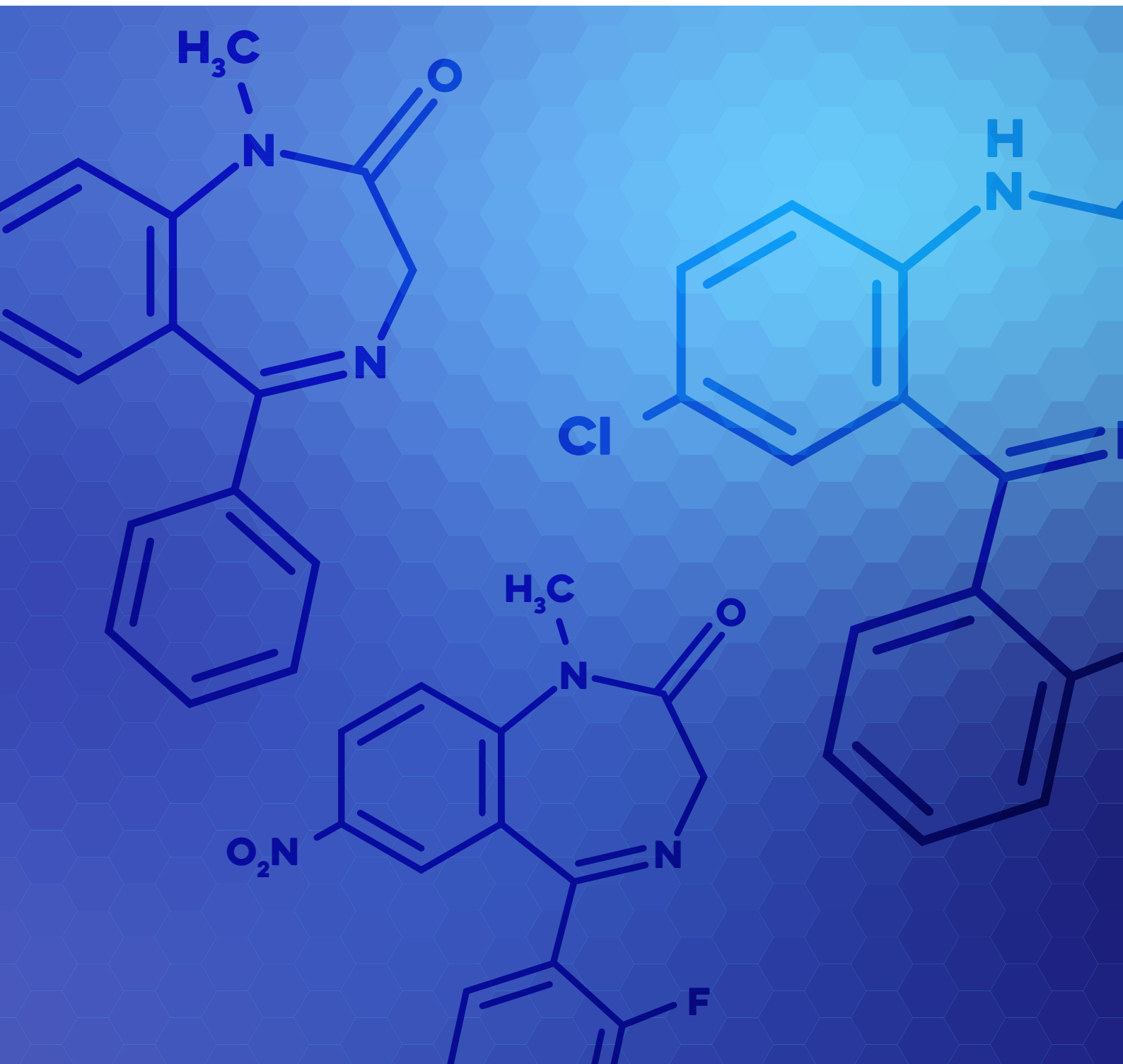




RACGP

# *Prescribing drugs of dependence in general practice, Part B*

## Benzodiazepines



## **Prescribing drugs of dependence in general practice, Part B – Benzodiazepines**

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*We recognise the traditional custodians of the land and sea on which we work and live.*

## *Foreword*

Benzodiazepines have a chequered clinical history and continue to produce polar opinions in the medical community. Benzodiazepines have been associated with both benefits and harms for patients, and a clear guide for accountable prescribing has been requested from multiple agencies.

Drug therapies will only ever have a partial role in managing complex bio-psychosocial issues that characterise mental health care. In the modern health environment, we have to explore and use non-drug therapies, and redefine the place of existing medications.

This guide represents a synthesis of the best available evidence for benzodiazepine use in the primary care setting. Consistent with all medications, prescribing benzodiazepines requires clear patient selection and ongoing clinical monitoring to optimise outcomes. The risk–benefit ratio of benzodiazepines changes considerably with concomitant psychoactive drugs, or comorbid alcohol or substance abuse or misuse.

In completing this guide, we acknowledge the work of the key advisers and reviewers, and the many people who have provided constructive feedback.

The Royal Australian College of General Practitioners (RACGP) welcomes feedback on this guide to continually improve services at the general practice level. Please use the feedback section on our website to help co-create this guide.

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# Acronyms

ADIS	Alcohol and Drug Information Service
ATODS	Alcohol, tobacco and other drugs
AUDIT	Alcohol Use Disorders Identification Tool
AWS	Alcohol Withdrawal Scale
CAS	Clinical Advisory Service
CBT	Cognitive behavioural therapy
CIWA-Ar	Clinical Institute Withdrawal Assessment of Alcohol State, revised
CNMP	Chronic non-malignant pain
CNS	Central nervous system
DACAS	Drug and Alcohol Clinical Advisory Service
DASAS	Drug and Alcohol Specialist Advisory Service
DSM	Diagnostic and Statistical Manual of Mental Disorders
GABA	Gamma-aminobutyric acid
GAD	Generalised anxiety disorder
GP	General practitioner
ICD	International Classification of Disorders
IDRS	Illicit Drug Reporting System
IDU	Injecting drug use
MOAI	Monoamine oxidase inhibitors
MBS	Medicare Benefits Schedule
MED	Morphine equivalent dose
NHS	National Health Service
NPS	National Prescribing Service
OCD	Obsessive compulsive disorder
OHS	Occupational health and safety
OTC	Over the counter
PBS	Pharmaceutical Benefits Scheme
PSIS	Prescription Shopping Information Service
PTSD	Post-traumatic stress disorder
S4	Schedule 4
S8	Schedule 8
SAD	Social anxiety disorder
SADQ	Severity of Alcohol Dependence Questionnaire
SNRI	Serotonin-norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
SUD	Substance use disorder
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
TCAs	Tricyclic antidepressants
TGA	Therapeutic Goods Administration
US	United States of America
WHO	World Health Organization

# Contents

<i>Foreword</i>	<i>i</i>
<i>Acknowledgements</i>	<i>ii</i>
<i>Acronyms</i>	<i>iv</i>
<i>Summary of recommendations</i>	<i>ix</i>
Wording of key principles and recommendations	ix
Key principles	ix
Treatment of insomnia	x
Treatment of anxiety disorders	xi
Treatment for alcohol withdrawal	xi
Discontinuing benzodiazepines	xi
<b>1. Introduction</b>	<b>1</b>
1.1 Aims	1
1.2 How to use this guide	2
1.3 Why do we need this guide?	2
1.3.1 Issues surrounding benzodiazepines	2
1.3.1.1 Variations in prescribing	2
1.3.1.2 Questions about over prescribing	2
1.3.1.3 Questions about safety of prescribing	4
1.3.1.4 Increasing awareness of problematic use, including misuse	6
1.3.2 The factors involved	6
1.3.2.1 Source of benzodiazepine misuse	6
1.3.2.2 Benzodiazepines are often combined with other drugs	7
1.4 Clinical pharmacology of benzodiazepines	7
1.4.1 Properties	7
1.4.2 Speed of onset	7
1.4.3 Metabolism and duration of activity	9
1.4.4 Tolerance	9
1.4.5 Equivalent dosages	10
1.5 Adverse effects of benzodiazepines	10
1.5.1 Adverse effects on mental health and functioning	10
1.5.1.1 Cognitive impairment	10
1.5.1.2 Anxiety	10
1.5.1.3 Depression	10
1.5.1.4 Paradoxical stimulation and disinhibition	10

1.5.2 Dependence, withdrawal syndrome and problematic use	11
1.5.2.1 Dependence – A contemporary understanding	11
1.5.2.2 Withdrawal syndrome	11
1.5.2.3 Incidence of withdrawal symptoms	11
1.5.2.4 Cravings and reinforcement	12
1.5.2.5 The spectrum of problematic use	12
1.5.2.6 Low-dose or therapeutic-dose dependence	12
1.5.2.7 Problematic benzodiazepine use	12
1.5.3 Morbidity and mortality	13
<b>1.6 Clinical governance</b>	<b>13</b>
1.6.1 Laws and regulations	13
1.6.2 General practice systems of care	14
1.6.2.1 Staff education and competency	14
1.6.2.2 Balancing patients' needs with practice capacity (risk stratification)	14
1.6.2.3 Care coordination	15
1.6.2.4 Practice policies and standards	16
1.6.2.5 Using and managing information	16
1.6.2.6 Quality improvement	17
1.6.3 Accountable prescribing of benzodiazepines	17
1.6.3.1 Evidence-based prescribing of benzodiazepines	18
1.6.3.2 Practical prescribing decisions	18
1.6.3.3 Assessing risk	18
1.6.4 Patient focus	21
1.6.4.1 Sharing prescribing decisions	21
1.6.4.2 Clinical responsibility in shared decision making	21
1.6.4.3 Aboriginal and Torres Strait Islander peoples	22
<b>2. Evidence-based guidance for benzodiazepines</b>	<b>23</b>
<b>2.1 Overview</b>	<b>23</b>
<b>2.2 Insomnia</b>	<b>24</b>
2.2.1 Background	24
2.2.2 Management of insomnia in general practice	25
2.2.2.1 Assessment and diagnosis	25
2.2.2.2 Acute insomnia	25
2.2.2.3 Chronic insomnia	26
2.2.2.4 Non-drug interventions	26
2.2.2.5 Drug therapy	26
2.2.3 Resources	27
<b>2.3 Anxiety disorders</b>	<b>28</b>
2.3.1 Background	28
2.3.2 Management of anxiety in general practice	29
2.3.2.1 Assessment and diagnosis	29
2.3.2.2 Cognitive behavioural therapy	29
2.3.2.3 Antidepressants	30
2.3.2.4 Benzodiazepines	30
2.3.3 Resources	31



<b>2.4 Alcohol withdrawal</b>	<b>31</b>
2.4.1 Background	31
2.4.2 Management of alcohol withdrawal in general practice	32
2.4.2.1 Assessment	32
2.4.2.2 Assisted withdrawal approaches	32
2.4.2.3 Benzodiazepines	32
2.4.2.4 Baclofen and carbamazepine	33
<b>2.5 Acute mania (bipolar disorder)</b>	<b>33</b>
2.5.1 Background	33
2.5.2 Management of manic episodes in general practice	33
<b>2.6 Epilepsy</b>	<b>34</b>
2.6.1 Background	34
2.6.2 Management of epilepsy in general practice	34
<b>3. Contraindications and precautions in special groups</b>	<b>35</b>
3.1 Overview	35
3.2 Paediatric patients	35
3.3 Women who are pregnant or breastfeeding	35
3.4 Older patients	36
3.4.1 Patients living in residential aged care facilities	36
3.5 Patients with chronic non-malignant pain	37
3.6 People with comorbidity – Mental illness and problematic drug use	37
3.7 Patients who misuse alcohol and/or other drugs (prescribed and illicit)	38
3.8 Prescribing to patients who drive	39
<b>4. Duration of benzodiazepine therapy</b>	<b>40</b>
4.1 Optimal duration of therapy	40
4.2 Prescribing benzodiazepines for longer than 4 weeks	40
4.3 Rationale for long-term benzodiazepine prescribing	41
4.4 Management of long-term benzodiazepine prescriptions	41
<b>5. Discontinuing benzodiazepines</b>	<b>42</b>
5.1 Discontinuing after short-term use	42
5.2 Discontinuing after longer term use – Withdrawal	42
5.2.1 Patients taking ‘therapeutic doses’	43
5.2.2 Patient taking high doses of benzodiazepines or who are users of illicit drugs (polydrug users)	43
5.3 General principles for the management of withdrawal of benzodiazepines	43
5.3.1 Resources	44
5.4 Tapering dosing	44
5.5 Additional pharmacotherapies	45
5.6 Should every patient be withdrawn?	45
<b>Resources</b>	<b>46</b>
Resource A. Examples of responses to patient requests for benzodiazepines	46
Resource B. Drug interactions	53
Resource C. State and territory contacts	54
Additional resources for Schedule 4 and Schedule 8 drug information	55

<b>Resource D. Communication with patients</b>	<b>56</b>
D.1 Benzodiazepine fact sheet for patients	56
D.2 Benzodiazepine reduction in the practice population	58
D.2A Practice letter to patients about benzodiazepine reduction	58
D.2B Practice guide to reduction and withdrawal of benzodiazepines (and Z drugs) in the practice population	58
D.3 Stopping benzodiazepines (benzodiazepine withdrawal) fact sheet for patients	63
D.4 Sleep hygiene and stimulus control fact sheet for patients	65
<b>Resource E. Practice policies and forms</b>	<b>67</b>
E.1 Practice policy example for repeat prescriptions	67
E.2 Prescription plan/agreement for a trial of longer term treatment	68
<b>Resource F. Drug and alcohol assessment tool</b>	<b>71</b>
Alcohol Use Disorders Identification Test	71
AUDIT questionnaire: Screen for alcohol misuse	71
Audit-C questionnaire	71
<b>Resource G. GP guide to behavioural therapy for insomnia</b>	<b>72</b>
Behavioural therapy for insomnia – Information for GPs	72
Sleep hygiene	72
Stimulus control	72
Stimulus control instructions	72
Sleep restriction therapy	73
Relaxation	73
Cognitive therapies	73
<i>Appendix A. Key terms and definitions</i>	<i>74</i>
A.1 Drugs of addiction and drugs of dependence	74
A.2 Tolerance, dependence, substance use disorder and withdrawal	74
A.3 Misuse, non-medical use and abuse	75
A.4 Drug-seeking behaviour	76
A.5 Prescriber behaviour	76
A.6 Staged supply	76
<i>Appendix B. Recommendations and grading</i>	<i>77</i>
B.1 Evidence-based statements and recommendations – Insomnia	77
B.2 Evidence-based statements and recommendations – Anxiety	78
B.3 Evidence-based statements and recommendations – Alcohol withdrawal	79
<i>Appendix C. Process of development</i>	<i>80</i>
<i>References</i>	<i>81</i>

## Summary of recommendations

Drugs of dependence have important therapeutic uses, but there is a need to ensure the supply of these medicines is clinically appropriate. A key measure is accountable prescribing that can be supported by a range of strategies at the practice level. Please refer to RACGP's *Prescribing drugs of dependence in general practice, Part A – Clinical governance framework* for information about these strategies.

Since 2002, approximately 7 million prescriptions for benzodiazepines have been dispensed in Australia each year, for conditions such as anxiety and insomnia. There is concern a portion of these prescriptions is causing or contributing to patient harm. This is a practical guide general practitioners (GPs) can use to minimise harm and maximise benefits to patients.

Evidence-based recommendations are collated here and there is further information in the body of the guide.

## Wording of key principles and recommendations

Within the key principles and recommendations, the term 'should' refers to a recommended action, 'must' refers to an obligation, 'must not' to a prohibition, and 'may' refers to a discretionary action.

Recommendations denoted with 'Rec' and a number are those taken from existing evidence-based guidelines and are accompanied by a link to the original source and grading. Each 'Rec' has a hyperlink allowing you to click through to the references. Other links are provided to sections in the body of the document. Recommendations without a 'Rec' are practice points.

For definitions of key terms, refer to [Appendix A](#).

## Key principles

Incorporating key principles of [accountable prescribing](#), [practice systems of care](#) and [patient-focused care](#):

1. [Prescription of benzodiazepines](#), as with any treatment, should be based on a comprehensive medical assessment; a diagnosis; thoughtful consideration of the likely risks and benefits of any medication, as well as alternative interventions; and a management plan derived through shared decision making and continual clinical monitoring.
2. GPs should be aware of the common [concerns](#) associated with benzodiazepines, such as potential [dependence](#), withdrawal, [problematic drug use](#) (including diversion and [misuse](#)) and known harmful effects, including falls, potential [cognitive decline](#) and [motor vehicle accidents](#). These risks should be [discussed with patients](#).
3. [Treatment seeks to maximise outcomes](#) for the health and social functioning of the patient while minimising risks. To minimise risks, benzodiazepines should be prescribed at the lowest effective dose for the [shortest clinical timeframe](#).
4. Avoid prescribing benzodiazepines to patients with [comorbid alcohol or substance use disorders](#) or polydrug use. GPs should consider seeking specialist opinion in the management of these patients. Patients who use two or more psychoactive drugs in combination (polydrug use) and those with a history of [substance misuse](#) may be more vulnerable to major harms.
5. Benzodiazepines are generally regarded by clinical practice guidelines as a short-term therapeutic option. Long-term use, [beyond 4 weeks](#), should be uncommon, made with caution and based on thoughtful consideration of the likely risks and benefits of benzodiazepines.
  - If alternatives to benzodiazepine treatment fail, have limited benefit or are inappropriate (either psychologically or pharmacologically), supervised benzodiazepine treatment may remain an acceptable long-term therapeutic option.

- Long-term benzodiazepine prescriptions should be at the lowest effective dose, preferably given intermittently, and regular attempts at reduction should be scheduled. Continued professional monitoring of health outcomes is required.
  - Benzodiazepines should be [prescribed from one practice and preferably one GP](#) and dispensed from one pharmacy.
6. GPs may wish to use the diagnosis of substance use disorder (SUD) rather than dependence, addiction or abuse; this is based on the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition's, (DSM-5's) sedative, hypnotic or anxiolytic use disorder criteria. This is a more neutral term that may reduce stigmatisation of patients with problematic use of benzodiazepines and other drugs or alcohol.
  7. GPs should develop strategies to manage [inappropriate requests for benzodiazepines by patients](#).
  8. All patients, including those who use benzodiazepines and other drugs or alcohol problematically, have the right to [respectful care](#) that promotes their dignity, privacy and safety.

## Treatment of insomnia

Insomnia is a common problem that can cause significant distress and reduced functioning. Chronic insomnia can be more challenging to manage, as it may be associated with an underlying cause, or be an independent disorder that can precipitate or worsen other comorbid conditions (eg depression). The understanding of chronic insomnia is still evolving.

The first step is comprehensive medical [assessment](#), including identification of any underlying issues, and diagnosis.

Where treatment is indicated:

- First-line therapy should be [non-drug interventions](#). Cognitive behavioural therapy (CBT), which may include stimulus control, sleep restriction, relaxation techniques and sleep hygiene education is well supported by evidence. It should therefore be offered to patients, including older adults. (Level A Evidence) [Rec 1](#).
- Decisions to prescribe pharmacological treatment should be made on an individual basis, after serious consideration of all risks and possible benefits.
- [Effective pharmacological therapies](#) include benzodiazepines and Z drugs (benzodiazepine receptor agonists), and both should be treated with the same cautions. (Level A Evidence) [Rec 2](#), [Rec 3](#).
- Short-term or intermittent dosing of benzodiazepines should be used to reduce the risk of tolerance and dependence. (Level B Evidence) [Rec 4](#), [Rec 5](#).
- Pharmacological treatment should be accompanied by specific patient education, regular review and continued efforts to employ the lowest effective dosage of medication, and to taper medication when conditions allow.

Note: When access to CBT is an issue, GPs and practice nurses may consider offering brief behavioural therapy to patients (refer to [www.racgp.org.au/your-practice/guidelines/handi/interventions/mental-health/brief-behavioural-therapy-for-insomnia-in-adults](http://www.racgp.org.au/your-practice/guidelines/handi/interventions/mental-health/brief-behavioural-therapy-for-insomnia-in-adults)).

## Treatment of anxiety disorders

Anxiety disorders are common and exist as a spectrum of conditions that vary from mild to severe. Comprehensive clinical [assessment](#) is the first step in management. Effective management requires obtaining a diagnosis and recognising that patients may not present with a single disorder (eg patients may experience generalised anxiety, panic disorder as well as depression).

Where treatment is indicated:

- First-line therapy for generalised anxiety disorder (GAD), panic disorder, and panic attacks should include [CBT](#) due to its effectiveness at reducing the symptoms of anxiety in the short and long term. (Level A Evidence) [Rec 6](#).
- Selective serotonin reuptake inhibitor (SSRI) and serotonin-norepinephrine reuptake inhibitor (SNRI) [medications](#) are effective across the range of anxiety disorders and are generally suitable for first-line pharmacological treatment of anxiety. (Level A Evidence) [Rec 7](#).
- [Benzodiazepine use](#) in anxiety disorders is mostly limited to severe or treatment-resistant cases.
- [Benzodiazepines](#) have proven benefit for GAD, social anxiety disorder and panic disorder. Benzodiazepines have not shown benefit for obsessive compulsive disorder (OCD) or post-traumatic stress disorder (PTSD). (Level A Evidence) [Rec 8](#).
- Short-term benzodiazepine use as occasional adjunctive therapy may be effective at reducing worsening of symptoms that can occur in the first few days to weeks of initiating antidepressant medication.

Note: When access to CBT is an issue, internet-based or computerised CBT programs have been shown to be effective (visit [www.racgp.org.au/your-practice/guidelines/handi/interventions/mental-health/internet-based-or-computerised-cbt-for-depression-and-anxiety](http://www.racgp.org.au/your-practice/guidelines/handi/interventions/mental-health/internet-based-or-computerised-cbt-for-depression-and-anxiety)).

