

Benzodiazepines and dementia

Benzodiazepines are a class of drugs commonly used to treat anxiety and insomnia. However, long-term regular treatment with benzodiazepines carries a number of risks. This sheet provides information about how these drugs work as well as the impact that they may have in respect to dementia risk and cognitive functioning.

What are benzodiazepines?

Benzodiazepines are psychotropic medications (that is, medications that impact on mood and behaviour) that have been in use since the 1960s primarily for the treatment of anxiety, panic disorders and insomnia. They are a ‘depressant’ medication, also known as ‘minor tranquilizers’ and can also be used for treatment of seizures, muscle spasms, alcohol withdrawal and as a preoperative medication for medical or dental procedures.

Benzodiazepines are widely available in Australia (Table 1) and are used regularly by around 15% of Australian adults aged 65 years and over.¹ Although prescribing rates have fallen over the past decade, there is a continued high rate of prescription among the population.^{2,3}

- 1 Windle A, Elliot E, Duszynski K, Moore V. Benzodiazepine prescribing in elderly Australian general practice patients. **Australian & New Zealand Journal of Public Health**. 2007;31(4):379–381.
- 2 Stephenson CP, Karanges E, McGreggor IS. Trends in the utilisation of psychotropic medications in Australia from 2000 to 2011. **Australian & New Zealand Journal of Psychiatry**. 2013;47(1):74–87.
- 3 Islam MM, Conigrave KM, Day CA, Nguyen Y, Haber PS. Twenty-year trends in benzodiazepine dispensing in the Australian population. **Internal Medicine Journal**. 2014;44(1):57–64.

Table 1. Benzodiazepines available in Australia^{4,5}

Main Use	Generic Name	Brand Name(s)
Anxiety, panic disorders	Alprazolam	Alprax [®] , Alprazolam Sandoz [®] , Chemmart Alprazolam [®] , GenRx Alprazolam [®] , Kalma [®] , Terry White Chemists Alprazolam [®]
Anxiety	Bromazepam	Lexotan [®]
	Oxazepam	Alepam [®] †, APO-Oxazepam [®] , Murelax [®] , Serepax [®]
Anxiety, seizures	Clobazam*	Frisium [®]
Seizures	Clonazepam	Paxam [®] , Rivotril [®]
Anxiety, alcohol withdrawal, sedation for short medical procedures, seizures, muscle spasm	Diazepam	Antenex [®] , APO-Diazepam [®] , Chemmart Diazepam [®] , GenRx Diazepam [®] , Ranzepam [®] , Terry White Chemists Diazepam [®] , Valium [®] , Valpam [®]
Anxiety, insomnia, sedation for short medical procedures	Lorazepam*	APO-Lorazepam [®] , Ativan [®]
Sedation for short medical procedures, seizures	Midazolam	B.Braun Midazolam [®] , Hypnovel [®] , Midazolam Alphapharm [®] , Midazolam Apotex [®] , Midazolam Sandoz [®]
Insomnia	Flunitrazepam	Hypnodorm [®]
	Nitrazepam	Alodorm [®] , Mogadon [®]
	Temazepam	APO-Temazepam [®] , Normison [®] , Temaz [®] , Temtabs [®]
	Triazolam*	Halcion [®]
Z Drugs[†] for insomnia	Zolpidem*	APO-Zolpidem [®] , Dormizol [®] , GenRx Zolpidem [®] , Somidem [®] , Stildem [®] , Stilnox [®] , Synthron Zolpidem [®] , Zolpibell [®] , Zolpidem Sandoz [®]
	Zopiclone	APO-Zopoclone [®] , Chemmart Zopiclone [®] , Imovane [®] , Imrest [®] , Terry White Chemists Zopiclone [®]

* Not listed on the Pharmaceutical Benefits Scheme (PBS)

† Z drugs have a similar action to benzodiazepines but are marketed for insomnia.

4 Australian Medicines Handbook. Adelaide: Australian Medicines Handbook Pty Ltd; 2016 [cited 2016 Apr 27]. Available from: <https://amhonline.amh.net.au/>

5 MIMS Online. MIMS Australia. 2016 [cited 2016 Apr 27]. Available from: <http://www.mimsonline.com.au>

How do benzodiazepines work?

Benzodiazepines slow down the activity of the central nervous system by enhancing the inhibitory effect of gamma-aminobutyric acid (GABA) in the brain, a chemical (neurotransmitter) that is used to control messages travelling from one cell to another.⁶ This action produces a calming effect in the brain, resulting in the various anti-anxiety, sedative or anti-seizure activity seen with these drugs. Benzodiazepines can target different GABA receptors in the brain and are also categorised according to the time it takes to produce an effect and for the drug to clear the body. Therefore, some benzodiazepines are better than others for treating particular conditions. For example, short-acting drugs tend to be used to treat insomnia whereas long-acting drugs are used to control anxiety.

What side-effects are associated with the use of benzodiazepines?

