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# Benzodiazepines

*Their role in aggression and why GPs should prescribe with caution*

## Background

Benzodiazepines are widely prescribed in Australia, despite concerns about their potential for abuse and dependence. Paradoxical reactions, disinhibition and amnesia are all associated with benzodiazepine use, misuse and intoxication. While violent and aggressive behaviour may be a consequence of such disinhibition, there is limited information available regarding the links between benzodiazepine use and violence.

## Objective

This article aims to examine the existing evidence on the relationship between benzodiazepines, violence and aggression.

## Discussion

While current evidence suggests that benzodiazepines rarely induce violence, it is important to note that the available literature is limited in its scope and that benzodiazepine related violence is often severe and of potential concern to frontline workers. Mediating risk factors for benzodiazepine related violence include concurrent alcohol use, benzodiazepine dose, a history of aggression and underlying impulsivity. Comprehensive assessment and alternate nonpharmacological treatment options should be considered before prescribing benzodiazepines within primary care.

**Keywords:** substance related disorder; benzodiazepines; prescriptions, drugs



Each year over 5 million prescriptions for benzodiazepines are subsidised through the Pharmaceutical Benefits Scheme (PBS),<sup>1</sup> accounting for approximately 4–5% of all prescriptions written by general practitioners.<sup>2</sup> Although not recommended as first line treatment for anxiety disorders, and despite significant risks of abuse and dependence with continued use, benzodiazepines are widely prescribed for managing anxiety, panic disorders and insomnia.

Between 2002 and 2007, diazepam was the most commonly prescribed anxiolytic followed by alprazolam and oxazepam, while temazepam and nitrazepam were the most widely used sedative hypnotics.<sup>3</sup> Although rates of sedative hypnotic use appear to be decreasing, prescriptions for anxiolytics are on the increase, particularly for those aged 30–65 years.<sup>3</sup> While benzodiazepine prescriptions decreased between 1999 and 2003, prescriptions for alprazolam increased from 243 026 to nearly 335 000,<sup>4</sup> with more than 400 000 prescriptions for alprazolam recorded by the PBS in 2010.<sup>1</sup> Although often perceived as a ‘safe’ long acting benzodiazepine,<sup>5</sup> clonazepam, which is less frequently prescribed, should still be used judiciously. Indeed, concerns about clonazepam misuse, particularly among forensic populations, led to its rescheduling as a PBS authority medication for epilepsy in Australia, and it is not recommended as a first line drug given the risk of abuse and efficacy of newer anticonvulsants.

Such high rates of benzodiazepine prescribing are concerning, given evidence of significant nonmedical use, abuse and other harm. Benzodiazepines are associated with addiction, overdose and other harms such as falls (particularly in the elderly) as well as abscess or tissue damage from unfiltered injecting.<sup>6–9</sup> In a study of people commencing drug treatment, nonmedical use of benzodiazepines was common, with GPs identified as the primary source of supply.<sup>10</sup> This highlights the importance of careful assessment when considering prescribing benzodiazepines within primary care, as well as the importance of following prescribing guidelines (*Table 1*).<sup>11</sup>

In addition to the risk of misuse and overdose, there is growing anecdotal evidence of a link between benzodiazepines and aggressive behaviour, particularly in relation to alprazolam. In a



**Table 1. RACGP guidelines for the rational use of benzodiazepines<sup>11</sup>**

Wherever possible avoid prescribing benzodiazepines to known polydrug users with dependence
When a program of benzodiazepine reduction is undertaken it should be with the patient's consent and cooperation
All patients prescribed benzodiazepines should be advised of the risk of dependence associated with long term use
Patients receiving prescriptions for benzodiazepines should be advised to obtain all prescriptions from the same doctor so that the risk of dependence can be monitored
Treatment review should include a review of the indication(s) for continued use of the benzodiazepine, medication dose and possible adverse effects. For all patients receiving long term benzodiazepines, review is particularly relevant
Nonmedication management for conditions such as anxiety and insomnia includes a clarification of the problem, counselling and specific advice, with referral where the diagnosis is uncertain, or where assistance in management is required
Detoxification from benzodiazepines may be facilitated by changing patients to long half life medications (eg. diazepam), and then slowly reducing the dose. One-to-one counselling may be supplemented by self help support programmes during withdrawal
The management of anxiety and insomnia should rely largely on nonpharmacological interventions
When benzodiazepines are prescribed, the lowest dose to achieve the desired outcome for the shortest duration necessary should be provided
For residents of aged care facilities, discontinuation of benzodiazepines can often be achieved gradually, provided the patient, family and nursing staff are cooperative. Medication may occasionally be required to control anxiety, agitation or other disturbed behaviours. Staff should be knowledgeable in appropriate management of challenging behaviours

