

BENZODIAZEPINES

KEY POINTS

- Benzodiazepines are generally regarded by clinical practice guidelines as only a short-term therapeutic option for anxiety and insomnia.
- Treating 13 patients with benzodiazepines for insomnia will improve sleep quality in one and there will likely be two patients with adverse effects.
- Non-pharmacological methods for insomnia (e.g. sleep hygiene, relaxation techniques) are often as effective as benzodiazepines.
- Abrupt discontinuation of benzodiazepines used for insomnia often results in short-term reduction of sleep quality.
- There is strong evidence that improvement in a range of neuropsychiatric functions occurs after discontinuation of benzodiazepines.
- Deprescribing of long term benzodiazepines for insomnia may take at least 6-8 weeks.
- Some patients reducing benzodiazepines may develop withdrawal symptoms and will require more gradual dose reduction.
- Providing patients with information regarding the risks of benzodiazepines in a structured format increases the efficacy of deprescribing.

CONTEXT

This guide considers the use of benzodiazepines for insomnia and anxiety.

RECOMMENDED DEPRESCRIBING STRATEGY

- Any patients taking benzodiazepines with overt adverse effects (daytime sedation, cognitive impairment, falls or dependence) may benefit from dose reduction and/or cessation.
- Many patients taking long-term benzodiazepines will gain benefits from cessation even though they do not have overt adverse effects.
- A tapering strategy should be used for all patients, but the duration and amount of tapering is variable.
 - The majority of patients will tolerate tapering by 15-20% per step over 6-8 weeks. One option (for patients using benzodiazepines for insomnia) is to advise not taking the agent one night a week for a week (or two), two nights the next week or two, three nights the next, etc. In most patients, this strategy will enable cessation.
 - If patients develop significant intolerant withdrawal or discontinuation symptoms, a return to the previous tapering step for a longer period of time (e.g. a month) often allows for a reattempt of dose reduction.

BENEFIT VERSUS HARM

	Favours Continuing Medication	Favours Deprescribing Medication
<p>Main Benefits</p> <ul style="list-style-type: none"> ➢ Short term relief of anxiety and/or insomnia 	<p>Increased Benefit</p> <ul style="list-style-type: none"> ➢ Intermittent low dose use 	<p>Decreased Benefits</p> <ul style="list-style-type: none"> ➢ Continuous use for more than 4 weeks
<p>Main Harms</p> <ul style="list-style-type: none"> ➢ Falls, cognitive impairment, dependence 	<p>Reduced Harms</p> <ul style="list-style-type: none"> ➢ Relatively young with healthy BMI 	<p>Increased Harms</p> <ul style="list-style-type: none"> ➢ Concurrent use of central depressant agents (e.g. opioids, antipsychotics, alcohol) ➢ Use in patients with high falls risk (e.g. frail elderly) ➢ Concurrent use of anticholinergic agents ➢ Use in patients with cognitive impairment ➢ Use in patients in first trimester of pregnancy ➢ Presence of renal and/or hepatic disease ➢ Presence of pulmonary disease or sleep apnoea

 EFFICACY

Benzodiazepines are widely used (and often misused) in Australia for a number of psychiatric conditions. These medications are generally effective, particularly when used short term, and are well tolerated by most people (in the short term). However, prolonged use is common and of concern due to a risk of dependence and an increased likelihood of other adverse effects, particularly sedation, falls, depression and cognitive impairment. Benzodiazepines were involved in approximately one third of drug induced deaths in Australia in 2016, commonly in combination with opioids.¹

Long term use should therefore be frequently re-evaluated with a view to dose minimisation or cessation if possible.

Benzodiazepines have anxiolytic, hypnotic, muscle relaxant and anticonvulsant properties. In terms of the use of benzodiazepines for psychiatric conditions, there is only demonstrated efficacy in four conditions: insomnia, panic disorder (PD), generalised anxiety disorder (GAD) and social anxiety disorder (SAD).²

The most common indications for the prescribing of benzodiazepines are insomnia and anxiety. As tolerance to the beneficial effects of benzodiazepines often develops, usually within weeks of commencement, short term use is recommended for these indications.