## Treatment for alcohol withdrawal

Benzodiazepines are an effective component of an alcohol withdrawal program. However, not every patient withdrawing from alcohol will require medication. Comprehensive medical [assessment](#) (including assessment of social support and the use of formal assessment tools) is required to determine the most appropriate approach for alcohol withdrawal (ie in the primary care or specialist alcohol services setting).

Where assisted withdrawal from alcohol is indicated:

- Benzodiazepines (eg diazepam, oxazepam) are the drugs of choice for treatment of acute [alcohol withdrawal](#) (including alcohol withdrawal delirium), but should be limited to a maximum of 7 days. (Level A Evidence) [Rec 9](#).

## Discontinuing benzodiazepines

When discontinuing benzodiazepines, consider using a stepped approach, starting with minimal interventions and moving to more intensive measures.

- Minimal [interventions](#) such as advisory letters or GP's advice should be considered as an initial step in benzodiazepine discontinuation.
- The strength of the GP–patient therapeutic alliance is an important positive factor that assists the successful withdrawal of benzodiazepines.
- If benzodiazepine use disorder has become moderate or severe, it can become a long-term and distressing problem. However, [gradual dose reduction interventions](#) are possible for many patients titrating the dose reduction against the level of withdrawal symptoms experienced. Additional psychological therapies increase the effectiveness of gradual dose reduction.
- Switching from a short half-life benzodiazepine to a long half-life benzodiazepine before gradual taper may assist patients with problematic withdrawal symptoms on reduction.



# 1. Introduction

The arrival of benzodiazepines into clinical practice in the 1960s was met with enthusiasm. It allowed doctors to offer patients a class of medication with a range of properties (eg sedative/hypnotic, anxiolytic, anticonvulsant, muscle relaxation) at a time when there were few effective therapeutic alternatives. Benzodiazepines were effective and appeared safe in comparison to barbiturates, chloral hydrate and other drugs, which were problematic due to toxicity and overdose.<sup>1</sup>

Due to the seeming paucity of side effects, rapid onset of effect and a pressing mental health need, benzodiazepines were quickly used and prescribed short- and long-term for anxiety, depression, insomnia, mental illness and neuromuscular conditions. By the 1970s, they were the most commonly prescribed drugs in the world.<sup>2</sup> In 1978, more than 2.3 billion doses of diazepam were sold in the US alone.<sup>3</sup>

In the 1980s, evidence of the addictive nature of benzodiazepines grew and it became generally accepted that benzodiazepines brought their own problems. In 1988, the Committee on Safety of Medicines (UK) published the first guideline for benzodiazepine use and recommended limiting the length of treatment to 2–4 weeks.<sup>4</sup> Since then, many international guidelines have advocated for the reduction in prescribing benzodiazepines, particularly short-acting benzodiazepines for long-term disorders such as anxiety.

However, there has been – and still is – a wide divergence between recommendations and clinical practice.

In Australia, nearly 7 million benzodiazepine prescriptions are currently recorded through the Pharmaceutical Benefits Scheme (PBS), Repatriation PBS and private scripts each year.<sup>5</sup> Benzodiazepines have remained a major anxiolytic therapy, and given the trend towards larger quantity scripts, not just for short-term use.<sup>5</sup>

There is growing apprehension in Australia regarding the harms associated with the sanctioned and unsanctioned use of benzodiazepines.<sup>6</sup> The misuse of alprazolam is particularly problematic. It appears to be disproportionately associated with misuse, fatal and non-fatal overdoses, paradoxical excitation, and withdrawal and rage responses, as well as traffic accidents and crime-related harms.<sup>7</sup>

The conditions where benzodiazepines are most commonly prescribed (ie anxiety and insomnia) remain sources of debate in medical circles. General practitioners (GPs) must consider multiple factors when prescribing benzodiazepines, including potential prescription abuse. Good clinical governance and an evidence-based approach remain key to safe and appropriate prescribing (refer to RACGP's *Prescribing drugs of dependence in general practice, Part A – Clinical governance framework*).

## 1.1 Aims

This guide aims to provide assistance to GPs in the appropriate prescribing of benzodiazepines in the context of general practice.

It is designed to discourage inappropriate use and reduce harms by providing GPs with:

- evidence of the advantages and disadvantages associated with the use of benzodiazepines
- support for appropriate prescribing of benzodiazepines within regulatory frameworks
- support for safer prescribing within their practices
- alternatives to benzodiazepines, including non-drug options
- tools for managing patients who are prescribed benzodiazepines such as objective goals and time limited prescribing
- tools for recognising and managing higher risk situations.

Implementing principles from this guide should reduce the risk that GPs will be involved in an adverse event associated with prescribing benzodiazepines.

## 1.2 How to use this guide

This guide is a reference to assist the management of benzodiazepine prescribing. It is part of a reference series on drugs of dependence. It is not a set of mandatory rules. Recommendations should be considered and implemented as required, and where appropriate to the individual practice and patient.

The appendices contain examples of some practice policies. These examples are not individually approved or endorsed by the RACGP Council, or by the RACGP *Standards for general practices* (4th edition) (the Standards). They are based on policies and practices from national and international sources. If practices wish to adopt any of these policies, they should be modified for relevance and applicability to the local context.

## 1.3 Why do we need this guide?

Drugs of dependence have important therapeutic uses and are highly beneficial to many individuals. The clinically appropriate supply of these medicines needs to be maintained.<sup>8</sup>

This guide is a resource to assist with the appropriate and accountable prescribing of benzodiazepines to prevent and reduce harms to patients, and to prevent medico-legal issues for GPs.

GPs need to be aware of the broad issues around benzodiazepine use in society, as well as specific problems at a patient level, and how to address these issues with practice-based interventions.

### 1.3.1 Issues surrounding benzodiazepines

#### 1.3.1.1 Variations in prescribing

Benzodiazepine prescribing rates vary between clinicians and practices. GPs vary in the extent to which they are willing to prescribe benzodiazepines. Some consider benzodiazepines to be extremely useful drugs for multiple situations, while others feel they have no place in general practice. Richard Balon wrote, '... benzodiazepines have been hesitantly lauded and frequently enthusiastically vilified ...'<sup>9</sup>

The range of approaches to prescribing benzodiazepines may be explained by the variation in attitudes to the drugs, the changing context of prescribing, differing perceptions of the role and responsibility of the GP (and the personal responsibility of the patient), issues around alternative treatment options, perceptions of patient expectations, non-clinical considerations (eg race, gender) and the doctor–patient relationship.<sup>8</sup>

#### 1.3.1.2 Questions about over prescribing

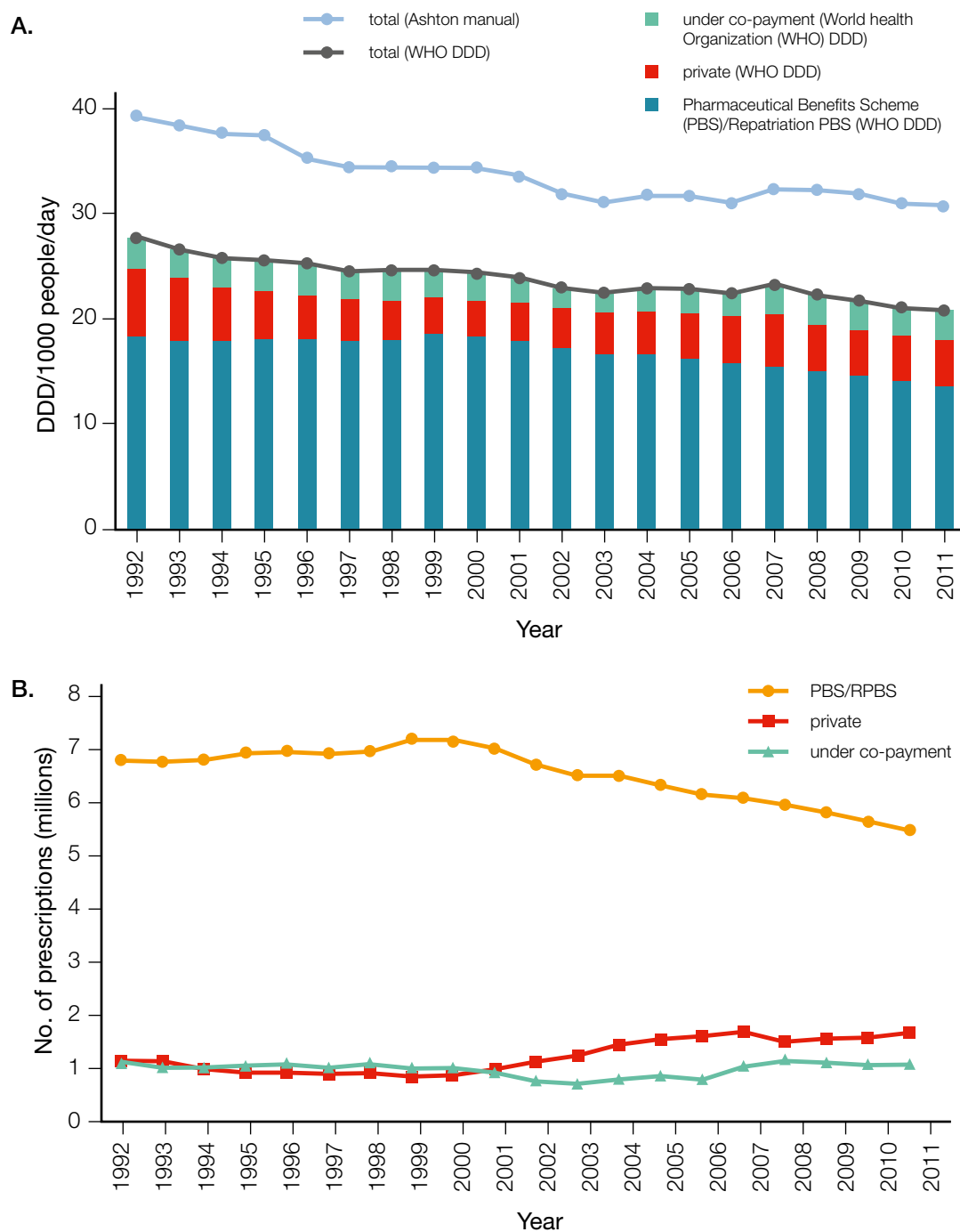
Comparing the prevalence of conditions for which benzodiazepines are indicated and the number of prescriptions dispensed, the evidence suggests that they may be over-prescribed and/or prescribed outside published guidelines.<sup>10</sup>

In 1991, there were an estimated 9.2 million benzodiazepine prescriptions dispensed from Australian retail pharmacies – enough to provide a daily dose for 3% of the adult population.<sup>5</sup> Since then there has been a modest declining trend in prescription numbers, although there are still approximately 7 million prescriptions for benzodiazepines written each year. Nearly 5 million prescriptions are subsidised through the PBS, and the rest are private or under co-payment prescriptions.<sup>11</sup> Since 2000, there has been a shift away from the PBS to private scripts.<sup>5</sup>

The modest decline can be partly explained by the use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). The use of SSRIs doubled between 2000–11, and have become the primary pharmacological treatments for anxiety disorders.<sup>5</sup>



Figure 1. Year-wise total dispensing of benzodiazepine derivatives in Australia between 1992 – 2011



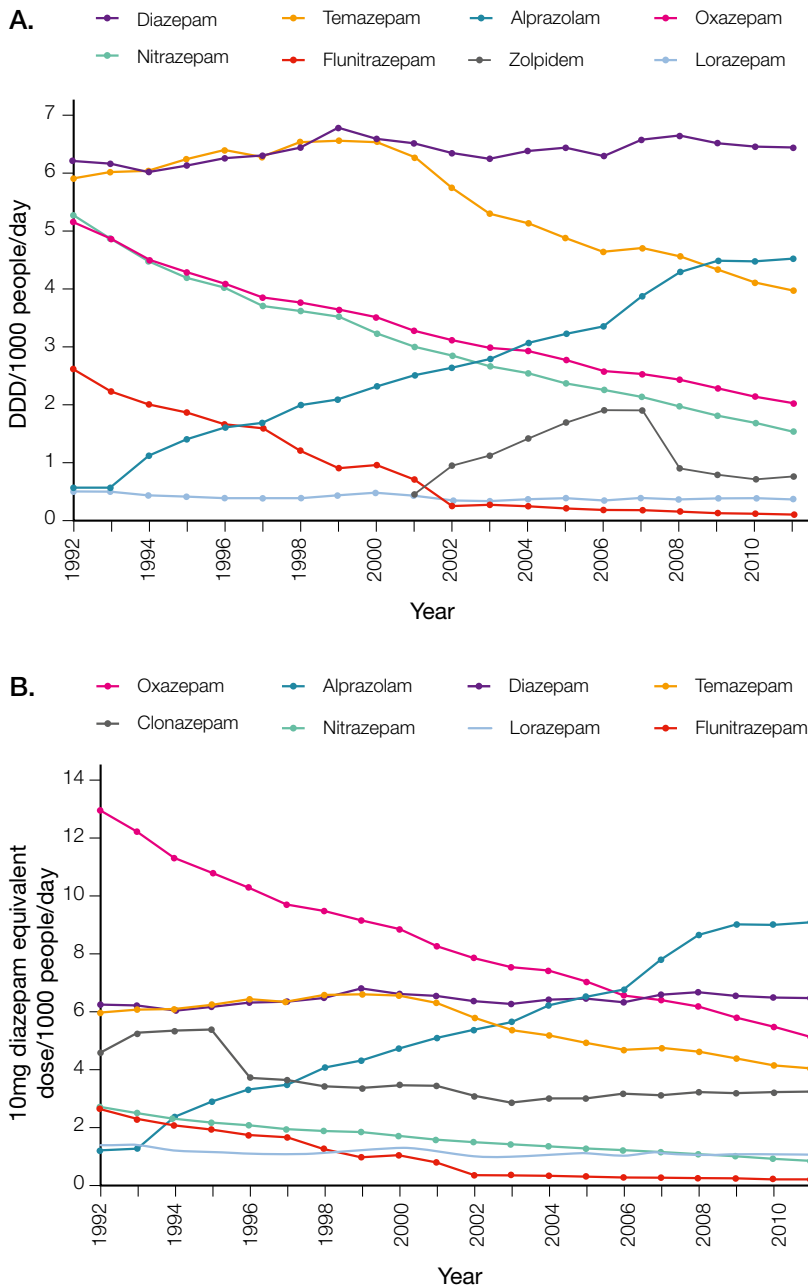
A. Defined daily dose (DDD)/1000 people/day

B. Number of prescriptions.

Reproduced with permission from Islam MM, Conigrave KM, Day CA, Nguyen Y, Haber PS. Twenty-year trends in benzodiazepine dispensing in the Australian population. *Intern Med J* 2013;44:57–64.

Despite a decrease in the prevalence of benzodiazepine prescriptions overall, diazepam and alprazolam prescribing increased.<sup>5</sup>

**Figure 2. Dispensing trend of major benzodiazepines in Australia between 1992 – 2011**



**A.** Defined daily dose (DDD)/1000 people/day

**B.** 10 mg diazepam dose/1000 people/day.

Reproduced with permission by Islam MM, Conigrave KM, Day CA, Nguyen Y, Haber PS. Twenty-year trends in benzodiazepine dispensing in the Australian population. *Intern Med J* 2013;55:57–64.

### 1.3.1.3 Questions about safety of prescribing

Coronial data reported in the Australian media have raised public concern about the safety of prescription medications. Based on Victorian drug-related death data,<sup>12</sup> prescription drugs are associated with 77% of all drug-related deaths.

Approximately half (48.8%) of all drug-related deaths are associated with benzodiazepines, which were identified as causal or contributory.

The number of deaths associated with benzodiazepines as a single drug is uncommon, and less than that from alcohol.

The most serious adverse events with benzodiazepines occur in the context of polydrug use (the use of more than one psychoactive substance in combination). The Coroner's Court of Victoria's figures suggest benzodiazepines, when used in conjunction with prescription or illicit opioids, are associated with a significant number of drug-related deaths.<sup>12</sup> Similar findings occur when used in conjunction with antidepressants and antipsychotic drugs.

In many of the benzodiazepine-related deaths (57%), there was a positive history of substance abuse.<sup>12</sup>

State coroners have called on the RACGP to address benzodiazepine prescribing by GPs following these benzodiazepine-related deaths.

Regulatory bodies are also reviewing benzodiazepines and how they are prescribed. As of February 2014, alprazolam has been rescheduled by the Therapeutic Goods Administration (TGA) to a Schedule 8 (S8) drug, due to concerns about misuse and harms. This followed a dramatic increase in the prescriptions for alprazolam (especially private prescriptions) – rising from 4.1% of the population in 1998 to 27.9% in 2010 – and a trend towards higher dose formulations.<sup>13–15</sup>

**Table 1. Drug related deaths in Victoria 2010<sup>12</sup>**

**1A. Drugs contributing to drug-related deaths**

	Number of deaths	Percentage of all drug-related deaths
Prescription drugs (alone or in combination with other drugs)	261	77.2%
Multiple drugs	215	63.6%
Single drug alone	123	36.4%
Prescription drugs alone	137	40.5%
Illicit drugs (alone or in combination with other drugs)	152	45%
Illicit drugs alone	50	14.8%
Alcohol (alone or in combination with other drugs)	82	24.3%
Alcohol alone	21	6.2%
<b>Total deaths*</b>	<b>338</b>	

**1B. Drug-related deaths associated with benzodiazepines**

Number of deaths	Number of deaths	Percentage of all drug related deaths	Percentage of benzodiazepine-related deaths
Total (causal or contributory)*	165	48.8%	100%
Combined with illicit or prescription opioids	136	40.2%	82.4%
Combined with substance abuse history	94	27.8%	57%
Combined with antidepressants	69	20.4%	41.8%
Combined with antipsychotics	47	13.9%	28.5%
Combined with alcohol	42	12.4%	25.5%
Benzodiazepines alone	5	1.5%	3%

\*Where an overdose involves more than one drug type, the death is counted under all contributing drug types. Therefore, individual data does not sum to the total.

### 1.3.1.4 Increasing awareness of problematic use, including misuse

Problematic use has been identified in men and women of all ages. According to the National Drug Strategy Household Survey, in 2010:<sup>16</sup>

- tranquilisers/sleeping pills (including benzodiazepines) were used for non-medical purposes by 3.2% of the Australian population aged 14 years and older at some stage in their lifetime
- benzodiazepines were used for non-medical purposes by 1.4% of Australians in the 12 months before the survey
- non-medical use of benzodiazepines is highest in people aged 20–29 (2.9%).

Awareness of diversion is relatively high, with benzodiazepines acknowledged as being among the most commonly diverted prescription medications (along with opioids) for illicit use.<sup>17</sup> However, unintentional misuse is less known. Australia is likely to have a large, but relatively hidden, population who unintentionally misuse benzodiazepines and who have developed an iatrogenic dependence.<sup>18</sup> Patients may also intentionally take medications outside of recommended use (eg larger doses) for what they consider to be a legitimate medical purpose (eg chronic insomnia).

Deliberate misuse of benzodiazepines for non-medical purposes occurs for a variety of reasons. People use benzodiazepines to:<sup>6,7</sup>

- enjoy the effects (especially taking large intermittent doses in a binge pattern)
- enhance an opiate effect
- help come down from stimulants
- combat opiate withdrawal symptoms
- substitute for their drug of choice.

The benzodiazepine, flunitrazepam, has been used to facilitate sexual assault.

The true prevalence of benzodiazepine misuse is unknown. However, the harms associated with non-medical prescription drug use, notably dependence and overdose, are well documented.<sup>17</sup>

## 1.3.2 The factors involved

### 1.3.2.1 Source of benzodiazepine misuse

In contrast to other drugs used for non-medical reasons, medical practitioners are the main source for benzodiazepine misuse.<sup>19</sup>

Individuals may obtain prescription medicines for non-medical purpose through a variety of means including:

- multiple doctors (doctor shopping or prescription shopping)
- drug theft (including from pharmacies)
- forgery of prescriptions
- inappropriate prescribing
- illicit market purchases
- procuring medicines from family, friends or acquaintances<sup>20</sup>
- bartering for sex or other services
- the internet.

In a survey of recent users of tranquilisers and sleeping pills for non-medical purposes, 71% thought these drugs were easy to obtain.<sup>16</sup> Patients are often highly skilled at obtaining prescriptions. They may present with a range of plausible and compelling reasons for why they should receive benzodiazepines. The most common is that they are benzodiazepine dependent and at risk of seizures if not prescribed the drug.<sup>21</sup> Patients often describe medical reasons for needing to take the medicine (eg epilepsy and anxiety).

### 1.3.2.2 Benzodiazepines are often combined with other drugs

Benzodiazepines are often used in combination with other drugs, including alcohol (polydrug use). This can dramatically increase the risk of harm (eg road traffic accidents and overdose). This also presents a medico-legal risk for prescribers (eg if the patient was not warned, concurrent drug or alcohol use was not assessed, or the risk or presence of substance use disorder [SUD] was not assessed).

A Melbourne study of adolescents who died of a drug overdose found a pattern of escalating attendance at general practices in the 6 months before death. The main reason for attendance was to obtain prescriptions for benzodiazepines.<sup>21</sup> Another study found 55% of heroin-related deaths and 88% of methadone deaths in Victoria involved benzodiazepines.<sup>22</sup> More than 90% of a cohort of heroin users in Sydney reported using benzodiazepines; 35% of the sample had injected benzodiazepines and 26% of those who had ever used benzodiazepines were diagnosed as dependent.<sup>23</sup> The 2011 Victorian Illicit Drug Reporting System (IDRS) – a sentinel survey of people who inject drugs – reported 92% of lifetime and 71% recent benzodiazepine use.<sup>24</sup>

## 1.4 Clinical pharmacology of benzodiazepines

Numerous benzodiazepines are available. They can be classified according to their main use, speed of onset, duration of action and drug half-life.

