Zolpidem and Zopiclone: Are They the Same?

Dr Lam Tat Chung, Paul
(林達聰醫生)

FRCP, FRCPsych, FHKAM (Medicine), FHKAM (Psychiatry)
Specialist in Psychiatry (Private Practice)
President

Zolpidem (Stilnox®) and zopiclone (Imovane™) are among the most frequently prescribed hypnotics in Western medicine (Note 1). They are the only z-drugs available in Hong Kong. Both drugs are believed to be good substitutes for benzothiazepines, with less tendency for abuse, addiction, dependence or withdrawal. (However this view is now under dispute.)

The two drugs are very similar. They are cheap, effective, well tolerated, and have short half-lives. But are they the same, or should a doctor choose one over the other when prescribing to a patient?

Zolpidem is an imidazopyridine compound that acts as an agonist on the alpha-1 subtype of the benzothiazepine site of the GABA-A receptor. Thus it has a specific effect on sedation and has no myorelaxant, anxiolytic and anticonvulsant properties. These give it a theorectical advantage over zopiclone, for instance, in patients with obstructive sleep apnoea.

Zopiclone is cyclopyrrolone compound that acts on alpha-1 and more broadly, on other alpha subtypes, making it more similar to a benzothiazine drug.

In response to reports of abnormal behaviours during sleep after taking these drugs, the US Food and Drug Administration (FDA) imposed a black box (ie, the most serious) warning in April 2019 cautioning on the use of z-drugs: "Serious injuries and death from complex sleep behaviours [Note 2] have occurred in patients with and without a history of such behaviours, even at the lowest recommended doses, and the behaviours can occur just after one dose. These behaviours can occur after taking these medicines with or without alcohol or other central nervous system depressants that may be sedating such as tranquilizers, opioids and anti-anxiety medicines."[1]

So far these are the similarities. Now let us look at the differences.

The FDA identified 62 cases of complex sleep behaviours that reported serious injuries or death after taking z-drugs (zolpidem, 61; eszopiclone, 3; zaleplon, 2) in 26 years (1992–2018).[1]

In a paper analysing the adverse drug reactions to z-drugs,[2] using the European Medicines Agency database from 2003–2017, the following results were obtained:

	Zolpidem	Zopiclone
Adverse drug reactions	206,315	65,140
No. of patients	4,374	1,760
Events per patient	47	37

Thus, the relative risk of zolpidem over zopiclone is 1.27, or 27% higher.

Further analysis revealed that the tendency for misuse, abuse and withdrawal was higher among zolpidem users than zopiclone users, but the reverse was true for overdose. Fatal outcome was 20.3% for those who took an overdose of zolpidem compared with 9.33% for those who took zopiclone.

A paper from South Korea in 2020 conducted a 12-year, population-based, retrospective cohort study on over 1 million people from 2002 to 2013. The adjusted hazard ratio of suicides associated with the use of zolpidem was 2.01.[3]

In a systematic review and meta-analysis in 2022, a significantly increased risk of suicide or suicide attempt was found among zolpidem users compared with non-users, with a pooled relative risk of 1.88. Furthermore, an increased risk of suicidal death was observed among zolpidem users compared with non-users, with a pooled relative risk of 1.82.[4]

In Australia, the Adverse Medicine Events Line reported 29 cases of neuropsychiatric reactions, including two deaths in the 3 years prior to November 2005. Twenty-six cases were related to zolpidem use and three to zopiclone.[5] The greatly increased risk of zolpidem cannot be attributed to more prescription of the drug, as shown in another paper[6] reporting that the prescription for zopiclone exceeded the prescription for zolpidem in Australia every year from 2011 to 2018.

Zopiclone is also the most commonly used hypnotic in the UK.[7] In Alberta, Canada, zopiclone had the highest frequency of use among hypnotics.[8] Zopiclone was prescribed to 47.4% of all patients using hypno-sedative medications in Alberta.[9] In Canada, zolpidem is only available as a sublingual tablet, and it is not covered by government insurance payment. Hence, its use is minimal.

A review of 29 psychoactive drugs (including the three z-drugs) in 2018 showed that zolpidem had the strongest evidence for medication-induced sleep walking (complex sleep disorder).[10]

In a comparison between zolpidem and zopiclone in elderly patients with Alzheimer's disease, zopiclone increased the main nocturnal sleep duration by 81 minutes, but there was no improvement for zolpidem.[11]

Eszopiclone administration to adult guinea pigs increased the mean duration of episodes of non–rapid eye movement (NREM) sleep, but not zolpidem administration.[12] NREM sleep promoted repair and regrowth of the body, building of bone and muscle, strengthening of the immune system and memory consolidation.

As with any other medication, drug interaction must be considered, as many patients are taking psychotropic drugs at the same time. The main concerns are competition in protein binding and the CYP450 enzymes. Co-administration with fluoxetine increased the half-life of zolpidem by 17%, and co-administration with sertraline increased zolpidem peak concentrations by 43%.[13] Co-administration with fluvoxamine and valproic acid[14] has been incriminated as the cause of sleep disorders. Two patients fatally shot their spouses after taking zolpidem with paroxetine.[15]

For my own clinic, I do not prescribe any zolpidem. I advise all my patients and colleagues not to take it. I have seen many cases (including doctors) who have gotten up to cook at night and then forgot to switch off the gas stove, or who have driven out and returned safely to their car parks but had amnesia for the episode.

