking a dose, or who live alone. These cautions apply with special force to patients taking another psychoactive drug.

If patients are prescribed z-drugs they should be made aware that sedation, confusion and disinhibition may occur. They should be advised to avoid alcohol. The hypnotic should be taken once the patient is in bed, not on the way to bed. Simple changes to the home environment, such as securing the bedroom door and windows, can reduce the risk of harm from sedation, disinhibition and confusion. It may be prudent to advise patients to make these changes, especially if they have a psychiatric illness that may predispose them to suicide or are taking multiple psychoactive drugs.

Conclusion

Evidence that z-drugs, especially zolpidem, commonly cause adverse effects not predictable from their pharmacology is weak. Zolpidem may cause hallucinations relatively frequently (as triazolam did), but reports of 'abnormal behaviour with amnesia' probably reflect predictable effects. Z-drugs have few advantages over benzodiazepines, and there is no good reason for their use in insomnia. If there were fewer prescriptions there would be fewer adverse events.

* 'Delayed sleep phase' refers to otherwise normal individuals whose natural sleep pattern is to go to sleep late – midnight or later – and wake up late – 9 am or later. If for social or occupational reasons getting up this late is unacceptable, the person typically attempts to go to sleep earlier in order to get up earlier, but when they are unable to go to sleep before their natural sleep time they may complain of insomnia.

† 'Constitutional short sleep need' refers to otherwise normal individuals who habitually sleep only a few hours a night (often four or five) but do not feel the need of more. This may cause a complaint of insomnia, typically when the person retires and no longer values their ability to study until midnight and then be up at 5 am to exercise before going to work.

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Further reading

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Self-test questions

The following statements are either true or false (answers on page 167)

1. Sedative drugs are likely to cause sleepwalking in people who have not previously sleepwalked.
2. Amnesia may be caused by micro-sleeps.