INSOMNIA

While hypnotics have been used for decades for insomnia, the studies that support this practice are limited to short term treatment and overall impact on sleep is moderate at best. Meta-analyses of sedative hypnotic use published in 2005 and 2007 identified that:^{3,4}

- The number of patients that would need to be treated with a sedative for one to have an improvement in sleep quality was 13 (95% CI 6.7-62.9).
- The increase in total sleep time with any sedative compared with placebo was 25.2 minutes (95%CI 12.8-37.8 minutes).
- There was a decrease in sleep latency (time trying to get to sleep) by approximately 10 minutes.
- The mean number of awakenings decreased by 0.63 (95%CI -0.48 - -0.77).

Tolerance to the hypnotic effects occurs rapidly and guidelines for pharmacological management of insomnia consistently recommend short term use only after attempts to use non-pharmacological methods (which have comparable efficacy to benzodiazepines).⁵ Suggested non-pharmacological therapies that have been shown to be effective for insomnia of different causes are shown in **Table 1** below.⁶

In people living with dementia, a Cochrane review found “a distinct lack” of evidence to help guide drug treatment of sleep problems in dementia patients. In particular, they found no trials of drugs that are widely prescribed for sleep problems, including the benzodiazepine and non-benzodiazepine hypnotics.⁷

ANXIETY

Anxiety disorders are a commonly occurring spectrum of conditions that vary from mild situational responses to stressors, to severe chronic anxiety with comorbid psychiatric illness. First-line therapy for GAD, PD, and panic attacks should include cognitive behaviour therapy (CBT) due to its effectiveness at reducing the symptoms of anxiety in the short and long term.⁸

Selective serotonin reuptake inhibitor (SSRI) and serotonin-norepinephrine reuptake inhibitor (SNRI) medications are effective across the range of anxiety disorders and are generally suitable for first-line pharmacological treatment of anxiety, particularly when there are elements of comorbid depression.

Short-term benzodiazepine use as occasional adjunctive therapy may be effective at reducing exacerbations of anxiety symptoms that can occur in the first few days to weeks of initiating antidepressant medication.⁹ Benzodiazepines are regarded by most clinical practice guidelines as a short-term therapeutic option.⁸ Use beyond four weeks is not recommended for most patients, as the risks of adverse effects associated with benzodiazepines outweighs the benefits in a number of patient groups (see adverse effect over).

WHAT IS THE CAUSE?	WHICH THERAPY AND WHAT APPROACH CAN I USE?
Lifestyle habits and environment not conducive to sleep	Advice on good sleep practices Practical tips on how to modify diet, exercise patterns, substance use, sleep-wake schedule, daytime napping, and sleep environment.
Negative thoughts or unrealistic expectations about sleep and the consequences of sleep loss	Cognitive therapy Techniques that replace distorted beliefs and attitudes with positive ones (e.g. reassure that <8 hours sleep a night is not necessarily detrimental).
Learned association between going to bed and being unable to sleep	Stimulus control Go to bed only when tired (and only use the bed for sleep or sex), get out of bed if not asleep within a perceived 20 minutes (do not watch the clock); repeat each night until a stable sleep-wake schedule is established.
Poor sleep drive results in broken sleep or excessive time spent in bed awake	Sleep restriction Restrict time in bed to actual sleep duration and have a set wake-up time; increase gradually as total sleep duration improves, and until the target sleep time is reached (not <5 hours).
Unable to mentally and/or physically wind down each night	Relaxation techniques Progressively focus on and relax each muscle group; taking deep breaths, relax and imagine something pleasant for as long as possible.