While benzodiazepines differ in their pharmacokinetics (absorption, distribution, metabolism, excretion), they all have similar pharmacodynamic properties and clinical actions.

### 1.4.1 Properties

Benzodiazepines have four basic properties that give rise to their clinical use:

- anxiolytic
- sedative/hypnotic
- anticonvulsant
- muscle relaxant.

Benzodiazepines can also produce anterograde and retrograde amnesia. This effect is used peri-procedurally.

These properties are the result of enhancement of activity of the major inhibitory neurotransmitter in the central nervous system (CNS), gamma-aminobutyric acid (GABA). Benzodiazepines bind to receptors on the GABA-A receptor complex causing inhibitory effects throughout the brain, including drowsiness and cognitive impairment (cerebral cortex), dampening of emotions such as fear and anxiety (mesolimbic dopamine system), memory impairment and anticonvulsant actions (hippocampus), and impairment of balance, motor control, muscle tone and coordination (cerebellum and other motor areas). These effects are non-selective.

Newer Z drugs (eg zolpidem and zopiclone) enhance the activity of GABA by binding at the same location as benzodiazepines. While these drugs have similar actions to benzodiazepines, they are marketed for insomnia due to their kinetic profile. High doses are required to produce the other actions such as decreased anxiety.<sup>25</sup> There is evidence Z drugs, which are now the most commonly prescribed hypnotic agents, share similar risks to benzodiazepines.<sup>26–29</sup>

### 1.4.2 Speed of onset

Benzodiazepines are rapidly absorbed orally. After ingestion, peak effects will occur within 30 minutes to 2 hours (refer to *Table 2*). The more fat-soluble drugs (eg diazepam) enter the CNS more rapidly.

Generic name	Trade name	Speed of onset, time to peak concentration	Elimination half-life	Approximate equivalent dose to diazepam 5 mg*	Comments
Diazepam	Antenex, Ducene, Vallium, Valpam	Rapid 30–90 minutes	Biphasic: rapid phase 3 hours; elimination half-life 20–48 hours	5 mg	Risk for accumulation because of long-acting metabolites (temazepam, desmethyldiazepam, oxazepam) Increased risk for abuse because of quick onset
Alprazolam	Alpraz, Kalma	Rapid-intermediate, 1 hour	6–25 hours	0.5 mg	Increased risk for abuse because of greater lipid solubility Clinically, non-medical users report onset of effects at 20 minutes and lasting up to 6 hours
Bromazepam	Lexotan	Rapid, 0.5–4 hours	20 hours	3 mg	
Clonazepam	Paxam, Rivotril	Intermediate, 2–3 hours	22–54 hours	0.25 mg†	Use caution in patients with liver disease
Flunitrazepam	Hypnodorm	Rapid, 1–2 hours	20–30 hours	*	
Lorazepam	Ativan	Intermediate, 2 hours	12–16 hours	1.0 mg†	Preferred for patients with liver impairment, as no active metabolites
Nitrazepam	Alodorm, Mogadon	Rapid, 2 hours	16–48 hours	5 mg	
Oxazepam	Alepan, Murelax, Serepax	Slow-intermediate, 2–3 hours	4–15 hours	15 mg	Preferred for patients with liver impairment, as no active metabolites
Temazepam	Euhypnos, Normison, Temaze, Temtabs	Intermediate, 30–60 minutes after tablets or 2 hours after capsules	5–15 hours	10 mg	Preferred for patients with liver impairment, as no active metabolites
Triazolam	Halcion	Rapid, 1–3 hours	Biphasic: rapid phase 2.5–3.5 hours; elimination half-life 6–9 hours	0.25 mg	Lacks active metabolites
Zolpidem	Stilnox	Rapid, 0.5–3 hours	2.5 hours	10 mg	
Zopiclone	Imovane	Rapid, 1.75 hours	5 hours	7.5 mg	

\*A broad review of published equivalents shows inconsistent data. The widely varying half-lives and receptor binding characteristics means that exact equivalence is difficult. †There is a wide variety of reported equivalence between clonazepam and other benzodiazepines. ‡Lorazepam may be relatively more potent at higher doses.

### 1.4.3 Metabolism and duration of activity

Benzodiazepines vary greatly in the speed at which they are metabolised and several different mechanisms are involved. Depending on their metabolic structure, benzodiazepines are short, medium or long acting (refer to *Table 2*).

For the majority of benzodiazepines, the elimination half-life is significantly longer than the duration of clinical action. As they are rapidly redistributed into fatty tissue after absorption, the noticeable clinical effects wear off after a few hours. However, the drugs may continue to exert subtle effects and, with repeated dosing, accumulation within the fatty tissue occurs and a steady state of blood concentration can be reached in approximately five half-lives. Due to slow leaching from fatty tissue, benzodiazepines may be detected in urine tests weeks to months after cessation of benzodiazepine use.

Benzodiazepines are metabolised by the liver and excreted renally. Metabolism may be impaired in patients with liver and/or kidney disease. Lorazepam, oxazepam and temazepam are metabolised by glucuronidation and therefore do not produce active metabolites. These are rarely susceptible to medication interactions, although their sedative effects remain synergistic. Some other benzodiazepines undergo metabolism by the cytochrome P450 (CYP450) 3A4 hepatic enzyme system and many are weak inhibitors of the CYP enzymes. Therefore, these benzodiazepines may have significant interactions with other drugs that are metabolised by these enzyme pathways.

Refer to [Resource B](#) for common drug–drug interactions.

### 1.4.4 Tolerance

Tolerance to all drugs of dependence develops with repeated use.<sup>31</sup> Steady state plasma concentrations of benzodiazepines and their metabolites are reached after about five elimination half-lives, usually a few days to 2 weeks after starting therapy. Within a few days of reaching a steady state of plasma concentration, patients may start to experience a loss of effect from benzodiazepines,<sup>32</sup> due to a range of neuroadaptive and physiological mechanisms.

Tolerance to the different benzodiazepine effects develops at different speeds and to different degrees, and may never be complete.<sup>2,32–34</sup> The degree of tolerance differs between patients.<sup>35</sup>

- A high proportion of patients with epilepsy develop tolerance to the anticonvulsant effects within a few weeks. This is similar to patients with spasticity disorders and the muscular relaxant effects.<sup>2</sup>
- Tolerance to the hypnotic effects is less clear. Some of the literature claims it develops rapidly,<sup>2</sup> while other authors claim it is slower.<sup>25</sup> The evidence is limited by the length of trials.<sup>32</sup> Sleep studies have shown that tolerance develops to the hypnotic effects of some rapidly eliminated benzodiazepines (eg triazolam) by 2 weeks, whereas for others (eg midazolam) tolerance emerges slowly and minimally.<sup>32,36</sup> Tolerance also appears to develop with the Z drugs, however to a low degree.<sup>3,32,36</sup>
- Tolerance to the anxiolytic and amnesic effects of benzodiazepines probably does not occur at all.<sup>32</sup> Although, there is some evidence that a slow (years) tolerance may develop.<sup>2,37</sup>

Long-term use of benzodiazepines may produce chronic changes in benzodiazepine-receptor functioning, which are thought not to fully return to their pre-addicted state after withdrawal and abstinence.<sup>38</sup>

There is a high degree of cross-tolerance between benzodiazepines and other sedative/hypnotic medications and alcohol.<sup>39</sup>

The development of tolerance is associated with escalation in dose, binge dosing and is one of the criteria for dependence<sup>31</sup> and SUD<sup>40</sup> (refer to *Table 3*). However, it is unusual for patients to steadily increase their dosage, even with long-term use, as might be expected with the development of tolerance.<sup>25,41</sup> Patients who are prescribed benzodiazepines for anxiety or sleep problems usually do not escalate their doses even over a lengthy period of use. However, high-dose benzodiazepine mono-dependence has been reported.<sup>3</sup>

Tolerance also makes it difficult to calculate equivalence.

### 1.4.5 Equivalent dosages

Equivalent doses are primarily used when making a transfer between drugs. Comparative oral doses of benzodiazepines are described in various sources, such as the Therapeutic Guidelines.<sup>35</sup> However, the clinical potency of different drugs varies among individuals and it is difficult to demonstrate equivalence with drugs having very different half-lives (refer to *Table 2*). Due to this and variations in metabolism among people, these equivalence tables should be used with caution.

## 1.5 Adverse effects of benzodiazepines

### 1.5.1 Adverse effects on mental health and functioning

While used commonly for mental illness, benzodiazepines are associated with a range of adverse effects on mental health and function.

#### 1.5.1.1 Cognitive impairment

Cognitive impairment is a broad term that encompasses several symptoms of benzodiazepine-induced CNS effects.<sup>42</sup>

Acute administration may induce dose-related sedation, drowsiness, learning impairment, psychomotor slowing and anterograde amnesia.<sup>33,43–48</sup>

Chronic cognitive effects are modified by tolerance to some, but not all of the acute effects.<sup>3</sup> A range of cognitive and psychomotor effects may persist after withdrawal.<sup>49</sup>

Long-term use of benzodiazepines has been associated with significant long-term cognitive impairment and increased risk of dementia in various studies.<sup>50–52</sup> The difficulty with these studies is symptoms that may naturally precede dementia for 10 years or more (eg anxiety, sleep disorders) are the very indications for which benzodiazepines are commonly prescribed.<sup>53</sup>

Other prospective trials show no association between benzodiazepines and accelerated cognitive decline.<sup>54</sup>

One aspect of psychomotor functioning that has received a lot of attention is driving ability. Benzodiazepines are associated with a 60–80% increase in the risk of traffic accidents, and taking alcohol and benzodiazepines together increases accident risk more than seven times.<sup>55</sup>

#### 1.5.1.2 Anxiety

Patients may experience new or worsened anxiety while taking benzodiazepines long term or after stopping long-term use (rebound anxiety).<sup>37,56</sup>

#### 1.5.1.3 Depression

Patients taking benzodiazepines may experience aggravated depression or depression that first appears during benzodiazepine use.<sup>37,57</sup> Benzodiazepines may cause and aggravate depression, possibly by reducing the output of neurotransmitters such as serotonin and noradrenaline.

#### 1.5.1.4 Paradoxical stimulation and disinhibition

Benzodiazepines may have a disinhibitory effect (especially at high doses), leading patients to behave out of character and potentially placing themselves in dangerous situations because of an impaired perception of inherent risk. Common scenarios involve high-risk sexual behaviour and reckless driving.<sup>42</sup> So called 'benzo binges' have been associated with shoplifting and other crimes.<sup>30</sup>

Patients may also experience paradoxical excitement with increased anxiety, insomnia, talkativeness, restlessness, mania, and occasionally rage and violent behaviour (known as the 'Rambo effect').<sup>7</sup>

Refer to [Precautions in special groups](#) interventions for further precautions and adverse effects.



## 1.5.2 Dependence, withdrawal syndrome and problematic use

### 1.5.2.1 Dependence – A contemporary understanding

Despite its familiarity and ubiquitous use, the concept of dependence is complex.

Historically, dependence has been defined in pharmacological terms. That is a state that develops during chronic drug treatment in which cessation elicits an abstinence reaction (withdrawal). This is time limited and reversible by renewed administration of the drug.

As awareness of problematic use grew, the definition of benzodiazepine dependence changed to include benzodiazepine addiction and abuse. Various definitions evolved with Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), International Classification of Disorders, 10th edition (ICD-10), World Health Organization (WHO) and leading authors describing it as a cluster of behavioural, cognitive and physiological phenomena that may develop after repeated substance use. This definition acknowledged that dependence is a complex condition that involves variable combinations of interacting patient and drug factors (eg [reinforcement](#), [tolerance](#), [withdrawal](#)).

This has created difficulties in determining incidence and prevalence of benzodiazepine dependence, caused inadvertent changes in reporting levels of adverse drug events<sup>58</sup> and difficulties in comparing dependence and withdrawal reactions in benzodiazepine alternative (eg SSRIs).

The DSM-5 criteria combine the former DSM-IV categories of substance abuse and substance dependence into a single condition of [SUD](#), measured on a continuum from mild to severe. The essential feature of SUD is a cluster of cognitive, behavioral and physiological symptoms indicating the individual continues using the substance despite significant substance-related problems.

### 1.5.2.2 Withdrawal syndrome

Benzodiazepine withdrawal syndrome is highly variable. It remains unclear why some long-term users can withdraw without difficulty, even after years of continuous use, while others undergo protracted agonies.<sup>59</sup>

The symptoms of withdrawal usually appear within 2–3 half-lives of the benzodiazepines being withdrawn.<sup>60</sup> They usually lessen and then disappear within a few weeks.<sup>60</sup> Sudden withdrawal of benzodiazepines can be associated with seizures.

The mildest form of withdrawal is rebound.<sup>3</sup> Rebound comprises of the original symptoms recurring transiently at a greater intensity.<sup>3</sup> Discontinuation of benzodiazepines is frequently associated with rebound anxiety and insomnia.<sup>36,61–66</sup> Withdrawal symptoms include irritability, paraesthesia, tinnitus, headaches, dizziness, poor memory, poor concentration, perceptual distortions, menstrual disturbances and sensory hypersensitivity.<sup>38,59,65,67</sup> Withdrawal symptoms can usually be minimised by gradual reduction.<sup>68,69</sup> There is evidence that some patients suffer protracted withdrawal symptoms that can continue for months to years after cessation.<sup>59</sup> There is debate about whether these persistent symptoms are withdrawal reactions, or simply features of an underlying disorder or worsening of that condition, which is triggered by treatment withdrawal.<sup>25</sup>

Short- and intermediate-acting benzodiazepines carry a greater risk of rebound and withdrawal than long-acting benzodiazepines. Withdrawal syndrome can appear while the patient is still taking medication. This may be because the patient avoids increasing the dose to cover increased tolerance,<sup>59</sup> or the patient is taking short-acting formulations and experiencing withdrawal as blood levels drop.

### 1.5.2.3 Incidence of withdrawal symptoms

The occurrence of withdrawal syndrome is related to high dosage and long-term use.<sup>3</sup>

Authors argue that based on the incidence of withdrawal symptoms, evidence of benzodiazepine dependence can be quite high. Withdrawal symptoms from benzodiazepines prescribed for insomnia can ensue after 4–6 weeks of use in approximately 15–30% of patients.<sup>70</sup> Others suggest

much higher incidences of withdrawal: in the order of 30–45% of patients who have used regular therapeutic doses of benzodiazepines for more than a few months.<sup>71</sup>

It has been debated whether this is a clinical problem.<sup>72</sup> For example, it has been suggested that in the absence of SUDs, the risk of addiction to benzodiazepines during long-term treatment of anxiety and related disorders has been exaggerated. In addition, the pharmacological dependence that develops when benzodiazepines are used long-term does not denote an all-encompassing preoccupation with and craving for benzodiazepines, nor does it create compulsive or uncontrollable benzodiazepine-seeking behaviour and adverse health and/or social consequences.<sup>73</sup>

#### 1.5.2.4 Cravings and reinforcement

The reinforcement potential of a drug is its ability to maintain or increase the frequency of drug-taking or drug-seeking behaviour. Drugs may have positive reinforcement potential by creating a reward (or 'high') or negative reinforcement potential by alleviating some form of distress (eg anxiety or withdrawal symptoms).<sup>57</sup>

Benzodiazepines predominantly demonstrate negative reinforcement effects.<sup>71</sup> By alleviating anxiety and withdrawal symptoms, it can encourage continued use. Used alone, and at therapeutic doses, they have not been associated with significant positive reinforcement for most patients (ie the drug itself does not encourage further use or dose escalation). Patients with a history of alcohol abuse, or even those with moderate alcohol consumption, appear to experience greater reinforcement effects with benzodiazepines. High doses may have positive reinforcing effects in some patients, particularly polydrug users.<sup>71</sup>

#### 1.5.2.5 The spectrum of problematic use

Problematic use rarely develops in patients taking a normal, therapeutic dose for short periods. However, particular patient populations may be more vulnerable to developing problematic use.

An original US report focusing specifically on the development of physiological dependence, especially at therapeutic doses, notes that benzodiazepines do not strongly reinforce their own use and are not widely abused drugs. When abuse does occur, it is almost always among individuals who are also actively abusing alcohol, opiates or other sedative hypnotics.<sup>74</sup>

#### 1.5.2.6 Low-dose or therapeutic-dose dependence

In cases of low-dose dependence, benzodiazepines were usually initiated for their anxiolytic or hypnotic effects. Doses may escalate slightly over years, however, prescriptions usually remain within therapeutically recommended limits.<sup>57</sup>

While high-dose dependence may be easier to recognise through drug-seeking behaviours, GPs should be aware of the more subtle behaviours of patients with low-dose dependence.

Patients with low-dose dependence tend to return at regular intervals to obtain repeat prescriptions, often before the previous supply has run out. They often carry their tablets around, and it is not uncommon for them to take an extra dose before an anticipated stressful event or a night in a strange bed. They have difficulty stopping the medication or reducing the dosage due to withdrawal symptoms.<sup>57</sup>

In contrast with patients with high-dose dependence (prescribed or recreational), patients with low-dose dependence tend not to abuse other drugs or alcohol.<sup>57</sup>

#### 1.5.2.7 Problematic benzodiazepine use

Based on the available epidemiological data, the prevalence of benzodiazepine abuse is generally low in the therapeutic setting (ie where the drug is correctly medically prescribed). The *American Psychiatric Publishing Textbook of Psychopharmacology* quotes prevalence of 0.6% for abuse and 0.5% for dependence among therapeutic users.<sup>75</sup> However, the incidences are much higher in people who abuse alcohol and other drugs.<sup>75</sup>

Supporting this, a 2013 study found most patients used benzodiazepines according to guidelines, and only 0.9% ended up as excessive users after 3 years.<sup>76</sup> Again, problematic use occurred mostly in individuals with alcohol and drug histories.

If benzodiazepine use disorder has become moderate or severe, it can become a long-term and distressing problem. There are several behaviours that indicate a patient may have problematic benzodiazepine use (eg escalating use patterns, drug-seeking behaviour and doctor or prescription shopping).<sup>77</sup>

GPs need to maintain vigilance in identifying SUDs, assist patients in recognising disordered use where it exists, set goals for recovery and assist patients to seek appropriate treatment.

### 1.5.3 Morbidity and mortality

Epidemiological studies have demonstrated an excess of consultations for accidents among persons taking benzodiazepines.<sup>78</sup>

In Victoria alone, benzodiazepines were involved in 3135 ambulance attendances in 2010–11 and 3440 in 2011–12. In terms of all alcohol and drug related attendances, they were the second most common only to alcohol. There was a disproportionate increase in the involvement of alprazolam compared to all benzodiazepines in ambulance attendances.<sup>79,80</sup>

In older patients, benzodiazepines are associated with higher risk of falls and subsequent injuries.<sup>81–83</sup>

The harmful effects of benzodiazepines, other than the risk of dependence with long-term use, have been associated (ie not proven cause and effect) with a 4–6-fold increased risk of death from all causes.<sup>84</sup>

Research has found patients prescribed hypnotic drugs (including benzodiazepines, Z drugs, barbiturates and sedative antihistamines) have an elevated risk of dying compared to those prescribed with no hypnotics.<sup>84</sup> There is a dose-dependent relationship, but even patients prescribed fewer than 18 hypnotic doses per year experienced increased mortality.<sup>84</sup> Note that this research did not find that hypnotic drugs were the cause of premature death – at best, it found a potential association.

Large cohort studies refute the relationship between benzodiazepine therapy and premature death. Emerging evidence suggests underlying psychiatric disorders are the principal determinant driving the association between hypnotics and mortality risk.<sup>85</sup>

## 1.6 Clinical governance

Please refer to RACGP's *Prescribing drugs of dependence in general practice, Part A – Clinical governance framework* for further information on clinical governance and its role in improving safety and quality for the use of drugs of dependence in general practice.

### 1.6.1 Laws and regulations

Most benzodiazepines are Schedule 4 (S4) 'prescription only' medicines. The exceptions are flunitrazepam and alprazolam, which are classed as S8 drugs.

Each state and territory has laws regulating the prescription of these medicines. Generally, there are tighter controls around the prescribing of S8 drugs and for prescribing to patients with known addiction. For example, GPs must seek a permit or an authority from the relevant state or territory health department when prescribing an S8 drug to persons who are drug dependent.

Some states have subsets of S4 drugs that involve prescribing restrictions or additional requirements; benzodiazepines often fall into this category.

GPs must be familiar with the relevant legislative requirements associated with writing prescriptions for S4 and S8 drugs.

State and territory departments and government-funded drugs of dependence units (or equivalent) can provide information regarding prescribing. Refer to [Resource C](#).

## 1.6.2 General practice systems of care

The quality and safety of patient care is no longer confined to the individual practitioner. General practices have responsibilities to work collaboratively with practitioners to address the safety and quality of health services provided in their facilities.

Practice systems of care around benzodiazepines can be put in place to maximise health outcomes and social functioning for patients while minimising drug and alcohol misuse, abuse, diversion and crime. Systems of care also provide the necessary infrastructure and support for GPs to perform their job efficiently and effectively.

### 1.6.2.1 Staff education and competency

Practices should ensure they have the level of knowledge among team members and practice capacity to address the issues associated with benzodiazepine prescribing (eg identification of patients with more complex needs and those at higher risk). Prescriber education is particularly important. The risk of benzodiazepine misuse and dependence is lower when the first-time prescriber is a specialist in general practice compared to a prescriber without specialty training.<sup>76</sup> GPs who are regularly involved in managing patients with problematic use of benzodiazepine or other drugs and alcohol should consider further training and developing good working relationships with addiction specialists.

