A GUIDE TO

deprescribing

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BENZODIAZEPINES

KEY POINTS

Cognitive Behavioural Therapy (CBT) is generally recommended as firstline therapy for anxiety and insomnia.

Benzodiazepines are recommended by clinical practice guidelines as only a short-term therapeutic option for anxiety or insomnia.

Non-pharmacological methods for insomnia (e.g. sleep hygiene, relaxation techniques) are often as effective as benzodiazepines.

Avoid starting benzodiazepines in older patients. If a benzodiazepine is absolutely necessary, use for a short time only, at a low dose and monitor the patient closely.

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.

Providing patients with information regarding the limitations and risks of benzodiazepines in a structured format increases the efficacy of deprescribing.

Success rates between 25% to 85% can be achieved with gradual taper strategies if patients are properly educated, provided with a clear plan for deprescribing, and informed about potential withdrawal symptoms.

CONTEXT

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

BENEFIT VERSUS HARM

	Favours Continuing Medication	Favours Deprescribing Medication
Main Benefits Short term relief of anxiety and/or insomnia	**Increased Benefit** • Intermittent low dose use	**Decreased Benefits** • Continuous use for more than 4 weeks
Main Harms Falls, cognitive impairment, dependence	**Reduced Harms** • Relatively young and robust	**Increased Harms** • 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

RECOMMENDED DEPRESCRIBING STRATEGY

- Any patient taking benzodiazepines with overt adverse effects (daytime sedation, cognitive impairment, falls or dependence) may benefit from dose reduction and/or drug cessation.
- Many patients taking long-term benzodiazepines will gain benefits from cessation even though they do not have overt adverse effects.
- Engaging the patient in a conversation about deprescribing a benzodiazepine is a critical first step. Concerns and questions from the patient, the family, and/or caregivers should be addressed.[31]
- Patients may benefit from psychotherapy while tapering off benzodiazepines. In a systematic review and metaanalysis, combining CBT with gradual tapering of the drugs over 3 months was more effective for stopping the drugs than gradual tapering alone.[68]
- A tapering strategy should be used for almost all patients, but the duration and amount of tapering is variable. Gradual tapering of benzodiazepines does not guarantee avoidance of withdrawal symptoms, but reduces the risk and severity (if they occur).[26]
- A frequently described approach is a dose reduction of 25% every 1 to 2 weeks,[55] while U.K. guidelines recommend reducing the daily dose by 10% to 20% every 2 weeks.[31]
  - 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 intolerance to withdrawal or severe discontinuation symptoms, a return to the previous tapering step for a longer period of time (e.g. a month) is appropriate, prior to re-attempting dose reduction.

EFFICACY

It should be firstly acknowledged that the balance of benefit and risk with benzodiazepine use is often disputed and undergoes periodic reconsideration,[1-11] yet the bulk of the available evidence calls for a cautious approach to their use, especially long term.[2,4,12] As with other drugs, there can be significant clinical benefits but also risks to patient safety, and an individualised approach is essential.

Benzodiazepines are widely used (and misused) in Australia for a number of 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, motor vehicle accidents, depression and cognitive impairment. Benzodiazepines were involved in over one-third of all unintentional drug-induced deaths in Australia in 2020, commonly in combination with opioids.[13] In late 2020, the United States Food and Drug Administration (FDA) updated a boxed warning for benzodiazepines, particularly emphasising the risks of co-administration with opioids.[12]

Benzodiazepines have anxiolytic, hypnotic, amnesic, muscle relaxant and anticonvulsant properties. In terms of their use for psychiatric conditions, there is only demonstrated efficacy in four conditions: insomnia, panic disorder (PD), generalised anxiety disorder (GAD) and social anxiety disorder (SAD).[5,14-17]

The most common clinical 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 (< 2-4 weeks) is recommended for these indications. The longer-term use of benzodiazepines should be frequently re-evaluated with a view to dose minimisation or cessation if possible.

