A GUIDE TO

deprescribing

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BENZODIAZEPINES

KEY POINTS

- **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.**
- **Benzodiazepines are generally regarded by clinical practice guidelines as only a short-term therapeutic option for anxiety.**
- **Discontinuation of benzodiazepines used for insomnia often results in short-term changes to sleep architecture.**
- **Some patients reducing benzodiazepines may develop withdrawal symptoms and will require more gradual dose reduction.**
- **Deprescribing of long term benzodiazepines for insomnia may take at least 6-8 weeks.**
- **Providing patients with information regarding the risks of benzodiazepines in a structured format increases the efficacy of deprescribing.**
- **There is strong evidence that improvement in a range of neuropsychiatric functions occurs after discontinuation of benzodiazepines.**

CONTEXT

This guide considers the use of benzodiazepines for insomnia and anxiety. Their use in alcohol withdrawal, epilepsy and management of acute mania is not discussed.

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. A 20-25% reduction every week or two is usually well tolerated.
- 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.

EFFICACY

Benzodiazepines are widely used (and often misused) in Australia and tend to be effective in the short term and have a good tolerability profile, again in the short term. Prolonged use, however, is cause for increasing concern. Dependence on benzodiazepines is more likely to occur with prolonged use. Other adverse effects such as sedation, increased risk of falls, depression and other CNS effects, can become problematic. Benzodiazepines were involved (causal or contributive) in approximately half of the drug-related deaths in Victoria in 2010.[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. Prescribing for insomnia and anxiety are the most common indications and tolerance to the effects of benzodiazepines has led to the recommendation of short term use for these indications.

The use of these agents in alcohol withdrawal, epilepsy and management of acute mania are not discussed in this document.

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:[2,3]

- 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).[4] Suggested non-pharmacological therapies that have been shown to be effective for insomnia of different causes are shown in **Table 1** below.[5]

In patients 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.[6]

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.[4]

ANXIETY

Anxiety disorders are common and are a spectrum of conditions that vary from mild situational responses to stressors to severe chronic anxiety with comorbid psychiatric illness.

First-line therapy for generalised anxiety disorder (GAD), panic disorder, 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.

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 co-morbid depression. Short-term benzodiazepine use as occasional adjunctive therapy may be effective at reducing worsening of anxiety symptoms that can occur in the first few days to weeks of initiating antidepressant medication.[7]

Benzodiazepines are generally regarded by clinical practice guidelines as a short-term therapeutic option.[8] Long-term use, beyond 4 weeks, should be uncommon, as the risk:benefit of benzodiazepines is an issue in a number of patient groups (see Adverse Effects below).

Benzodiazepine use in anxiety disorders is mostly limited to severe or treatment-resistant cases. They have more benefit for generalised anxiety disorder (GAD), social anxiety disorder and panic disorders than for obsessive compulsive disorder (OCD) or post-traumatic stress disorder (PTSD).[10, 11, 12, 13]

ADVERSE EFFECTS

Adverse effects of benzodiazepines have only been adequately studied in the short term. Few studies have specifically addressed adverse effects associated with long term usage. Some of the adverse effects can subside due to tolerance in a similar way to the desired effect of the medication. Most often, subjective feelings of dysphoria and heaviness, along with sedation rapidly subside with continuous treatment.[14]

In addition to the sedating adverse effects, there is a risk of physical and psychological addiction with long-term use. The impact of these adverse effects is greater in certain subgroups:

- 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.

In a meta-analysis of sedative hypnotic use in older people published in 2005, Glass et al[2] identified that:

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

Long term use of benzodiazepines has been implicated in reduction of cognition.[15] A case control study has found that there may be an increased incidence of dementia in patients who take benzodiazepines for 6 months or more.[16]

Debate regarding the causality in this observational study is ongoing.[17] It remains unclear whether benzodiazepines increase risk of dementia or are prescribed to combat pre-clinical symptoms of dementia.

