

Benzodiazepines

BENZODIAZEPINES are minor tranquillisers widely used in clinical practice for sedation and relief of anxiety. They are also widely used for illicit or non-prescribed purposes. The first benzodiazepine (chlordiazepoxide) was marketed in 1959 as a safe alternative to barbiturates. This was followed by the introduction of many related compounds that achieved immense popularity to become the most commonly prescribed class of drugs in the 1970s and 1980s.

Benzodiazepines are CNS depressants. They have antianxiety, anticonvulsant, hypnotic and muscle relaxant properties. Their use results in performance deficits (including memory impairment, motor incoordination, decreased reaction time and ataxia).

PHARMACOLOGY

Benzodiazepines enhance the effects of gamma-aminobutyric acid (GABA) which is the main inhibitory neurotransmitter in the CNS. Benzodiazepines bind to receptors on the GABA-A receptor complex (Cape et al., 2002).

ABSORPTION

Benzodiazepines are relatively lipophilic (fat soluble) and most are poorly water soluble with the exception of midazolam (used in anaesthetic practice but also as a 'date rape' drug). They are

generally rapidly and fully absorbed orally with peak plasma concentrations from ½ to 2 hours after ingestion. The more lipophilic agents e.g. diazepam are absorbed faster than the relatively more hydrophilic agents e.g. oxazepam (Cape et al., 2002).

DISTRIBUTION

Benzodiazepines rapidly enter the CNS and are then distributed to less vascular adipose tissue. They all cross the placental barrier and can result in neonatal drowsiness, respiratory depression, hypotonicity and withdrawal (Therapeutic Guidelines Ltd., 2000).

METABOLISM

Benzodiazepines must be converted to water soluble compounds before renal excretion. They are metabolised by both oxidation, which may produce active compounds, and by glucuronidation which inactivates them. Active metabolites may have longer half-lives than the parent drug resulting in prolonged effects (especially with chronic dosing).

PATTERNS OF USE

- in 2001, 1.1% of Australians aged 14 years or over reported use of tranquillisers or sleeping pills in the previous 12 months for non-medical purposes, with peak use reported amongst those aged 20–29 years
- while there is little overall difference in prevalence of tranquilliser or sleeping pill use between men and women (M: 1.2%; F: 1.0%), men aged 20–29 were more likely than women of the same age to use these drugs (3.0% and 2.2% respectively)
- across age groups, people aged 40 years or over had the highest proportion of people

who reported use of prescription drugs for non-medical purposes every day, or every week (AIHW, 2001)

- according to the Australian Statistics on Medicines (PBS, 1998), a total of 8.89 million prescriptions for benzodiazepines were dispensed through Australian pharmacies in 1998 (including PBS/RPBS, private and under co-payment prescriptions)
- the use of night-time sedation with benzodiazepines increases markedly with age
- long-term use of benzodiazepines remains common

EFFECTS OF BENZODIAZEPINES

All are sedating, anxiolytic and anti-convulsant.

Short-term Effects

- drowsiness, lethargy, fatigue
- motor incoordination, decreased reaction time and ataxia
- impaired cognition and memory (especially anterograde amnesia)
- confusion
- muscle weakness or hypotonia
- depression
- nystagmus, vertigo
- dysarthria, slurred speech
- blurred vision, dry mouth
- headaches
- paradoxical euphoria, excitement, restlessness, hypomania and extreme disinhibited behaviour (especially high dose, users may feel 'invulnerable, invincible and invisible')
- potentiation of other CNS depressants e.g. alcohol and opioids increasing likelihood of respiratory depression

(Victoria Police, 2002; Cape et al., 2002)

Long-term Effects

Similar to short-term effects (with no known organ toxicity) plus:

- tolerance to sedative/hypnotic and psychomotor effects (conflicting evidence whether tolerance develops to anxiolytic actions and effects on memory)
- emotional blunting (inability to feel normal highs or grief due to inhibition of arousal)
- menstrual irregularities, breast engorgement
- dependence (may develop after 3–6 weeks at therapeutic doses)

(Cape et al., 2002)

pared with normal subjects. Rebound insomnia frequently occurs on cessation of benzodiazepines

- polydrug use, or concurrent use of benzodiazepines, alcohol or opioids, increases the risk of overdose
- dependence and withdrawal can occur even when recommended doses are used (Busto et al., 1986) (i.e., within 3–6 weeks)
 - withdrawal symptoms may be apparent while the patient is still taking medication, possibly because the patient avoids increasing the dose to cover increased tolerance (Ashton, 1991) or due to the short half-life of some drugs
- adverse mood effects with inability to experience emotions or unwanted stimulation or aggression

USES AND PROBLEMS

Uses

Clinically useful in the treatment of anxiety and insomnia because of their efficacy, at least in the short-term, and relative safety compared to the barbiturates or tricyclic antidepressants.

Other uses in clinical practice include the treatment of alcohol withdrawal (to prevent delirium tremens), epilepsy, tremor and agitation in psychiatric disorders.

