

Z drugs: their properties and use in treating insomnia

Steve Chaplin BPharm, MSc, Sue Wilson PhD and David Nutt DM, FRCP, FRCPsych, FMedSci

KEY POINTS

- the Z drugs, zaleplon, zolpidem and zopiclone, are nonbenzodiazepine short-acting hypnotics that act on the benzodiazepine receptor
- they are indicated for short-term treatment of insomnia in adults
- zopiclone has the longest duration of action, which means it is suited to patients who complain of waking throughout the night
- zolpidem has a rapid absorption and short duration of action, and is suitable when getting off to sleep is the primary concern
- zaleplon is ultra-short acting and therefore can be taken during the night (until five hours before required to drive, etc); this is suitable in patients whose sleep disturbance is intermittent
- Z drugs should be used at a reduced dose in patients with hepatic impairment and avoided in those with severe hepatic impairment
- no dose adjustment is recommended for zolpidem in patients with renal impairment, zopiclone should be initiated at a low dose and zaleplon should be avoided in patients with severe renal impairment
- Z drugs are contraindicated in unstable myasthenia gravis, acute or severe respiratory depression, obstructive sleep apnoea and psychotic illnesses

Steve Chaplin, Sue Wilson and Professor David Nutt provide an overview of the properties of Z drugs and how they compare in the short-term treatment of insomnia.

The *BNF* states that treatment with a hypnotic should be reserved for acutely distressed patients. It may be helpful in cases of short-term insomnia, when it should be taken intermittently and preferably for no more than one week, with a maximum duration of three weeks. Treatment may be appropriate for transient insomnia (eg due to shift work or jet lag), when a short-acting agent should be chosen.

Zaleplon (Sonata), zolpidem and zopiclone (Z drugs) are nonbenzodiazepine short-acting hypnotics that act on the benzodiazepine receptor. Zaleplon has the fastest onset of action and the shortest half-life. Due to its short duration of action, prescribers should consider an alternative hypnotic if early morning waking is a problem and patients should be advised not to take a second dose in the same night. All Z drugs should be given in reduced doses for elderly people.

Z drugs are mainly eliminated by hepatic metabolism. Due to the risk of precipitating coma, they should be used cautiously and at a reduced dose in patients with hepatic impairment, and they should be avoided in patients with severe hepatic impairment.

Clearance of zaleplon is reduced in patients with renal impairment and, though no dose reduction is necessary in those with mild or moderate impairment, it should be avoided in patients with severe impairment. No dose adjustment is recommended for zolpidem in patients with renal impairment whereas treatment with zopiclone should be initiated at a low dose.

The Z drugs are contraindicated in patients with unstable myasthenia gravis, acute or severe respiratory depression or obstructive sleep apnoea. They should not be prescribed for children. Zolpidem is additionally contraindicated in patients with psychotic illness.

Zaleplon and zolpidem should be used with caution in patients with depression and all should be prescribed with caution in patients with muscle weakness, myasthenia gravis or a history of drug or alcohol misuse. Prolonged use may be associated with a risk of tolerance and withdrawal symptoms; tapering the dose on discontinuation may be considered for zolpidem

	Generic/brand	Dose	Licensed duration ^a	Cost ^b
Zaleplon	Sonata	10mg at bedtime or after going to bed if difficulty sleeping elderly: 5mg	2 weeks	£3.76 (10mg, 2 weeks) £3.12 (5mg, 2 weeks)
Zolpidem	generic	10mg at bedtime elderly or debilitated patients: 5mg	4 weeks	90p (10mg, 2 weeks) 96p (5mg, 2 weeks)
Zopiclone	generic	7.5mg at bedtime elderly: 3.75mg, increase if necessary	4 weeks	71p (7.5mg, 2 weeks) 74p (3.75mg, 2 weeks)

^aBNF states preference for 1 week and maximum of 3 weeks ^bprices MIMS May 2013

Table 1. Dose, licensed duration and costs of the three Z drugs

	No. scrips (000s)	NIC (£000s)
Zaleplon	0.7	3.6
Zolpidem	747	1082
Zopiclone	5525	7498

Table 2. GP prescriptions and net ingredient cost (NIC) for Z drugs in England, 2011

and zopiclone but is not suggested for zaleplon.

The *BNF* includes Z drugs with other hypnotics in its classification of drug

interactions. Potentially clinically significant interactions with this class may occur with other drugs that affect their hepatic metabolism (notably macrolide antibiotics, rifampicin and some antivirals), and the CNS depressant effects of antidepressants and antipsychotics may be enhanced. Alcohol also enhances the sedative effects of Z drugs.

The *BNF* advises warning patients of the risk of drowsiness during the following day only for zolpidem and zopiclone; however, the SPC for zaleplon advises caution for patients performing skilled tasks (with-

out referring specifically to hangover effects).

The Z drugs have a common spectrum of adverse effects involving the CNS and gastrointestinal tract. All may be associated with paradoxical effects (excitability, hostility) and sleep walking; treatment should be discontinued if these occur.

Declaration of interests

None to declare.

Steve Chaplin is a pharmacist who specialises in writing on therapeutics

Place in therapy

In the treatment of insomnia, when there is distress and impairment of daytime function in spite of good sleep habits, there are two choices of treatment with a good evidence base.

The first is cognitive behavioural therapy designed for insomnia (CBTi), which usually includes stimulus control, sleep restriction and cognitive work focussing on pre-sleep anxiety. This therapy is not widely available in UK. The other is to use a licensed hypnotic drug with a pharmacological profile that minimises daytime hangover as far as possible. The drugs available that fit this profile are the three Z drugs, zopiclone, zolpidem and zaleplon.

Zopiclone has the longest duration of action, which means it is used when patients complain of waking throughout the night, but some patients will have morning sleepiness and there is evidence that it may impair driving the next day.

Zolpidem has a rapid absorption and short duration of action. It should be taken at bedtime when getting off to sleep at night is the primary concern, as it does not impair next-day function.

Zaleplon is ultra-short acting and because of this can be taken during the night (until five hours before driving, etc). This is useful in patients whose sleep disturbance is intermittent: they can choose to use it only if sleep eludes them and

thus have confidence and control over dosing.

Indeed, with the advice about length of continuous dosing in the *BNF*, prescription of intermittent use of the Z drugs is sensible and acceptable to patients.

Declaration of interests

None to declare.

Sue Wilson is senior research fellow at Imperial College London, and David Nutt is professor of neuropsychopharmacology at Imperial College London and honorary consultant psychiatrist, Central and North West London NHS Trust