Practices should promote the development of competency in prescribing benzodiazepines. Where potentially inappropriate and suboptimal prescribing is identified, practices and GPs have an opportunity to engage in education and support, and improve patient outcomes.

### Dependence programs

Access to relevant programs is limited in some areas of Australia. Practices may wish to consider supporting GP-based benzodiazepine detoxification programs in-house. Benzodiazepine detoxification typically requires significant and frequent communication with patients, more regular visits with the GP and other clinical staff, on-call mechanisms and management of patients who are often highly anxious.<sup>86</sup> Suitably qualified staff, organised support and ongoing quality assurance arrangements may be required. GPs involved in this type of program should feel comfortable prescribing adjunct medications.<sup>86</sup>

### 1.6.2.2 Balancing patients' needs with practice capacity (risk stratification)

Patients should be appropriately evaluated to determine the complexity of services required.

One of the goals in the initial assessment of a patient is to obtain a reasonable assessment of clinical complexity/risk in the context of concurrent SUD or psychopathology. In this context, patients can be stratified into three basic groups. The following will offer a practical framework to help determine which patients may be safely managed in the primary care setting, should be co-managed with specialist support and should be referred on for management in a specialist setting.

GPs with advanced training in addiction medicine and/or mental health management are suited to taking on higher responsibilities under this model.

- **Group I – Managed in primary care:** Patients with no evidence of past or current history of SUD or mental illness, apart from the presenting problem.

- **Group II – Managed in primary care with specialist support:** Patients may have a past history of a treated SUD or a significant family history of problematic drug use. They may also have a past or concurrent psychiatric or chronic pain disorder. While not actively addicted, patients are at increased risk, which may be managed in consultation with appropriate specialist support.
- **Group III – Managed by specialist services:** This group of patients represents the most complex cases to manage because of an active SUD or major, untreated psychopathology. These patients are either actively misusing prescription drugs or pose significant risk to both themselves and to the practitioners, who may lack the resources or experience to manage them.

It is important to remember that all groups can be dynamic. Group II can become Group III with relapse to active addiction, while Group III patients can move to Group II with appropriate treatment. In some cases, as more information becomes available to the practitioner, the patient who was originally thought to be low risk (Group I) may be reclassified as Group II or even Group III. It is important to continually reassess risk over time.<sup>87</sup>

### 1.6.2.3 Care coordination

A key message from inter-professional dialogue is that all health professionals (eg psychiatrists, pharmacists, GPs, nurses) have difficulties when dealing with high-risk patients and prescribing benzodiazepines.<sup>88</sup> There should be an agreed set of professional standards regarding communication and transfer of care. In particular, the responsibility of ongoing prescribing duties should be explicit.

Prescribing may be initiated and recommended by other specialists, or during hospital in-patient care. When prescribing is transferred from secondary to primary care, the following information should be relayed to the GP:

- indication for use
- expected length of treatment
- when the treatment will be reviewed and by whom
- advice about withdrawal if indicated
- clear indications of the GP's role
- clear agreement on roles of all clinicians between GP and secondary care
- clear indications of support and referral pathways to the secondary service.

GPs should take care when patients on high doses of benzodiazepines are transferred from secondary care without a therapeutic rationale for clinical benefits or planned withdrawal schedule. GPs are not required to continue prescriptions commenced elsewhere if they are not comfortable doing so. However, GPs should not undermine the professional advice of colleagues, and should attempt immediate contact by telephone to clarify the management plan when there are concerns.

With continued monitoring of care, issues may arise which should prompt specialist review or immediate transfer to hospital (refer to RACGP's *Prescribing drugs of dependence in general practice, Part A – Clinical governance framework*). The following should prompt consideration for referral to specialist mental health services:<sup>89</sup>

- insufficient experience to manage the patient's condition requiring benzodiazepine therapy, or insufficient practice infrastructure to provide ongoing recall and review
- multiple attempts at treatment have not resulted in sustained improvement
- severe coexisting depressive symptoms or a risk of suicide
- evidence of problematic drug use

- comorbid physical illness and concomitantly prescribed treatments which could interact with prescribed psychotropic medication
- proposed interventions are not available within primary care services.

#### 1.6.2.4 Practice policies and standards

General practices should have agreed clinical policies regarding prescribing benzodiazepines to improve the quality and consistency of prescribing, and improve safety for patients and practice staff.

Practices should consider having policies regarding:

- the management of patients according to mental illness and use of drugs of dependence to provide the appropriate level of service internally and externally
- repeat scripts for benzodiazepines (refer to [Resource E.1](#))
- limitations for registrar prescribing of benzodiazepines (refer to RACGP's *Prescribing drugs of dependence in general practice, Part A – Clinical governance framework*).

Simple, practice-based interventions can be quite effective. [Practice-based letters](#) sent to a general practice population have repeated proven effectiveness in reducing benzodiazepine use in older patients.<sup>90</sup> A 10-year follow-up in the Netherlands after such an intervention revealed 60% of these patients remained abstinent of benzodiazepine use.<sup>91</sup> Those who returned to benzodiazepine therapy often did so at lower doses. Simple educational interventions may also reduce inappropriate benzodiazepine use.<sup>90,92</sup>

Benzodiazepine misuse might not be a highly visible problem in every practice, however all practices should be involved in supporting steps to reduce inappropriate benzodiazepine use in their practice and community. Each general practice should assess their own needs and develop policies that suit their circumstances.

#### 1.6.2.5 Using and managing information

To help GPs manage prescribing risks, practices should have infrastructure (computer based or other) that provides:

- standardised patient information on benzodiazepines, including the effects on driving and operating machinery (refer to [Resource D.1](#))
- a treatment plan when there is a clinical decision to continue benzodiazepines. The plan should clearly outline the responsibilities of the patient and the practice, and include an agreement to review and monitor clinical progress against therapeutic goals
- access to high-quality information systems and/or prescription shopping hotlines to assist in curtailing prescription abuse
- mechanisms/processes within the practice to share information regarding benzodiazepine abuse/misuse
- formalised benzodiazepine withdrawal guidelines within the practice (refer to [Resource D.2B](#))
- standardised patient information on sleep hygiene methods (refer to [Resource D.4](#)).

### 1.6.2.6 Quality improvement

Quality improvement measures around benzodiazepine prescribing include developing policies or an audit, communicating with patients and managing risks.

Further information about quality improvement can be found in the RACGP's *Prescribing drugs of dependence in general practice, Part A – Clinical governance framework*.

## 1.6.3 Accountable prescribing of benzodiazepines

### ✓ Key points

- Prescribing benzodiazepines, as with any treatment, should be based on a comprehensive medical assessment, a diagnosis, thoughtful consideration of the likely risks and benefits of any medication as well as alternative interventions, and a management plan derived through shared decision making and continual clinical monitoring.
- GPs should be aware of the concerns associated with benzodiazepines such as potential dependence, withdrawal, problematic drug use (including diversion and misuse), and known harmful effects, including falls, potential cognitive decline and motor vehicle accidents. These risks should be discussed with patients.
- GPs may wish to use the diagnosis of SUD rather than dependence, addiction or abuse. This is based on the [DSM-5](#) sedative, hypnotic or anxiolytic use disorder criteria. This is a more neutral term that may reduce stigmatisation of patients with problematic use of benzodiazepines and other drugs/alcohol.
- Treatment seeks to maximise outcomes for the health and social functioning of the patient while minimising risks. To minimise risks, benzodiazepines should be prescribed at the lowest effective dose, for the shortest clinical time frame.
- Once started, some patients find it hard to stop benzodiazepines. Therefore, prescription should be accompanied with a plan to reduce and cease benzodiazepines.
- Patients who use two or more psychoactive drugs in combination (polydrug use), and those with a history of substance misuse may be more vulnerable to major harms. Significant caution should be taken if prescribing benzodiazepines to patients with comorbid alcohol/substance abuse or polydrug use. GPs should consider seeking specialist opinion in management of these patients.
- Benzodiazepines are generally regarded by clinical practice guidelines as a short-term therapeutic option. Long-term use, [beyond 4 weeks](#), should be uncommon, made with caution and based on thoughtful consideration of the likely risks and benefits of benzodiazepines.
  - If alternatives to benzodiazepine treatment fail, have limited benefit or are inappropriate (either psychologically or pharmacologically), supervised benzodiazepine treatment may remain an acceptable long-term therapeutic option.
  - Long-term benzodiazepine prescriptions should be at the lowest effective dose, preferably given intermittently, and regular attempts at reduction should be scheduled. Continued professional monitoring of health outcomes is required.
  - Benzodiazepines should be [prescribed from one practice and preferably one GP](#), with prescriptions dispensed from one pharmacy.
- GPs should develop strategies to manage [inappropriate requests for benzodiazepines by patients](#).



### 1.6.3.1 Evidence-based prescribing of benzodiazepines

The evidence base for benzodiazepine use continues to evolve, but despite the length of time they have been used in clinical practice, the evidence remains incomplete in many areas.<sup>93</sup> The clinical recommendations and practice points presented in this guide are based on the best available evidence.

With respect to benzodiazepine therapy, recommendations based on these randomised controlled studies do not always reflect clinical reality. It is recognised that randomised controlled trials are generally a maximum of 12 weeks and performed in restricted patient groups with little comorbidity or other features resembling conventional clinical samples.<sup>94</sup>

### 1.6.3.2 Practical prescribing decisions

Good prescribing practice involves careful and considered diagnosis; clear therapeutic goals; the use of non-drug therapies where suitable; prescribing appropriate types, formulations and amounts of medication; explaining the effects of medications and any risk of dependence; and implementing regular medication reviews.

The risks of problematic use and diversion make prescribing benzodiazepines more challenging.

The short-term use of benzodiazepines can be helpful for symptomatic relief across a wide range of clinical conditions. Given the potential for harm with benzodiazepine use, clinical discipline is required. The immediate relief with benzodiazepines is tempting, yet the best outcomes are often achieved with non-drug treatment. However, these interventions take time, may not be available in a timely fashion, and involve engagement and effort from patients.

While the thrust of this guide is that benzodiazepines should generally be prescribed less, care should be exercised when changing from one psychoactive substance to another or when using combination therapies. All psychoactive drugs have risks and benefits. Some non-benzodiazepine drugs also have problems with dependence and problematic use (eg quetiapine). There is consensus that although benzodiazepines have been problematic, when prescribing is placed in the broader historical context and the types of patients prescribed benzodiazepines are considered, it is apparent that other psychotropic drugs have raised similar problems.<sup>58,95–99</sup>

### 1.6.3.3 Assessing risk

Patients who previously misused drugs (eg opioids, anti-alcohol or smoke cessation treatments) have a higher risk of becoming excessive users compared to patients who have not previously misused drugs.<sup>76</sup> Greater challenges exist for patients already prescribed benzodiazepines for some time. Once a benzodiazepine prescription has been started, it may be harder to stop.

To minimise harms associated with prescription drug misuse, GPs need to maintain vigilance in identifying SUDs, assist patients in recognising disordered use where it exists, set goals for recovery and assist patients to seek appropriate treatment.

### Recognising patients with problematic benzodiazepine use

There are several behaviours that indicate a patient may have problematic benzodiazepine use, such as escalating use patterns, drug-seeking behaviour and doctor or prescription shopping.<sup>77</sup>

Drug-seeking behaviours that indicate risk, but are less predictive of problematic use include:

- attending early for prescription renewal
- complaining aggressively about the need for higher doses
- hoarding drugs during periods of reduced symptoms
- requesting specific drugs
- acquiring similar drugs from other medical sources
- escalating unsanctioned doses 1–2 times



- using the drug to treat other symptoms
- selling prescription drugs.

Drug-seeking behaviours that are highly predicative of problematic use include:

- forging prescriptions
- stealing or borrowing another patient's drugs
- injecting oral formulations
- obtaining prescription drugs from non-medical sources
- abusing illicit drugs concurrently
- escalating unsanctioned doses multiple times
- losing prescriptions repeatedly.

Patients may be extremely convincing, using plausible stories and even manipulating a GP's discomfort with confrontation to obtain medication.<sup>77</sup>

For ways to manage patient who may be drug seeking, refer to patient scripts in [Resource A](#).

Patients with previous substance use problems, or those who use antipsychotic medication, are at increased risk of disordered benzodiazepine use.<sup>76</sup> However, any patient can develop problematic use, and so universal precautions are important when considering prescribing.

### Assessment of substance use disorder

The DSM-5 criteria combine the old DSM-IV categories of substance abuse and substance dependence into a single condition of SUD, measured on a continuum from mild to severe.<sup>40</sup>

The essential feature of SUD is a cluster of cognitive, behavioral and physiological symptoms indicating the individual continues using the substance despite significant substance-related problems.<sup>40</sup>

Using the term SUD should:

- reduce confusion associated with the terms dependence, addiction and abuse (which have been inconsistently and often incorrectly used to describe points on a spectrum of disordered use)
- be more acceptable to patients and their carers – a diagnosis of being 'drug dependent' may be confronting and create stigma.

Diagnosis of SUD requires the presence of at least two of 11 criteria, across four categories: impaired control, social impairment, risky use and pharmacology. Based on the total number of criteria the patient has, the substance use disorder can be classified as mild (2–3 symptoms), moderate (4–5 symptoms) or severe (6 or more symptoms). It is hoped these severity classifiers may help to clarify treatment options (refer to *Table 3*).

Although the term SUD is a helpful addition, the term dependence will necessarily be used when discussing any 'drug of dependence'.

**Table 3. DSM-5 criteria for diagnosing a sedative, hypnotic or anxiolytic use disorder**

A problematic pattern of sedative, hypnotic or anxiolytic use leading to clinically significant impairment or distress, as manifested by at least two of the following 11 criteria, occurring within a 12-month period:

Impaired control criteria	<ol style="list-style-type: none"> <li>1. Sedatives, hypnotics or anxiolytics are often taken in larger amounts or over a longer period than was intended</li> <li>2. There is a persistent desire or unsuccessful efforts to cut down or control sedative, hypnotic or anxiolytic use</li> <li>3. A great deal of time is spent in activities necessary to obtain the sedative, hypnotic or anxiolytic; use the sedative, hypnotic or anxiolytic; or recover from its effects</li> <li>4. Craving or strong desire or urge to use the sedative, hypnotic or anxiolytic</li> </ol>
Social impairment criteria	<ol style="list-style-type: none"> <li>5. Recurrent sedative, hypnotic or anxiolytic use resulting in a failure to fulfil major role obligations at work, school or home (eg repeated absences from work or poor work performance related to sedative, hypnotic or anxiolytic use; sedative-, hypnotic- or anxiolytic-related absences, suspensions or expulsions from school; neglect of children or household)</li> <li>6. Continued sedative, hypnotic or anxiolytic use despite having persistent or recurrent social or interpersonal problems caused by or exacerbated by the effects of sedatives, hypnotics or anxiolytics (eg arguments with a spouse about consequences of intoxication; physical fights)</li> <li>7. Important social, occupational or recreational activities are given up or reduced because of sedative, hypnotic or anxiolytic use</li> </ol>
Risky use criteria	<ol style="list-style-type: none"> <li>8. Recurrent sedative, hypnotic or anxiolytic use in situations in which it is physically hazardous (eg driving an automobile or operating a machine when impaired by sedative, hypnotic or anxiolytic use)</li> <li>9. Sedative, hypnotic or anxiolytic use is continued despite knowledge of having persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the sedative, hypnotic or anxiolytic</li> </ol>
Pharmacological criteria	<ol style="list-style-type: none"> <li>10. Tolerance, as defined by either of the following: <ol style="list-style-type: none"> <li>a. A need for markedly increasing amounts of the sedative, hypnotic or anxiolytic to achieve intoxication or desired effect</li> <li>b. A markedly diminished effect with continued use of the same amount of the sedative, hypnotic or anxiolytic</li> </ol> <p><b>Note:</b> This criterion is not considered to be met for individuals taking sedatives, hypnotics or anxiolytics under medical supervision</p> </li> <li>11. Withdrawal, as manifested by either one of the following: <ol style="list-style-type: none"> <li>a. The characteristic withdrawal syndrome for sedatives, hypnotics or anxiolytics (refer to Criteria A and B of the criteria set for sedative, hypnotic or anxiolytic withdrawal in DSM-5 pp 557–558)</li> <li>b. Sedatives, hypnotics or anxiolytics (or a closely related substance, such as alcohol) are taken to relieve or avoid withdrawal symptoms</li> </ol> </li> </ol>

**Specifiers:**

**In early remission:** After full criteria for sedative, hypnotic or anxiolytic use disorder were previously met, none of the criteria for sedative, hypnotic or anxiolytic use disorder have been met for at least 3 months but for less than 12 months (with the exception that criterion 4 may be met)

**In sustained remission:** After full criteria for sedative, hypnotic or anxiolytic use disorder were previously met, none of the criteria for sedative, hypnotic or anxiolytic use disorder have been met at any time during a period of 12 months or longer (with the exception that criterion 4 may be met)

**In a controlled environment:** This additional specifier is used if the individual is in an environment where access to sedatives, hypnotics or anxiolytics is restricted

**Current severity:**

**Mild:** Presence of 2–3 symptoms

**Moderate:** Presence of 4–5 symptoms

**Severe:** Presence of 6 or more symptoms

## 1.6.4 Patient focus

### ✓ Key points

- All patients, including those who use benzodiazepines and other drugs and alcohol problematically, have the right to respectful care that promotes their dignity, privacy and safety.

#### 1.6.4.1 Sharing prescribing decisions

Treatment and care of patients should take into consideration their needs and preferences. Clinical options and patient information should be culturally appropriate. It should be accessible to people with individual needs including those with physical, sensory or learning disabilities, and those who do not speak or read English.

Fully informing patients about the benefits and drawbacks of benzodiazepines may improve shared decision making between the patient and doctor. While there are time constraints in a consultation, this approach may reduce GPs' workload with fewer patients returning for repeat prescriptions.<sup>8</sup>

Non face-to-face methods of communication can also be useful. For example, a study involving direct delivery of an educational tool on benzodiazepines to older patients increased their risk perception of inappropriate prescriptions.<sup>100</sup>

Exploring patient preferences, ideas and expectations during a consultation may lead to fewer benzodiazepine prescriptions. Evidence suggests doctors sometimes assume patients want drug treatment and/or would be resistant to withdrawal, whereas some patients prefer not to use medication or wish to discontinue drugs.<sup>8</sup>

Patients need good information and access to alternative treatments including CBT for insomnia and anxiety. These interventions may be made available in the practice or through local services. There are many resources available on the internet (eg computer-based anxiety therapies).

#### 1.6.4.2 Clinical responsibility in shared decision making

While most patients' involvement with drugs of dependence is clinically driven, there can be elements of manipulation (and rarely criminal intent) behind patients' requests for benzodiazepines.

The important caveat when prescribing drugs of dependence relates to healthcare benefits. Some patients with drug dependency may request higher doses on the basis that they are making a choice as an informed patient, or as harm minimisation.

Patients have a right to good healthcare, but not a right to drugs of dependence. Patients need to be informed of this at the beginning of any trial using drugs of dependence. If the clinician feels further therapy is detrimental to a patient's health, then clinical withdrawal of medication should begin.

Doctors typically have a strong desire to alleviate a patient's distress and suffering. The psychological phenomenon of transference in addiction, pain and mental illness can result in doctors having difficulty in these clinical areas. Some GPs may find it difficult to set boundaries for patients, and are therefore at risk of being pressured to prescribe inappropriately. Other GPs may have difficulty saying 'no' or believe they are 'helping' or taking a harm minimisation approach by giving in to a patient's requests for drugs.

All practitioners express difficulty responding to patients who use manipulative behaviour (eg threatening to self-harm if they do not receive medication). GPs should educate themselves about appropriate responses to common manipulative behaviours used to access drugs of dependence. To aid GPs' negotiation skills, scripted replies have been developed to help with appropriate responses in difficult situations (refer to [Resource A](#)).

### 1.6.4.3 Aboriginal and Torres Strait Islander peoples

There is very little literature on benzodiazepine use in Aboriginal and Torres Strait Islander peoples. While the clinical recommendations in this guide are the same for all patients, there is a need to understand the complex cultural context of Aboriginal and Torres Strait Islander peoples to build an effective therapeutic alliance. Working with local, respected Aboriginal Health Workers and/or drug and alcohol workers is crucial for comprehensive bio-psychosocial care.

#### Resources

The *Working Together* book is relevant in understanding and providing mental health care to Aboriginal and Torres Strait Islander peoples. This is available at <http://aboriginal.telethonkids.org.au/media/699863/Working-Together-Book.pdf>

The *Handbook for Aboriginal Alcohol and Drug Work* includes useful information on benzodiazepines. This is available at [http://ses.library.usyd.edu.au/bitstream/2123/8339/6/2012-handbook\\_online-version3.pdf](http://ses.library.usyd.edu.au/bitstream/2123/8339/6/2012-handbook_online-version3.pdf)

## *2. Evidence-based guidance for benzodiazepines*

### 2.1 Overview

The evidence base for benzodiazepine use continues to evolve, but despite the length of time they have been used in clinical practice, the evidence remains incomplete in many areas.<sup>93</sup> The clinical recommendations and practice points presented in this guide are based on the best available evidence.

Benzodiazepines are used for a broad range of conditions including:

- insomnia
- anxiety disorders
- alcohol withdrawal
- mania/hypomania
- epilepsy
- acute seizures
- arousal/agitation in the in-patient setting
- palliative care
- musculoskeletal disorders.

Insomnia and anxiety disorders are commonly managed in general practice and are the main focus of this chapter. Alcohol withdrawal may be managed in general practice and is covered briefly. However, GPs wishing to manage patients withdrawing from alcohol will need to consult other resources.

