

Appropriate and cost-effective prescribing of hypnotics and anxiolytics

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. Benzodiazepines are only recommended as a short-term measure for crises in anxiety. The 2019 Public Health England (PHE) report, 'Dependence and withdrawal associated with some prescribed medicines - an evidence review' states that the fall in benzodiazepines has continued from 2008 and the longer-term increase in Z-drugs, which peaked in 2014 when they replaced benzodiazepines for insomnia, has started to fall.²

This bulletin reviews current evidence and offers advice on managing new patients and chronic hypnotic users.

Implementation resources are available to support audit and review of patients. Further resources are available in the PrescQIPP resources on dependency forming medicines, including the benzodiazepine deprescribing algorithm available at: <https://www.prescqipp.info/our-resources/bulletins/bulletin-256-dependence-forming-medications/>

Recommendations

- For new patients, offer non-drug measures such as a 'good sleep hygiene guide' before prescribing medication. Identify and treat any underlying causes.^{1,3}
- Do not offer a benzodiazepine for the treatment of generalised anxiety disorder in primary or secondary care except as a short-term measure during crises⁴ or as single doses for fear or anxiety prior to surgery.⁵ A stepped-care model is used to offer the least intrusive, most effective intervention for people with GAD. Education and low-intensity psychological interventions such as individual non-facilitated self-help are offered before drug treatment.⁴
- 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.⁵
- Avoid benzodiazepines in patients with significant pulmonary disease, respiratory depression, obstructive sleep apnoea, and severe hepatic disease, and for those taking other hypnotics, (tricyclic) antidepressants, antihistamines, and opioids.²
- 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.³
- Do not routinely add hypnotics to repeat prescribing systems.
- Benzodiazepines and the Z-drugs should only be prescribed after informed consent from the patient or carer if the individual is not of sufficient age or understanding.

Recommendations

- 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.^{1,6}
- Avoid long acting hypnotics, e.g. nitrazepam due to an increased risk of residual effects the following day.⁵
- 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 Where communication is difficult with the patient due to cognitive impairment, ensure supported shared decision making with carers.
- Implement a practice policy in line with the above recommendations, considering patient contracts as appropriate.⁷
- 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

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.^{1,3}

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 categorised as:

- Short term if insomnia lasts between one and four weeks.
- Long term (or persistent) if insomnia lasts for four weeks or longer.³

Co-morbid or secondary insomnia is 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 co-morbidity is identified. Commonly, the person has conditioned or learned sleep difficulties, with or without heightened awakening in bed.

- Typically, primary insomnia has a duration of at least one month.
- Primary insomnia accounts for about 15–20% of long-term insomnia.^{1,3}

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 (see attachment 1).³ 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 (for example, <https://www.nhs.uk/Livewell/insomnia/Documents/sleepdiary.pdf>) can be used and can help identify possible causes.³

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.^{1,8-14} The term hypnotic refers to short acting benzodiazepines (temazepam, loprozalam, lormetazepam) and the Z-drugs (zopiclone, zolpidem, and zaleplon (now discontinued)). Use would be for no more than four weeks with benzodiazepines, or two to four weeks with Z-drugs.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.³

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.⁵

Nitrazepam has a prolonged action and may give rise to residual effects the following day; repeated doses tend to be cumulative.⁵ Use of nitrazepam should be avoided, especially in the elderly.¹⁵ 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.⁵

The NICE technology appraisal (TA77) 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.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.¹

Generalised anxiety disorder

Generalised anxiety disorder (GAD) is one of a range of anxiety disorders that includes panic disorder (with and without agoraphobia), post-traumatic stress disorder, obsessive-compulsive disorder, social phobia, specific phobias (for example, of spiders) and acute stress disorder. Anxiety disorders can exist in isolation but more commonly occur with other anxiety and depressive disorders.⁴

A stepped-care model is used to organise the provision of services and to help people with GAD, their families, carers and practitioners to choose the most effective interventions.⁴ For people with GAD whose symptoms have not improved after education and active monitoring (Step 1), offer one or more of the following as a first-line intervention, guided by the person's preference (Step 2):

- Individual non-facilitated self-help
- Individual guided self-help
- Psychoeducational groups

For people with GAD and marked functional impairment, or those whose symptoms have not responded adequately to step 2 interventions:⁴

Offer either (Step 3):

- An individual high intensity psychological intervention or
- Drug treatment

High-intensity psychological interventions

If a person with GAD chooses a high-intensity psychological intervention, offer either cognitive behavioural therapy (CBT) or applied relaxation.⁴