INSOMNIA

Non-pharmacological approaches (**Table 1**) are preferred. Cognitive behavioural therapy (CBT), which includes sleep hygiene, stimulus control and sleep restriction, is recommended as a firstline therapy for insomnia (and anxiety),[11,15,16,18-24] although up to 40% of patients with insomnia will have ongoing symptoms despite CBT. It performs at least as well as pharmacotherapy in the short term, with superior results in the long term.[20]

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.[33]

If drug therapy is considered, it is important to evaluate the underlying nature of the patient's insomnia and what the intended outcome of the therapy is. Short-term drug therapy (up to four weeks) may be appropriate in acute insomnia with an identifiable precipitating factor or illness.[18]

While hypnotics are frequently used for insomnia, the studies that support this practice are limited to short-term treatment and the overall impact on sleep is moderate at best,[25-27] with suggestions that a "placebo response" is a major contributor to their perceived effectiveness in practice.[26] Meta-analyses of hypnotic use have identified that:[28-30]

- 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 mean increase in total sleep time with any sedative compared with placebo was 25.2 minutes (95%CI 12.8-37.8 minutes) and temazepam provided a mean increase of 28.5 minutes;
- there was a decrease in sleep latency (i.e. time to get to sleep) of approximately 10 minutes and temazepam provided a mean decrease of 16.3 minutes compared to placebo;
- the mean number of awakenings decreased by 0.63 (95%CI -0.48 to -0.77); and
- sleep efficiency (calculated as the percentage of time in bed spent as sleep time) was 4.9% greater with temazepam than placebo.

Long-term treatment of insomnia with benzodiazepines is not recommended because of the lack of evidence, side effects, and risks of tolerance and dependence.[19] It has been shown that after 24 weeks of chronic benzodiazepine intake, the subjective sleep quality drops to a level below baseline.[19] Guidelines for the pharmacological management of insomnia consistently recommend short-term use only,[16,18-22,25,26,31,32] after attempts to use sleep hygiene (e.g. avoiding bright lights, having a consistent sleep schedule, positioning clocks away from the bed, avoiding caffeine and electronics before bed) and other non-pharmacological methods (which have comparable efficacy to benzodiazepines).[24] Suggested non-pharmacological approaches that have been demonstrated to be effective for insomnia of different causes are shown in Table 1.[33]

Systematic reviews have noted a paucity of evidence to guide the drug treatment of sleep problems in patients with dementia.[34,35]

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 CBT due to its effectiveness in the short and long term.[5,11,15,23]

Selective serotonin reuptake inhibitor (SSRI) (first line) and serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressant medications are effective across the range of anxiety disorders and are generally suitable for long-term pharmacological treatment of anxiety, particularly when there are elements of comorbid depression.[15]

The role of benzodiazepines in anxiety disorders is controversial.[1-5,7-11,23] While they are rapidly acting, relatively well tolerated and effective for the prominent symptoms of anxiety, they should not be used as first-line therapy because of potential harms (including increased risk of falls, memory problems, accidents, daytime sedation and dependence, and the potential adverse interactions with alcohol and opioids).[2,4,5,15]

Benzodiazepines should be given very cautiously and never as monotherapy.[5] Their use should usually be restricted to acute crises and the immediate short term. For instance, short-term use of a benzodiazepine may be needed as an adjunct to an antidepressant for anxiety that is severe and disabling, or causing the patient unacceptable distress, due to the delayed onset of effect of the antidepressant,[15] and the potential for transient worsening of anxiety in some cases soon after commencing an antidepressant. A dilemma, however, is that this combination is not particularly safe in the elderly, especially if continued. There is a five-fold increased risk (odds ratio (OR) = 4.7, 95%CI 1.7-13) of hip fracture, equating to one extra hip fracture for every 17 patients aged 80 years and over who are treated for a year with the combination of a benzodiazepine and an SSRI.[36] The patient's risk of falling should be assessed before prescribing the combination.

Use beyond four weeks is not recommended for most patients with anxiety, as the risks of adverse effects typically outweigh the benefits.[2] However, maintenance therapy, subject to periodic reassessment may be appropriate in patients who have not responded to other treatments and in those who are on a long-term regimen, at a stable dosage and have a good clinical response[15]

ADVERSE EFFECTS

There is a causal association between benzodiazepine use and motor vehicle accidents, falls and bone fractures.[37]

Some adverse effects of benzodiazepines may subside due to tolerance, in a similar way that tolerance develops to the desired effects. Most often, subjective feelings of dysphoria, heaviness, and sedation rapidly subside with continuous treatment.[32]

The impact of the adverse effects of benzodiazepines is greater in certain subgroups:

- pregnancy: there is increased risk of foetal abnormalities in the first trimester;
- alcohol consumption or combination with opioids: increased risk of excessive sedation and respiratory depression;
- renal and/or hepatic disease: clearance of the agents or their active metabolites will be compromised;
- pulmonary disease/sleep apnoea: benzodiazepines are respiratory suppressants; and
- older adults: as a consequence of multiple comorbidities and medicines, and CNS changes associated with aging, the risk of adverse effects is increased in older adults, especially those over 75 years of age.

