Appropriate and cost-effective prescribing of short acting hypnotics

The National Institute for Health and Care Excellence (NICE) TA77 recommends hypnotics to be prescribed for up to two weeks only, after non-drug measures have failed and the patient’s insomnia is severe, disabling or causing the patient extreme distress.\(^1\) This is due to concerns over hypnotic dependence. This bulletin reviews current evidence and offers advice on managing new patients and chronic hypnotic users.

**Recommendations**

- For new patients, offer non-drug measures such as a ‘good sleep hygiene guide’ before prescribing medication. Identify and treat underlying causes.\(^1,2\)

- Benzodiazepines and the Z–drugs (zopiclone and zolpidem) should be avoided in the elderly, because the elderly are at greater risk of becoming ataxic and confused, leading to falls and injury.\(^3\)

- Should a prescription be considered appropriate (non-drug measures have failed and the patient’s insomnia is severe, disabling or causing extreme distress), use a benzodiazepine or Z-drug at the lowest dose and for up to two weeks only.\(^2\)

- Do not routinely add hypnotics to repeat prescribing systems.

- As there is little to choose between short acting benzodiazepines and Z-drugs, choose a hypnotic with the lowest acquisition cost. Currently, generic zopiclone 7.5mg tablets are the lowest cost hypnotic.\(^1,4\) Avoid long acting hypnotics, e.g. nitrazepam due to increased risk of residual effects the following day.\(^3\)

- If a patient does not respond to one Z-drug, do not switch to another hypnotic in an attempt to get a response as there is no evidence to suggest that switching works.\(^1\)

- For chronic hypnotic users, review their need for a hypnotic and offer them support to withdraw from their hypnotic.\(^5\)

- Implement practice policy in line with above recommendations, considering patient contracts as appropriate.\(^5\) Practice policies include management of “out of hours” and emergency patient requests.

- Review prescribing of hypnotics for patients discharged from secondary care.

- Collaborate with substance misuse services, community mental health teams and voluntary agencies if necessary.

**Background**

Insomnia is a disturbance of normal sleep patterns commonly characterised by difficulty in initiating sleep (sleep onset latency) and/or difficulty maintaining sleep (sleep maintenance). However, insomnia is highly subjective. Although most healthy adults typically sleep between seven and nine hours per night,
patterns vary greatly between people. In any given person there are variations from night to night. Insomnia can have a number of different causes.\textsuperscript{1,2}

Insomnia can be categorised according to duration or likely duration. Definitions of duration of insomnia vary widely in the literature; for the purpose of this topic, insomnia is categorized as:

- **Short term** if insomnia lasts between one and four weeks.
- **Long term (or persistent)** if insomnia lasts for four weeks or longer.\textsuperscript{2}

Primary insomnia can be differentiated from insomnia associated with factors such as personal circumstances, physical or psychiatric co-morbidities, concomitant drug treatments or substance abuse (drugs, nicotine, alcohol or caffeine). Underlying causes should be identified and treated.

Primary insomnia is insomnia that occurs when no comorbidity is identified. Commonly, the person has conditioned or learned sleep difficulties, with or without heightened arousal in bed.

- Typically, primary insomnia has a duration of at least one month.
- Primary insomnia accounts for about 15–20\% of long term insomnia.\textsuperscript{1,2}

The NICE Clinical Knowledge Summary (CKS) on managing insomnia advises that non-drug therapies should initially be explored. This includes advice on bedtime routine and relaxation techniques\textsuperscript{2} (see appendix 1, page 10). CKS notes that there is insufficient evidence to assess the effectiveness of sleep hygiene as a single intervention. However, its use is widely supported by expert opinion in current literature and guidelines. Sleep diaries (appendix 2, page 11) can be used and can help identify possible causes.\textsuperscript{1,2}

If non-drug measures have failed and the patient's insomnia is severe, disabling or causing extreme distress, hypnotic therapy may be used. Hypnotic therapy should then only be prescribed for short periods of time only, in strict accordance with the licensed indications.\textsuperscript{1,6-12} The term hypnotic refers to short acting benzodiazepines (temazepam, loprazolam, lormetazepam) and the Z-drugs (zopiclone, zolpidem, and zaleplon (now discontinued)). This would be for no more than four weeks with benzodiazepines, or two to four weeks with Z-drugs.\textsuperscript{1} Licensed treatment lengths are set out in table 1.

