Graylands Hospital Drug Bulletin
Focus on Benzodiazepines

North Metropolitan Health Service – Mental Health March 2015 Vol 22 No.1 ISSN 1323-1251

Introduction

Benzodiazepines (BZDs) are one of the most commonly prescribed medications for the treatment of insomnia and anxiety.[1] They are also frequently used to treat psychiatric emergencies, epilepsy, severe muscle spasm, acute alcohol withdrawal, anaesthesia and intensive care.

However, the use of BZDs is often controversial as they are widely acknowledged to be addictive and withdrawal symptoms can occur after 4-6 weeks of continuous use. This had led to the recommendation that they should not be used as hypnotics or anxiolytics for longer than 4 weeks.[2] In older age, BZDs also have serious adverse effects, including increased risk of falls, road traffic accidents and cognitive impairment.[3,4]

More recently the risks of long term BZD use have received greater focus with new evidence demonstrating a link between BZD use and the development of Alzheimer's disease[5] and also increased risk of mortality.[6]

Given the wide spread usage of these medications and the associated risk, this bulletin reviews BZDs with particular emphasis upon adverse effects, dependence and abuse potential.

Mechanism of action

The great breakthrough in our understanding in the mechanism of action of BZDs came in the mid-1970s when biologists at Hoffman-La Roche demonstrated that BZDs exert their psychotropic effects by potentiating Gamma-aminobutyric acid (GABA) neurotransmission.[7]

GABA is one of the most abundant neurotransmitters in the CNS (more than 200-1000 times more abundant than acetylcholine or serotonin) with high concentrations in the cortex and limbic system.

BZDs bind to the $GABA_A$ receptor, reducing the quantity of GABA required to open the chloride channel, hyperpolarise the neuron and inhibit neurotransmission.[8] BZDs act on GABA-A receptors that include subunits of the alpha-1, alpha-2, alpha-3, and other classes.

The Non-BZD hypnotics such as zolpidem and zopiclone (Z-drugs) are more selective for the alpha-1 subclass which seems to drive sleepiness but not anti-anxiety.

Table 1: BZDs and relative half-lives[9,10]

Drug name	Half-life (hours)
Short-acting	
Triazolam	2
Alprazolam	6-12
Oxazepam	4-15
Temazepam	8-22
Medium-acting	
Bromazepam	10-20
Lorazepam	10-20
Long-acting	
Clobazam	12-60
Clonazepam	18-50
Diazepam	20-100
Flunitrazepam	18-26
Nitrazepam	15-38

Benzodiazepine use in Psychiatry

Sleep disorders

BZDs are effective hypnotics and are widely used in the treatment of sleep disorders. They can reduce the time taken to fall asleep, increase duration and efficacy of sleep, and reduce periods of wakefulness after the onset of sleep.[11]

BZDs suppress stage 3 and 4 of sleep, but only cause a slight decrease in REM sleep. These drugs are generally only recommended for short-term therapy due to the development of tolerance and dependence. BZDs with a short half-life can facilitate falling asleep with a lower risk of residual daytime drowsiness.

Non-BZD hypnotics such as zolpidem and zopiclone (Z-drugs) are becoming more widely used but may be just as likely as the BZDs to cause dependence and withdrawal.

The National institute of Health & clinical Excellence (NICE) carried out a technology appraisal on the newer hypnotics in 2004 ,and reported that

there was a lack of compelling evidence to distinguish between the Z-drugs and the short-acting BZD hypnotics, and concluded that prescribing decisions should be made on a cost basis.[12]

Anxiety

BZDs provide rapid symptomatic relief from acute anxiety states.[13] However, due to their potential to cause physical dependence and withdrawal symptoms, guidelines recommend that they should only be used to treat anxiety that is severe, disabling or subjecting the individual to extreme distress.[9]

A recent meta-analysis systematically reviewed 27 randomised controlled trials of drug treatment for generalised anxiety disorder (GAD).[14] The only BZD included was lorazepam. Fluoxetine was ranked first for response and remission and pregabalin for tolerability. Lorazepam showed up poorly but data for it were limited and the authors did not comment further.

NICE recommends that BZDs should not be used to treat panic disorder.[15]

Psychosis

BZDs are commonly used in the context of psychotic disorders and schizophrenia as adjunctive treatment, particularly when patients display agitated, violent and aggressive behaviours.