The following sections demonstrate how benzodiazepines fit into the context of treatment for a range of conditions, but do not represent comprehensive guidance. Additional resources are provided for each condition.

## 2.2 Insomnia

### ✓ Key points

- Insomnia is a common problem seen in general practice. The understanding of chronic insomnia is still evolving.
- In acute insomnia, sleep often returns to normal once the precipitating factor has resolved.
- In chronic insomnia, treatment is focused on addressing underlying comorbid precipitants (where present), and psychological and behavioural management.
- Pharmacotherapy for acute and chronic insomnia may be necessary for severe or resistant cases of insomnia. The decision to prescribe should be on an individual basis and involve serious consideration of all risks and possible benefits.
- Benzodiazepines and Z drugs have been shown to be effective treatments and may be prescribed for short-term or intermittent use. Harm, such as dependence and adverse events, may occur with both drug groups.
- Dose reduction and cessation should be discussed with the patient on first prescription and commenced once sleep patterns return to normal.
- Pharmacological treatment should be accompanied by specific patient education and regular review.

	Evidence statements	Grade
Rec 1	Cognitive behavioural therapy (CBT) based treatment packages for chronic insomnia, including sleep restriction and stimulus control, are effective and therefore should be offered to patients as first-line treatment. <sup>101</sup>	A
Rec 2	Z drugs and short-acting benzodiazepines are efficacious for insomnia. <sup>101</sup>	A
Rec 3	Prescription of zolpidem and zopiclone should be treated with the same caution as benzodiazepines. <sup>102</sup>	A
Rec 4	Intermittent dosing may reduce the risk of tolerance and dependence. <sup>101</sup>	B
Rec 5	If hypnotics are to be used for treating insomnia, it is recommended that treatment is short term (not more than 4 weeks) and at the lowest possible dose. <sup>103</sup>	B

To see the original source of the recommendations and grading, as well as supporting sources, click on the recommendation number in the left column.

### 2.2.1 Background

Sleep disturbance is the third most common psychological reason for patient encounters in general practice. Population surveys found 13–33% of adult Australians have regular difficulties getting to sleep or staying asleep.<sup>104</sup>

Insomnia is defined in DSM-5 as a difficulty in getting to sleep, staying asleep or having non-restorative sleep despite having adequate opportunity for sleep, together with associated impairment of daytime functioning, with symptoms being present for at least 4 weeks.<sup>40</sup>

**Acute insomnia** meets the DSM-5 definition of insomnia, but with symptoms occurring for less than 4 weeks.<sup>40</sup> It is experienced by up to 80% of the population at some stage, generally due to one or more precipitating factors.<sup>105</sup>

Factors that can precipitate acute insomnia include:<sup>104</sup>

- physiological – hyperarousal due to stress, being ‘on-call’, caring for a sick child/relative, being in a strange situation (eg in hospital)
- pharmacological – prescribed drugs (eg newly prescribed diuretic causing nocturia) and non-prescribed drugs
- physical – coughing, environment (eg noise, temperature)
- disruption of circadian rhythm (eg jet lag).

Provided patients adhere to good sleep habits, most will return to normal sleep once the precipitating factor has resolved or diminished.<sup>106</sup>

**Chronic insomnia** was previously viewed as a sleep disturbance that was secondary to a medical condition, psychiatric illness, sleep disorder or medication, and would improve with treatment of the underlying disorder.<sup>107,108</sup> However, evidence over the last 20 years indicates this view is incorrect. It is now recognised that insomnia may be an independent disorder.<sup>108–110</sup> The understanding of chronic insomnia continues to evolve. Insomnia may have some similarities with depression in that they both represent long-term disorders for which many patients require maintenance treatment.

Chronic insomnia may occur in the absence of coexisting conditions. When coexisting conditions exist, insomnia may persist despite successful treatment of the coexisting condition. Treatment directed at the insomnia, rather than the comorbidity, may be necessary. Since insomnia can precipitate, exacerbate or prolong comorbid conditions, treatment of insomnia may in turn improve comorbidities.

Chronic insomnia is unlikely to resolve spontaneously.<sup>111</sup>

## 2.2.2 Management of insomnia in general practice

When patients present with insomnia to GPs in Australia, few (0.8%) receive a referral for specific non-drug therapy.<sup>112</sup> All guidelines strongly recommend psychological and behavioural management.<sup>68,102,108,113</sup>

### 2.2.2.1 Assessment and diagnosis

Assessment and diagnosis of insomnia requires:<sup>111</sup>

- understanding the patient's typical sleep pattern over an extended time frame (weeks to months) – a sleep diary can help assessment
- identifying contributing lifestyle factors (eg caffeine, nicotine, pets in the bedroom)
- understanding the patient's beliefs and concerns about sleep
- determining the effects of poor sleep on the patient (eg poor memory, fatigue, work absence, accidents)
- identifying comorbid conditions – this may be aided by the Auckland Sleep Questionnaire, which is a validated screening tool.<sup>114</sup>

### 2.2.2.2 Acute insomnia

Treatment is focused on avoiding or withdrawing the precipitant, if possible. All patients should receive basic behavioural counselling on sleep hygiene and stimulus control.

Drug treatment may be indicated as an adjuvant to non-drug therapies for acute insomnia that is severe, disabling and causing distress. Benzodiazepines and Z drugs are the most effective drugs.<sup>25</sup> The short-term use of benzodiazepines as hypnotic agents should only be one aspect of general management,<sup>25</sup> with a clear endpoint of drug cessation once sleep patterns return to normal.

### 2.2.2.3 Chronic insomnia

Management of chronic insomnia starts with addressing any relevant, underlying problems that are present, such as:

- pharmacological – prescribed drugs (eg some antidepressants, withdrawal of sedatives) and non-prescribed drugs (eg caffeine, alcohol)
- physical (eg pain, respiratory and cardiovascular disorders, neurological disorders, movement disorders, restless leg syndrome and other sleep disorders)
- psychiatric disorders (eg depression, anxiety, dementia and substance misuse)
- disruption of circadian rhythm (eg shift work).

### 2.2.2.4 Non-drug interventions

First-line therapy for chronic insomnia should be non-drug interventions that are supported by evidence in achieving sustained improvements in sleep parameters.<sup>115,116</sup> Interventions include:

- CBTs<sup>18,117</sup> (eg stimulus control, sleep restriction therapy, relaxation techniques, cognitive therapy and sleep hygiene education)<sup>111</sup>
- brief behavioural therapy (ie modification of waking behaviours that affect the physiological systems regulating sleep)<sup>118–121</sup>
- exercise.<sup>122</sup>

Psychological and behavioural treatments administered weekly over a 4–8-week period have shown robust and stable improvements in sleep continuity for up to 2 years.<sup>123</sup> These therapies are now available online, which has vastly improved access.

Refer to [Resource G](#) for a GP guide to behavioural therapies for insomnia.

### 2.2.2.5 Drug therapy

For patients who continue to have insomnia that is sufficiently burdensome to warrant other interventions, reasonable approaches include continued behavioural therapies, medication or both.<sup>108</sup>

Recommendations in guideline on the use of medication for chronic insomnia vary. This is primarily due to the lack of evidence from extended trials that adequately compare long-term risks and harms of these medications. Some guidelines suggest avoidance of hypnotic drugs as far as possible,<sup>102</sup> while others make a considered judgement on the risks and benefits.<sup>68,108,113</sup>

The decision to treat chronic insomnia must weigh any potential serious side effects associated with pharmacologic therapy against potential health risks of not providing treatment. This includes decreased quality of life, increased risk for psychiatric comorbidities and SUD, and decreased performance. The approach should be individualised according to the patient's values and preferences, the availability of advanced behavioural therapies, the severity and impact of the insomnia, and the potential benefits versus the risks, costs and inconveniences.<sup>108</sup>

Pharmacological treatment should be accompanied by specific patient education, regular review and continued effort to employ the lowest effective maintenance dosage of medication, and to taper medication when conditions allow.<sup>113</sup>

- **Benzodiazepines** – May have a place in the treatment of severe acute insomnia or treatment-resistant chronic insomnia. For patients with sleep onset insomnia, a short-acting medication is a reasonable choice for an initial trial of pharmacologic therapy. This may improve the insomnia with less residual somnolence the following morning. For patients with sleep maintenance insomnia, a longer-acting medication is preferable for an initial trial of pharmacological therapy.<sup>108</sup>
- **Z drugs** – Have been shown to be effective in the treatment of insomnia in the short term. However, there is very limited evidence that they retain their efficacy during long-term



treatment.<sup>123</sup> Z drugs are associated with issues relating to adverse events, rebound insomnia, development of tolerance and SUD, and need to be carefully monitored in individual patients.<sup>123</sup> Zolpidem's black box warning states, 'Zolpidem may be associated with potentially dangerous complex sleep-related behaviours which may include sleep walking, sleep driving and other bizarre behaviours. Zolpidem is not to be taken with alcohol. Caution is needed with other CNS depressant drugs. Limit use to four weeks maximum under close medical supervision'.<sup>124</sup>

Psychological and behavioural treatments produce comparable outcomes to Z drugs during active treatment and have better durability beyond the active administration of treatment.<sup>123</sup>

Prescription of zolpidem and zopiclone should be treated with the same precautions and patient management as benzodiazepines.<sup>102</sup>

- **Melatonin** – An endogenous hormone associated with the control of circadian rhythms and sleep regulation. Melatonin levels may be reduced in middle-aged and elderly patients with insomnia. Supplementation with melatonin has been shown to improve limited aspects of sleep in 30–50% of patients over 55 years of age.<sup>106,125,126</sup> Data from clinical trials are variable. Some showed that some patients gain clinically significant improvements in quality of sleep and morning alertness with prolonged-release melatonin, but many patients in the clinical trials did not respond to treatment.<sup>35</sup> Melatonin does not appear to be addictive or cause withdrawal effects when stopped.<sup>125</sup> There is a lack of long-term study data.

At the time of writing, melatonin is available in Australia as a prolonged-release formulation for short-term treatment of primary insomnia, characterised by poor sleep quality in patients aged 55 years or older.<sup>35</sup> The recommended dose is 2 mg orally at bedtime, and at present, there is insufficient evidence to support treatment beyond 3 weeks.<sup>35</sup>

In a European campaign to reduce benzodiazepine and Z drug usage, the availability of prolonged-release melatonin was shown to positively contribute to success.<sup>127</sup>

- **Other prescription medications** – Includes antipsychotics (eg quetiapine, olanzapine). Studies demonstrating the usefulness of these medications for either short- or long-term management of insomnia are lacking. Furthermore, these agents have significant risks and therefore, their use in the treatment of chronic insomnia (without a relevant comorbid condition) cannot be recommended.<sup>107</sup> Numerous other medications have a sedating effect, but are not recommended for routine use in patients with insomnia. These include antidepressants, diphenhydramine and antipsychotics.<sup>108</sup>
- **Over-the-counter (OTC) medications** – Such as antihistamines or antihistamine/analgesic type drugs, and herbal and nutritional substances (eg valerian) are not recommended in the treatment of chronic insomnia due to the relative lack of efficacy and safety data.

## 2.2.3 Resources

- Medical Journal of Australia supplement, Sleep Disorders: A practical guide for Australian health care practitioners, available at [www.sleephealthfoundation.org.au/files/MJA%20Supplement/MJA\\_Supplement\\_final.pdf](http://www.sleephealthfoundation.org.au/files/MJA%20Supplement/MJA_Supplement_final.pdf)
- Australasian Sleep Association, Insomnia, available at [www.sleep.org.au/documents/item/355](http://www.sleep.org.au/documents/item/355)
- Australian Prescriber, Cognitive behaviour therapy in medical practice, available at [www.australianprescriber.com/magazine/24/2/33/7](http://www.australianprescriber.com/magazine/24/2/33/7)
- Australian Psychological Society, Managing insomnia: What we've learnt in the last 10 years, available at [www.psychology.org.au/inpsych/2014/april/bartlett](http://www.psychology.org.au/inpsych/2014/april/bartlett)
- RACGP Handbook of non-drug interventions (HANDI), Brief behavioural therapy for insomnia in adults, available at [www.racgp.org.au/your-practice/guidelines/handi/interventions/mental-health/brief-behavioural-therapy-for-insomnia-in-adults](http://www.racgp.org.au/your-practice/guidelines/handi/interventions/mental-health/brief-behavioural-therapy-for-insomnia-in-adults)
- South Australian kit – Insomnia management kit, available at [www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/clinical+resources/clinical+topics/substance+misuse+and+dependence/sleep+problems+-+insomnia+management+kit](http://www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/clinical+resources/clinical+topics/substance+misuse+and+dependence/sleep+problems+-+insomnia+management+kit)

## 2.3 Anxiety disorders

### ✓ Key points

- Anxiety disorders are common and exist as a spectrum of conditions that vary from mild to severe.
- Comprehensive clinical [assessment](#) is the first step in management. Effective management requires obtaining a diagnosis, and recognising that patients may not present with a single disorder (eg patients may experience generalised anxiety, panic disorder as well as depression).
- Where treatment is indicated:
  - First-line therapy for generalised anxiety disorder (GAD), panic disorder, and panic attacks should include [CBT](#) (due to its effectiveness at reducing the symptoms of anxiety in the short and long term).
  - SSRI and SNRI [medications](#) are effective across the range of anxiety disorders and generally suitable for first-line pharmacological treatment of anxiety.
  - Short-term benzodiazepines as occasional adjunctive therapy may be effective at reducing worsening of symptoms that can occur in the first days to weeks of initiating antidepressant medication, and therefore aid adherence
  - [Benzodiazepine use](#) in anxiety disorders is mostly limited to severe or treatment-resistant cases.
  - Patients who use two or more psychoactive drugs in combination (polydrug use) may be more vulnerable to major harms.

	Evidence statements	Grade
Rec 6	Cognitive behavioural therapy is recommended as one of the treatments of choice for generalised anxiety disorder, panic disorder, and panic attacks due to its effectiveness at reducing the symptoms of anxiety in the short and long term, although patient preference must be taken into consideration. <sup>64</sup>	A
Rec 7	Consider an selective serotonin reuptake inhibitor (SSRI) for first-line drug treatment, as SSRIs are effective across the anxiety and related disorders, in short and long term, and are generally well tolerated. <sup>128</sup>	A
Rec 8	Benzodiazepines have evidence of benefit in generalised anxiety disorder, social anxiety disorder and panic disorder, but not obsessive compulsive disorder or post-traumatic stress disorder. <sup>94</sup>	A/B

To see the original source of the recommendations and grading, as well as supporting sources, click on the recommendation number in the left column.

### 2.3.1 Background

Anxiety disorders include GAD, panic disorder, OCD, PTSD, phobias and SAD.

In 2007, anxiety disorders were the most common self-reported mental disorder in Australia, affecting 14% of people aged 16–85 years.<sup>129</sup> Anxiety disorders may be prominent in depressive conditions and other chronic health diseases. Anxiety and related disorders often become chronic.

Not all patients with anxiety symptoms require treatment. Anxiety symptoms exist on a continuum and many people with milder degrees of anxiety, particularly recent onset and association with stressful situations will recover without intervention.<sup>89</sup> The need for treatment is determined by the severity and persistence of symptoms, the presence of comorbid mental or physical illness, the level of disability and the impact on social functioning. Treatment should aim to achieve full remission of symptoms and return of function, rather than just symptom improvement and distress reduction.<sup>130</sup>

Randomised controlled trials across a range of anxiety disorders often demonstrate a high placebo response, which indicates that non-specific effects can play a large part in improvement.<sup>128</sup>

Approaching anxiety disorders systematically involves identifying and treating any comorbidities, providing patient education and appropriate psychological and pharmacological interventions. These should be evidence-based and patients should receive ongoing monitoring to determine whether treatment aims are being achieved.<sup>130</sup>

## 2.3.2 Management of anxiety in general practice

For a comprehensive review of management of anxiety disorders, GPs are advised to review individual clinical guidelines.

Benzodiazepine use in anxiety disorders is mostly limited to severe, or treatment-resistant, cases. Patients with a history of significant mental illness who use two or more psychoactive drugs (polydrug use) may be more vulnerable to major harms. Significant caution should be taken if prescribing benzodiazepines to patients with comorbid alcohol or SUDs, or polydrug use. GPs should consider seeking specialist opinion in the management of these patients.

### 2.3.2.1 Assessment and diagnosis

Comprehensive clinical assessment is the first step to developing a diagnosis and determining the patient's level of disability. In milder, recent onset anxiety disorders, consider 'watchful waiting' (support, addressing social factors and monitoring).<sup>89</sup>

It is important to detect comorbid depression. Depression should be treated if depressive symptoms are moderate or severe.

Most guidelines recommend CBT as first-line non-drug therapy, while SSRIs and SNRIs are the drugs of first choice. Benzodiazepine recommendations are generally limited to severe or treatment-resistant cases. However, the efficacy of psychological and pharmacological approaches is similar in the acute treatment of mild to moderate anxiety disorders.<sup>89,94,131</sup>

The selection of an initial treatment modality should be guided by considerations including the patient's needs and preferences, the risks and benefits for the patient, the patient's past treatment history, the presence of comorbid general medical and other psychiatric conditions, cost and the local availability of evidence-based psychological interventions.

Where appropriate and available, patients should be offered a choice of evidence-based treatment approaches.

### 2.3.2.2 Cognitive behavioural therapy

All major guidelines recommend CBT as the first-line intervention for anxiety disorders.<sup>64,89,94,130</sup>

CBT is a multimodal intervention. Specific techniques used in the therapy include education, self-monitoring, relaxation training, cognitive restructuring, exposure to imagery and anxiety-producing situations, and relapse prevention. CBT has been shown to be an effective stand-alone treatment for GAD.<sup>132</sup> Comorbidity does not decrease the treatment effects of CBT.

CBT for most anxiety, and related disorders, can be delivered effectively in individual or group therapy formats.<sup>130</sup> There are also an increasing number of self-directed formats that require minimal or no therapist contact, which have been shown to be effective.<sup>130</sup> These include bibliotherapy (self-help books) and internet or computer-based programs.<sup>133,134</sup>

A combination of medication and cognitive behaviour or exposure therapy has been shown to be a clinically desired treatment strategy.<sup>94</sup> However, combination therapy results have been conflicting,<sup>135,136</sup> and results vary for different anxiety disorders. While current evidence does not support the routine combination of CBT and pharmacotherapy as initial treatment for all anxiety disorders, there is support for combined use in panic disorders, with or without agoraphobia.<sup>137,138</sup>

Benzodiazepines are generally avoided in patients with anxiety disorders who are undergoing CBT. This is due to their potential interference with motivation and learning, which are required for CBT to be effective. Some authors are now challenging this,<sup>73</sup> however there is sparse trial evidence to support a conclusion. More research is needed to ascertain if these treatment modalities can be combined effectively.

CBT protocols for anxiety usually involve 10–14 weekly sessions, but briefer strategies of 6–7 sessions have been shown to be as effective. Unfortunately, a lack of access to trained clinicians may be an issue in some areas and therefore lead to the majority of patients with anxiety being treated with medications.<sup>139</sup> Online CBT programs have shown efficacy, and may be suitable for patients who cannot access face-to-face therapy, or who prefer treatment in their own homes, in their own time.

### 2.3.2.3 Antidepressants

Note that anxiety disorders show a strong placebo response, especially at mild to moderate levels of symptom severity.<sup>89</sup> If pharmacotherapy is indicated, the SSRIs and SNRIs are preferred agents.<sup>140</sup> Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MOAI) are other alternatives.

Although preferred over benzodiazepines, there are limited studies comparing head-to-head effectiveness with antidepressants. Reviews of the studies performed suggest comparative effectiveness of benzodiazepines to older and new antidepressants.<sup>141–142</sup>

In trials of benzodiazepines and newer antidepressants, benzodiazepines have demonstrated comparable or greater improvements with fewer adverse events in patients suffering from GAD or panic disorder.<sup>141</sup> Efficacy of benzodiazepines for panic disorder is comparable to SSRIs, SNRIs and TCAs.<sup>143</sup> Similarly, the incidence of withdrawal symptoms from antidepressants seems to occur at similar levels to benzodiazepines.<sup>96</sup>

Reviewers have suggested the major change in prescribing pattern from benzodiazepines to newer antidepressants in anxiety disorders has occurred in the absence of comparative data of high-level of proof.<sup>141,144</sup>

However, SSRIs and SNRIs remain recommended first-line treatments by international guidelines for anxiety disorders.<sup>143</sup>

Short-term benzodiazepines as occasional adjunctive therapy may be effective at reducing worsening of symptoms that can occur in the first days to weeks of initiating antidepressant medication.

### 2.3.2.4 Benzodiazepines

Benzodiazepines are not indicated for 'mild' anxiety.

Benzodiazepines may be used (as monotherapy or in combination with antidepressants) for patients with very distressing or impairing symptoms whom rapid symptom control is critical.<sup>143</sup>

Benzodiazepines have evidence of benefit for GAD, social anxiety disorder and panic disorder, but not for OCD or PTSD.<sup>64,94</sup> Trials have been conducted with clonazepam, diazepam and lorazepam, which have demonstrated the efficacy of these compounds in managing panic disorder clonazepam for SAD, diazepam and bromazepam for GAD.<sup>3</sup>

The benefit of a more rapid response to benzodiazepines must be balanced against the possibilities of troublesome side effects (eg sedation) and physiological dependence that may lead to difficulty discontinuing the medication.<sup>143</sup> Note that:

- Due to its rapid onset and offset of action, alprazolam is the benzodiazepine most commonly prescribed for panic disorders. However, in a meta-analysis, it has not been shown to have better efficacy than other benzodiazepines for panic disorders, and it does have a greater risk of dependence, problematic use and withdrawal.<sup>145</sup>
- Although tolerance is less of an issue with anxiety, patients are at risk of dependence and other harms (eg depression, increased anxiety, accidents).