NICE CKS states that if a benzodiazepine or Z-drug is prescribed for short term insomnia, the exact duration will depend on the underlying cause, but treatment should not continue for longer than two weeks.\textsuperscript{2}

The British National Formulary (BNF) states that benzodiazepines and the Z–drugs should be avoided in the elderly, because the elderly are at greater risk of becoming ataxic and confused, leading to falls and injury. Where a hypnotic is used for short term use, it should not be given for more than three weeks (preferably only one week). Intermittent use is desirable with omission of some doses. A short acting drug is usually appropriate.\textsuperscript{3}

Nitrazepam has a prolonged action and may give rise to residual effects the following day; repeated doses tend to be cumulative.\textsuperscript{5} Use of nitrazepam should be avoided, especially in the elderly.\textsuperscript{13} Loprazolam, lormetazepam and temazepam act for a shorter time and they have little or no hangover effect, however withdrawal phenomena are more common with the short acting benzodiazepines.\textsuperscript{3}

NICE guidance on generalised anxiety disorder (GAD) in adults recommends that benzodiazepines should not be offered for the treatment of GAD in primary or secondary care, except as a short term measure during crisis.\textsuperscript{14}

NICE technology appraisal (TA) guidance states that there is no compelling evidence of a clinically useful difference between the ‘Z-drugs’ and shorter acting benzodiazepine hypnotics from the point of view of their effectiveness, adverse effects, or potential for dependence or abuse.

- There is no evidence to suggest that if people do not respond to one of these hypnotic drugs, they are likely to respond to another.\textsuperscript{1}
• The drug with the lowest purchase cost (taking into account daily required dose and product price per dose) should be prescribed.¹

• Switching from one of these hypnotics (Z-drugs) to another should only occur if a patient experiences adverse effects considered to be directly related to a specific agent. These are the only circumstances in which the drugs with the higher acquisition costs are recommended.³

Evidence on risks

Risks associated with the long-term use of benzodiazepines and Z-drugs have been well recognised for many years. These include falls, accidents, cognitive impairment, dependence and withdrawal symptoms.¹,⁵,¹⁵ Concerns over dependence led the Committee on Safety of Medicines, as early as 1998, to advise that benzodiazepines should be restricted to severe insomnia and that treatment should be at the lowest dose possible and not be continued beyond four weeks.¹⁵

This risk is greater in the elderly. The BNF states that benzodiazepines and the Z–drugs should be avoided in the elderly, because the elderly are at greater risk of becoming ataxic and confused, leading to falls and injury.³

Treatment benefits may be small and may not justify the increased risks in this population, particularly in those at risk of cognitive impairment or falls. A meta-analysis of 13 studies (4,378 participants) reported that Z-drugs reduced polysomnographic sleep latency by 22 minutes and subjective sleep latency by seven minutes.¹⁶

Recent observational studies suggest that benzodiazepine use is associated with an increased risk of mortality or dementia. However, published evidence on the relationship between benzodiazepines and dementia is limited and inconsistent. A population based cohort study of 34,727 patients demonstrated that people who were prescribed anxiolytic and hypnotic drugs had a significantly increased risk of death from any cause over a seven year period; there were approximately four excess deaths linked to drug use per 100 people followed for an average of 7.6 years after their first prescription.¹⁷

A prospective population based cohort study (1,063 people aged 65 years and over (mean age 78.2 years) showed that new use of benzodiazepines was associated with a 60% increased risk of dementia compared with non-users. The total study duration was 20 years, including a five year observation period and a 15 year assessment period. Patients were eligible for the study if they were dementia free at five years and did not start taking hypnotics until at least year three.¹⁸

A Canadian observational case-control study (using data from a prescription drug insurance plan; 8,980 people aged 66 years or over) investigated the link between past benzodiazepine use and the risk of Alzheimer’s disease. The study showed a cumulative and dose effect association between benzodiazepine use and the risk of developing Alzheimer’s along with a greater risk with long acting benzodiazepines. However potential biases in the study limit the conclusions that can be drawn.¹⁹