Problems Associated with Benzodiazepines

- short- or long-term patterns of benzodiazepine use is associated with excess sedation, cognitive impairment, and increased risk of accidents (Oster et al., 1990). Advise patients of risks when driving or operating machinery
- adverse sleep effects. Studies amongst people with sleeping disorders have demonstrated that insomnia sufferers who use benzodiazepines have a similar quantity but poorer quality of night-time sleep com-

HIGH RISK GROUPS

- elderly:
 - higher risk of falls and fractures amongst the elderly (Leipzig et al., 1999). Through long-term use, many elderly patients have become dependent on benzodiazepines as a sleep aid and therefore find cessation very difficult. Accumulation of doses can readily cause oversedation and increase the risk of accidents
 - are higher users of prescribed medications for the management of chronic disease. Use of benzodiazepines in combination with some medications places the patient at increased risk of negative side effects and/or dependence
- polydrug and injecting users:
 - high-dose use, particularly amongst polydrug users, may result in extremely disinhibited, or uncharacter-

istic behaviour. Described as the 'Rambo syndrome', a person may engage in assaults, shoplifting or other activities, in full view of witnesses, and be unable to recall any events related to the offence

- benzodiazepine use appears to be increasing amongst injecting drug users, and is associated with a higher rate of HIV risk-taking behaviour (Darke et al., 1992)
- risk of overdose in people using heroin is increased when other CNS depressants, such as alcohol and benzodiazepines, are used (Zador et al., 1996)

PRESCRIBING BENZODIAZEPINES

Rational Use of Benzodiazepines

The following guidelines (RACGP, 2000) are recommended when prescribing benzodiazepines:

- avoid prescribing benzodiazepines to people suspected of using other psychoactive drugs
- advise all patients prescribed benzodiazepines of the risk of dependence
- to prevent inadvertent dependence, encourage patients to see the same doctor for repeat prescriptions
- prescribe benzodiazepines in the lowest possible dose for the shortest possible time
- reduce benzodiazepine dose only with the patient's consent and cooperation
- rely on non-pharmacological approaches to manage anxiety and insomnia
- before writing a repeat prescription for benzodiazepines, undertake a review of all medications (and ask about visits to other general practitioners)

To reduce access and harm resulting from the prescribing of multiple, single, high-dose prescriptions, write short-term prescriptions and encourage regular review. There is a high risk associated with prescribing large quantities of benzodiazepines (and other drugs of dependence).

Precautions

Benzodiazepines should be used with caution in patients:

- with renal failure
- with liver disease
- with respiratory disease
- in late pregnancy
- who are breastfeeding

Drug Interactions

Refer to Table 11–1.

Use in Management of Anxiety and Insomnia

Benzodiazepines are effective for relief of anxiety symptoms and will induce sleep if given in sufficient doses (Therapeutic Guidelines Ltd., 2000). Research has questioned the efficacy of prescribing benzodiazepines for symptom reduction in anxiety management, with studies demonstrating that counselling alone has similar, if not greater efficacy (Catalan et al., 1984).

Benzodiazepines have demonstrated efficacy in the short-term management of insomnia, however similar results have not been demonstrated for periods longer than two weeks (NHMRC, 1991). Insomnia should be regarded as a symptom requiring assessment and evaluation, rather than a diagnosis per se. A sleep-wake history may reveal the patient to:

- be functioning normally on the amount of sleep obtained

- have unrealistic expectations of the requirements for sleep
- have a disorder of the sleep–wake schedule (including problems associated with shift work) which is not improved with hypnotics
- have a specific sleep disorder such as sleep apnoea or narcolepsy, in which case hypnotics are contraindicated

Finally, many patients who have taken benzodiazepines for periods in excess of 4–6 months have unwittingly become, dependent and experience withdrawal insomnia (Busto et al., 1986; Therapeutic Guidelines Ltd., 2000).

MANAGEMENT AND INTERVENTION STRATEGIES

Reviewing Benzodiazepines in Long-term Users: A Staged Approach

- advise the patient you want to review their benzodiazepine medication with them
- assess dosage and pattern of use
- assess use of alcohol and other psychotropics
- assess withdrawal symptoms
- assess reported and observed side effects

Table 11–1
Drug interactions

Interacting drug	Mechanism of interaction	Clinical effect
Alcohol or other CNS depressants	additive effect	increased sedation
Antacids, anticholinergics	decreased absorption	delayed onset of acute clinical effects of benzodiazepines
Oral contraceptives, isoniazid	reduction in metabolism	prolongation of elimination half-life and effect of benzodiazepine
Cimetidine	inhibition of metabolism	increased toxic effects due to elevated plasma concentrations of diazepam
Rifampicin	increased metabolism	elimination half-life of benzodiazepine shortened
Digoxin	protein binding diazepam altered	increased digoxin levels
L-dopa	unknown	exacerbation of parkinsonian symptoms
Disulfiram	decreased metabolism	increased effects of benzodiazepine

Source: Norman et al. (no date, p. 37)

