BEDTIME WITHOUT BENZODIAZEPINES AND 'ZZZ-DRUGS'

CASE SCENARIO

Harry, aged 79, regularly presents to collect his temazepam 10 mg prescription with directions '10 mg nocte when required'. At his most recent visit, he mentions that he is regularly waking to use the bathroom due to increased bladder frequency (2–3 times per night) and wonders if he should increase his dose so that he stops waking so regularly. You confirm that Harry has been taking temazepam for 6 years and you ask how helpful this medicine has been since he started.

Introduction

Sleep complaints are common, with up to 60% of Australians experiencing difficulty falling asleep, maintaining sleep, or waking too early multiple times per week.[1]

Insomnia that is acute or short term tends to resolve once the precipitating factor(s) subside.[2] However, when symptoms occur at least 3 nights per week (with adequate opportunity for good sleep) and are associated with significant daytime impairment (e.g. fatigue, difficulty concentrating) for longer than 3 months, it is termed 'chronic insomnia'.[3,4] Recent estimates suggest 10–15% of Australian adults experience chronic insomnia at any given time.[1,5–8]

Treatment of insomnia

Cognitive behavioural therapy for insomnia (CBTi) is recommended as first-line treatment for insomnia, however most individuals (90%) attending primary care are prescribed a benzodiazepine or alternative pharmacotherapy such as a non-benzodiazepine hypnotic (zolpidem or zopiclone, known as the Z-drugs).[9–11] Benzodiazepines and these Z-drugs are together referred to as benzodiazepine receptor agonists (BZRAs).[12–14]

SPONSORSHIP INFORMATION

A national education program for pharmacists funded by the Australian Government under the Quality Use of Diagnostics, Therapeutics and Pathology program.

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OUR AUTHORS

DR ERIN OLDENHOF (she/her)
BA(Psych)(Hons), DPsych (Clin)

STACEY PUTLAND (she/her)
BPharm, AACPA, MPS

OUR REVIEWERS

HANA NUMAN (she/her)
BPharm (NZ), PGDipClinPharm (NZ), MPS (NZ)

Quality Use of Medicines for Insomnia and Sleep Health (QUMISH) Steering Committee

CONFLICTS OF INTEREST:
Erin is employed by Reconnexion to support individuals dependent on benzodiazepines and z-drugs to safely stop their medication.

Stacey is employed by the Australasian Sleep Association to manage a grant project specifically focused on upskilling pharmacists on insomnia management and sleep health.

LEARNING OBJECTIVES

After reading this article, pharmacists should be able to:

- Discuss risks associated with benzodiazepine receptor agonist use
- Provide recommendations for evidence-based treatments for insomnia
- Discuss symptoms associated with withdrawal from long-term benzodiazepine receptor agonist therapy
- Explain how pharmacists can help manage withdrawal from long-term benzodiazepine receptor agonist therapy.

Competency standards (2016) addressed: 1.1, 1.5, 1.6, 2.2, 3.1, 3.2, 3.5

Accreditation number: CAP2409DMEO

Accreditation expiry: 31/8/2027

While effective in the short term at improving sleep onset, BZRAs do not treat the underlying cause of insomnia, and are associated with a wide range of potential adverse effects and risks of harm.[15–17] These include both cognitive and physical effects such as fatigue, dizziness, risk of falls and fractures in older adults, cognitive deficits (i.e. memory problems), motor vehicle accidents, and worsening mood and sleep.[18,19]

Importantly, BZRAs can cause tolerance and dependence, which can potentially produce significant withdrawal symptoms on cessation. Guidelines recommend BZRAs be used intermittently or short term only (not more than 4 weeks) at the lowest possible dose.[20,21] However, it is not unusual for people to be prescribed these medicines long term, and dependence is observed at similar rates across long-term users of all types of BZRAs.[22–26]

A role for pharmacists

Pharmacists can play a variety of roles in the quality use of medicines for insomnia, such as BZRAs. Studies have shown positive results when pharmacists work collaboratively with general practitioners by conducting medication reviews and providing deprescribing recommendations for BZRAs, and even demonstrate that pharmacists can lead deprescribing efforts with additional training.[27–29]