A randomised controlled trial (RCT) of older people assessed the effects of short term treatment with sedative hypnotics (n=2511). The authors concluded that any treatment benefits were small and may not justify the increased risks in this elderly population, particularly in those at risk of cognitive impairment or falls. This was a reasonably well conducted review and the results appear reliable.²⁰

The risks associated with motor vehicle accidents and benzodiazepines and Z-drugs are well known.²¹,²²

A new offence of driving with certain controlled drugs above specified limits in the blood came into force in March 2015. Prescription drugs covered by the new offence include amphetamine (e.g. dexamphetamine or selegiline), clonazepam, diazepam, nitrazepam, lorazepam, methadone, morphine or opiate and opioid-based drugs (e.g. codeine, tramadol or fentanyl), oxazepam and temazepam. Although only a few benzodiazepines and opioids are included in the list above, all benzodiazepines and opioids can impair driving ability.²³
Circadin®

Melatonin is a pineal hormone which is licensed for the short term treatment of insomnia in adults over 55 years. The European Medicines Agency (EMA) concluded that the two pivotal trials, Neurim VII and Neurim IX used in the license application for prolonged release (PR) melatonin (Circadin®) demonstrated a statistically significant effect on the rate of responders, based on both combined criteria of "quality of sleep" (QOS) and "behaviour following wakefulness" with a 14% difference compared to placebo in a pooled analysis (20% for Neurim VII and 11% for Neurim IX). The treatment effect size was considered to be small. Comparison between zolpidem and Circadin® on QOS appears to be similar in magnitude and variability. Overall the EMA concluded that the results in the different studies suggest that melatonin PR is efficacious, with a small effect size in a relatively small fraction of patients.

Circadin® (Melatonin PR) can be given up to a maximum of 13 weeks and may appear to be an option, where there is a concern over dependence. Circadin® has a restricted license (should only be used in patients aged over 55 years), the treatment effect is small and in addition is more expensive than other hypnotics, such as zopiclone. NICE CKS does not recommend melatonin for the short term treatment of insomnia. However, for people over 55 years of age with persistent insomnia, modified-release melatonin may be considered. The recommended initial duration of treatment is three weeks. If there is a response to treatment, it can be continued for a further ten weeks.

As melatonin (standard release) is available as an unlicensed special, following MHRA guidance, MTRAC issued guidance that "it is important to ensure that the licensed product available in the UK is used wherever possible. This includes off-label use of the licensed product, if deemed suitable by the clinician." For further information on melatonin refer to PrescQIPP bulletin 108 melatonin (SPOT-List) https://www.prescqipp.info/melatonin-spot-list/category/217-melatonin-spot-list
Table 1: Benzodiazepines, Z-drugs and melatonin PR comparison

<table>
<thead>
<tr>
<th>Hypnotic</th>
<th>Drug class</th>
<th>Half–life(^{1,6,12,24,27})</th>
<th>Dose(^{6,12,24})</th>
<th>Dose in elderly(^{6,12,24})</th>
<th>Licensed Length of treatment(^{6,12,24})</th>
<th>Weekly cost Drug Tariff December 2016(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loprazolam</td>
<td>Benzodiazepine (short acting)</td>
<td>11.7 hours</td>
<td>1mg increasing to 1.5mg or 2mg if needed.</td>
<td>Elderly: 1mg Frail: 0.5mg Hepatic: caution</td>
<td>Treatment should not normally be continued beyond four weeks.</td>
<td>£4.50</td>
</tr>
<tr>
<td>Lormetazepam</td>
<td>Benzodiazepine (short acting)</td>
<td>11 hours</td>
<td>0.5mg – 1.5mg at bedtime</td>
<td>0.5mg</td>
<td>Few days to two weeks, with a maximum of four weeks including the tapering off process</td>
<td>£1.70 (1mg)</td>
</tr>
<tr>
<td>Temazepam</td>
<td>Benzodiazepine (short acting)</td>
<td>8-15 hours</td>
<td>10-20mg</td>
<td>5mg</td>
<td>Chronic use not recommended</td>
<td>£0.58 (10mg)</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>Benzodiazepine (long acting)</td>
<td>15-38 hours</td>
<td>5 -10mg</td>
<td>2.5mg – 5mg</td>
<td>Should not extend beyond four weeks and treatment should be gradually withdrawn</td>
<td>£0.30 (5mg)</td>
</tr>
<tr>
<td>Zopiclone</td>
<td>Z-drug</td>
<td>3.5–6.5 hours</td>
<td>7.5mg</td>
<td>3.75mg</td>
<td>2–5 days for transient insomnia and 2–3 weeks for short term insomnia.</td>
<td>£0.29</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>Z-drug</td>
<td>2.5 hours</td>
<td>10mg</td>
<td>5mg</td>
<td>Few days to two weeks, maximum four weeks including tapering off.</td>
<td>£0.30</td>
</tr>
<tr>
<td>Melatonin PR</td>
<td>Pineal hormone</td>
<td>3.5-4 hours</td>
<td>2mg, 1-2 hours before bedtime</td>
<td>2mg</td>
<td>Maximum 13 weeks</td>
<td>£3.59</td>
</tr>
</tbody>
</table>
Withdrawal regimens

