



National Prescribing Service Limited

NPS Position Statement

July 2008

Zolpidem and sleep-related behaviours

Review and implications for insomnia management

Summary

- In February 2008 the Therapeutic Goods Administration (TGA) placed a boxed warning on the product information of medicines containing zolpidem. The warning:
 - highlights potentially dangerous sleep-related behaviours that may be linked to zolpidem use
 - advises that zolpidem should not be taken with alcohol, and that caution is needed with concurrent use of other CNS depressants
 - recommends limiting use to a maximum of 4 weeks.
- In postmarketing reports zolpidem has been associated with a variety of bizarre sleep-related events — such as sleepwalking, sleep-eating and sleep-driving — with patients having no subsequent memory of the event.
- Sleep-related events have been reported with other hypnotics, but the pattern of reports with zolpidem has been interpreted by the TGA as signalling increased risk with this medicine. While these behaviours are considered rare, the incidence is uncertain. A causal link between zolpidem and these behaviours has not been established.
- If a sleep-related event occurs during use of zolpidem (or another hypnotic), stop the medicine to avoid potential harms to the patient and the community.
- Sleep-related events can occur with therapeutic doses of zolpidem in people without predisposing factors. However, the risk is probably increased by alcohol, other CNS depressants, and high doses of zolpidem.
- Non-drug therapies are recommended as initial treatment for insomnia.
- Reserve short-acting benzodiazepines (e.g. temazepam), zolpidem, or zopiclone for short-term severe insomnia, and for intermittent use in chronic severe insomnia unresponsive to non-drug therapies.
- The risks associated with hypnotics generally outweigh any benefits they provide with continuous long-term use.
- There is no convincing evidence that the benefit–harm profile of zolpidem or zopiclone is more favourable than that of short-acting benzodiazepines. Tolerance, dependence, withdrawal symptoms and morning sedation have also been reported with zolpidem and zopiclone.
- For all hypnotics, use the lowest dose for the shortest time possible (ideally for less than 2 weeks) and re-evaluate within 7–14 days of starting therapy.

What is the evidence to link zolpidem with bizarre sleep-related behaviours?

The evidence linking zolpidem with bizarre sleep-related behaviours consists of postmarketing surveillance, particularly in Australia, and published case reports. Although sleep-related behaviours have been reported with other hypnotics¹, the Therapeutic Goods Administration (TGA) considers that the pattern of reports with zolpidem signals an increased risk of these events with this medicine. The incidence of these events is not known, but the wide international use of zolpidem over the last 15 years suggests that they are rare.

Adverse events reported to the TGA in the first year zolpidem was marketed in Australia (2000) showed an unusual pattern of psychiatric and neurological reports.² By February 2007, there were 16 reports of sleepwalking, including 2 reports of sleep-driving.³ These reports drew substantial media interest, and 12 months later more than one-third of all reports to the TGA for zolpidem (392 of 1032) described a sleep-related event (10% of all reports were for sleep-driving).⁴ Note that an increased rate of reporting alone does not prove causality, as individual cases may have confounding factors. Also, the rate of reporting does not suggest actual incidence, as many external factors are known to influence reporting, such as media attention, marketing, and other factors.

Published reports of sleepwalking⁵, phone conversations⁶ and hallucinations⁷ emerged with zolpidem in the mid-1990s. Since then, other unusual sleep-related events have been described internationally, including

preparing and eating food⁸⁻¹², compulsive house cleaning¹⁰, sleep-driving³, and house painting³, in addition to reports of sleepwalking.¹³⁻¹⁶

People exhibiting these sleep-related behaviours have consistently reported no memory of the event. Most events occurred after the first dose of zolpidem or within a few days of starting therapy.^{2,5,14,15} In most cases the behaviour resolved when zolpidem was stopped.

Report suspected adverse reactions to the TGA online (www.tgasime.health.gov.au) or by using the 'Blue Card' distributed with *Australian Prescriber*. For information about reporting adverse reactions, see the TGA website (www.tga.gov.au).

Avoid use of alcohol, other CNS depressants, and higher-than-recommended doses of zolpidem

Alcohol use, other CNS depressants, and taking more than the recommended dose of zolpidem are likely to increase risk of these events.^{*17} A history of restless legs syndrome⁹, drug and alcohol abuse¹³, mental illness^{8,13,14,16}, or sleepwalking^{5,14} may be predisposing factors, but their relative contribution is uncertain. Reports have involved people who did not drink alcohol at the time of taking zolpidem, who took a therapeutic dose or who had no history of sleepwalking or other obvious risk factors.⁴

What is the advice of regulatory authorities?

As part of ongoing monitoring of the safety of zolpidem, the TGA noted the continued reporting of adverse events throughout 2007. In February 2008, the TGA moved to increase the warnings about zolpidem by imposing a boxed warning at the start of the product information of all medicines containing zolpidem.⁴ The warning states that:

- zolpidem may be associated with potentially dangerous complex sleep-related behaviours, which may include sleepwalking, sleep-driving, and other bizarre behaviours
- zolpidem is not to be taken with alcohol
- caution is needed with other CNS depressants
- use should be limited 4 weeks maximum under close medical supervision.