BZDs are often combined with antipsychotics for this purpose, however, a recent Cochrane review concludes that there is no convincing evidence that combining an antipsychotic and a BZD offers any advantage over the BZD alone.[16]

BZDs are also used in a significant minority of patients with psychosis who fail to respond to antipsychotic treatment.[17]

Additionally, there is limited evidence that some refractory patients may benefit from a combination of antipsychotic and BZD.[17]

Other beneficial effects

BZDs have anticonvulsant and muscle relaxant effects that are considered to be independent of their anxiolytic actions. These effects can be valuable in the emergency treatment of seizures or in the management of muscle spasms.

BZDs are also sometimes used as part of induction procedures prior to anaesthesia. BZDs (mainly diazepam) are also useful in managing withdrawal from alcohol.

Risks of benzodiazepines

BZDs are generally very well tolerated. Particularly when given in low doses for short periods of time. However, they may be associated with a number of adverse effects.

Oversedation, Falls & hip fractures, Road traffic accidents

The most common side effect of BZDs is sedation. Although, tolerance appears to develop after a few weeks, but some residual effects may remain. Signs of oversedation may include drowsiness, poor concentration, incoordination, muscle weakness, dizziness and mental confusion.

Oversedation persists longer and is more marked in the elderly and may contribute to falls and fractures. In the elderly the use of BZDs has been associated with at least a 50% increase in the risk of hip fracture.[18]

Acute confusional states have also occurred in the elderly even after small doses of BZDs. Oversedation from BZDs contributes to accidents at home and at work and studies from many countries have shown a significant association between the use of BZDs and the risk of serious road traffic accidents (RTAs).[19] People taking BZDs should be warned of the risks of driving and of operating machinery.

A study from Scotland of 19,386 drivers involved in RTAs found BZDs were associated with an increased risk of a crash (odd ratio for RTA 1.62: 95% CI 1.24 to 2.12).

The increased risk was significant for long half-life drugs used as anxiolytics, and the short half-life hypnotic, zopiclone.

Table 2: Adverse effects of BZDs

Sedation	GI disturbances
Drowsiness	Paradoxical
Incoordination	disinhibition
Ataxia	Incontinence
Memory impairment	Jaundice
Muscle weakness	Depression
Headaches	Emotional blunting
Diplopia	Respiratory depression

Cognitive effects

Long-term treatment with BZDs has been described as causing impairment in several cognitive domains, such

as visuospatial ability, speed of processing, and verbal learning.

An extensive study comprised a meta-analysis of the cognitive effects of long-term BZD use.[4] Thirteen studies were identified and the data were combined so that each study only contributed one outcome variable relating to cognitive function. The duration of BZD use ranged from 1 to 34 years.

These users were consistently more impaired than controls across all of the cognitive categories evaluated. The mean weighted effect size was -0.74 (SD+/-0.25) and all these differences were significant.

The authors point out the relative paucity of studies but conclude that long-term BZD use and cognitive impairment associated with this use, "have numerous implications for the informed and responsible prescription of these drugs."

Disinhibition

There seems to be an association between BZD use and subsequent aggressive behaviour. This is called disinhibitory or paradoxical reactions. These reactions may include acute excitement, hyperactivity, increased anxiety, vivid dreams, sexual disinhibition, hostility and rage.[20]

The overall incidence remains uncertain and varies widely depending on the population studied. Estimates of incidence range from less than 1% to at least 20% of those taking BZDs.[21] But those with impulse control problems, neurological disorders, learning disabilities, adolescents and the elderly are at significant risk.[20]

Alzheimer's disease

Observational studies published in 2012 have suggested a link between long term BZD use and the future development of Alzheimer's disease.[22]

More recently a case control study from Canada showed a cumulative and dose effect association between BZD use and the risk of developing Alzheimer's disease.[5]

The risk of Alzheimer's disease increased with prolonged exposure to BZDs; OR 1.32 (CI 1.01-1.74) for between 3 and 6 months use and OR 1.84 (CI 1.62-2.08) for exposure longer than 6 months.

The association for AD was also stronger for long-acting (half-life of 20 hours or more) BZDs than short-acting agents. The interpretation of these findings is strengthened by rigorous methods and they took significant steps to reduce potential biases and confounders.

Premature mortality

The association of premature mortality and BZD use is controversial. Although two studies in older populations did not report a significant association between BZD use and mortality [23] four others (in younger samples) found evidence of significantly increased mortality.