Benzodiazepine and Z-drug withdrawal syndrome may develop at any time up to three weeks after stopping a long acting benzodiazepine (e.g. nitrazepam), but may occur within a day in the case of a short-acting one (loprazolam, lormetazepam, temazepam). It is characterised by insomnia, anxiety, loss of appetite and of body-weight, tremor, perspiration, tinnitus, and perceptual disturbances. Some symptoms may be similar to the original complaint and encourage further prescribing; some symptoms may continue for weeks or months after stopping benzodiazepines. states

Benzodiazepine and Z-drug withdrawal should be flexible and carried out at a “reduction” rate that is tolerable for the patient. The rate should depend on the initial dose of benzodiazepine, duration of use, and the patient’s clinical response. Withdrawal symptoms for long term users usually resolve within six-18 months of the last dose. Some patients will recover much more quickly, others may take longer. The addition of beta-blockers, antidepressants and antipsychotics should be avoided where possible. Counselling can be of considerable help both during and after the taper. states

Practice review process

Various approaches to reducing hypnotic prescribing can achieve significant success. Withdrawal approaches as outlined in NICE CKS can be found in appendix 3, page 12. The All Wales Medicine Strategy Group (AWMSG) has produced a very comprehensive education pack with best practice examples that have been used to help with the problem of long term prescribing of hypnotics and anxiolytics. It is available on their website at: http://www.awmsg.org/docs/awmsg/medman/Educational%20Pack%20-%20Material%20to%20Support%20Appropriate%20Prescribing%20of%20Hypnotics%20and%20Anxiolytics%20across%20Wales.pdf

A reduction in benzodiazepine and Z-drug prescribing can be achieved through:

- **Appropriate initiation**: only initiate therapy according to practice policy (attachment 2) and ideally issue no more than two weeks supply. Upon treatment initiation, provide verbal and written information to patients regarding the complications of long term use and associated side effects such as tolerance, dependence and withdrawal (attachment 5).

- **Review of existing patients** with the aim to withdraw treatment or reduce dosage where appropriate. An audit of patients on long term use is provided in attachment 1. The following patients (as described in the All Wales education pack) may be excluded or referred to substance misuse services:
  - Potential substance misusers, i.e. patients on multiple drugs of abuse.
  - Patients unwilling to participate in a managed withdrawal programme.
  - Patients who may be diverting their supply.
  - Patients who are terminally ill, or with serious physical illness such as ischaemic heart disease.
  - Patients with severe mental health problems.

Agree the practice withdrawal process and policy (attachment 2) and patient contract (attachment 3). Initiate the withdrawal process (appendix 3): Attach a letter (attachment 4) and/or information leaflet (attachment 5) to every hypnotic prescription.

Community pharmacy support in identifying suitable patients for withdrawal and supporting withdrawal should be implemented (attachment 6).

