

# BENZODIAZEPINES

## KEY POINTS

- For every 6 patients treated with benzodiazepines for insomnia, one will have an adverse effect.
- Treating 13 patients with benzodiazepines will improve sleep quality in one.
- Non-pharmacological methods (eg. sleep hygiene, relaxation techniques) are often as effective as benzodiazepines.
- Discontinuation of benzodiazepines often results in short term changes to sleep architecture.
- Some patients may develop true withdrawal symptoms and will require more gradual dose reduction.
- Deprescribing of long term benzodiazepines for insomnia may take at least 6-8 weeks.

## CONTEXT

This guide considers the deprescribing of benzodiazepines for insomnia.

## RECOMMENDED DEPRESCRIBING STRATEGY

- 1 Any patients taking benzodiazepines with overt adverse effects (daytime sedation, cognitive impairment, falls or dependence) may benefit from dose reduction and/or cessation.
- 2 Many patients taking long term benzodiazepines will benefit from dose reduction even though they do not have overt adverse effects.
- 3 A tapering strategy should be used for all patients, but the duration and amount of tapering is variable.
- 4 The majority of patients will tolerate tapering by 15-20% per step over 6-8 weeks. One option 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.
- 5 If patients develop significant intolerant withdrawal or discontinuation symptoms, a return to the previous tapering step for a longer period of time (eg. a month) often allows for a reattempt of dose reduction.

## EFFICACY

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.

### 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<sup>1,2</sup> identified that:

- 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 an decrease in sleep latency (time trying to get to sleep) by approximately 10 minutes.

continued page 2 >

WHAT IS THE CAUSE?	WHICH THERAPY AND WHAT APPROACH CAN I USE?
Lifestyle habits and environment not conducive to sleep	<b>Advice on good sleep practices</b> 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	<b>Cognitive therapy</b> 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	<b>Stimulus control</b> 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	<b>Sleep restriction</b> 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	<b>Relaxation techniques</b> 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.<sup>3</sup>

< EFFICACY continued from page 1

■ 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).<sup>3</sup> Suggested non-pharmacological therapies that have been shown to be effective for insomnia of different causes are shown in **Table 1**.

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.<sup>4</sup>

## ADVERSE EFFECTS

Adverse effects of benzodiazepines have been only adequately studied in the short term, and no 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.<sup>5</sup>

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.<sup>1</sup> 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,<sup>6</sup> and 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.<sup>7</sup> Debate regarding the causality in this observational study is ongoing,<sup>8</sup> and it remains unclear whether benzodiazepines increase risk of dementia or are prescribed to combat pre-clinical symptoms of dementia. It is fairly certain, however, that improvement in a range of neuropsychiatric functions occur after discontinuation of benzodiazepines.<sup>9,10</sup>

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%.<sup>11</sup>

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 and 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 BEFORE DEPRESCRIBING

### IN FAVOUR OF DEPRESCRIBING

- ✓ Some patients may be aware of being dependent on benzodiazepines for insomnia and may be amenable to a weaning regimen.

### AGAINST DEPRESCRIBING

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

## RESOURCES

- ✓ QUICK REFERENCE GUIDE
- ✓ ANTIHYPERTENSIVES GUIDE
- ✓ ANTIPLATELET AGENTS GUIDE
- ✓ ANTIPSYCHOTICS GUIDE
- ✓ BENZODIAZEPINES GUIDE
- ✓ BISPHOSPHONATES GUIDE
- ✓ STATINS GUIDE
- ✓ VITAMIN D & CALCIUM GUIDE



[www.consultantpharmacyservices.com.au](http://www.consultantpharmacyservices.com.au)



primary  
health  
TASMANIA

phn  
TASMANIA

An Australian Government Initiative

[www.primaryhealthtas.com.au](http://www.primaryhealthtas.com.au)



## DISCONTINUATION SYNDROMES

Cessation of benzodiazepines often results in problems with recurrence 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 occur to sleep. Sleep latency is increased, sleep is more disturbed and overall sleep is shorter in duration.<sup>12</sup> 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.<sup>13</sup> While it is difficult to predict which patients are more likely to become dependent, those who take higher doses, use high potency compounds (eg. 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. Patients often experience increases in sensory acuity, often with photophobia and increased sensitivity to everyday sounds.<sup>14</sup> Symptoms generally subside in 2-4 weeks but can be more prolonged. An appropriate tapering schedule can minimise and sometimes avoid these withdrawal effects.

## REFERENCES

1. Jennifer Glass, Krista L Lancôt, Nathan Herrmann, Beth A Sproule, Usoa E Busto. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits BMJ. doi:10.1136/bmj.38623.768588.47 (published 11 November 2005).
2. Buscemi N, Vandermeer B, Friesen C, et al. The efficacy and safety of drug treatments for chronic insomnia in adults: a meta-analysis of RCTs. J Gen Intern Med 2007; 22:1335.
3. NPS News Number 67, 2010. Addressing hypnotic medication use in primary care. Available at [www.nps.org.au](http://www.nps.org.au)
4. McCleery J, Cohen DA, Sharpley AL. Pharmacotherapies for sleep disturbances in Alzheimer's disease. Cochrane Database of Systematic Reviews 2014, Issue 3. Art. No.: CD009178. DOI: 10.1002/14651858.CD009178.pub2.
5. Lader, M. Benzodiazepine harm: how can it be reduced? Br J Clin Pharmacol. 2014 Feb; 77(2): 295-301.
6. Billotti de Gage S. et. al. Benzodiazepine use and risk of dementia: prospective population based study. BM 2012; 345:
7. Yaffe K, Boustani M Benzodiazepine use and risk of Alzheimer's disease: case-control study. BMJ 2014; 349 doi: 10.1136/bmj.g5205 (Published 9 September 2014).
8. NPS Medicinewise. Do benzodiazepines increase risk of dementia? 31 October 2014. Available at [www.nps.org.au](http://www.nps.org.au)
9. Barker M et al. Cognitive effects of long term benzodiazepine use: A meta-analysis. CNS Drugs 2004;18: 37-48.
10. Verdaux H et al. Is benzodiazepine use a risk factor for cognitive decline and dementia? A literature review of the epidemiological studies. Psychol Med 2005; 35: 307-15.
11. Marlies R. de Jong, Maarten Van der Elst and Klaas A. Hartholt. Drug-related falls in older patients: implicated drugs, consequences, and possible prevention strategies. Ther Adv Drug Saf (2013) 4(4) 147-154.
12. Dikeos DC et al. The pharmacology of insomnia: efficacy and rebound with hypnotic drugs. Primary Care Companion. Clin Psychiatry 2002; 4(Suppl 1): 27-32.
13. Lader M. Long-term anxiolytic therapy: the issue of drug withdrawal. J Clin Psychiatry 1987; 48 (Suppl): 12-16.
14. Ashton H. Benzodiazepine withdrawal: outcome in 50 patients. Br J Addict 1987; 82: 655-71.