When benzodiazepines are prescribed short term for severe anxiety, they are generally used in conjunction with other interventions including counselling or antidepressants (where appropriate), to reduce the risk of symptom recurrence<sup>89</sup> or to alleviate and prevent the worsening of anxiety<sup>130</sup> that may occur at the start of antidepressant therapy.<sup>146</sup>

Rarely, ongoing therapy with benzodiazepines may be necessary in patients with severe, treatment-resistant anxiety. Although concerns have surrounded the risks of tolerance and SUD with long-term use of benzodiazepines, there is little evidence of tolerance to their anxiolytic effects.<sup>35</sup> Problematic use is a risk in those with a history of SUD, but is otherwise uncommon.<sup>147</sup>

The decision to treat chronic anxiety with benzodiazepines must weigh the risks and benefits of benzodiazepine therapy. Concerns about potential problems in long-term use should not prevent their use in patients with persistent, severe, distressing and impairing anxiety symptoms,<sup>147</sup> or in patients who are resistant to, or cannot tolerate, multiple first-line therapies.<sup>130</sup> Ongoing supervision is required.

### 2.3.3 Resources

- Australian Prescriber, Cognitive behaviour therapy in medical practice, available at [www.australianprescriber.com/magazine/24/2/33/7](http://www.australianprescriber.com/magazine/24/2/33/7)
- RACGP Handbook of non-drug interventions (HANDI), Depression and anxiety: internet based or computerised CBT (iCBT or CCBT), includes relevant website links, available at [www.racgp.org.au/your-practice/guidelines/handi/interventions/mental-health/internet-based-or-computerised-cbt-for-depression-and-anxiety](http://www.racgp.org.au/your-practice/guidelines/handi/interventions/mental-health/internet-based-or-computerised-cbt-for-depression-and-anxiety)

## 2.4 Alcohol withdrawal

### ✓ Key points

- Benzodiazepines are an important component of alcohol withdrawal programs, but not every patient requires medication.
- Benzodiazepines are generally only used as first-line options for acute treatment in a controlled environment for alcohol withdrawal.

	Evidence statements	Grade
Rec 9	Benzodiazepines (eg diazepam, oxazepam) are the drugs of choice for treatment of acute alcohol withdrawal (including alcohol withdrawal delirium), but for a maximum of 7 days. <sup>148</sup>	A

To see the original source of the recommendations and grading, as well as supporting sources, click on the recommendation number in the left column.

### 2.4.1 Background

Alcohol dependence is characterised by craving, tolerance, preoccupation with alcohol and continued drinking in spite of harmful consequences (eg liver disease). From a clinical perspective, alcohol dependence can be subdivided into mild, moderate or severe categories. People with mild dependence (based on alcohol dependence assessment tools) usually do not need assisted alcohol withdrawal. People with moderate dependence usually need assisted withdrawal, which can be managed in a community setting. People who are severely alcohol dependent need assisted alcohol withdrawal, typically in an in-patient or residential setting.<sup>149</sup>

The onset of alcohol withdrawal is usually 6–24 hours after the last drink. In some severely dependent drinkers, withdrawal can occur while the patient is still intoxicated due to drops in blood alcohol level.<sup>30</sup>

About 95% of people with alcohol dependence can stop drinking without major withdrawal symptoms (ie delirium, seizures).<sup>30</sup> Supportive care alone is often effective in minor alcohol withdrawal. Medication may not be necessary with lower daily alcohol consumption or for periodic drinkers. Seizures (usually a single episode) occur in approximately 5% of people with alcohol dependence when withdrawing from alcohol, and delirium tremens are typically seen in the most severe forms of alcohol withdrawal.<sup>30</sup>

## 2.4.2 Management of alcohol withdrawal in general practice

Alcohol dependence may require complex multidisciplinary therapy, including social support systems.

### 2.4.2.1 Assessment

Formal assessment tools can help determine if the patient is best suited to alcohol withdrawal in the primary care or specialist alcohol services setting.

The routine screening tool is the Alcohol Use Disorders Identification Tool (AUDIT or AUDIT-C) (refer to [Resource F](#)). Other tools include Severity of Alcohol Dependence Questionnaire (SADQ) to assess the severity of dependence; and the Clinical Institute Withdrawal Assessment of Alcohol State, revised (CIWA-Ar) or Alcohol Withdrawal Scale (AWS) for severity of withdrawal.

Patients may be suitable for home alcohol withdrawal if they:

- have no history of seizures or delirium tremens
- do not pose a suicide risk
- have social support
- show no significant polydrug misuse
- are not dependent on benzodiazepines.<sup>149</sup>

### 2.4.2.2 Assisted withdrawal approaches

When conducting an assisted withdrawal from alcohol, there are three commonly used approaches:<sup>30</sup>

- benzodiazepine loading – involves giving a large dose (up to 80 mg of diazepam) on day one in an in-patient setting, and then no further benzodiazepines
- tapering dose regimes – a predetermined (fixed) dose of benzodiazepine is administered in tapering doses over 2–6 days
- symptom-triggered sedation – doses of benzodiazepine are administered according to the severity of withdrawal symptoms.

There is limited evidence for selecting one approach over another, however, the first approach is more suited to an in-patient setting. In a comparison of fixed schedule and symptom triggered regimens, the latter two approaches were favoured.<sup>150</sup>

### 2.4.2.3 Benzodiazepines

Benzodiazepines have been shown to be one of the most effective drug classes in the management of alcohol withdrawal syndrome. The rationale of the use of benzodiazepines is to modulate CNS hyperactivity due to the alcohol withdrawal, by interacting with GABA receptors.<sup>150</sup>

A 2010 systematic review found benzodiazepines have a protective benefit against alcohol withdrawal symptoms, in particular seizures (when compared to placebo), and have a potentially protective benefit for many outcomes when compared with other drugs. This review did not find a statistical significance among the performance of different benzodiazepines.<sup>150</sup>

Avoid prescribing benzodiazepines to patients who are dependent on alcohol before enrolling them in, or referring them to, community withdrawal. Prescribing a 'small dose of diazepam' to help patients who claim to have stopped or reduced their alcohol consumption should also be avoided. Benzodiazepines can increase alcohol cravings and relapse rates.<sup>151</sup>

#### 2.4.2.4 Baclofen and carbamazepine

Baclofen has been used to rapidly reduce symptoms of severe alcohol withdrawal syndrome. However, the evidence for recommending baclofen is insufficient to support its use in most situations.<sup>152</sup> Carbamazepine has been effective in trials, but its role is as yet unclear.<sup>153</sup> These, and several other drugs, may be useful adjuncts but cannot currently be recommended for clinical monotherapy.

## 2.5 Acute mania (bipolar disorder)

### ✓ Key points

- Benzodiazepines can be used to calm or sedate and control aggressive, overactive or disturbed behaviour in manic episodes until a mood stabiliser takes effect.

### 2.5.1 Background

Bipolar disorder is a recurrent, disabling condition. Patients experience periods of mania or hypomania, depression and mixed episodes or 'dysphoric mania' (both manic and depressive symptoms). Bipolar disorder is commonly subdivided into bipolar disorder I (at least one manic episode) and bipolar disorder II (hypomania and depression only).<sup>154</sup>

Bipolar disorder has a lifetime prevalence of up to 1.6%.<sup>154</sup>

### 2.5.2 Management of manic episodes in general practice

For acutely manic patients, referral to a specialist psychiatric service for in- or out-patient care is recommended.<sup>154</sup>

There are two components to managing acute mania with medication:<sup>154</sup>

- mood stabilisation with drugs (eg lithium, sodium valproate, carbamazepine) or one of the new second-generation antipsychotics
- adjunct therapy to control acute agitation while mood stabilisers start to take effect (about 1 week for most patients).

Adjunct therapy usually consists of an antipsychotic or benzodiazepine (or a combination). This calms or sedates the person with mania as a temporary measure, until the mood stabiliser starts to be effective.<sup>154</sup>

In most cases, the benzodiazepine or antipsychotic would be withdrawn once the acute episode has resolved, and then only the mood stabiliser continued. It is common practice to taper down and discontinue benzodiazepines within 2–3 weeks of achieving adequate symptom control in mania.<sup>154</sup>



## 2.6 Epilepsy

### ✓ Key points

- Clonazepam has been the most commonly used benzodiazepine for the long-term treatment of epilepsy.

Evidence statements	Grade
Carbamazepine, sodium valproate, lamotrigine and oxcarbazepine can all be regarded as first-line treatments for partial and secondary generalised seizures. <sup>155</sup>	A
Sodium valproate and lamotrigine are drugs of choice for primary generalised seizures and should also be prescribed if there is any doubt about the seizure type and/or syndrome classification. <sup>155</sup>	A

### 2.6.1 Background

Epilepsy affects approximately 224,000 Australians (1 in 100) and is the most common chronic brain disorder. Nearly 10% of Australians will have a seizure during their lifetime, and one-third of those will be diagnosed with epilepsy.<sup>156</sup>

### 2.6.2 Management of epilepsy in general practice

In acute epilepsy, diazepam, lorazepam and midazolam are the drugs most commonly used to control prolonged seizures.<sup>155</sup>

In chronic epilepsy, the use of benzodiazepines is now rare. They have limited usefulness in long-term management due to the rapid development of tolerance to anticonvulsant effects and the associated side effects (eg sedation and psychomotor slowing).<sup>155</sup>

Benzodiazepines are considered adjunct to standard antiepileptic drugs, and used when these have failed to achieve acceptable control.<sup>155</sup>

Benzodiazepines for seizure prophylaxis should only be used on advice from a specialist neurologist or paediatrician.

Prescription of benzodiazepines for epilepsy within Australia requires an authority prescription. Take care with monitoring and detecting problematic use.



## 3. Contraindications and precautions in special groups

### 3.1 Overview

Benzodiazepines should not be prescribed, or prescribed with extreme caution, to:

- women who are, or may be, pregnant
- patients with active SUDs, including alcohol (unless it is a part of an alcohol withdrawal program)
- patients with medical or mental health conditions that may be worsened by benzodiazepines (eg fibromyalgia, chronic fatigue syndrome, depression, bipolar disorder or impulse control disorders)
- patients being treated with opioids for chronic pain or addiction
- patients experiencing grief reactions, as benzodiazepines may suppress and prolong the grieving process.

### 3.2 Paediatric patients

Benzodiazepines are generally not recommended for use in children.

Benzodiazepines may cause aggression, anxiety, nervousness and disinhibition in children and adolescents. Routine use for anxiety disorders cannot be recommended.<sup>157</sup>

The use of benzodiazepines in the paediatric population is clinically limited.<sup>158</sup> Control of acute febrile or epileptic seizures is the primary indication. Seizures commonly occur in the paediatric populations and while most self-terminate within 5 minutes, those lasting longer may warrant medication to control the seizure and avoid status epilepticus (and neurological compromise).<sup>159</sup> Buccal or intranasal midazolam and buccal or rectal diazepam are effective for the treatment of acute seizures in children.<sup>160</sup>

Note that children may have access to benzodiazepines through their parents, their peers or potentially via the internet.

### 3.3 Women who are pregnant or breastfeeding

Benzodiazepines should be avoided during pregnancy and breastfeeding. Non-drug approaches for anxiety and insomnia are preferred.

Women who become pregnant and are already taking benzodiazepines should be tapered down to the lowest effective dose, or have it completely withdrawn. With good withdrawal management, there is no evidence that withdrawal is likely to cause problems with the pregnancy.<sup>38</sup>

As benzodiazepines are highly fat soluble, they rapidly cross the placenta. Benzodiazepines taken early in pregnancy have been linked to congenital abnormalities (eg oral clefts, pyloric stenosis and alimentary tract atresia).<sup>161</sup> This association is considered controversial, and data published in the last 10 years do not indicate an absolute contradiction to benzodiazepines in the first trimester.<sup>162</sup> However, avoiding benzodiazepines or tapering off (completely or to the lowest possible dose) is recommended.<sup>163</sup>

Benzodiazepines taken later in pregnancy (late third trimester), during labour or while breastfeeding are associated with risks to the fetus/neonate. They can cause neonatal drowsiness, respiratory depression, poor temperature regulation, poor feeding, hypotonicity ('floppy baby syndrome') and neonatal withdrawal syndrome.<sup>35,164</sup>

Neonates exposed in utero may benefit from breastfeeding to reduce neonatal withdrawal.<sup>165,166</sup>

Where a hypnotic is necessary, zolpidem has been suggested.<sup>163</sup> However, two studies have reported an association between zolpidem and an increased risk of adverse pregnancy outcomes, including small-for-gestational age, low birth weight and preterm deliveries.<sup>35</sup>

Note that women misusing benzodiazepines during pregnancy may also be using other drugs including alcohol.

## 3.4 Older patients

Patients over 60 years of age have the most significant risk of harm with benzodiazepine use (particularly if the patient has additional risk factors for cognitive or psychomotor adverse events) relating to falls, fractures and cognitive decline.<sup>50,167</sup>

Benzodiazepines are used by approximately 15% of people over 65 years of age in Australia.<sup>168</sup> Use of benzodiazepines in this age group is often chronic, despite the combination of harms associated with long-term, physiological changes with ageing (eg hepatic metabolism impairment) and the potential for multiple coexisting pathologies and drug interactions.

Older patients are more sensitive to the CNS depressant effects of psychotropic medications including benzodiazepines. This may result in confusion, night wandering, amnesia, pseudo-dementia<sup>38</sup> (refer to [1.5.1.1 Cognitive impairment](#)), ataxia, falls and fractures.

In older patients, all psychotropic medications have been associated with an increased risk of fractures. The risk increase is moderate and similar across all psychotropic medications. One meta-analysis demonstrated that the relative risk of fractures was 1.34 (95% CI=1.24–1.45) for benzodiazepines, 1.60 (95% CI=1.38–1.86) for antidepressants, 1.59 (95% CI=1.27–1.98) for antipsychotics and 1.38 (95% CI=1.15–1.66) for opioids.<sup>169</sup>

Older people presenting with anxiety symptoms should be treated initially with antidepressants and psychological therapies, rather than benzodiazepines.<sup>170</sup>

Sedative use for insomnia has shown statistically significant improvements in sleep, but the magnitude of effect is small and the benefits of these drugs may not justify the increased risk.<sup>167</sup> Clinical judgement is required.

Zolpidem and other Z drugs have become preferred drugs to manage insomnia. They are widely used among older adults because of perceived improved safety profiles compared with traditional benzodiazepines. However, accumulating data in recent years in patients over 65 years of age suggest possible safety concerns of these medications (zolpidem specifically) including effects on balance and memory and increased fracture risk. Until better studies or pharmacovigilance data become available to guide patient selection for prescribing zolpidem and other Z drugs, judicious use of these hypnotic agents in older adults is warranted.<sup>171</sup>

Reduction in the use of benzodiazepines in the elderly is a worthwhile goal if this can be achieved without psychotropic substitution. Older patients require planned interventions including CBT and stepped-dose reduction to reduce long-term benzodiazepine prescription.

### 3.4.1 Patients living in residential aged care facilities

Prescribing for patients living in residential aged care facilities (RACFs) (and other residential facilities) carries all of the risks associated with benzodiazepine use in older patients and presents further special difficulties.

Accreditation of RACFs has resulted in a heightened awareness of the facility's responsibilities for quality use of medicines.

Medication may occasionally be required to control anxiety, agitation or other disturbed behaviours. Staff should be knowledgeable in the appropriate management of challenging behaviours. Where staff have received education in geriatric care, and where the organisational culture is supportive, there is less use of benzodiazepines.<sup>170</sup>

In a study of sleep quality in patients using benzodiazepines in RACFs, patients who were long-term users slept more poorly than those who were non-users. The effects were worse in patients taking long-acting benzodiazepines.<sup>172</sup> Although patients, doctors, nursing staff and families often fear the consequences of benzodiazepine withdrawal in older patients, there is no evidence that patients experience an 'unmasking' of depression or anxiety.<sup>173</sup>

Successful reduction in the rates of benzodiazepine use in RACF patients results in benefits (eg increased mobility and alertness, reduced incontinence and improved wellbeing).<sup>174</sup> Discontinuation of benzodiazepines can often be achieved gradually in RACFs, providing patient, family and nursing staff are cooperative.<sup>175</sup>

Benzodiazepines have been associated with increased fracture risk in patients living in RACFs. However, a reduction in benzodiazepine use may not lead to a decrease in fracture risk if substitution medications are used.<sup>176</sup> Reduction in benzodiazepine use for RACF patients is worthwhile if it can be achieved without psychotropic drug substitution.

### 3.5 Patients with chronic non-malignant pain

Use of multiple psychoactive medications (including benzodiazepines) is common in people who have chronic non-malignant pain (CNMP). Where available, it is advisable that a specialist pain or addiction service becomes involved in the care of these patients.<sup>177</sup>

The relationship between pain, mental illness, SUD and dependence, and the social environment are complex. A range of addictive drugs has been misused in the context of CNMP including alcohol, benzodiazepines, cannabis, opioids and stimulants. Estimates of dependence (on any drug including alcohol) among people with chronic pain varies. In patients on long-term opioids, prevalence of DSM-5 opioid-use disorder may be as high as 26%.<sup>178</sup>

Benzodiazepines have little place in the management of chronic musculoskeletal pain. There is sparse evidence that these are clinically effective as muscle relaxants. The decision to use benzodiazepines in the context of multiple sclerosis or muscle disorders should be taken on a case-by-case basis with specialist consultation.

There is a strong association between sleep disturbance and CNMP. Evidence suggests that pain and sleep exist in a complex relationship in which pain causes sleep disturbance and sleep disturbance intensifies pain. This association can impair a patient's daily function and decrease quality of life.<sup>179</sup> Assessment of a patient's sleep disturbance involves review of the contributing impacts of lifestyle, comorbid anxiety or depression, and uncontrolled pain to focus management on an individualised basis.

Benzodiazepines present additional risk for someone being prescribed opioids in terms of overdose (fatal and non-fatal) and psychomotor impairment. Driving presents a particular risk.

CBT can be useful in addressing emergent anxiety symptoms. Simple reassurance and attention to sleep hygiene can be effective with managing the emergent sleep disturbance.

### 3.6 People with comorbidity – Mental illness and problematic drug use

For the purposes of this guide, comorbidity will refer to situations where people have problems related both to their use of substances (from hazardous through to harmful use and/or dependence) and to their mental health (from problematic symptoms through to highly prevalent conditions such as depression and anxiety, and to the low-prevalence disorders such as psychosis).<sup>177</sup>

While it is common to refer to a patient's psychiatric disorder or SUD as primary or secondary, this may have limited clinical use. It is important to establish whether substance use may be contributing to the patient's psychiatric problems.<sup>177</sup>

Symptoms of psychiatric disorders (eg depression, anxiety and psychosis) in patients misusing drugs and/or alcohol are the rule rather than the exception. In addition, these psychiatric disorders increase the risk of harmful substance use and patients may be physically unwell. These patients are often the most challenging to engage and treat, and their prognosis is frequently poor.<sup>177</sup>

The number of placebo-controlled trials is small, and there remains little evidence to guide treatment.<sup>177</sup> Available evidence suggests that a substantial proportion of patients with a comorbid SUD mental illness who are treated with benzodiazepines will develop some form of dependence. Therefore, benzodiazepines should largely be avoided, except in the context of withdrawal.<sup>180</sup>

Patients with personality disorders have a higher risk of dependence and dose escalation, hence benzodiazepines should be avoided in this group.

## 3.7 Patients who misuse alcohol and/or other drugs (prescribed and illicit)

Patients who have problematic drug use belong to a complex group at high risk of adverse events. A common drug combination that should be noted is alcohol and benzodiazepines.<sup>180</sup> When benzodiazepines are combined with other CNS depressants (eg alcohol, opioids), patients are at risk of respiratory depression, heavy sedation, coma and death. It has been reported that the use of antidepressant drugs in combination with benzodiazepines may also increase the risk of overdose, especially in the case of older TCAs.<sup>181</sup> Alcohol and benzodiazepines can produce cross tolerance, and regular use of both can make withdrawal more severe and/or protracted.<sup>180</sup>

Apart from the risk of overdose, harms associated with polydrug use (particularly among people who inject drugs) include a higher rate of infectious and metabolic complications, as well as psychiatric, social and forensic consequences, with an increasing cost to society.<sup>182,183</sup> People who are participating in medication-assisted opioid dependence treatment, and who take benzodiazepines regularly or intermittently, tend to do very poorly, with a higher risk of adverse outcomes.<sup>21</sup>

There is little evidence to guide practitioners in the management of this often difficult-to-treat population. However, when treating polydrug users, it is recommended not to initiate prescription of benzodiazepines. For polydrug users already taking them, it is recommended to reduce and cease prescription of benzodiazepines in a supervised manner.<sup>153</sup>

Therapeutic monitoring and prescribing should only occur if GPs have extensive experience in addiction medicine, or in conjunction with specialist supervision. When working with known polydrug users, it is essential to collaborate with local drug and alcohol services, and to provide clear guidelines on the accepted harm-minimisation strategies. Clear boundaries are crucial.

Maintenance benzodiazepine prescribing in illicit drug users cannot be recommended on the basis of existing evidence. Although it may reduce illicit benzodiazepine use in some patients,<sup>153</sup> it may not be in the best interests of the patient or the wider community. The very rare exception would be under explicit agreement concerning specified short-term indications (such as outpatient alcohol withdrawal) as advised by a drug and addiction medicine specialist with daily, or at most weekly, dosing at a nominated pharmacy and monitoring with urinary drug test. Drug screens may be useful to monitor other benzodiazepines and drug use, especially in this population.