Table 1: Educational, behavioural and cognitive therapies for insomnia.¹¹

 ADVERSE EFFECTS

The adverse effects of benzodiazepines have been only adequately studied in the short term. Few studies have specifically addressed adverse effects associated with long term usage. Epidemiologic and experimental data has demonstrated a causal association between benzodiazepine use and motor vehicle accidents, falls and bone fractures.¹⁰

Some adverse effects may subside due to tolerance, in a similar way that tolerance develops to the desired effect of the medication. Most often, subjective feelings of dysphoria, heaviness, and sedation rapidly subside with continuous treatment.¹¹

This is because GABA receptors become less responsive with prolonged use of benzodiazepines, making the inhibitory effects of GABA less effective. In addition, negative feedback mechanisms cause a reduction in production of GABA, resulting in tolerance to its sedating and anxiolytic effects. However, enhancement of GABA's inhibitory activity also results in reduced production of excitatory neurotransmitters, which results in some of the long term side effects of benzodiazepines including ataxia, memory loss, confusion and possibly depression.

The impact of these adverse effects is greater in certain subgroups as outlined in **Table 2** below.

SUBGROUP AT HIGHER RISK	Reason for higher risk
PREGNANCY	there is increased risk of foetal abnormalities in the first trimester.
ALCOHOL CONSUMPTION	increased risk of excessive sedation and respiratory depression
RENAL AND/OR HEPATIC DISEASE	metabolic clearance of the agents will be compromised.
PULMONARY DISEASE/SLEEP APNOEA	benzodiazepines are respiratory suppressants
OLDER ADULTS	As a consequence of multiple comorbidities and CNS changes associated with aging, the risk of adverse effects is increased in older adults, especially those over 75 years of age

Table 2: Subgroups of people at high risk of benzodiazepine adverse effects

The use of benzodiazepines in older people is particularly problematic. A meta-analysis of sedative-hypnotic use in this population identified that:

- the most common adverse effects recorded were drowsiness or fatigue, headache, nightmares, nausea and other gastrointestinal disturbances
- the number needed to harm for sedative hypnotics compared to placebo was 6 (95%CI 4.7-7.1)
- adverse cognitive effects were significantly more common with sedative use than placebo.³

IMPAIRED COGNITION

Benzodiazepine use is frequently implicated in impairing cognition. Whilst this is most common in people using high doses long term, it may also occur with low doses over the short term, particularly in older adults. Whilst these effects typically resolve with discontinuation, there is concern that benzodiazepine use may contribute to dementia, with a number of observational studies associating an increased incidence of dementia with benzodiazepine use.¹⁰ Meta-analyses of several of these studies reported an increased odds of developing dementia of between 49% and 78% in users of benzodiazepines.^{12,13} However, it should be acknowledged that these studies have not definitively demonstrated that benzodiazepine use causes dementia, and the potential for reverse causality (e.g. benzodiazepine use was treating symptoms associated with preclinical dementia) cannot be excluded.

FALLS

Benzodiazepines are associated with an increased risk of falls. Multiple meta-analyses have found an increased relative risk of falls associated with sedative/hypnotic use. For example, a 2013 meta-analysis reported an overall increase in risk of at least one fall during the reported trial periods (often 6 months or less) of between 35% and 60%.¹⁴

DEPENDENCE

In addition to the above range of adverse effects, regular benzodiazepine use commonly results in the development of psychological and physical dependence. The likelihood of this occurring increases with duration of use and is also higher in elderly patients and those with multiple medical conditions.