In a prospective study of 3434 patients aged 65 or over without dementia at study enrolment, cumulative use of total standardised doses of benzodiazepines over a 10-year window was examined in relation to development of dementia and cognitive trajectory.[18] Over a mean follow-up of 7.3 years, 797 (23.2%) people developed dementia (of which 637 were of the Alzheimer's type). Interestingly, there was no relationship between the highest rate of benzodiazepine use (more than 120 standardised doses ~4 months of daily use) and the development of dementia. Low-level use (1-30 standardised doses) and moderate use (30-120 doses) was, however, associated with an increased risk of dementia with hazard ratios of 1.25 (95% CI 1.03-1.57) and 1.31 (95% CI 1.00-1.71).[18]

Despite these varying results, there is strong evidence that improvement in a range of neuropsychiatric functions occurs after discontinuation of benzodiazepines.[19,20]

Benzodiazepines are associated with an increased risk of falls. Multiple meta-analyses of the impact of drugs on falls found increased relative risk of falls associated with sedative/hypnotic use. These were reviewed recently and an overall increase in risk of at least one fall during the reported trial periods (often 6 months or less) was between 35% and 60%.[21]

With prolonged use of benzodiazepines, GABA receptors become less responsive, making the calming effects of GABA less effective. In addition, negative feedback mechanisms result in reduced production of GABA, resulting in tolerance to the sedating and anxiolytic effects. Enhancement of GABA's inhibitory activity results in reduced production of the excitatory transmitters. This results in some of the long term side effects of benzodiazepines which include ataxia, memory loss, confusion and possibly depression.

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, including depression.

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). [22,23,24,25,26]

Three studies that utilised a relatively minimal intervention, that of a patient directed letter from their prescriber (with or without a follow-up consultation), were reviewed together.[27] All three studies reported significant reductions in benzodiazepine use with cessation of the benzodiazepine in 20-35% of subjects in the intervention groups compared to 10-15% of the "usual care" groups at six-month follow-up. A pooled risk difference of 8% (95% CI 3-13%) gave a NNT of 12.

A more intensive strategy, involved the use of a "deprescribing patient empowerment intervention" which involves an education package for patients that describes the risks associated with benzodiazepines and a stepwise tapering protocol. At 6 months, 37.8% of the intervention group had either discontinued (40/148; 27%) benzodiazepine use or reduced the dose of benzodiazepine (16/148; 10.8%). Usual treatment results were 4.5% (7/155) cessation and 6.5% (10/155) dose reduction (ARR 27%; NNT=3.7). Of interest, in multivariate sub-analyses, age greater than 80 years, sex, duration of use, indication for use, dose, previous attempt to taper and concomitant polypharmacy (10 drugs or more per day) did not have a significant interaction effect with benzodiazepine therapy discontinuation.[28]

A multicentre three arm study used a similar strategy, providing to patients in a structured interview:[29]

- 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).

These authors found that at 12 months, 162 of 369 patients (45%) that received the education (some with further follow-up) had ceased their benzodiazepine(s), compared with 26 of 173 (15%) in the control group (ARR 30%; NNT 3.3).[29]

It seems relatively clear, therefore, that informing patients taking long-term benzodiazepines has a significant impact on successful deprescribing. 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.[30]

IN FAVOUR OF DEPRESCRIBING

- Patients who are aware of dependence on benzodiazepines may be amenable to a weaning regimen.
- Informing patients of the potential harms of benzodiazepine use increases the likelihood of long term discontinuation.

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

Cessation of benzodiazepines when used for insomnia often results in problems with recurrence (in an exaggerated form) of the insomnia as a part of a discontinuation syndrome. As physical and psychological dependence on benzodiazepines is common, many patients also undergo some withdrawal symptoms.

DISCONTINUATION

After stopping benzodiazepines, insomnia can return in an exaggerated form and short term changes to sleep can occur. Sleep latency is increased, sleep is more disturbed and overall sleep is shorter in duration.[31] Although these changes are of short duration (less than a week), the recommencement of benzodiazepines is a common response to the signs.

WITHDRAWAL

About 20% of long term users of benzodiazepines become physically addicted and attempts to withdraw the drug are associated with frank withdrawal symptoms.[32] 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 2**). Patients often experience an increase in sensory acuity, often with photophobia and increased sensitivity to everyday sounds.[8, 33]

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[30]

RESOURCES

- QUICK REFERENCE GUIDE
- GENERAL INFORMATION
- ALLOPURINOL
- ANTIHYPERTENSIVES
- ANTIPLATELET AGENTS
- ANTIPSYCHOTICS
- BENZODIAZEPINES
- BISPHOSPHONATES
- CHOLINESTERASE INHIBITORS
- GLAUCOMA EYE DROPS
- NSAIDS
- OPIOIDS
- PROTON PUMP INHIBITORS
- STATINS
- SULPHONYLUREAS
- VITAMIN D AND CALCIUM

AUTHORSHIP

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