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 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); and
- adverse cognitive effects were significantly more common with sedative use than placebo.[29]

In fact, adverse drug events associated with benzodiazepine use as hypnotics are more than twice as likely to occur compared with enhanced quality of sleep.[26]

IMPAIRED COGNITION

Benzodiazepine use is frequently implicated in cognitive impairment. 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.[29,37-39]

Studies in mice indicate that benzodiazepines may impair the structural plasticity of dendritic spines, contributing to cognitive impairment.[40]

Whilst these cognitive effects typically resolve with discontinuation, there has been concern that benzodiazepines may contribute to the development of dementia, with a number of reports associating an increased incidence of dementia with benzodiazepine use.[41-46] However, this association has been questioned,[23,47,48] particularly when relying on data from observational studies, with their inherent methodological limitations e.g. the potential for reverse causality (benzodiazepine use was for treating symptoms associated with pre-clinical dementia). A recent meta-analysis including data from 35 studies found that an observed association between benzodiazepine use and increased risk of dementia did not persist after exclusion of studies with potential reverse causation and confounding by indication.[48]

FALLS

Benzodiazepines are associated with an increased risk of falls.[18] Multiple meta-analyses have confirmed an increased relative risk of falls associated with benzodiazepine use.[49,50] For example, a 2018 meta-analysis reported an overall mean increase in the risk of fall by 42% (OR = 1.42, 95%CI 1.22-1.65).[49]

Similarly, meta-analyses show an increased risk of hip fracture in patients taking benzodiazepines compared with non-users.[51-53]

It should, however, be noted that lack of sleep has also been associated with an increased risk of falls.[18]

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. It is estimated that dependence develops in nearly half of patients who use benzodiazepines for longer than 1 month. Tolerance to the sedative effects may occur rapidly within 2 to 4 weeks, but the risk of other adverse effects can persist.[26]

FACTORS TO CONSIDER

The discontinuation of benzodiazepines has been a focus for improved medication use for decades and they have typically been the highest priority drug group for a deprescribing clinical practice guideline, according to doctors, pharmacists, and nurses.[25,26] Many discontinuation strategies have been employed for long-term adult users, with most studies utilising dose tapering either alone or as part of other interventions (usually psychotherapy).[9,10,25,26,54-62]

Relatively simple interventions may reduce many patients' use of benzodiazepines.[61] 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.[63]

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.[64] At 6 months, 37.8% of the intervention group had either discontinued or reduced their benzodiazepine (of 148 participants, 40 [27%] ceased and 16 [10.8%] reduced doses). 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 influence benzodiazepine therapy discontinuation.

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; and
- a self-help leaflet to assist with sleep quality (for those taking benzodiazepines for insomnia).[65]

At 12 months, 162 of 369 patients (45%) who received the education (some with further follow-up) had ceased their benzodiazepine(s), compared with 26 of 173 (15%) in the control group (NNT 3.3).[65]

Based on published studies, it is apparent that patient education regarding the long-term use of benzodiazepines has a significant impact on successful deprescribing.[56,61] 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.[66]

There is limited data regarding the pharmacological management of benzodiazepine cessation.[9] A 2018 Cochrane review evaluated the benefits and harms of pharmacological interventions to facilitate discontinuation of benzodiazepines in chronic users.[58] The interventions assessed included valproate, tricyclic antidepressants, pregabalin, carbamazepine, paroxetine and flumazenil. Most studies were of low quality and had 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.

CBT may be effective for discontinuing benzodiazepines, both in the short term and in the long term.[11,55,61,62,67,68]

A recent systematic review found that deprescribing benzodiazepines improves cognitive function across multiple domains.[26] One study examining the effects of withdrawing chronic temazepam and 'Z drugs' (e.g. zopiclone and zolpidem) in older adults found that, 6 months after the cessation of hypnotics, patients experienced shorter sleep-onset latency and less difficulty in initiating sleep disturbance than at baseline, with reduced daytime fatigue and enhanced quality of life.[21,70]

IN FAVOUR OF DEPRESCRIBING

Patient willingness to change has been positively associated with successful cessation of benzodiazepines.[11,59]

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 ongoing 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.