FACTORS TO CONSIDER

The discontinuation of benzodiazepines has been a focus of improved medication use for decades. A number of discontinuation strategies have been employed for adult long-term users. A recent review of the clinical evidence and guidelines for benzodiazepine discontinuation found that most studies utilised dose tapering either alone or as part of other interventions (usually psychotherapy).¹⁵⁻¹⁹

Relatively simple interventions may effectively reduce many patients' use of benzodiazepines. For example, studies that utilised patient-directed letters from their prescriber (with or without a follow-up consultation) reported significant reductions in benzodiazepine use. In these studies, cessation of benzodiazepines occurred in 20 to 35% of subjects in the intervention groups, compared to 10 to 15% of the "usual care" groups at six month follow-up, with a number needed to treat (NNT) of 12.²⁰

Tannebaum et al utilised a more intensive strategy involving a "deprescribing patient empowerment intervention" to reduce benzodiazepine use. This consisted of an education package for patients that described the risks associated with benzodiazepines and a stepwise tapering protocol.²¹

At 6 months, 37.8% of the intervention group had either discontinued benzodiazepine use or reduced the dose of benzodiazepine (of 148 participants, 40 [27%] ceased and 16 [10.8%] reduced doses). The NNT for this study was 3.7. Of interest, in multivariate sub-analyses, age >80 years, sex, duration of use, indication for use, dose, previous attempt to taper, and concomitant polypharmacy (defined as ≥ 10 drugs per day) did not have a significant interaction effect with benzodiazepine therapy discontinuation.²¹

A similar study utilised a structured interview to provide patients with:

- information regarding benzodiazepine dependence and withdrawal symptoms
- information regarding the risks of long term use on memory, cognition, falls and accidents
- reassurance about reducing medication
- a patient self-help leaflet to assist with sleep quality (for those taking benzodiazepines for insomnia).

At 12 months, 162 of 369 patients (45%) that received the education (some with further followup) had ceased their benzodiazepine(s), compared with 26 of 173 (15%) in the control group (ARR 30%; NNT 3.3).²²

A 2017 systematic review assessed seven studies that reported on interventions to deprescribe benzodiazepines and other hypnotics amongst older people.²³ Mixed interventions, such as patient education and tapering, pharmacological substitution with psychological support, and tapering with psychological support, were associated with discontinuation rates between 27 and 80%.

Based on these data, **it is apparent that patient education regarding the long-term use of benzodiazepines has a significant impact on successful deprescribing.** Such interventions are of low cost, easily integrated into regular care and involve patients in therapeutic decision-making. The Royal Australian College of General Practitioners (RACGP) has developed patient fact sheets on both the use and cessation of benzodiazepines, along with sample letters for patient mailouts and sample dose reduction strategies for particular agents.⁸

IN FAVOUR OF DEPRESCRIBING

- ✔ Patient willingness to change has been positively associated with successful cessation of benzodiazepines.³⁰
- ✔ Some patients may be aware of being dependent on benzodiazepines and may be amenable to a weaning regimen.
- ✔ There is evidence that informing patients of the potential harms of benzodiazepine use increases the likelihood of long term discontinuation.
- ✔ Lower baseline benzodiazepine doses and shorter durations of use are associated with greater rates of successful cessation and lower risks of resumption.

AGAINST DEPRESCRIBING

- ✘ Short term benzodiazepine use may be appropriate for patients with a self-limiting stressor.
- ✘ Patients receiving benzodiazepines for other significant indications (muscle spasm) may require continuation of the agents.

 DISCONTINUATION SYNDROMES

Sudden cessation of benzodiazepines in tolerant patients result in them being exposed to hypoactive GABA and hyperactive glutamatergic excitation, which causes discontinuation symptoms.²⁴ This may even occur in patients who have only used low doses for a few weeks. Discontinuation symptoms include recurrence, rebound and withdrawal.

Recurrence involves the person experiencing symptoms identical to those for which the benzodiazepine was initially prescribed.

Rebound symptoms reflect the inverse of the therapeutic effect of benzodiazepines, such as increased anxiety, insomnia and restlessness. For example, insomnia can return in an exaggerated form with changes to sleep patterns. Sleep latency is increased, sleep is more disturbed, and overall sleep is shorter in duration.²⁵ Although these changes are of short duration (usually less than a week), the recommencement of benzodiazepines is a common patient response to these symptoms.