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- assess history of depression
- assess other medical problems (e.g. pain)
- discuss long-term use with the patient
- discuss withdrawal symptoms with the patient
- finalise the management plan
- fatigue
- tinnitus
- hyperacusis, photophobia, perceptual disturbances
- depersonalisation, derealisation
- blurred vision

(Mant & Walsh, 1997; NPS News, 1999)

Dependence and Withdrawal

- tolerance and withdrawal from benzodiazepines can occur in individuals who have been taking therapeutic doses of benzodiazepines for two or more weeks
- it is estimated that symptoms may occur in up to 45% of patients discontinuing low therapeutic doses and up to 100% of patients for high doses
- there is a significant risk of withdrawal if benzodiazepines are discontinued abruptly, particularly in the sick and elderly.

Symptoms of withdrawal

Commonly include:

- insomnia
- anxiety
- irritability
- restlessness
- agitation
- depression
- tremor
- dizziness

Less common but medically serious:

- seizures (high dose ± alcohol)
- delirium

Other symptoms include:

- muscle twitching and pains
- anorexia, nausea
- metallic taste

Principles when helping the patient withdraw from benzodiazepines

- withdrawal must be gradual (e.g. 10–20% per week, slowing reduction at lower doses e.g. < 15 mg diazepam)
- a reducing regime will generally take 6–8 weeks (or longer especially with higher doses)
- make a contract with the patient
- gradually reduce the patient's dose using a set reducing dosage over a set time period (e.g. reduce the most important dose of the day by ¼ of the tablet)
- consider converting the patient to a benzodiazepine with a long half life e.g. diazepam, to reduce the severity of withdrawal symptoms (see benzodiazepine equivalence table below)

Table 11–2
Benzodiazepine equivalence table

5 mg diazepam	= 0.5–1 mg alprazolam
	= 3–6 mg bromazepam
	= 10 mg clobazepam
	= 0.5 mg clonazepam
	= 1–2 mg flunitrazepam
	= 1 mg lorazepam
	= 5–10 mg nitrazepam
	= 15–30 mg oxazepam
	= 10–20 mg temazepam
= 0.25 mg triazolam	

- titrate the dosage reduction according to patient symptoms
- discuss sleep and stress management, diet and exercise
- review regimen weekly
- provide support, reassurance and explanation

(NPS News, 1999)

Dose equivalents are approximate, some drugs at higher doses may be more potent.

Aged Care Residential Facilities

Prescribing for residents in aged care facilities (and other residential facilities) presents special difficulties. Accreditation of aged care facilities has heightened awareness of responsibilities of the facility for quality use of medicines (Australian Pharmaceutical Advisory Committee, 1997). This responsibility includes drug utilisation review by an accredited pharmacist. The use of benzodiazepines is lower where staff have received education in geriatric care and where the organisational culture is supportive (Roberts et al., 1998).

Benefits for the elderly in aged care accommodation following successful reduction in rates of benzodiazepine use include:

- increased mobility
- increased alertness
- reduced incontinence
- improved wellbeing (Gilbert et al., 1993)

BENZODIAZEPINE MISUSE

Habitual Drug Users ('Doctor Shoppers')

Almost all GPs come across patients who may be obtaining prescriptions from several doctors.

The following may help in responding effectively (Mant et al., 1997):

- do not prescribe a benzodiazepine on the first visit
- there is rarely a valid indication for benzodiazepines in young people
- say 'no' from the start to the patient's requests for the prescription, whilst offering your help as a doctor
- take the opportunity to discuss risks associated with drug use and consider referral to a specialist agency

Drug Dependent Patients

The RACGP (2000) has endorsed the following protocol for prescribing benzodiazepines in high doses on a regular basis the definition of which is 'more than three occasions per month for more than two months in any one year.' There are high risks with patients seeking large quantities of benzodiazepines (and other drugs of dependence) from one prescriber or from multiple prescribers. Most high dose users cannot be managed with an ordinary script.

The protocol aims include the support of quality medical practice, reducing overdose deaths and indiscriminate prescribing to polydrug users while reducing barriers to doctors seeing drug-dependent patients.

A protocol for prescribing benzodiazepines in high doses on a regular basis (RACGP, 2000) follows.

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Where relevant and appropriate the following should be undertaken and adequately documented in the medical record:

- a full history, including use of alcohol and other drugs and psychiatric comorbidity
- adequate physical examination
- problem/diagnosis list
- management plan, which should include the following:
 - consultation with another medical practitioner with experience in management of drug dependence
 - communication with other prescribers, notably methadone prescriber
 - supply of specified small quantities (e.g. daily), whether at the surgery or, if applicable, at a community pharmacy.
 - communication with the Health Insurance Commission to clarify whether the patient is seeing multiple doctors for prescriptions for benzodiazepines and/or narcotic analgesics
 - monitoring of consumption where applicable by the Health Insurance Commission, with agreement by the patient to attend only one doctor and one pharmacy and signed consent to the doctor receiving feedback on actual consumption for the period of the contract

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