Savings

This bulletin focuses on the safe and appropriate use of hypnotics and aims to reduce the overall use of hypnotics. A reduction in benzodiazepine and Z-drug prescribing can be achieved as described above. In England and Wales, the total annual spend for hypnotics is over £45.1 million (ePACT August to October 2016). If a 40% reduction in prescribing is achieved by reviewing and stopping hypnotic prescribing then the annual savings would be over £18 million, which equates to £29,532 per 100,000 patients.
Where an appropriate clinical decision has been made to prescribe a short acting benzodiazepine or a Z-drug, use the least costly hypnotic.\(^1\)

Currently, zopiclone 7.5mg tablets are the least costly option followed by zolpidem 10mg tablets and temazepam 20mg tablets. Prescribers should note that temazepam is a schedule 3 controlled drug because of its abuse potential. Long acting benzodiazepines nitrazepam and flunitrazepam should be avoided as they can lead to residual effects the next day especially in the elderly. Current spend on long acting benzodiazepines is almost £3.2 million and use should be reviewed.

**Summary**

- Insomnia is a common complaint and non-drug measures such as advice on bedtime routine and relaxation techniques are advocated for the initial management in NICE guidance. If non-drug measures fail and the insomnia is severe, disabling and causing the patient severe distress then up to a two week course of a hypnotic may be tried. Hypnotics used, include short-acting benzodiazepines, Z-drugs (zopiclone, zolpidem) and melatonin MR. The problems of benzodiazepines and Z-drugs are well known and include development of tolerance, dependence potential and withdrawal causing rebound insomnia. Benzodiazepines and the Z–drugs should be avoided in the elderly, because the elderly are at greater risk of becoming ataxic and confused, leading to falls and injury.

- Circadin® (Melatonin MR) may appear to be an option where there is a concern over dependence, however the licensing authority noted that the treatment effect was small and it is more expensive than other hypnotics. In line with NICE TA77, because of the lack of compelling evidence to distinguish between Z-drugs or the shorter-acting benzodiazepine hypnotics, the drug with the lowest purchase cost (taking into account daily required dose and product price per dose) should be prescribed.

**References**


Additional PrescQIPP resources

- Briefing
- Data pack
- Audit, contracts, letters, policy, tools

Available here: [https://www.prescqipp.info/hypnotics/category/97-hypnotics](https://www.prescqipp.info/hypnotics/category/97-hypnotics)

Information compiled by Anita Hunjan, PrescQIPP Programme, December 2016 and reviewed by Katie Smith, Senior Medicines Evidence Reviewer, February 2017.

Non-subscriber publication June 2017.

Contact help@prescqipp.info with any queries or comments related to the content of this document.

This document represents the view of PrescQIPP CIC at the time of publication, which was arrived at after careful consideration of the referenced evidence, and in accordance with PrescQIPP’s quality assurance framework.

The use and application of this guidance does not override the individual responsibility of health and social care professionals to make decisions appropriate to local need and the circumstances of individual patients (in consultation with the patient and/or guardian or carer). [Terms and conditions](#)
Appendix 1: NHS Clinical Knowledge Summaries, Insomnia – Management: What advice should I give regarding good sleep hygiene?

Available at [http://cks.nice.org.uk/insomnia - !scenario](http://cks.nice.org.uk/insomnia - !scenario)

Sleep hygiene aims to make people more aware of behavioural, environmental, and temporal factors that may be detrimental or beneficial to sleep.

Advise the person to:

- Establish fixed times for going to bed and waking up (and avoid sleeping in after a poor night's sleep).
- Try to relax before going to bed.
- Maintain a comfortable sleeping environment: not too hot, cold, noisy, or bright.
- Avoid napping during the day.
- Avoid caffeine, nicotine, and alcohol within six hours of going to bed.
- Consider complete elimination of caffeine from the diet.
- Avoid exercise within four hours of bedtime (although exercise earlier in the day is beneficial).
- Avoid eating a heavy meal late at night.
- Avoid watching or checking the clock throughout the night.
- Only use the bedroom for sleep and sexual activity.

NHS Choices - [http://www.nhs.uk/Conditions/Insomnia/Pages/Prevention.aspx](http://www.nhs.uk/Conditions/Insomnia/Pages/Prevention.aspx)

Sleeping well leaflet - [www.rcpsych.ac.uk/healthadvice/problemsdisorders/sleepingwell.aspx](http://www.rcpsych.ac.uk/healthadvice/problemsdisorders/sleepingwell.aspx)
# Appendix 2: Daily sleep diary


## Daily Sleep Diary

Complete the diary each morning ("Day 1" will be your first morning). Don’t worry too much about giving exact answers, an estimate will do.