Drug treatment

If a person with GAD chooses drug treatment, offer a selective serotonin reuptake inhibitor (SSRI) as first line choice. Do not offer a benzodiazepine for the treatment of GAD in primary or secondary care except as a short-term measure during crises. Benzodiazepines are associated with a poorer outcome in the long term and should not be prescribed for the treatment of individuals with panic disorder.⁴

For information on depression and anxiety refer to PrescQIPP bulletin 237: Antidepressants <https://www.prescqipp.info/our-resources/bulletins/bulletin-237-antidepressants/>

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.^{1,5,16,17} The elderly are at greater risk of becoming ataxic and confused, leading to falls and injury.⁵ 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.¹⁶

Treatment benefits may be small and may not justify the increased risks in the elderly 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.¹⁸

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.¹⁹

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.²⁰

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.²¹

A meta-analysis of randomised controlled trials (RCTs) studied the risks and benefits of using any pharmacological treatment for insomnia for at least five consecutive nights in people aged 60 or over with insomnia and otherwise free of psychiatric or psychological disorders. (n=2471). 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.²²

The risks associated with motor vehicle accidents and benzodiazepines and Z-drugs are well known.²³⁻²⁵ A new offence of drug driving came into force in March 2015. There are eight prescription drugs included in the list with limits in micrograms per litre (µg/L) of blood, including:

- clonazepam 50 µg/L
- diazepam 550 µg/L
- flunitrazepam 300 µg/L
- lorazepam 100 µg/L
- methadone 500 µg/L
- morphine 80 µg/L
- oxazepam 300 µg/L
- temazepam 1000 µg/L

Amphetamine (e.g. dexamphetamine or selegeline) limit 250µg/L was added in April 2015.²⁵ Although only a few benzodiazepines and opioids are included in the list above, all benzodiazepines and opioids can impair driving ability.⁵

In addition, PHE states that benzodiazepines should be avoided in patients with significant pulmonary disease, respiratory depression, obstructive sleep apnoea, and severe hepatic disease, and for those taking other hypnotics, (tricyclic) antidepressants, antihistamines, and opioids.²

Public Health England in its evidence review on dependence and withdrawal summarises the following:²

- Always consider the risk of harm against the potential benefits from short-term or intermittent use
- Consider alternatives including referral for psychological therapy, since the first-line intervention for generalised anxiety disorder, panic disorder and panic attacks is Cognitive Behavioural Therapy (CBT)
- When a benzodiazepine is indicated, inform the patient that treatment will be at the lowest effective dose for as short a time as possible (2 to 4 weeks)
- Make the first prescription for no longer than 7 to 14 days, with no issue of a repeat prescription
- Offer support for long-term patients in the form of a slow and gradual reduction in dosing (taper) to avoid withdrawal symptoms

Melatonin

Melatonin is a pineal hormone.⁵ Circadin® (melatonin) prolonged-release (P/R) 2mg tablets are licensed for the short term treatment of insomnia in adults over 55 years.²⁶ The European Medicines Agency (EMA) concluded that the two pivotal trials, Neurim VII and Neurim IX used in the license application for 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 P/R is efficacious, with a small effect size in a relatively small fraction of patients.²⁷ Circadin® (Melatonin P/R) 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.^{6,26} NICE CKS does not recommend melatonin for the short term treatment of insomnia.³ However, for people over 55 years of age with persistent insomnia, P/R 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.³

Melatonin is included with the other hypnotics when NICE warns of the risks of hypnotics. These risks include falls, cognitive impairment, dependence and withdrawal symptoms.¹⁷

For further information on melatonin, unlicensed melatonin formulations and use of melatonin in children refer to PrescQIPP bulletin 245 melatonin [<https://www.prescqipp.info/our-resources/bulletins/bulletin-245-melatonin/>]

Table 1 provides a comparison of half-lives and licensed treatment lengths for benzodiazepines, Z-drugs and melatonin.