However, a recent review showed pharmacists might have the greatest impact through consumer education, as this process can also facilitate shared decision-making and create an open dialogue.[30] As a standalone intervention, education can see nearly half (45%) of long-term BZRA patients reduce their medication.[31,32]

Patient education is key

Creating motivation for change

Patient education is essential when initiating the deprescribing process. Research with long-term BZRA users found that one of the reasons they continue BZRAs is because the underlying issue persists.[33] This can lead to the belief that they need their medication to sleep and, for many, creates a preoccupation about the impacts of poor sleep if they stop.[34]

Nonetheless, many adults who hold these beliefs also want to reduce their medication and don't like having to rely on it to sleep.[33,35,36] This paradox between 'needing' a medication but not wanting to rely on it illustrates why many will require effective treatment for their insomnia before they can stop their BZRA.[34]

Education around the risk of harm is key for motivating change. With long-term use, tolerance to the sedative effects of BZRAs can occur, and the risk of dependence increases.[37] This means that for many, the BZRA may simply be staving off withdrawal rather than providing any real therapeutic benefit.[33] By focusing on a patient's concerns about ongoing BZRA use, pharmacists can draw attention to the incongruence between the patients beliefs and behaviour, an important step towards eliciting motivation to engage with interventions like CBTi.[24]

Although tempting to problem-solve on the spot, research tells us that patients

need time after receiving new information, and that education alone rarely leads to immediate behaviour change.[38] Pharmacists will be more successful if they resist the urge to recommend BZRA cessation before the patient is ready.[39,40]

Delivering tailored education

In addition to information about the harms of long-term BZRA use, pharmacists should also provide more specific information regarding their use. For example, other risks such as the risk of worsening sleep quality (i.e. less time spent in deep and rapid eye movement (REM) sleep), daytime sleepiness and risk of motor vehicle accidents (particularly with new prescriptions and in older adults), and reported parasomnias (e.g. sleepwalking and bizarre sleep behaviours).[41–45] Planting the seed for BZRA cessation requires not only increasing the salience of the harms but also decreasing the perceived benefits of continued use.

Guidance on carrying out a gradual dose reduction (GDR – see further information below) while supporting the development of skills necessary to navigate the tapering process is another important component of patient education.[31]

Before initiating a GDR, patients may require a period of stabilisation where they take a consistent dose at set times of the day. This process can help offset psychological dependence resulting from any 'when necessary' (PRN) use and provides a steady baseline from which to begin the taper.[17,46] Engaging with CBTi at this stage can be useful to build the patient's self-efficacy for sleep. Evidence shows that those able to make positive changes to sleep habits before reducing their BZRA use are more likely to have success when they do reduce.[47] This is useful for patients not ready to change their BZRA use, as CBTi builds skills and confidence that will benefit them through withdrawal.

Why CBTi?

CBTi is the first-line treatment for chronic insomnia. In the short term, it can be as effective as BZRAs at improving sleep onset, but unlike BZRAs, there are few adverse effects, and the benefits are sustained long term.[48–51]

CBTi combines several components, including education on sleep and healthy sleep behaviour, stimulus control therapy (i.e. strengthening bed/bedroom cues for sleep), bedtime restriction therapy, cognitive restructuring (i.e. identifying and challenging of thoughts, feelings and behaviours which impact sleep) and relaxation therapy. »

Sessions aim to identify and target the underlying causes of insomnia and can lead to large and sustained improvements in insomnia and associated mental/physical symptoms.[52]

Accessing CBTi

Although individually delivered and face-to-face is arguably the most effective way to deliver CBTi, access via Medicare Benefits Schedule (MBS) referral is low (<1%), with cost and limited availability of trained clinicians significant barriers.[11,53,54] As such, online and digital formats are increasingly common, with a range of evidence-based self-managed CBTi apps and programs available that demonstrate similar reductions in insomnia severity (see: *www.sleepprimarycareresources.org.au/insomnia/cbti/referral-to-digital-cbti-programs*).[55,56]

Regardless of the format, supporting consumer choice is important, as many individuals will engage with multiple modalities at the same time.[56]

Withdrawal from long-term BZRA use

There will always be some degree of hesitation or fear about reducing BZRAs; however, with sufficient time, planning, and support, most patients (up to 88%) can successfully reduce or withdraw from their BZRA use.[57]

Every conversation with a patient about their BZRA is potentially a step towards reducing use, and pharmacists should aim to routinely provide education in a supportive and non-judgemental manner when they dispense a BZRA.