The TGA also encourages doctors to use zolpidem in accordance with the approved indication, only where

clinically indicated, and for short periods of time. Pharmacists are encouraged not to dispense more than a single pack at a time.

A warning about complex sleep behaviours had previously been added to the Australian product information of all sedative-hypnotic drug products. In addition to warning about concurrent use of alcohol and CNS depressants, the statement advises that¹⁷:

- the risk of these events appears to be increased at doses exceeding the maximum
- events can occur in both sedative/hypnotic naïve and sedative-experienced patients
- if a patient reports a sleep-driving episode, discontinue treatment because of the risk to the patient and the community.[†]

*The recommended maximum dose of zolpidem is 12.5 mg immediately before bedtime (modified-release tablet).¹⁸

† Gradual withdrawal may be required for continuous long-term use.

Treating insomnia

There are many potential causes of insomnia that should be addressed before making a treatment decision. Sleeping difficulties may be caused by psychiatric disorders (particularly depression), environmental factors, substance abuse, medicines, chronic pain states, cardiac and respiratory failure, sleep apnoea, and restless legs syndrome.^{19,20}

Use non-drug therapies first

Non-drug therapies are accepted as the first choice for insomnia because they may be useful and do not have the risks associated with drug therapy.²¹ A systematic review of 6 clinical trials showed a modest beneficial effect on sleep maintenance with combined behavioural therapies.²²

Sleep hygiene principles and stimulus-control advice (resetting cues for sleep) are simple strategies that may be useful for the short- or long-term management of insomnia. Some fundamental principles include^{19,20}:

- going to bed only when you feel sleepy
- using the bedroom for sleep and not to read or watch TV in bed
- avoiding caffeine, nicotine and alcohol
- exercising regularly, but not in the late evening

- getting out of bed and going to another room if not asleep after 20 minutes
- getting up at the same time each morning
- avoiding daytime sleep.

Sleep restriction therapy aims to improve the percentage of time that is spent in bed asleep, monitoring progress by using a sleep diary. The first step is to delay normal sleep time, after which regular adjustments are made to increase the length of sleep.^{19,21}

Cognitive therapy aims to modify irrational beliefs about sleep. It may require referral to a psychologist.^{20,21} Medicare rebates for cognitive behavioural therapies are available for eligible patients.

Relaxation therapies aim to reduce physiological, cognitive or emotional arousal before bed.^{20,21}

Regular exercise may be useful for improving chronic insomnia in older adults with sedentary lifestyles and has a variety of other health benefits.²¹

The Australasian Sleep Association has further information on non-drug therapies for insomnia, including contact details for Insomnia Treatment Services (refer to their website at www.sleepaus.on.net). Note that the National Prescribing Service does not endorse any individuals or their services.

Place of medicines in insomnia

Reserve drug therapy with short-acting benzodiazepines (e.g. temazepam), zolpidem, or zopiclone for short-term severe insomnia if the cause is likely to resolve within a short time (i.e. within 2 weeks), and for intermittent use in chronic severe insomnia unresponsive to non-drug therapies.¹⁹ The risks associated with hypnotics (particularly the potential for dependence) generally outweigh any benefit they provide with continuous long-term use.²¹

There is no convincing evidence that the benefit-harm profile of zolpidem or zopiclone is more favourable

than that of short-acting benzodiazepines.²³ Like the benzodiazepines, zolpidem and zopiclone can also cause tolerance, dependence, withdrawal symptoms, and morning sedation.²⁴ If drug therapy is appropriate, use the lowest effective dose for the shortest possible time.^{18,19}

To help patients withdraw from long term benzodiazepines, see the guide in *NPS News 4* at www.nps.org.au.

Information for patients

Provide patients seeking treatment for insomnia with information about non-drug therapies. See *MedicinesTalk* Spring 2004 'Getting a good night's sleep' at www.nps.org.au, which provides information for patients with insomnia.

If prescribing a hypnotic, advise patients to:

- take no more than their prescribed dose (even if it does not appear to work)
- take the medicine immediately before getting into bed
- avoid drinking alcohol close to taking the medicine, and avoid taking the medicine if they have been drinking alcohol or believe they still have alcohol in their bloodstream
- avoid taking the medicine if they do not intend to stay in bed a full night (7–8 hours)

Inform patients about the potential problems of the medicine, including the risk of dependence. Discuss a short duration of therapy, ideally less than 2 weeks, and the need for re-evaluation if they perceive no improvement within 7–14 days of starting therapy.

When considering or prescribing zolpidem:

- discuss the possibility of sleep-related behaviours, as these are potentially dangerous to the patient and others²⁵
- discuss and provide a copy of the NPS fact sheet produced on this topic at www.nps.org.au.

Discuss the consumer medicine information (CMI) leaflet for the medicine you prescribe.

References

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.