Table 1. Benzodiazepines, Z-drugs, and melatonin comparison

Hypnotic	Drug class	Half life ^{1,8-14,26,28-30}	Dose ^{8-14,26,29,30}	Dose in elderly ^{8-14,26,29,30}	Licensed Length of treatment ^{8-14,26,29,30}	Weekly cost ⁶
Loprazolam	Benzodiazepine (short acting)	11.7 hours	1mg increasing to 1.5mg or 2mg if needed.	1mg	Treatment should not normally be continued beyond four weeks.	£5.63 (1mg)
Lormetazepam	Benzodiazepine (short acting)	11 hours	0.5mg – 1.5mg at bedtime	0.5mg	Few days to two weeks, with a maximum of four weeks including the tapering off process.	£3.02 (1mg)
Temazepam	Benzodiazepine (short acting)	7-11 hours	10-20mg	10mg	Few days to two weeks, with a maximum of four weeks including the tapering off process.	£0.41 (10mg)
Nitrazepam	Benzodiazepine (long acting)	24 hours	5-10mg	2.5mg–5mg	Should not extend beyond four weeks and treatment should be gradually withdrawn.	£0.25 (5mg)
Zopiclone	Z-drug	3.5–6.5 hours	7.5mg	3.75mg	2–5 days for transient insomnia and 2–3 weeks for short term insomnia.	£0.29 (7.5mg)
Zolpidem	Z-drug	2.5 hours	10mg	5mg	Treatment should be as short as possible and should not exceed four weeks including the period of tapering off.	£0.43 (10mg)
Melatonin PR (Circadin®)	Pineal hormone	3.5-4 hours	2mg, 1-2 hours before bedtime	2mg	Maximum 13 weeks	£3.59
Melatonin 3mg tablets (Colonis Pharma Ltd)	Pineal hormone	30-60 minutes	3mg-6mg	3mg-6mg	For the short-term treatment of jet-lag in adults: 5 days course and maximum 16 courses per year	£15.17 (3mg)
Melatonin 1mg/ml oral solution (Colonis Pharma Ltd)	Pineal hormone	30-60 minutes	3mg-6mg	3mg-6mg	For the short-term treatment of jet-lag in adults: 5 days course and maximum 16 courses per year.	£18.20 (3mg)

Withdrawal regimens

Refer to attachment 2 for withdrawal process.

Medical management of benzodiazepine withdrawal should be individually tailored to the patient. It usually often involves switching to a longer-acting benzodiazepine in order to achieve a smooth decline in blood and tissue concentrations during benzodiazepine withdrawal.³¹ Benzodiazepines should be prescribed on a slow dose taper, maintaining the dose if symptoms become uncomfortable or increasing the dose if symptoms become intolerable, and sometimes with additional prescribing for symptomatic relief.²

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, lorazepam, 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.⁵

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 to eighteen months of the last dose.⁵ Some patients will recover more quickly, others may take longer. The addition of beta-blockers, antidepressants and antipsychotics should be avoided where possible.³²

Counselling can be of considerable help both during and after the taper.⁵

Practice review process

Various approaches to reducing hypnotic prescribing can achieve significant success. Withdrawal approaches can be found in Benzodiazepines: How they work and how to withdraw (The Ashton Manual).²⁸ A practice guide for hypnotics and anxiolytics can be found at: http://www.wales.nhs.uk/sites3/Documents/582/Guide_Hypnotics%20%26%20Anxiolytics%20Practice%20Guide_version02.pdf

A deprescribing benzodiazepine and Z-drug algorithm is available as part of the dependence forming medications project www.prescqipp.info

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

- Appropriate initiation: only initiate therapy according to practice policy (attachment 3) 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 1).
- 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 attachments 4-6. The following patients (as described in the All Wales education pack) may be excluded or referred to commissioned CCG services (e.g. homeless, substance misuse) or GP specialists for the development of actions plans⁷:
 - » 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 3) and patient contract (attachment 7).
- Initiate the withdrawal process (attachment 2).
- Attach a letter (attachment 8) and/or information leaflet (attachment 1) to every hypnotic prescription.

Community pharmacy support in identifying suitable patients for withdrawal and supporting withdrawal should be implemented (attachment 9). (The community pharmacy medicines use review (MUR) service is being decommissioned from the end of 20/21 financial year.)³³

Examples of self care resources for insomnia are provided in attachment 10.

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 £55.7 million (NHSBSA Sep - Nov19). If a 40% reduction in prescribing is achieved by reviewing and stopping hypnotic prescribing then the annual savings would be over £22 million, which equates to £88,305 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 temazepam 10mg tablets and zolpidem 10mg tablets. Prescribers should note that temazepam is a schedule 3 controlled drug because of its abuse potential. Long acting benzodiazepines nitrazepam and flurazepam should be avoided as they can lead to residual effects the next day especially in the elderly. There should be no NHS prescriptions issued for flurazepam as it is included in Part XVIII A of the Drug Tariff (the blacklist).⁶ Current spend on long acting benzodiazepines is £2.4 million and their 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 P/R. 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 P/R) 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 the daily required dose and product price per dose) should be prescribed.

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 Briefing	https://www.prescqipp.info/our-resources/bulletins/bulletin-258-hypnotics/
 Implementation tools	
 Data pack	https://pdata.uk/views/B258_Hypnotics/FrontPage?:iid=1&:is-GuestRedirectFromVizportal=y&:embed=y

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