Up to 30% of patients who take benzodiazepines for just 4–6 weeks will experience withdrawal symptoms when they stop, and after 6 months of regular use, up to 80% of patients will experience withdrawal.[15,58]

While the withdrawal sequalae from nonbenzodiazepine hypnotics (i.e. zolpidem and zopiclone) is less understood, and often only associated with high doses used over longer periods of time, guidelines indicate they should still be treated with the same level of caution as benzodiazepines.[21,59,60]

Many patients will hesitate to even consider reducing their BZRA for fear of discontinuation symptoms. While withdrawal symptoms are common, their severity varies greatly. Some patients experience little to no discomfort during their BZRA taper and require minimal support from healthcare professionals after receiving written or verbal recommendations. For others, withdrawal is complicated by discontinuation syndromes, and for a small number (10–15%) withdrawal can become protracted, lasting many months or even years.[61] In those experiencing complicated or protracted withdrawal, often this is precipitated by their medication being reduced too quickly.[61]

A GDR can reduce the severity of withdrawal symptoms and, consequently,

increase the likelihood of successful cessation. The recently released *Maudsley Deprescribing Guidelines* recommend that a GDR should be designed around a patient's risk of withdrawal, with reduction rates varying between 5–20% (depending on patient factors) of the total dose every 1–4 weeks, and stipulate that this should be guided by the patient's experience.[62] Pharmacists should refer to current, specialised references in regard to appropriate tapering and deprescribing of BZRAs.[12]

Withdrawal is not a linear process, and a GDR requires regular review and adjustment based on how the patient is managing their symptoms.[63] By normalising the need to pause or even reinstate a previous dose, pharmacists can reduce the likelihood that patients will interpret these setbacks as evidence that they cannot stop their BZRA. Pharmacists can provide ongoing support to patients tapering their medication by understanding the need for an individualised approach and advocating for flexible tapering plans with their prescriber.

Pharmacists' skills and knowledge in compounding can also offer patients options when they get to lower doses or where proprietary formulations are limiting. In some cases, patients may also benefit from staged supply, such as when they are having difficulty regulating their own use.

Managing withdrawal symptoms

While it is difficult to predict who will be successful and why, patients trying to reduce their BZRA are best equipped when they are properly educated about the deprescribing process and informed about potential withdrawal symptoms (see Table 1).

When reducing BZRAs, most patients will experience some degree of rebound insomnia, which involves the recurrence of their original symptoms at a greater intensity.[64,65] While longer duration of use and higher doses are typically associated with more severe withdrawal, these risk factors can often be mitigated by a slower reduction rate. Notably, older adults appear to tolerate withdrawal just as well as their younger counterparts.[66,67] The acute severity of withdrawal symptoms may be mitigated in older adults due to the protracted clearance of BZRAs in older age.[68] »

Through difficult periods, patients may seek means for symptom relief. Monitoring potential compensation with other over-the-counter sedatives (e.g. doxylamine) or increased alcohol use can help track how a patient is coping with their reduction. Most patients will benefit from reassurance that their symptoms will pass with time, however pharmacists need to strike the right balance between normalising the ups and downs of withdrawal and referring on for further investigation when necessary.[63]

While recommended in some guidelines, switching to a long-acting BZRA is unlikely to improve the outcome, particularly when switching from a short-acting BZRA taken once at night for insomnia.[69,70]

Currently no medication is approved in Australia to support BZRA withdrawal, therefore non-pharmacological strategies are key to managing symptoms (e.g. relaxation and mindfulness practice, a balanced diet, abstaining from alcohol, regular exercise, and support groups).[71]

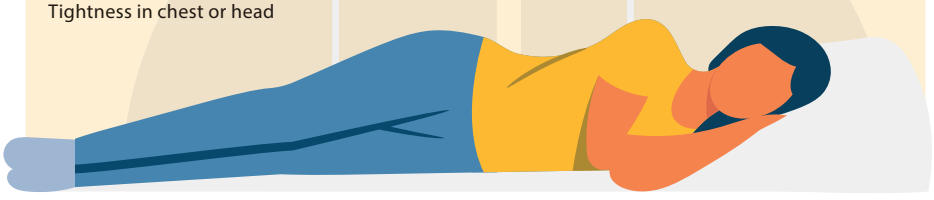
There is good evidence, however, that CBTi leads to increased success with BZRA cessation.[72–74] It is proposed that as CBTi treats the underlying psychological and behavioural factors perpetuating insomnia, it can render the medication redundant, diminishing the psychological dependence and reducing the likelihood of relapse.[73]