More recently, a retrospective cohort study from the UK assessed the risk of death in people aged over 16 years who were taking BZDs. Patients registered with one of 273 GP practices were identified from the General Practice Research Database.

The cohort included 34,727 patients who had received at least 2 prescriptions for an anxiolytic or hypnotic drug between Jan 1998 and Dec 2001. These were compared with 69,418 controls matched by age, sex and general practice that were not prescribed these drugs.

After an average of 7.6 years, prescription of an anxiolytic, a hypnotic or both was associated with double the risk of death from any cause compared with no prescription for these drugs (hazard ratio [HR] adjusted for sex, age, sleep disorders, anxiety disorders, other psychiatric disorders, comorbidities and prescription of other drugs=2.08, CI 2.02 to 2.15, $p<0.001$).

BZDs were the most commonly prescribed class of drug (76% of patients), followed by Z drugs (39%) and other drugs (21%).

Dependence and Withdrawal

Of all the issue surrounding the BZDs, dependence and withdrawal have occasioned the greatest continuing concern. BZDs are widely acknowledged to be addictive and withdrawal symptoms can occur after 4-6 weeks of continuous use.

Table 5: Characteristics of BZD withdrawal

Physical	**Psychological**
Muscle stiffness	Anxiety/insomnia
Weakness	Nightmares
GI disturbances	Depersonalisation
Paraesthesia	Decreased memory
Flu-like symptoms	Delusions & hallucinations
Visual disturbances	Depression

Short acting drugs such as alprazolam or lorazepam are associated with more problems on withdrawal than longer acting drugs such as diazepam.

Management of BZD withdrawal

Withdrawal of the BZD drug can be managed in primary care if the patients in consideration are willing. Clinicians should seek opportunities to explore the possibilities of BZD withdrawal with patients on long term prescriptions.

Switching to diazepam

Patients who take short or intermediate acting BZDs should be offered an equivalent dose of diazepam (which has a longer half-life and therefore causes less severe withdrawal). It is also available in variable strengths and formulations.

See Table 4 below for approximate dose conversions of BZDs when switching to diazepam.

Table 4: Switching from BZDs to diazepam[9,10]: Doses

BZD	Approx dose (mg)equivalent to 10mg diazepam
Alprazolam	0.5
Bromazepam	3
Clobazam	10
Clonazepam	0.25
Flunitrazepam	0.5
Lorazepam	1
Nitrazepam	5
Oxazepam	15
Temazepam	10
Triazolam	0.25

Extra precautions apply in patients with hepatic dysfunction as diazepam and other long-acting drugs may accumulate to toxic levels. Diazepam substitution may not be appropriate in this group of patients.

Gradual dosage reduction

It is generally recommended that the dosage should be tapered gradually. The NPS provides guidance on how to withdraw patients from BZDs.

"Guidelines for withdrawing patients from BZDs, including prescribing pointers, complementary therapies, and BZD dose equivalents."

http://www.nps.org.au/__data/assets/pdf_file/0020/15761/news04_benzodiazepines_0699.pdf

Table 6 – Recommendations for reducing dosage of BZDs[24]

- Estimate the average daily intake of BZDs.
- Calculate an equivalent dose of diazepam and substitute diazepam for the BZD.
- Give diazepam in 3-4 divided doses per day at fixed times.
- Reduce dose by between 10-20% at weekly intervals. Reduction may need to be slower when the dose is down to 15 mg daily.
- Regularly review and titrate dose to the severity of withdrawal symptoms.
- In general practice a reducing regime will generally take 6-8 weeks, but may take 3-4 months or even a year.
- Sometimes, even when the dose is reduced by only a small amount, withdrawal symptoms re-emerge. In this case, the dose may be held at a plateau for 1-2 weeks or even increased for a few days before the reduction regime is resumed.

Conclusion

BZDs are effective medications and when used appropriately (i.e. short term use, within their dose and licensed indications) are generally well tolerated. However, longer term use, and the use in the elderly especially, requires a very close examination of the risk/benefit profile for each drug.

Particularly given the risks of dependence, tolerance and newer evidence suggesting that this class of medications may increase the risk of developing dementia and premature mortality.

This Drug Bulletin was written by Barrat Luft, & reviewed by the Graylands Pharmacy Department. For references or any Psychiatric Drug Information enquiries please contact the Statewide Psychiatric Drug Information Service on (08)93476400
druginformation.graylands@health.wa.gov.au