recent study investigating benzodiazepine use and crime in a forensic population,<sup>12</sup> we elicited concerns about benzodiazepine related violence from a range of workers within primary health, legal and forensic settings (Table 2).

The remainder of this article aims to disentangle these concerns by analysing the available literature on benzodiazepine use and violence and provide some practical information to assist GPs in identifying and managing individuals at risk of benzodiazepine related aggression and violence.

### **What is the evidence for benzodiazepine related aggression?**

Although benzodiazepines are traditionally prescribed as anxiolytic and sedating agents, both animal<sup>13</sup> and human<sup>14</sup> studies document increased levels of anger, hostility and aggression following benzodiazepine use. Reports of such reactions date back to the 1960s,<sup>15</sup> with early studies documenting diazepam induced

rage attacks and 'egodystonic hatefulness',<sup>16</sup> while chlordiazepoxide and clorazepate were associated with aggressive outbursts.

According to the available evidence, such 'paradoxical' reactions are rare. Miller<sup>17</sup> reported that only around 1% of patients receiving chlordiazepoxide or diazepam developed aggressive reactions, while Dietch and Jennings<sup>18</sup> found that out of 11 717 patients receiving alprazolam, only four reported aggressive reactions. While many single dose studies emphasise the low prevalence of such aggressive reactions, there is consistent evidence of a correlation between aggression and benzodiazepine intake in both animal and human studies.<sup>19,20</sup> In a controlled laboratory study, Pagano<sup>21</sup> found that male subjects who were administered 10 mg of diazepam displayed significantly higher levels of aggression than those administered 5 mg or placebo. It is unclear whether this increased tendency for aggression would translate to real-world violence, particularly as many drug-using patients consume substantially higher doses of benzodiazepines. In a sample of patients stabilised on buprenorphine substitution pharmacotherapy, the median dose of diazepam consumed by participants (acquired from a range of sources) was 30 mg. Several patients reported taking diazepam equivalents of over 500 mg.<sup>22</sup>

A review of the available literature reveals that there is limited real-world, up-to-date research investigating the relationship between benzodiazepine use and violent behaviour. Previous research has primarily focused on single dose studies administered to healthy volunteers in controlled environments or acute administration experiments in animal models. The findings of these studies are difficult to translate to patients encountered in primary care.

Daderman and Lidberg<sup>23</sup> conducted one of the few studies of benzodiazepine related violence in a clinical population. In a sample of 42 Swedish male juvenile offenders, 19 were identified with a history of frequent intoxication with flunitrazepam. The authors found that almost all individuals in this group had been previously sentenced for serious violent offences. They also found that the combination of flunitrazepam with alcohol was associated with a reduction in episodic memory and an increase in impulsive violence. Psychiatric vulnerability played a role in this population with those scoring highly on boredom, susceptibility and verbal aggression being at greatest risk of violence. While this study occurred in individuals with violent criminal histories, it suggests that certain short acting benzodiazepines can increase impulsive violence and induce memory loss in susceptible individuals.