Lesson: When prescribing z-drugs, your informed choice matters.

To earn 1 CME point, take the "Self-Study CME" quiz for this article on page 132.

Note 1. Zopiclone is used in Europe, while eszopiclone, a stereoisomer, is used in the US.

The European Medicines Agency determined that there is no advantage of eszopiclone over zopiclone.

Note 2. Please see "Complex Sleep Behaviours and Sleepwalking" at the bottom of this page.

A complete list of references can be downloaded from www.SOPHYSICIANSHK.org

Clinical Notes in Psychiatry and Neurology

Complex Sleep Behaviours and Sleepwalking: The Confusion of Two Confusional States

Dr Lam Tat Chung, Paul
(林達聰醫生)

FRCP, FRCPsych, FHKAM (Medicine), FHKAM (Psychiatry)
Private Specialist
Email: drtclam@netvigator.com

Parasomnias are disorders characterised by abnormal behaviours occurring in association with sleep. They are divided into two types:

- Rapid eye movement sleep (REM) behaviour disorders, including restless leg syndrome, sleep paralysis, nightmares, and REM sleep behaviour disorder
- Non–rapid eye movement sleep (NREM) behaviour disorders

The following Table (see next page) gives the details on the types of NREM disorders as defined by ICSD-3 (International Classification of Sleep Disorders) and DSM-5 (Diagnostic and Statistical Manual).

Both classifications of NREM disorders include sleepwalking and exclude conditions due to medication use. In DSM-5, there is a differential diagnosis of medication-induced complex behaviours. In sleepwalking, the patient is deeply asleep and cannot be easily woken up. There is complete amnesia for the event. The patient will not answer questions or follow instructions. They can sometimes perform complex behaviour like driving a car, although they can fall off a balcony and injure themselves. Their awareness is diminished, so they are in a confused state. They are totally amnesic for the episode. When they awake, they will become totally awake quickly.

In complex sleep behaviour due to drugs (frequently z-drugs), the patient is not in a state of sleep. They are in a state of decreased consciousness. They may be able to react to the environment, like answering some questions and driving a car with or without accident. Their level of consciousness may fluctuate and may last for a long time (eg, days). They may have total or partial amnesia.

Here is the issue: The two different conditions are often confused, even in learned journal papers. Many authors talk about sleepwalking or sleep driving after taking z-drugs, but in fact these are complex sleep behaviours. The word 'sleep' here means that the abnormal behaviour occurs after the patient goes to sleep, not that the patient is in a state of sleep.

It is important to make the distinction. Quoting a paper from *Sleep Medicine Reviews*[1]:

The term sleep driving should be reserved for patients who have signs, symptoms and history consistent with sleep walking and related disorders. Driving while impaired following abuse or misuse of z-drugs or other sedative hypnotics should not be attributed to sleep or sleepwalking. The data reviewed in this article suggest that the majority of cases should be labelled simply as "drug-related impaired driving".

Reference

1. Pressman M. Sleep Med Rev 2011;15:285-292.

Table. International diagnostic criteria for non-rapid eye movement sleep parasomnias according to ICSD-3 and DSM-5.

Definition	
ICSD-3	
Clinical manifestation	A. Recurrent episodes of incomplete awakening from sleep B. Inappropriate or absent responsiveness to efforts of others to intervene or redirect the person during the episode C. Limited (eg, a single visual scene) or no associated cognition or dream imagery D. Partial or complete amnesia for the episodes Notes: • The events usually occur during the first third of the major sleep episode. • The individual may continue to appear confused and disoriented for several minutes or longer following the episode.
Exclusion	E. The disturbance is not better explained by another sleep disorder, mental disorder, medical condition, medication or substance abuse.
Subtypes	• Sleep terror • Sleepwalking • Confusional arousal – Sleep-related abnormal sexual behaviours
DSM-5	
Clinical manifestation	A. Recurrent episodes of incomplete awakening from sleep, usually occurring during the first third of the major sleep episode, accompanied by either one of the following: – Sleepwalking: repeated episodes of rising from bed during sleep and walking about. While sleeping, the individual has a blank, staring face; is relatively unresponsive to the efforts of others to communicate with him or her; and can be awakened only with great difficulty – Sleep terrors: recurrent episodes of abrupt terror arousals from sleep, usually beginning with panicky scream. There is intense fear and signs of autonomic arousal, such as mydriasis, tachycardia, rapid breathing and sweating, during each episode. There is relative unresponsiveness to efforts of others to comfort the individual during the episodes B. No or little (eg, only a single visual scene) dream imagery is recalled. C. Amnesia for the episodes is present.
Distress/ Disability	D. The episodes cause clinically significant distress or impairment in social, occupational or other important areas of functioning.
Exclusion	E. The disturbance is not attributable to the physiological effects of a substance (eg, a drug of abuse, a medication). F. Coexisting mental and medical disorders do not explain the episodes of sleepwalking or sleep terrors.
Subtypes	• Sleep terror type • Sleepwalking type – With sleep-related eating – With sleep-related abnormal sexual behaviours

DSM, Diagnostic and Statistical Manual; ICSD, International Classification of Sleep Disorders