WITHDRAWAL

There is limited data regarding pharmacological management of benzodiazepine cessation. A 2018 Cochrane review evaluated the benefits and harms of pharmacological interventions to facilitate discontinuation of benzodiazepines in chronic users.²⁶ The interventions assessed included valproate, tricyclic antidepressants, pregabalin, carbamazepine, paroxetine and flumazenil. Whilst over 30 studies involving over 2000 participants were evaluated in this review, most studies were of low quality and small sample sizes, and the review was unable to draw firm conclusions as to the appropriateness or effectiveness of these interventions in reducing benzodiazepine use.

About 20% of long term users of benzodiazepines become physically addicted and attempts to withdraw the drug are associated with frank withdrawal symptoms.²⁵ While it is difficult to predict which patients are more likely to become dependent, those who take higher doses, use high potency compounds (e.g. alprazolam) and have used the agents for prolonged periods of time are more likely to become dependent.

Withdrawal symptoms include anxiety, insomnia, nightmares, changes to memory and concentration as well as muscle spasms (see **Table 3**). Patients often experience an increase in sensory acuity, often with photophobia and increased sensitivity to everyday sounds.⁸

The duration of withdrawal symptoms is often dependent upon the agent. Withdrawal from benzodiazepines with short half-lives (e.g. oxazepam, alprazolam) usually improves significantly within four to five days; withdrawal from long half-life benzodiazepines (e.g. diazepam) usually subsides after two to four weeks, but can be prolonged. An appropriate tapering schedule can minimise and sometimes avoid these withdrawal effects. Whilst there is no evidence regarding the most suitable benzodiazepine tapering regimen, factors that may indicate a slower tapering regimen will be required include high dose, high potency and prolonged duration of benzodiazepine use.

ANXIETY SYMPTOMS		DISTORTED PERCEPTIONS	MAJOR INCIDENTS (MAINLY WHEN HIGH DOSES ARE STOPPED ABRUPTLY)
PSYCHOLOGICAL	PHYSICAL		
<ul style="list-style-type: none"> ■ Anxiety ■ Panic attacks ■ Insomnia ■ Poor memory ■ Depression ■ Paranoia ■ Intrusive memories ■ Cravings ■ Nightmares ■ Excitability ■ Agoraphobia ■ Social phobia ■ Obsessions ■ Rage, aggression ■ Irritability 	<ul style="list-style-type: none"> ■ Agitation ■ Tremor ■ Headache ■ Weakness ■ Dizziness ■ Nausea ■ Vomiting ■ Diarrhoea ■ Constipation ■ Palpitations ■ Rashes ■ Tingling, numbness, altered sensation ■ Fatigue ■ Flu-like symptoms 	<ul style="list-style-type: none"> ■ Hypersensitivity to sound, light, touch, taste ■ Abnormal body sensation e.g. itching, pain, stiffness, blurred vision, paraesthesia, muscle twitching, tinnitus, burning sensations ■ Feeling self or world to be abnormal (depersonalisation or derealisation) 	<ul style="list-style-type: none"> ■ Fits (1-2% of patients) ■ Delirium (rare) ■ Transient hallucinations (visual, tactile, auditory) or illusions (rare) ■ Psychosis (very rare)

Table 3: Acute withdrawal effects after ceasing benzodiazepines⁸

RESOURCES

- GENERAL INFORMATION
- ALLOPURINOL
- ANTIHYPERGLYCAEMICS
- ANTIHYPERTENSIVES
- ANTIPSYCHOTICS
- ASPIRIN
- BENZODIAZEPINES
- BISPSPHONATES
- CHOLINESTERASE INHIBITORS
- GLAUCOMA EYE DROPS
- NSAIDS
- OPIOIDS
- PROTON PUMP INHIBITORS
- STATINS
- VITAMIN D AND CALCIUM

AUTHORSHIP

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