### **Risk factors for benzodiazepine related aggression**

From a practical primary healthcare perspective, it is important to note that the contribution of benzodiazepines to violence or aggression is



**Table 2. Worker concerns regarding benzodiazepine related violence<sup>12</sup>**

'I have a few clients who have y'know caused property damage and smashed windows and things like that and they are not quite sure what they were doing or why they did it. I had one client who set fire to his oven under the influence of Xanax and didn't quite know what he was doing. He was passed out when the smoke alarm went off so his neighbour came and pulled him out of his flat and he also called me one day and said that he had just woken up covered in blood and didn't know what he had been doing.' (Forensic counsellor)

'Long term clients that we know really, really well, and have extremely good relationships with suddenly exploding in anger and wrecking our shop, throwing chairs around, being verbally abusive, threatening, just going off and then coming back the next day and denying that they were even in the service. "Me, no way? I would never do that to you!" Yes you bloody well did!' (NSP worker)

'It's probably the aggressive response that they have when they have actually been quite violent toward people but again that brings up that very, very complex social question, do people pop a Xanax and then give themselves permission at some point to let loose this aggressive underlying part of themselves that was there anyway?' (Detox manager)

'The other thing is petty violence if you like. So getting into street fights, getting into fights at the boarding house. I think they are the two most common, I mean usually you end up with the person being beaten up invariably.' (General practitioner)

complex and mediated by a number of risk factors. Lion<sup>24</sup> suggested that aggressive outbursts may result from an interaction between the pharmacological profile of the benzodiazepine, other co-occurring drug use and the patient's personality. Paton<sup>25</sup> suggested that other risk factors for adverse reactions include the presence of central nervous system degenerative disease, a learning disability or difficulty with impulse control. Hall and Zisook<sup>26</sup> found that occasions where benzodiazepines had been implicated in aggression, rage and hostile behaviour were rare and had mainly occurred in the context of high dose use (ie. more than the prescribed amount). Alcohol has consistently been found to increase benzodiazepine related violence and aggression.<sup>23</sup>

Personality factors may also mediate acts of violence in the context of concurrent alcohol and benzodiazepine use,<sup>25</sup> with those with poor impulse control or a history of aggression associated with the greatest risk. Consistent with this notion, Cole et al<sup>27</sup> found that alprazolam worsened symptoms in patients with post-traumatic stress disorder and increased impulsive behaviour in those with borderline personality disorder. Particular caution is therefore required when prescribing benzodiazepines to patients with multiple psychiatric diagnoses or where impulsivity is a prominent symptom (eg. borderline personality disorder, impulse control disorder).

## Practical steps for reducing benzodiazepine related harm

- Take a comprehensive substance use history that includes periods of alcohol and prescription drug misuse
- Avoid benzodiazepines in patients with a history of substance misuse, aggression, violent forensic history or psychiatric disorders that include poor impulse control
- Consider nonpharmacological options, such as psychological approaches for patients with anxiety, and sleep hygiene and relaxation techniques for those with sleep difficulties and insomnia
- Prescribe small quantities for a short period of time at the lowest possible dose
- Have an agreement that the patient will only see one doctor and one pharmacy, and that benzodiazepine treatment will be reviewed if there are concerns about risk, with clear documentation and explanation to the patient
- Monitor patients prescribed benzodiazepines closely (eg. weekly reviews)
- Use urine drug screens where there is risk of substance use, before commencing and as a monitoring tool during benzodiazepine therapy
- Use jurisdictional drugs and poisons services, prescription shopping programs and PBS prescription releases to monitor medications used by the patient.

## Conclusion

The prescribing of benzodiazepines and their role in aggression and crime is a complex issue. While there is some evidence that benzodiazepines increase the risk of aggression among people with specific personality factors, the existing literature is limited, and definitive conclusions are difficult to make. Until the link between benzodiazepines and violence can be better understood, vigilant prescribing is an important preventive strategy.

## Summary of important points

- Benzodiazepines are widely prescribed despite recommendations to the contrary.
- Although benzodiazepine related violence and aggression is relatively rare, it can be of a high severity.
- Existing evidence does not adequately address the issue of benzodiazepine related aggression that is experienced by frontline workers.
- In Australia, GPs are the main source of benzodiazepines for those that misuse them. Cautious prescribing includes careful history and examination and assessment of risk.
- A clear management plan should include patient information on the potential harms associated with benzodiazepines and emphasising reasons for short treatment durations.
- Quality patient focused care involves weighing up the balance between the modest benefits of benzodiazepines with the substantial risks and harms in some patients.



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Conflict of interest: Professor Lubman has received honorarium for talks by AstraZeneca.

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