## 3.8 Prescribing to patients who drive

Summarising the extensive literature on benzodiazepines and driving, the risk of accident increases proportionally to dose. However, there is no dose without increased risk – including stable, longer term dosing. Risk is highest at initiation, with long-acting benzodiazepines and when benzodiazepines are taken with other sedatives, especially alcohol.

Benzodiazepines have especially been shown to impair vision, attention, information processing, memory, motor coordination and combined-skill tasks. All drivers should be advised of increased crash risk when taking benzodiazepines. Patients who experience any degree of sedation should be cautioned not to drive.

According to Austroads, a person is not fit to hold an unconditional licence if they have an alcohol disorder or other SUD (eg substance dependence, heavy frequent alcohol or other substance use) that is likely to impair safe driving.<sup>184</sup>

The state or territory driver licensing authority may consider a conditional licence. This is subject to periodic review, taking into account the nature of the driving task and information provided by the treating doctor as to whether the following criteria are met:<sup>184</sup>

- the person is involved in a treatment program and has been in remission\* for at least 1 month
- there is an absence of cognitive impairments relevant to driving
- there is absence of 'end-organ effects' that impact on driving.

\* Remission is attained when there is abstinence from the use of impairing substance(s) or where substance use has reduced in frequency to the point where it is unlikely to cause impairment. Remission may be confirmed by biological monitoring for the presence of drugs.

Some patients with SUD will continue to drive after being warned not to do so. If GPs are aware that a patient continues to drive in a dangerous way, they should:

- more strongly recommend the patient stops
- advise the patient that the GP has an obligation to report behaviours that are dangerous to the patient and others
- consider reporting dangerous behaviour to state or territory licensing authorities.

This is a difficult situation as it will damage the doctor–patient relationship. However, in some cases the risk of damaging the relationship is outweighed by the risk of the patient (and others) being hurt or killed. If in doubt, contact your medical indemnity provider.

## 4. *Duration of benzodiazepine therapy*

### 4.1 Optimal duration of therapy

Guidelines and formularies typically give durations of 1–4 weeks for benzodiazepine therapy, depending on the indication. Short-term therapy is generally advised to reduce the risk of dependence and withdrawal, as well as other potential harm such as cognitive impairment. Short-term therapy does not reduce the risk of accidents or falls.

Dependence is recognised as a risk in some patients who receive treatment for longer than 1 month, and health professionals should be conscious of this when considering the relative benefits and risks of treatment.<sup>25</sup>

The 1–4 week time frame is not based on risk–benefit data; rather that no substantive placebo-controlled trials of hypnotics have been carried out for longer than a few weeks. The available evidence does not suggest there is an unfavourable risk–benefit transition at 3–4 weeks for any agent.<sup>101</sup>

Patients who are prescribed benzodiazepines for problems relating to anxiety or sleep usually do not escalate their doses even over a lengthy period of use.<sup>185</sup> A 2013 study found most patients use benzodiazepines according to guidelines, and only 0.9% ended up as excessive users after 3 years.<sup>76</sup> Excessive use occurred mostly in individuals with alcohol and drug histories.

Lacking the means to determine the optimal duration of therapy, a rational approach is to allow the duration of treatment to be determined by a series of risk–benefit decisions and shared decision making, with periodic trials of tapering and discontinuing medication to determine whether continued therapy is indicated.<sup>101,186</sup> This approach provides an ‘exit strategy’ and thereby addresses concerns that once started, hypnotic therapy could be unending.<sup>101</sup>

Clinical discipline and accountable prescribing are essential when considering long-term benzodiazepine therapy.

### 4.2 Prescribing benzodiazepines for longer than 4 weeks

While the optimum duration of therapy is not clear from the evidence, there are very few specific indications for the chronic use of benzodiazepines. The decision to prescribe benzodiazepines longer term should be uncommon and made with caution. Assume that all patients are at risk of dependence.

Benzodiazepines may be used for longer than 4 weeks in selected cases. Patients who are terminally ill or severely handicapped, where it is clear that the benefits outweigh the risks and side effects, or where a detailed individual assessment has been made with a patient and their family or carers.

Benzodiazepines may also be indicated in certain neurological disorders (eg stiff person syndrome) and in neuromuscular conditions where spasticity is problematic. Increasingly, benzodiazepines are being used off-label for indications (eg drug-induced movement disorders, restless legs syndrome, acute psychotic agitation, terminal agitation, nausea and vomiting, intractable pruritus and intractable hiccup).<sup>187</sup>

Recommendations supporting the long-term use of benzodiazepines for any mental illness or chronic sleep disorder come from evidence limited to shorter time frames. Hence, longer duration of prescribing should occur in conjunction with heightened clinical surveillance.

The principles of universal precautions apply. Ensure a clear diagnosis is formed, comprehensive assessment is undertaken, clear treatment plan is discussed with the patient and information is provided to the patient to enable informed consent. The negotiated treatment plan will have clearly defined time limit and goals of treatment.

## 4.3 Rationale for long-term benzodiazepine prescribing

Benzodiazepines are generally regarded by clinical practice guidelines as a short-term therapeutic option. Long-term use, beyond 4 weeks, is not generally advocated by clinical practice guidelines, hence long-term therapy should be uncommon and made with caution.

Prescribing benzodiazepines, like other aspects of clinical practice, should be based on thoughtful consideration of the likely risks and benefits, and the risks and benefits of alternative interventions. This decision should be made in conjunction with the patient and their carers, where appropriate.<sup>100</sup> Benzodiazepines may be prescribed longer term where:

- patients do not respond to, or cannot tolerate, numerous first-line therapies<sup>130,188</sup>
- use is intermittent
- specialists make a recommendation and are able to provide a rationale of therapy.

For some patients, benzodiazepine alternatives fail, have limited benefit, are unavailable or clinically inappropriate. If there is no history of drug dependence, positive indicative 'lifestyle' factors are present and a clinical decision for benzodiazepine treatment can be justified, then long-term therapy should not necessarily be regarded as a deviation from good clinical practice.<sup>25</sup> Supervised benzodiazepine treatment may remain an acceptable long-term therapeutic option for some patients.

## 4.4 Management of long-term benzodiazepine prescriptions

Many patients are able to safely take short courses of benzodiazepines, or to use them intermittently longer term, on a 'as required' basis and to stop them when no longer needed.<sup>25,113</sup>

In a situation where the clinical decision is that the ongoing use of a benzodiazepine is the most appropriate management, this requires ongoing monitoring of health outcomes and continuing vigilance for potential hazards throughout treatment.<sup>25</sup>

The responsible specialist or GP should clearly outline a prescribing plan that should be documented in the patients' notes or management plan.

The prescribing plan may include instructions that:

- regular prescription reviews take place
- no repeat prescriptions will be made without face-to-face contact
- all prescriptions will be made by one doctor within a single practice
- one pharmacy will dispense all medication.

Benzodiazepine prescriptions should be at the lowest effective dose and given intermittently, with regular reviews of the treatment plans and regular attempts at withdrawal.

At the time of benzodiazepine prescription renewal or medication review, GPs should continue to discuss the risks of long-term benzodiazepines and the benefits of discontinuation (eg cognition, mood, sleep and energy level) and advise the patient to reduce or discontinue the benzodiazepines if there are issues. GPs should document this communication.

Patients should be monitored closely for problematic use or any [therapeutic dose dependence behaviour](#). Any escalation of dose or inappropriate use would lead to a complete review of prescribing and attempted withdrawal of benzodiazepine, along with a review of alternative therapy.

Refer to [Resource E.2](#) for an example of a prescription plan/agreement.

All GPs should develop strategies to manage inappropriate requests for benzodiazepines.



## 5. Discontinuing benzodiazepines

### 5.1 Discontinuing after short-term use

For patients on less than 4 weeks of benzodiazepine therapy, it should be possible to stop medication without tapering. Caution should be exercised with patients who are at risk of seizures.

### 5.2 Discontinuing after longer term use – Withdrawal

Withdrawal is possible for most patients on longer term benzodiazepines, although the process of reduction may be difficult and lengthy. The withdrawal process is aided by a good therapeutic alliance between the GP and patient, with specialist support where needed. Discontinuation is usually beneficial as it is followed by improved psychomotor and cognitive functioning, particularly in the elderly.<sup>189</sup> Up to 15% of patients who experience withdrawal will go on to have protracted symptoms lasting months to years.<sup>2</sup>

Withdrawal strategies will vary with the type of dependence (therapeutic dose, prescribed high dose, recreational high dose or polydrug). Withdrawal symptoms are highly variable and each patient will need tailored withdrawal management that will also address any underlying problems. Withdrawal symptoms may appear in 1–2 days for agents with shorter half-lives, but may not appear until 3–7 days for agents with longer half-lives.

**Table 4. Acute withdrawal symptoms**

Anxiety symptoms		Distorted perceptions	Major incidents Mainly when high doses are stopped abruptly
Psychological	Physical		
<ul style="list-style-type: none"> <li>• Anxiety</li> <li>• Panic attacks</li> <li>• Insomnia</li> <li>• Poor memory</li> <li>• Depression</li> <li>• Paranoia</li> <li>• Intrusive memories</li> <li>• Cravings</li> <li>• Nightmares</li> <li>• Excitability</li> <li>• Agoraphobia</li> <li>• Social phobia</li> <li>• Obsessions</li> <li>• Rage, aggression</li> <li>• Irritability</li> </ul>	<ul style="list-style-type: none"> <li>• Agitation</li> <li>• Tremor</li> <li>• Headache</li> <li>• Weakness</li> <li>• Dizziness</li> <li>• Nausea</li> <li>• Vomiting</li> <li>• Diarrhoea</li> <li>• Constipation</li> <li>• Palpitations</li> <li>• Rashes</li> <li>• Tingling, numbness, altered sensation</li> <li>• Fatigue</li> <li>• Flu-like symptoms</li> </ul>	<ul style="list-style-type: none"> <li>• Hypersensitivity to sound, light, touch, taste</li> <li>• Abnormal body sensation eg itching, pain, stiffness, blurred vision, paraesthesia, muscle twitching, tinnitus, burning sensations</li> <li>• Feeling self or world to be abnormal (depersonalisation or derealisation)</li> </ul>	<ul style="list-style-type: none"> <li>• Fits (1–2% of patients)</li> <li>• Delirium (rare)</li> <li>• Transient hallucinations (visual, tactile, auditory) or illusions (rare)</li> <li>• Psychosis (very rare)</li> </ul>

Reproduced with permission from Ford C, Law F. Guidance for the use and reduction of misuse of benzodiazepine prescribing and other hypnotics and anxiolytics in general practice. 2014.<sup>38</sup>



Protracted benzodiazepine withdrawal symptoms include:<sup>30</sup>

- anxiety
- depression
- diarrhoea, constipation, bloating
- insomnia
- irritability
- muscle aches
- poor concentration and memory
- restlessness
- less commonly, perceptual disturbances and panic attacks
- occasionally, seizures and symptoms of psychosis.

The symptoms and duration of benzodiazepine withdrawal can vary, mostly impacted by the level of dose reduction. Although, other contributing factors can include a history of polydrug dependence, seizures, anxiety, depression or trauma, or when the total daily dose is not clear (due to doctor shopping or illegal purchase).

### 5.2.1 Patients taking ‘therapeutic doses’

For patients who have early/mild dependence, minimal interventions such as advisory letters, other information provision or GP advice should be offered. Where dependence is established, gradual dose reduction of prescribed benzodiazepine is recommended (both grade A recommendations from the British Association for Psychopharmacology).<sup>153</sup>

Switching from a short half-life benzodiazepine to a long half-life benzodiazepine before gradual taper should be reserved for patients having problematic withdrawal symptoms on reduction (grade D recommendation from the British Association for Psychopharmacology).<sup>153</sup>

Additional psychological therapies increase the effectiveness of gradual dose reduction, particularly in patients with insomnia and panic disorder. Consideration should be given to targeted use of these interventions (grade B recommendation from the British Association for Psychopharmacology).<sup>153</sup>

### 5.2.2 Patient taking high doses of benzodiazepines or who are users of illicit drugs (polydrug users)

So called ‘harm-reduction dosing’ or maintenance prescribing of benzodiazepines for patients using polydrugs cannot be recommended on the basis of existing evidence, as prescribing benzodiazepines does not appear to prevent use of other drugs.<sup>153</sup> There is some evidence that maintenance dosing of benzodiazepines may reduce high-dose problematic benzodiazepine use in some patients (grade D recommendation from the British Association for Psychopharmacology).<sup>153</sup>

## 5.3 General principles for the management of withdrawal of benzodiazepines

If dependence on benzodiazepines has become established, it is often difficult to treat and can become a long-term, distressing problem.<sup>25</sup> All patients with dependence should be encouraged to discontinue the drug and offered a detoxification program at regular intervals. For some patients, discontinuation will be difficult, but the effort should be made. For other patients, a reduction in dose, rather than discontinuation, will be the first goal.

Evidence-based recommendations for general practice management of benzodiazepine withdrawal are difficult due to a lack of data. The following are general principles:

- Review the patients' prescription records and discuss the situation to those receiving long-term benzodiazepines.
- Send patients letters suggesting methods of tapering off benzodiazepines (this may be enough to motivate them to withdraw).
- Teach patients ways to deal with anxiety and insomnia (either as primary conditions or due to withdrawal).
- Acknowledge that withdrawing from benzodiazepines can be stressful.
- Encourage family and friends to provide encouragement and practical help during withdrawal.
- Refer patients to appropriate services (eg psychologist or support groups). Only refer to drug or alcohol dependence services if the service has shown specific interest in benzodiazepine dependence or the patient also has a drug or alcohol problem.
- Advise patients to make changes in lifestyle such as regular exercise.
- Advise patients to avoid alcohol.
- Advise patients to avoid mild stimulants (eg coffee and chocolate [theobromine]) as these can cause anxiety, panic and insomnia.
- Postpone advice on smoking cessation until after the benzodiazepine has been withdrawn.<sup>189</sup>

Benzodiazepine reduction requires a team approach with regular communication between the prescriber and other practitioners involved in the patient's care (eg pharmacist, counsellor, psychiatrist, addiction services).

### 5.3.1 Resources

Specialist services such as Reconnexion, [www.reconnexion.org.au](http://www.reconnexion.org.au), offer free telephone support (1300 273 266) to help with benzodiazepine withdrawal.

## 5.4 Tapering dosing

The clearest strategy for withdrawing benzodiazepines in primary care is to taper the medication.<sup>189</sup>

Slow discontinuation of benzodiazepines is recommended to avoid withdrawal symptoms (eg rebound anxiety, agitation, insomnia or seizures) particularly when use exceeds 8 weeks. However, clear evidence for the optimal rate of tapering is lacking. The British National Formulary recommends a minimum of 6 weeks,<sup>190</sup> while Lader recommends a maximum of 6 months.<sup>189</sup> The exact rate of reduction should be individualised according to the drug, dose and duration of treatment (refer to *Table 5*).

Two-thirds of patients can achieve cessation with gradual reduction of dose alone. Others need additional psychological therapies and a limited number of patients benefit from additional pharmacotherapy.<sup>191</sup> CBT performed in a single, extended (20-minute) consultation with a GP, with a handout, has been shown to increase non-use at 1 year from 15% to 45%.<sup>192</sup> A systematic review comparing routine care to brief interventions, gradual dose reduction and psychological interventions found all interventions increased benzodiazepine discontinuation over routine care, with gradual dose reduction plus psychological interventions the most effective.<sup>191</sup>

All patients on a reduction regime must obtain prescriptions from one prescriber and through one pharmacy, where time-limited dispensing may be required (eg once or twice a week at a specified time). Plans should be in place to cover absences of the usual prescribing doctor from the practice. Consider working closely with the patient's pharmacist with staged supply or supervised dosing to assist the patient with dose reduction and cessation, if they are unable to manage this themselves.

**Table 5. Recommendations for tapering benzodiazepines**

Duration of use	Recommended taper length	Comments
<6 to 8 weeks	Taper may not be required	Depending on clinical judgment and patient stability/preference, consider implementing a taper, particularly if using a high-dose benzodiazepine or an agent with a short or intermediate half-life, such as alprazolam or triazolam
8 weeks to 6 months	Slowly over 2–3 weeks	Go slower during latter half of taper. Tapering will reduce, not eliminate, withdrawal symptoms. Patients should avoid alcohol and stimulants during benzodiazepine withdrawal
6 months to 1 year	Slowly over 4–8 weeks	
>1 year	Slowly over 2–4 months	

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A common first step in withdrawal is to substitute diazepam for the benzodiazepine being taken.<sup>189</sup> The slower elimination of diazepam creates a smoother taper in blood level.<sup>102</sup>

Refer to [Resource D.2B](#) for withdrawal protocols.

## 5.5 Additional pharmacotherapies

Pharmacotherapy interventions have limited use in benzodiazepine withdrawal. Generally, other drugs are used to address symptoms rather than substitute for benzodiazepines.

**Carbamazepine** – Carbamazepine has shown some usefulness, however, there is not enough evidence to recommend its use.<sup>193</sup>

**Antidepressants** – There is limited evidence that antidepressants help in benzodiazepine withdrawal, unless depression (or anxiety disorders/panic disorders) are present or emerge during withdrawal.<sup>191,193</sup>

**Melatonin** – Melatonin may help benzodiazepine reduction in older people with insomnia.<sup>194</sup>

## 5.6 Should every patient be withdrawn?

There may be a small number of patients whose quality of life improves with the stable use of benzodiazepines. This may justify long-term therapy. The decision to continue long-term benzodiazepine treatment needs to be clearly documented. The decision may also involve a second opinion by a specialist in an area relevant to the patient's needs. These patients still require regular, ongoing review and re-assessment of the risks and benefits of benzodiazepine use.

Attempts at withdrawal are more likely to succeed if the patient is able to contemplate the ultimate goal of cessation, and the doctor and patient are able to work together in a productive therapeutic relationship to achieve this.

Some patients struggle to reduce and cease benzodiazepine use. However, this group can often reduce their daily dose markedly and this is accompanied by a decrease in risk and side effects. They may continue on low-dose benzodiazepines (eg 2–5 mg diazepam daily) for an extended period. Continued regular review may assist in the majority who will successfully cease benzodiazepines in the longer term. This decision should be made on a case-by-case basis.

For patients who have complex, multiple morbidities, GPs should seek advice from mental health and addiction specialists, as well as other relevant specialists (eg neurologists) to assist with development of the best plan to assist the patient.

## Resources

### Resource A. Examples of responses to patient requests for benzodiazepines

#### Purpose

To provide GPs with examples of responses to specific inappropriate and maladaptive patient requests for benzodiazepines.

#### Reducing the incidence of requests

Before the actual consult, there are a number of things that practices can do to decrease the incidence of inappropriate and maladaptive requests for medications:

- When new patients make an appointment, ask the receptionist to give the following information, 'The doctor, when seeing you for the first time, will do a detailed assessment and may need additional information from your previous doctors prior to making any treatment decisions, including prescribing medicines'.
- Inform patients of practice-wide policies regarding prescribing, including reviewing prescribing for existing patients. This may involve a sign in the waiting room.
- Develop clear plans for all staff on how to respond to requests for benzodiazepines using scripted response.

#### Example responses to inappropriate requests for medications

Alprazolam and temazepam are frequently used in the scenarios below, but may be substituted for other benzodiazepines. Some responses are specific for alprazolam or temazepam as both medications have undergone changes to their Pharmaceutical Benefits Scheme (PBS) listing and Therapeutic Goods Administration (TGA) scheduling.

Table A.1 gives some examples of responses to patient requests and includes a rationale for the response. Note that all responses are examples only and should be adapted to individual clinical circumstances.

**Table A.1. Sample responses to inappropriate requests for medications**

Patient request	Sample responses	Comments
I need something to help me to sleep.	Sometimes poor sleep indicates more serious underlying problems. Can you tell me more about your sleep issues? or What have you tried to help you sleep? or Sleeping tablets have been used in the past to help people with sleeping problems. However, we now know these can have side effects and can be risky so we don't always prescribe them.	You need to make a detailed assessment and diagnose the condition rather than treating a symptom. Don't assume that if someone asks you to assist them with sleep that they are looking for sleeping tablets. Offer a hierarchy of alternatives, including sleep hygiene and cognitive behaviour therapy (CBT). Give the patient written information.
Ok, you won't give me alprazolam, how about some Serepax or Rivotril?	This is clearly an inappropriate request. We don't just prescribe the medications people ask for. My job as a professional is to make a diagnosis and do what I think is best for my patients.	You can only legally prescribe drugs for the medical treatment of a patient under your care, and must take all reasonable steps to ensure a therapeutic need exists. You can't legally prescribe drugs merely to support the drug dependence of a person.