If the patient is unwilling to cease benzodiazepines, discontinuation is unlikely to be successful.[11]

An alternative treatment strategy should be developed before ceasing benzodiazepines. If the agents are deprescribed before an alternative intervention is implemented, then the patient's only treatment for their condition is being stopped and long-term discontinuation is unlikely.[6]

Patients receiving benzodiazepines for other significant indications (e.g. muscle spasm) may require continuation of the agents. As mentioned previously, continued therapy, subject to periodic reassessment may be appropriate in some patients with anxiety who have not responded to other treatments and who are on a long-term regimen, at a stable dosage.

DISCONTINUATION SYNDROMES

Sudden cessation of benzodiazepines may cause discontinuation symptoms, including 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. Although these changes are of short duration (usually less than a week), the recommencement of benzodiazepines is a common patient response to these symptoms. Again, patient education and engagement are critical.

WITHDRAWAL

The experience of discontinuing from long-term benzodiazepine therapy differs markedly among patients.[10,11] Some can cease benzodiazepines with few or only mild symptoms, whereas others endure prolonged periods of severe symptoms.

It is worth noting that the fear of benzodiazepine withdrawal symptoms motivates some patients to continue taking the drugs even when they do not seem to benefit from treatment. Such patients are often hypervigilant about any bodily changes and likely to misinterpret minor symptoms during minimal dose reductions as signs of withdrawal, which reinforces the erroneous notion that they will never be able to cease them.[11]

Over one-third of people report withdrawal symptoms when discontinuing benzodiazepines.[71] While it is difficult to predict which patients are more likely to become dependent and subsequently develop frank withdrawal symptoms, those who take higher doses, use high-potency compounds (e.g. alprazolam) and have used the agents for prolonged periods of time are at greater risk.

Withdrawal symptoms include anxiety, insomnia, nightmares, irritability, changes to memory and concentration, myoclonic jerks, palpitations, and sensory disturbances, such as photophobia and hyperacusis (oversensitivity to certain frequency sounds and volume ranges) (see **Table 2**).[60,66,71]

ANXIETY SYMPTOMS		DISTORTED PERCEPTIONS	MAJOR INCIDENTS (MAINLY WHEN HIGH DOSES ARE STOPPED ABRUPTLY)
PSYCHOLOGICAL	PHYSICAL		
■ Anxiety ■ Panic attacks ■ Insomnia ■ Poor memory ■ Depression ■ Paranoia ■ Intrusive memories ■ Cravings ■ Nightmares ■ Excitability ■ Agoraphobia ■ Social phobia ■ Obsessions ■ Rage, aggression ■ Irritability	■ Agitiation ■ Tremor ■ Headache ■ Weakness ■ Dizziness ■ Nausea ■ Vomiting ■ Diarrhoea ■ Constipation ■ Palpitations ■ Rashes ■ Tingling, numbness, altered sensation ■ Fatigue ■ Flu-like symptoms	■ 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)	■ Fits (1-2% of patients) ■ Delirium (rare) ■ Transient hallucinations (visual, tactile, auditory) or illusions (rare) ■ Psychosis (very rare)

Table 2: Acute withdrawal effects after ceasing benzodiazepines[60,66]

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 or avoid withdrawal effects. Recommendations on the pace of dosage reduction range widely, from reducing the initial benzodiazepine dose by 50% approximately every week to reducing the daily dose by between 10% and 25% every 2 weeks.[9] 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. Switching from short-acting to longacting benzodiazepines prior to tapering has not been shown to improve rates of successful cessation or reduce the incidence or severity of withdrawal symptoms.[26,55]

It is contended that most patients will be able to withdraw over a period of up to 8 weeks (**Table 3**), and that prolonged reductions (over many months) should generally be avoided to prevent the withdrawal of treatment from becoming the patient's main preoccupation.[9]

Duration of use	Recommended duration of tapering	Comments
< 6 to 8 weeks	May not be required	Consider tapering benzodiazepine, particularly if patient is taking a high-dose benzodiazepine or a medicine with short or intermediate half-life
8 weeks to 6 months	Slowly over 2–3 weeks	
6 months to 1 year	Slowly over 4–8 weeks	Tapering will minimise withdrawal symptoms Advise patients to avoid alcohol and stimulants
> 1 year	Slowly over 2–4 months	

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