Knowledge to practice

Pharmacists routinely encounter patients taking long-term BZRAs for insomnia and are in an ideal position to identify potential tolerance (e.g. dose escalation) and dependence (e.g. what happens if they miss a night, drug-seeking behaviour). Pharmacists should explore the patient's understanding of the risks associated with prolonged BZRA use and provide education on reduction and withdrawal where appropriate. Pharmacists also play an important role in providing education on evidence-based treatment for insomnia (i.e. CBTi). Pharmacists should be aware of referral options to access CBTi and BZRA dependence support so these can be provided to patients where necessary. Please see 'Further information and resources' on p41 for resources for deprescribing, evidence-based treatment of insomnia, CBTi, and health professional and patient support services.

Table 1 – Examples of benzodiazepine withdrawal symptoms

COMMON	LESS COMMON	RARE
Abdominal pain and cramps*	Aching jaw	Blackouts
Agoraphobia	Confusion*	Sinus pain
Anxiety*	Constipation	Blood noses
Blurred vision	Cravings	Rectal bleeding
Dizziness*	Diarrhoea	Heavy periods
Extreme lethargy	Dry mouth	Burning sensations (along spine, around mouth)
Feelings of unreality	Hallucinations*	Breast discharge
Gastrointestinal problems*	Hyperactivity	Swollen breasts
Insomnia*	Urinary incontinence/ frequency/urgency	Hair loss
Irritability*	Increased saliva	Hypersensitivity to touch
Lack of concentration	Changes to taste or appetite	Seizures*
Lack of coordination and/or balance	Numbness	
Muscle aches	Paranoia	
Nausea*	Pins and needles	
Nightmares	Sore mouth/tongue	
Panic attacks	Suicidal thoughts*	
Restlessness*	Tinnitus	
Tightness in chest or head		



**Also observed with nonbenzodiazepine hypnotics (i.e. zolpidem or zopiclone)*
Reference: *Reconnexion[17], AMH[20], Maudsley Deprescribing Guidelines[62], Cosci et al[75], Schifano et al[76]*

Conclusion

Pharmacists play a pivotal role in sleep health education for all patients. Routinely engaging patients in conversations about their sleep and BZRA use not only opens a dialogue and builds rapport but also provides a stepwise approach for pharmacists to address an often-complex issue, and represents a patient-centred approach to quality use of medicines. Each interaction builds on previous conversations to facilitate collaborative and informed decision-making, laying the foundation to support patient choice and motivation to reduce BZRA use.

CASE SCENARIO CONTINUED

You learn that Harry has already increased his dose a couple of times over the past 2 years (currently taking 20 mg every night). After you inform Harry that he has likely developed a tolerance to the medicine, and provide more information about the adverse effects of long-term use, Harry discloses that he has had a couple of falls recently. You confirm that this may be a result of the medicine, and then explore if he has tried any other options for insomnia management. Harry is curious to learn that CBTi is more effective than temazepam but only wants to do it in person. You recommend he speak to his GP about his recent falls and actual temazepam use, to discuss accessing subsidised psychologist sessions for CBTi under a Mental Health Treatment Plan and for the support available to help him reduce his temazepam dose. »