Benzodiazepines can have an important role in the short-term treatment of numerous conditions and in general have acceptable side-effect profiles. For example, some people can experience drowsiness, nausea or reduced co-ordination. However, long-term and regular use often leads to tolerance and dependence and for some individuals, ceasing or reducing the dose of long-term benzodiazepine treatment can result in severe withdrawal symptoms.⁷ As such, some benzodiazepines (alprazolam and flunitrazepam) are scheduled as a drug of addiction.^{8,9}

What are the implications of benzodiazepines in respect to dementia risk?

There is significant debate about the impact of benzodiazepines on people's likelihood of developing dementia and as study findings are mixed, further research is required before any conclusion can be made.

6 Therapeutic Guidelines. Psychotropic. eTG Complete. November 2015 [cited 2016 Apr 27]. Available from: <https://tgldcdp.tg.org.au/etgcomplete>

7 Schweizer E, Rickels K. Benzodiazepine dependence and withdrawal: a review of the syndrome and its clinical management. *Acta Psychiatrica Scandinavica*. 2007;98(s393):95-101.

8 Prescribing drugs of dependence in general practice, Part B – Benzodiazepines. Melbourne: The Royal Australian College of General Practitioners; 2015 [cited 2016 Apr 27]. Available from: <http://www.racgp.org.au/your-practice/guidelines/drugs-of-dependence-b/1-introduction/>

9 NSW Ministry of Health. Prescribing of benzodiazepines alprazolam and flunitrazepam; 2013 [cited 2016 Apr 27]. Available from: <http://www.health.nsw.gov.au/pharmaceutical/Documents/guide-flunitraz-alpraz.pdf>

There is some convincing evidence from studies that have followed participants for over 15 years that long term use of benzodiazepines is likely to increase the risk of dementia.^{10,11} Further, literature reviews have reported that long-term users of benzodiazepines have a 1.5- to 2-fold increase risk of developing dementia compared with those who have never received benzodiazepines.^{12,13}

In contrast, findings from a recent prospective study following participants for an average of seven years did not find any association between the highest level of benzodiazepine use and dementia or cognitive decline. Contrary to expectations, this study reported a small increased risk for dementia in people with low (up to one month) or moderate (one to four months) use of benzodiazepines.¹⁴ Still, others have suggested that benzodiazepines might even be protective against dementia.¹⁵

It is possible that the apparent association between benzodiazepine use and dementia could be better explained by the fact that the very early symptoms of dementia (whether diagnosed as dementia or otherwise) are often treated with these medications. The increased risk of dementia associated with low levels of benzodiazepine use may suggest that people in the very early stages of dementia could be more sensitive to the effects of benzodiazepines on cognitive functioning, resulting in the discontinuation of the drug and therefore, low levels of use.¹⁶

10 Billioti de Gage S, Bégaud B, Bazin F, Verdoux H, Dartigues J, Pérès K, et al. Benzodiazepine use and risk of dementia: prospective population based study. **BMJ**. 2012;345:e6231.

11 Gallacher J, Elwood P, Pickering J, Bayer A, Fish M, Ben-Shlomo Y. Benzodiazepine use and risk of dementia: evidence from the Caerphilly Prospective Study (CaPS). **Journal of Epidemiology & Community Health**. 2012;66(10):869–873.

12 Zhong G, Wang Y, Zhang Y, Zhao Y. Association between benzodiazepine use and dementia: A meta-analysis. **PLoS ONE**. 2105;10(5):e0127836. doi:10.1371/journal.pone.0127836

13 Billioti de Gage S, Pariente A, Bégaud B. Is there really a link between benzodiazepine use and the risk of dementia? **Expert Opinion in Drug Safety**. 2015;14(5):733–47

14 Gray SL, Dublin S, Yu O, Walker R, Anderson M, Hubbard RA, Crane PK, Larson EB. Benzodiazepine use and risk of incident dementia or cognitive decline: prospective population based study. **BMJ** 2016;352:i90. [cited 2016 Apr 27]. Available from: <http://www.bmj.com/content/352/bmj.i90>

15 Fastbom J, Forsell Y, Winblad B. Benzodiazepines may have protective effects against Alzheimer disease. **Alzheimer Disease & Associated Disorders**. 1998;12(1):14–17.

16 Gray SL, Dublin S, Yu O, Walker R, Anderson M, Hubbard RA, Crane PK, Larson EB. Benzodiazepine use and risk of incident dementia or cognitive decline: prospective population based study. **BMJ** 2016;352:i90. [cited 2016 Apr 27]. Available from: <http://www.bmj.com/content/352/bmj.i90>

What are the impacts of benzodiazepines on cognitive functioning?