<table>
<thead>
<tr>
<th>Your Name___________________________</th>
<th>The date of Day 1_______________</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enter the Weekday (Mon, Tues, Wed, etc.)</strong></td>
<td>Day 1</td>
</tr>
<tr>
<td>1 At what time did you go to bed last night?</td>
<td></td>
</tr>
<tr>
<td>2 After settling down, how long did it take you to fall asleep?</td>
<td></td>
</tr>
<tr>
<td>3 After falling asleep, about how many times did you wake up in the night?</td>
<td></td>
</tr>
<tr>
<td>4 After falling asleep, for how long were you awake during the night in total?</td>
<td></td>
</tr>
<tr>
<td>5 At what time did you finally wake up?</td>
<td></td>
</tr>
<tr>
<td>6 At what time did you get up?</td>
<td></td>
</tr>
<tr>
<td>7 How long did you spend in bed last night (from first getting in, to finally getting up)</td>
<td></td>
</tr>
<tr>
<td>8 How would you rate the quality of your sleep last night?</td>
<td>1</td>
</tr>
<tr>
<td>V. Poor</td>
<td></td>
</tr>
</tbody>
</table>
## Appendix 3: Reducing and stopping benzodiazepines and Z-drugs

### How to assess someone who wants to stop benzodiazepines or Z-drugs:

- Decide if the person can stop their current benzodiazepine or Z-drug without changing to diazepam.
- Switching to diazepam is recommended for:
  - People using the short-acting potent benzodiazepines (e.g. lorazepam).
  - People using preparations that do not easily allow for small reductions in dose (that is alprazolam, flurazepam, loprazolam and lormetazepam).
  - People taking temazepam or nitrazepam who choose to withdraw from diazepam after discussing the advantages and disadvantages.
  - People experiencing difficulty or who are likely to experience difficulty withdrawing directly from temazepam, nitrazepam, or Z-drugs, due to a high degree of dependency (associated with long duration of treatment, high doses and a history of anxiety problems).
- Seek specialist advice (preferably from a hepatic specialist) before switching to diazepam in people with hepatic dysfunction as diazepam may accumulate to a toxic level in these individuals. An alternative benzodiazepine without active metabolites (such as oxazepam) may be preferred.
- Negotiate a gradual drug withdrawal schedule (dose tapering) that is flexible. Be guided by the person in making adjustments so that they remain comfortable with the withdrawal.
- Titrate the drug withdrawal according to the severity of withdrawal symptoms, e.g. withdrawal should be gradual (dose tapering, such as 5–10% reduction every 1–2 weeks, or an eighth of the dose fortnightly, with a slower reduction at lower doses), and titrated according to the severity of withdrawal symptoms. See withdrawal regimes below. Drug withdrawal may take three months to a year or longer. Some people may be able to withdraw in less time.
- Review frequently, to detect and manage problems early and to provide advice and encouragement during and after the drug withdrawal.
- If they did not succeed on their first attempt, encourage the person to try again.
- Remind the person that reducing benzodiazepine dosage, even if this falls short of complete drug withdrawal, can still be beneficial.
- If another attempt is considered, reassess the person first, and treat any underlying problems (such as depression) before trying again. If they did not succeed on their first attempt, encourage the person to try again.

- **Approximate equivalent doses, “diazepam” 5 mg:**
  - loprazolam 0.5–1 mg.
  - lormetazepam 0.5–1 mg.
  - nitrazepam 5 mg.
  - temazepam 10 mg.

Withdrawal regimens can be found at:


**Further resources for patients**

Benzodiazepines - [www.rcpsych.ac.uk/mentalhealthinfo/treatments/benzodiazepines.aspx](http://www.rcpsych.ac.uk/mentalhealthinfo/treatments/benzodiazepines.aspx)

Stopping benzodiazepines and Z-drugs -

Battle against tranquillisers - [http://bataid.org](http://bataid.org)