FURTHER INFORMATION AND RESOURCES

- **Reconnexion** (*www.reconnexion.org.au*) is a specialist benzodiazepine dependency service in Victoria. It provides free counselling, telephone and email support, community information and education for health professionals.
- **Alcohol Drug Information Service (ADIS):** Phone 1800 250 015, 24 hours a day, 7 days a week, for patient information, support or treatment referrals regarding benzodiazepine use.
- For people seeking psychological assistance while trying to withdraw from benzodiazepines or for insomnia treatment, the **Australian Psychological Association** can assist with finding a psychologist (*https://psychology.org.au*).
- **NPS MedicineWise** provides a range of resources for health professionals and consumers to manage benzodiazepine dependence (*www.nps.org.au/benzodiazepine-dependence*).
- **The Royal Australian College of General Practitioners – Prescribing drugs of dependence in general practice: Part B – Benzodiazepines** provides evidence-based recommendations on treatment of relevant conditions and discontinuing therapy (*www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/drugs-of-dependence/part-b/summary-of-recommendations*).
- **Primary Health Tasmania – A guide to deprescribing benzodiazepines** (*www.primaryhealthtas.com.au/wp-content/uploads/2023/03/A-guide-to-deprescribing-benzodiazepines.pdf*).
- **The Maudsley Deprescribing Guidelines: Antidepressants, Benzodiazepines, Gabapentinoids and Z-drugs.** Wiley Blackwell; 2024.
- **Deprescribing.org – Benzodiazepine & Z-Drug (BZRA) Deprescribing Algorithm** (*https://deprescribing.org/wp-content/uploads/2019/03/deprescribing_algorithms2019_BZRA_vf-locked.pdf*).
- **Sleep Health Foundation** (*www.sleephealthfoundation.org.au*) and the **Australasian Sleep Association** (*https://sleep.org.au*) – insomnia resources for consumers and healthcare providers.
- An up-to-date list of digital CBTi programs is available on the **Sleep Health Primary Care Resources** page (*www.sleepprimarycareresources.org.au/insomnia/cbti/referral-to-digital-cbti-programs*).
- Online self-help program for managing benzodiazepine withdrawal can be accessed via **HealthZone** (*https://bdz.healthzone.org.au*).

UP TO
1.5
CPD
CREDITS
GROUP 2

KEY POINTS

- **BZRAs are routinely prescribed to manage insomnia.**
- **BZRAs should only be used short term or intermittently for insomnia (maximum 4 weeks) at the lowest possible dose but are often prescribed for longer periods. Dependence and tolerance can occur.**
- **CBTi is the first-line treatment for insomnia and is available in a range of formats to suit consumer preferences.**
- **Withdrawing from BZRAs requires an individualised approach, some patients can cease these easily while others will require many months (if not years).**
- **Pharmacists can support BZRA cessation through patient education and appropriate referral.** AP

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ASSESSMENT QUESTIONS

Each question has only one correct answer.

1 Which ONE of the following is *CORRECT* regarding BZRA use?

A BZRAs treat the triggers of insomnia and are generally well tolerated.

B BZRAs are not associated with withdrawal symptoms when used as recommended.

C Potential adverse effects include falls, memory impairment and sleep quality disturbance.

D BZRAs are recommended for at least 4 weeks' use.

2 Common withdrawal symptoms from BZRAs include:

A Seizures, lethargy and loss of taste.

B Insomnia, dry mouth and suicidal thoughts.

C Restlessness, insomnia and anxiety.

D Pins and needles, blood in the stool and abdominal pain.

3 Arna, 55 years old, has been taking oxazepam for over 3 years after the loss of her partner led to chronic insomnia. Which ONE of the following is *MOST* appropriate regarding the evidence-based treatment for insomnia, and recommendations for the withdrawal of her oxazepam?

A Switching to a long-acting BZRA increases the likelihood of successful cessation in most patients.

B CBTi is as effective as BZRAs and sustains these effects after therapy is complete and can lead to greater chance of successful BZRA withdrawal.

C Tapering plans should be followed strictly to ensure patients withdraw from their BZRA successfully in a timely manner to minimise risk.

D CBTi should be delayed until after BZRA cessation as evidence shows that it is not effective when used concurrently.

4 Pharmacists can be pivotal in assisting patients to successfully reduce and/or cease their BZRAs. Which ONE of the following is *MOST* appropriate when considering the role of the pharmacist in this area?

A Providing education to patients, conducting medication reviews and providing deprescribing recommendations are key areas in which pharmacists can enact change.

B Pharmacist education on BZRAs should be specific to deprescribing to be successful.

C Highlighting and addressing a patient's concerns about ongoing BZRA use can often cause patients to avoid reduction and/or cessation.

D Pharmacist education on BZRA cessation is most effective when patients are first educated on the benefits of BZRA cessation, irrespective of their readiness to change.