Benzodiazepines can have a negative impact on mental abilities and cognitive functioning. The side-effects can include confusion, disorientation, inattention or reduced co-ordination. This can have potentially very serious implications for people who are already living with dementia or mild cognitive impairment, and for older people who may be at greater risk of adverse health outcomes such as falls¹⁷ and subsequent injuries including fractures. An impairment in cognitive and psychomotor functioning may also impact on driving ability; benzodiazepines are associated with a 60-80% increase in the risk of traffic accidents.¹⁸

There has been debate about whether or not these side-effects are temporary (disappearing when medication stops), lasting, or are a result of the underlying conditions such as anxiety or insomnia that the medications are being used to treat. Studies have shown that most people recover some but not all of their cognitive functioning after stopping benzodiazepines, but that the impact is relatively minor for most people.¹⁹

Should benzodiazepines be prescribed and what are the alternatives?

Benzodiazepines should be used with caution, particularly in patients who have cognitive impairment or who are over the age of 60 years. This is because older people:

- May have difficulty eliminating the drug from their system, due to the physiological changes associated with ageing;
- Are most at risk of harm from using benzodiazepines in relation to falls, fractures and cognitive decline; and

17 Woolcott JC, Richardson KJ, Wiens MO, Patel B, Marin J, Khan KM, Marra CA. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. **Archives of Internal Medicine.** 2009;169(21):1952-60.

18 Prescribing drugs of dependence in general practice, Part B – Benzodiazepines. Melbourne: The Royal Australian College of General Practitioners; 2015 [cited 2016 Apr 27]. Available from: <http://www.racgp.org.au/your-practice/guidelines/drugs-of-dependence-b/1-introduction/>

19 Stewart SA. The effects of benzodiazepines on cognition. **Journal of Clinical Psychiatry.** 2005;66(Suppl. 2):9-13.

- May have other existing medical conditions and taking medications that could interact with benzodiazepine treatment.^{20,21}

It is generally recommended that benzodiazepines (if required) should be prescribed at the lowest dose possible and for short periods of time (e.g. two-four weeks), as part of a broader treatment plan.²² Reduction in the use of benzodiazepines for older people is a worthwhile goal as it usually leads to improved cognitive and psychomotor functioning.

Newer ‘Z drugs’ (e.g. zolpidem and zopiclone), which also target GABA receptors, can be used to treat insomnia. Although these drugs were initially believed to have improved safety profiles compared with traditional benzodiazepines, there is increasing evidence to suggest that ‘Z drugs’ carry similar risks. Therefore, these drugs should also be used with caution in older adults, and psychological therapies such as sleep restriction and stimulus control should be offered to patients as first-line treatment.²³

Current guidelines recommend that older people presenting with anxiety symptoms should be treated initially with psychological therapies and/or anti-depressants rather than benzodiazepines.²⁴ Further, clinical practice guidelines indicate that for people with dementia who also have depression or anxiety, interventions such as music, support and counselling should be considered in the first instance. Other classes of anti-depressant drugs can be trialled if non-pharmacological treatments are inappropriate or have failed.²⁵

20 Therapeutic Guidelines. Psychotropic. eTG Complete. November 2015 [cited 2016 Apr 27]. Available from: <https://tgldcdp.tg.org.au/etgcomplete>

21 Prescribing drugs of dependence in general practice, Part B – Benzodiazepines. Melbourne: The Royal Australian College of General Practitioners; 2015 [cited 2016 Apr 27]. Available from: <http://www.racgp.org.au/your-practice/guidelines/drugs-of-dependence-b/1-introduction/>

22 Australian Medicines Handbook. Adelaide: Australian Medicines Handbook Pty Ltd; 2016 [cited 2016 Apr 27]. Available from: <https://amhonline.amh.net.au/>

23 Prescribing drugs of dependence in general practice, Part B – Benzodiazepines. Melbourne: The Royal Australian College of General Practitioners; 2015 [cited 2016 Apr 27]. Available from: <http://www.racgp.org.au/your-practice/guidelines/drugs-of-dependence-b/1-introduction/>

24 *ibid*

25 Guideline Adaption Committee. Clinical Practice Guidelines and Principles of Care for People with Dementia. Sydney: NHMRC Partnership Centre for Dealing with Cognitive and Related Functional Decline in Older People; 2016. [cited 2016 Apr 27]. Available from: http://sydney.edu.au/medicine/cdpc/documents/resources/LAVER_Dementia_Guidelines_recommendations_PRVW5.pdf

What questions should you ask your doctor about any drug being prescribed?

- What are the potential benefits of taking this drug?
- How long before improvement may be noticed?
- What action should be taken if a dose is missed?
- What are the known potential side-effects?
- If there are side-effects, should the dose be reduced or should the drug be stopped?
- If the drug is stopped suddenly, what happens?
- What other drugs (prescription and over-the-counter) might interact with the medication?
- How might this drug affect other medical conditions?
- Are there any changes that should be reported immediately?
- How often will a visit to the doctor be needed?
- Is the drug available at a subsidised rate?

This sheet is not intended to provide general or individual medical advice. Individuals concerned about their own or others medication should consult their GP or specialist.

Further Information

Dementia Australia offers support, information, education and counselling. Contact the National Dementia Helpline on **1800 100 500**, or visit our website at dementia.org.au



For language assistance phone the Translating and Interpreting Service on **131 450**