**Table A.1. Sample responses to inappropriate requests for medications**

Patient request	Sample responses	Comments
No, I've tried all this. The only thing that works for me is a sleeping pill. I want medication.	<p>Have you used medication before? Who prescribed it to you?</p> <p>or</p> <p>I am concerned about that, as a request like this can sometimes be a sign of dependence on the medication. Can we talk about how much you are taking?</p> <p>or</p> <p>Sleeping pills are not the first choice in treating insomnia. These come with risks and limitations.</p> <p>or</p> <p>Sleeping medicines only provide a short-term benefit. If you're having trouble sleeping, it may be because you've become dependent on them. Using non-drug methods has been shown to have a better long-term benefit.</p> <p>or</p> <p>It's my/our practice's policy not to prescribe sleeping tablets.</p> <p>or</p> <p>I am concerned that providing ongoing medication is not good for your overall health. Can we trial a graduated withdrawal program, or can I refer you to a specialist?</p> <p>or</p> <p>Your sleep problems can be a result of your drug use. Giving tablets is just treating a symptom. I'd like to get to the cause and help you with your drug problem.</p> <p>or</p> <p>Thank you for coming to see me. It was nice to meet you. I am unable to prescribe the medications that you requested today because I don't believe it is in your best interest and that's not the way we now practice medicine. I have mentioned alternative methods of exploring and treating your problem. Please give my advice some further thought and if you decide you would like to avail yourself of the treatment that I am able to offer you, I look forward to seeing you again. In that case, please make another appointment.</p>	<p>A patient asking for medication (especially specific medication) is a possible red flag that the patient is drug seeking.</p> <p>Ask the patient why they have not returned to the doctor who previously prescribed medication to them. Stress the advantages of continuity of care.</p> <p>Ask the patient about what sleep hygiene practices they have tried and gauge their knowledge. Provide further information about sleep hygiene as needed.</p> <p>Educate the patient about the problems associated with sleeping tablets, including abnormal sleep often with early awakening, as well as the risks.</p> <p>Play a broken record on this advice. Remember, patients may no longer derive any relief from the medication, but they feel very much worse when they stop it.</p> <p>If the patient does not accept your advice and continues to pressure you, one last resort option is to stand up from your chair while maintaining eye contact with the patient, walk to and open the door of your consulting room and say something like, 'Thank you for coming to see me ... (or) It was nice to meet you ... I am unable to prescribe the medications that you request today because I don't believe it is in your best interest .... if you decide ... '</p>
Doctor, I need a script for my panic attacks.	<p>Let's first talk about what you have been experiencing to ensure we have the right diagnosis. Then we'll talk about which treatment is most likely to help you.</p> <p>Medication is not necessarily the first option in treating this condition and in some cases it can actually be a cause of anxiety.</p>	<p>Panic attacks are a symptom, not a condition, and their cause needs to be diagnosed.</p>

**Table A.1. Sample responses to inappropriate requests for medications**

Patient request	Sample responses	Comments
I want/need a prescription for alprazolam (or other benzodiazepines).	<p>We don't prescribe this medication(s). Let's talk about how I can help you with your sleep problem without drugs.</p> <p>or</p> <p>The rules around these medications have changed due to the range of harms they were causing.</p> <p>or</p> <p>I'm sorry, it's my/our practice policy not to prescribe alprazolam.</p> <p>or</p> <p>I don't prescribe these medications. But I'd like to know more about why you are on these medications, and the best way to manage this. Can we talk about how you came to be on these tablets?</p> <p>or</p> <p>I am concerned about that. Sometimes a request of this nature is a sign that someone has become dependent on the medication. Can we talk about how much you are using?</p>	<p>Provide sleep hygiene leaflet and CBT information.</p> <p>Alprazolam has been rescheduled as Schedule 8 (S8) drug.</p>
Why don't you prescribe sleeping tablets?	<p>We prescribed them in the past, but we have generally reduced their use (to very specific circumstances).</p> <p>or</p> <p>We now realise they only provide short-term benefits and can lead people to adopt unhealthy and unsafe ways of dealing with their sleep and other life problems.</p> <p>or</p> <p>The health department has warned us not to prescribe some benzodiazepines as they are causing serious problems.</p> <p>If really being pushed inappropriately:</p> <p>I am sorry, you are asking me to do something which I consider to be inappropriate or unsafe.</p> <p>While I can understand your situation, I cannot prescribe outside legal frameworks or if I consider that the medication will not help.</p>	<p>It is preferable that you openly and honestly communicate your true clinical concerns about the medication requested; advising the patient of the time limited 'benefit' and the serious risks. Emphasise your duty of care to 'first do no harm' and help.</p> <p>If you do not feel confident or able to have this frank discussion with the patient at this time, you may alternatively provide literature that explains this clinical perspective. Some clinicians find it helpful to provide a letter jointly signed by an authoritative source ('borrowed protection*'). This may sometimes be necessary when a patient is demonstrating apparent drug-seeking behaviour and persisting in their pressure on you to prescribe inappropriately, especially if they are asking you to do something that is medically unsound or even unethical. This response can offload the pressure being placed on you and deflect it back onto the patient.</p>
<p>(In a patient with substance use disorder [SUD])</p> <p>But the tablets/capsules have helped me cut down my morphine use.</p>	<p>This is a serious problem and benzodiazepines have never been shown to help.</p> <p>If you have a morphine problem, you need proper treatment. I think you need the best help you can get. I can treat you for morphine dependence with a more effective treatment, or, if after further assessment, I think you need specialised treatment, I can refer you for specialist help.</p>	<p>There is no evidence that prescribing benzodiazepines helps heroin or morphine users control their opioid use. On the contrary, these drugs are commonly used to supplement, boost or counteract the effects of other unsanctioned drug use.</p> <p>There is ample evidence that benzodiazepine use by opioid users causes harm.</p>

**Table A.1. Sample responses to inappropriate requests for medications**

Patient request	Sample responses	Comments
But Dr X prescribes them (Dr X being someone in your practice or one nearby).	<p>That's Dr X's decision, but the other doctors in this practice don't prescribe them.</p> <p>or</p> <p>That's Dr X's decision, but other doctors in this practice insist on continual monitoring of patients they prescribe this medication.</p> <p>or</p> <p>That's Dr X's decision, but other doctors in this practice have very strict prescribing criteria.</p> <p>or</p> <p>If that doctor prescribed it for you before, it may be best for you to go back to him/her. They know your history better than I do, and it's best to continue with the one doctor</p>	<p>Discuss this issue with Dr X. Develop a practice policy (or local area policy) if your ability to handle requests for drugs is compromised.</p> <p>Dr X can contact the Clinical Director of the <a href="#">Alcohol and Drug Services</a> for advice about appropriate prescribing of benzodiazepine medications.</p> <p>Ask the patient why they have not returned to the doctor who previously prescribed the medication. Stress the advantages of continuity of care.</p>
Why don't you prescribe alprazolam?	<p>I am sorry, it's my/our practice policy not to prescribe alprazolam.</p> <p>or</p> <p>Xanax, one of the brands of alprazolam, has been taken off the market in Australia and there have been restrictions placed on this medication because of concerns on safety. Many people have suffered significant side effects from this drug and there have been a number of deaths.</p>	<p>Refer to the guide on prescribing S8 opioids and drugs of dependence.</p> <p>Remember that alprazolam can only be prescribed as a PBS benefit on an Authority prescription for one indication, 'Panic disorder where other treatments have failed or are inappropriate'. Other anxiety disorders are not included in that indication.</p>
If I don't get alprazolam I'll be desperate. I'll have to go and <prostitute myself, do an armed hold-up, go back to using drugs>.	<p>That'll be completely your decision, and not something I can support. However, I can help you with your drug problem and sleeping/anxiety problem without the need for alprazolam.</p> <p>If the patient threatens to harm you or your staff:</p> <p>This practice takes these sorts of threats seriously and has serious consequences. Are you sure about what you just said?</p> <p>or</p> <p>Activate practice duress alarms or processes.</p> <p>or</p> <p>I do not believe it is safe or appropriate to prescribe the medication you are asking me to prescribe under these conditions.</p> <p>or</p> <p>This practice takes these sort of threats seriously. I am sorry, I cannot supply the services that are necessary for your care. I cannot continue with this consultation, thank you.</p>	<p>It is not possible to establish or maintain a genuinely therapeutic relationship<sup>†</sup> with any patient who uses such emotional manipulation to influence your clinical decision making.</p> <p>Continue to offer the patient help. There is no need to accept responsibility for another's behaviour or threat. Be very clear and firm, though empathetic, in your responses.</p> <p>You may elect to call the police if you consider the threat to be a serious one. You can call staff at your local drug of dependence unit to notify them of the events and your clinical actions. They will provide you with advice and support.</p>



**Table A.1. Sample responses to inappropriate requests for medications**

Patient request	Sample responses	Comments
<p>(In a patient with [SUD])</p> <p>I'm trying to get off drugs and I need some help with sleep.</p>	<p>If you've got a problem with drug dependence, there's a very significant, and proven, risk of you becoming dependent on other drugs too. Have you seen a specialist about this lately?</p> <p>or</p> <p>I want to help you get off drugs, but it would be a breach of my duty of care to you to prescribe this medication.</p> <p>I wouldn't be doing the right thing by you if I prescribe this medication.</p> <p>Sleeping drugs cause their own problems, and can make things worse rather than better.</p> <p>You will have some sleep problems when you are withdrawing from opioid medications like morphine, but this will improve with time as your body recovers from the effects of this medication. What you tell yourself, your self-talk, is very important during this time. When you experience difficulties settling off to sleep, reframe the situation by reminding yourself that these symptoms are a result of your body repairing itself, like the itch you experience when a sore is healing. Remind yourself these are 'good' symptoms rather than 'bad' or sinister ones.</p> <p>Your sleep problem is a common side effect of using sedative drugs like morphine, sleeping tablets or alcohol – it's due to a rebound effect resulting in increased alertness after a period of sedation. It's much better to treat the cause rather than the symptom.</p> <p>You're going to have this sleep problem as long as you continue using these medications or drinking. I can help you (or refer you for help) with your drug problem if you like.</p> <p>If you are unable to sleep, you need to remain positive. Tell yourself: 'If I am unable to sleep tonight, I am not going to let it worry me because it won't do me any serious harm. I will just get up and read or do something else that relaxes me'.</p>	<p>There is no evidence that prescribing benzodiazepines for the treatment of heroin or morphine addiction is any use at all. There is ample evidence of the harm, including increasing the risk of overdose, confusion, amnesia, falls and accidents, risky sexual behaviour and increased needle sharing.</p> <p>It is important to say these things to the patient in a firm, unwavering and confident manner so the patient understands you mean what you say and there is no room for negotiation.</p> <p>Drugs can interfere with sleep either as a result of stimulation (caffeine, nicotine or other stimulants) or as a response to varying levels of sedation (rebound insomnia) associated with declining blood levels (trough levels) with alcohol, opioid or benzodiazepine medications.</p> <p>Reinforce the principles of sleep hygiene, including never napping during the day no matter how tired the patient feels and getting out of bed to do something relaxing after 30 minutes of trying to get to sleep and trying again when feeling ready to sleep.</p> <p>Talk to the patient about the use of de-catastrophising techniques.</p>
<p>You prescribed alprazolam for me before, why not now?</p>	<p>These sorts of drugs are for short-term use only. If you're asking for a repeat, we haven't solved your sleep problem (or anxiety problem) and you are on a pathway to developing a new problem.</p> <p>Alprazolam has been found to be so problematic that has now been reclassified to a more dangerous drug group.</p> <p>We need to find a more effective longer term solution that is not associated with harm.</p>	<p>Prescribing hypnotics for drug-dependent patients creates an expectation of further prescribing, and causes hostility and aggression when expectations aren't met.</p>



**Table A.1. Sample responses to inappropriate requests for medications**

Patient request	Sample responses	Comments
(In a patient with SUD) I'm trying to cut down my drug use but you won't help me.	If you have a drug addiction problem, benzodiazepines are one of the least effective and most dangerous drugs to use. I know you want me to give you the best treatment, but benzodiazepines will not help.	Offer help or refer them to <a href="#">Alcohol and Drug Information Service (ADIS)</a> , for counselling and referral.
Why do you want to change my medications now? You have been prescribing alprazolam for my panic attacks, temazepam for my sleeping problems, diazepam for my anxiety and clonazepam for that seizure that I had a long time ago. I need these medications and I might die if you stop them.	<p>I know that I have been prescribing these medications for you for many years now.</p> <p>However, I have been giving a lot of thought to your health problems and I have been doing some reading on the latest medical literature and speaking to some experts in the field.</p> <p>As you know, medical research continues to reveal new things that change the way we think and practice medicine. I have realised the medications I am prescribing for you are no longer in your best interests.</p> <p>Because I care about you, I need to do something about that. It is my ethical duty to provide you with nothing but the best possible medical care that I can. So, we need to make a number of changes over the next several (2–3) months.</p> <p>I'd like to tell you about the reasons we need to make these changes and how your health will actually improve over time as a result of these changes.</p> <p>I will be there to guide and support you all the way and a medical colleague who specialises in making these sorts of medication changes has offered his/her support and advice as we go. Let's now discuss how we are going to make these changes to your treatment and map this out.</p>	<p>Doctors often find it difficult to make changes in their prescribing of analgesic and psychotropic medications, particularly when they are pressed for time, and when their patients express strong emotional attachment to these medications and a deep fear of change.</p> <p>While prescribing benzodiazepine medications in the long term does not generally represent good clinical practice, prescribing multiple benzodiazepines is poor clinical practice.</p> <p>Doctors need be aware of the evidence and have confidence in their clinical judgement when making changes to medications and other treatments.</p> <p>Doctors also need to learn to manage their emotions when responding to the emotions and pressures of patients.</p> <p>It can be important to play a broken record of positive reinforcement on the benefits of altering treatment to one that is consistent with evidence and careful clinical assessment of the patients' circumstances.</p> <p>It is important to document changes to a treatment plan.</p> <p>A copy of this treatment plan should be provided to the patient so there is clarity, transparency and certainty in what is to be offered in the new treatment plan.</p> <p>If the patient declines to comply with this change of treatment plan, the doctor must then consider whether to continue providing suboptimal care, and whether it is possible to maintain a genuine therapeutic relationship.</p> <p>While recognising that practical challenges may arise in rural and remote areas, it may be appropriate for the doctor to ask the patient to go away and think about what is proposed and return when they are ready to embark upon the new treatment plan.</p>
Please give me <drug name> just this once and I won't ask again	<p>I'm sorry but we don't prescribe those drugs in our practice.</p> <p>I am concerned about that, as sometimes a request like this can be a sign that a patient has become dependent on the medication. Can we talk about how much you are taking?</p>	<p>You may use 'we' and 'our practice' to suggest a collective decision and if you do not have confidence to say 'no' when under such emotional pressure. This avoids direct confrontation.</p> <p>However, it is better to own your clinical decisions and to communicate them in a confident, positive light.</p>

**Table A.1. Sample responses to inappropriate requests for medications**

Patient request	Sample responses	Comments
(In a patient with SUD) I've been waiting for hours to see you and you won't even help.	I am sorry you had to wait. I am very keen to help you, but your treatment depends on finding the best solution to your problem. Now let's talk about your problem and explore ways I can help you.	Some patients may use waiting time to coerce doctors. This can be averted by a sign in the waiting room indicating that particular drugs are not prescribed by doctors in the practice. Never allow yourself to be a 'victim' of inappropriate or manipulative patient behaviour.
Ok, if you can't give me temazepam, could you please prescribe some deptran or seroquel? Another doctor gave me that to help me sleep.	I'm sorry, we can help you with your sleep problem, but we can't prescribe other drugs that might also cause harm.	Many drugs prescribed for insomnia, including antidepressants such as doxepin and antipsychotic medications like seroquel or zyprexa are misused by injecting drug users (IDUs). It is important not to substitute benzodiazepines with drugs (eg antidepressants and major tranquillisers) that may cause a range of serious side effects, especially when misused.
If I don't get benzos I'm going to fit. I had a seizure once before when I was detoxing (or withdrawing).	I'm sorry to hear that. But in that case, you must be dependent on benzodiazepines. We're not allowed to prescribe drugs to sustain drug dependence (consider showing the patient the relevant section of the legislation). You need referral for detoxification. I can offer you three options for help: <ul style="list-style-type: none"> <li>I can arrange treatment.</li> <li>I can give you a specialist contact to call for advice.</li> <li>If, after further assessment, I believe it is appropriate and safe for you, I might be able to offer you out-patient withdrawal.</li> </ul>	Benzodiazepine withdrawal for drug-seeking patients requires close supervision. Specialist withdrawal management is highly advisable where there is any history of severe or complicated withdrawal (eg seizures or delirium) where the patient has been taking diazepam 50 mg daily or more or its equivalent dose for other benzodiazepine medications, where there is significant comorbidity, where there is unsanctioned or hazardous alcohol or other drug use in the patient's present living environment or where there is a past history of failed ambulatory withdrawal management.

**A note on staff safety**

All practices must implement strategies to ensure the occupational health and safety (OHS) of general practitioners (GPs) and other members of the practice team. This includes having a risk management strategy that details the necessary steps to protect doctors and practice staff from potential patient violence.

A doctor duress system is recommended in each consulting room and doctors should feel confident to use it in any situation where they feel under threat.

For tips on minimising risks of violence, practices can refer to *General Practice – A safe place: tips and tools*, available at [www.racgp.org.au/your-practice/business/tools/safetyprivacy/gpsafeplace](http://www.racgp.org.au/your-practice/business/tools/safetyprivacy/gpsafeplace)

For advice on managing aggressive, violent or threatening patients, refer to [www.miga.com.au/library/10RRAR08.pdf](http://www.miga.com.au/library/10RRAR08.pdf)

**\*Borrowed protection**

If you have reason to believe you may be at immediate risk, or if you do not feel confident to manage a particular clinical circumstance safely or effectively, it may be wise to tell the patient that it is not your responsibility for the decision, but defer to a 'higher', less identifiable authority. For example, 'I can't prescribe X because of health department regulations.' Using 'borrowed protection' should be limited to when you feel it is absolutely necessary. It is usually therapeutically more appropriate for you to communicate clearly and with confidence that you will not prescribe particular medications when you do not believe this is in the best interests of the patient, and then also explain alternative treatment approaches. This approach lets the patient know that you believe in yourself as a clinician and that you are confident and competent as a doctor.

**\*The presence of a therapeutic doctor–patient relationship in a consultation is a key to recognising a patient who wants help and a person seeking drugs.**

The establishment of a therapeutic relationship requires mutual openness and truth telling. A relationship in which a patient tells a doctor what medications they want, regardless of the clinical circumstances, is not a therapeutic one. A patient who is not open to an honest discussion about the benefits, risks and harms associated with their prescribed and non-prescribed medications, or to treatment goal setting and planning, is not engaging in treatment. They are not demonstrating they are ready to join the doctor in a genuine therapeutic relationship.

When this relationship does not exist, the challenge for the GP is to speak and work with the drug-seeking person in a way that is insightful and sensitive to their circumstances and to encourage and motivate them to accept constructive, safe and appropriate clinical assistance.

This tool has been adapted with permission from the work of Adrian Reynolds, Clinical Director, Alcohol and Drug Service, Department of Health & Human Services, Tasmania and Dr Malcolm Dobbin, Senior Medical Advisor (Alcohol and Drugs), Department of Human Services, Victoria.

## Resource B. Drug interactions

Clinically significant medication interactions with benzodiazepines.

Drugs that increase serum levels of benzodiazepines (through action on hepatic metabolic pathways)	Drugs that have sedative effects significantly enhanced by benzodiazepines
<ul style="list-style-type: none"><li>• Ketoconazole</li><li>• Itraconazole</li><li>• Macrolides</li><li>• Fluoxetine</li><li>• Cimetidine</li></ul>	<ul style="list-style-type: none"><li>• All full-agonist opioids, including methadone</li><li>• Partial agonist opioids such as buprenorphine</li><li>• Alcohol</li><li>• Antipsychotics or other sedating medication</li><li>• Barbiturates</li><li>• Sedating anti-histamines</li></ul>

## Resource C. State and territory contacts

State/ territory	Legislation	Contact (web)	Legislative contact (phone)	24-hour clinical advisory services
Australian Capital Territory	<i>Medicines, Poisons and Therapeutic Goods Act 2008</i> <a href="http://www.legislation.act.gov.au/a/2008-26/default.asp">www.legislation.act.gov. au/a/2008-26/default.asp</a>	Pharmaceutical Services <a href="http://health.act.gov.au/health-services/population-health/health-protection-service/pharmaceutical-services/pharmaceutical-services">http://health.act.gov.au/health- services/population-health/health- protection-service/pharmaceutical- services/pharmaceutical-services</a>	Pharmaceutical Services Section, ACT Health 02 6205 0998	DACAS – Australian Capital Territory 03 9418 1082
New South Wales	<i>Poisons and Therapeutic Goods Act 1966</i> <a href="http://www.austlii.edu.au/au/legis/nsw/consol_act/patga1966307">www.austlii.edu.au/au/ legis/nsw/consol_act/ patga1966307</a>	Pharmaceutical Services <a href="http://www.health.nsw.gov.au/pharmaceutical/pages/default.aspx">http://www.health.nsw.gov.au/ pharmaceutical/pages/default.aspx</a>	Pharmaceutical Services Unit, Legal and Regulatory Services Branch, NSW Health 02 9391 9944	DASAS 02 9361 8006 (Sydney) 1800 023 687 (Rural)
Northern Territory	<i>Medicines, Poisons and Therapeutic Goods Act 2014</i> <a href="http://notes.nt.gov.au/dcm/legislat/legislat.nsf/d989974724db65b1482561cf0017cbd2/86a3e80a889a330369257d4f001810d5?OpenDocument">http://notes.nt.gov.au/ dcm/legislat/legislat.nsf/d9 89974724db65b1482561c f0017cbd2/86a3e80a889a 330369257d4f001810d5? OpenDocument</a>	Poisons Control <a href="http://www.health.nt.gov.au/Environmental_Health/Medicines_and_Poisons_Control/index.aspx">www.health.nt.gov.au/ Environmental_Health/Medicines_ and_Poisons_Control/index.aspx</a>	Poisons Control Unit, Department of Health and Community Services 08 8922 7341	DACAS – Northern Territory 1800 111 092
Queensland	<i>Health (Drugs and Poisons) Regulation 1996</i> <a href="http://www.legislation.qld.gov.au/LEGISLTN/CURRENT/H/HealDrAPOR96.pdf">www.legislation.qld.gov.au/ LEGISLTN/CURRENT/H/ HealDrAPOR96.pdf</a>	Medicines Regulation and Quality <a href="http://www.health.qld.gov.au">www.health.qld.gov.au</a>	Medicines Regulation and Quality, Queensland Health 07 3328 9890	GPs can phone ADIS 1800 177 833 to be put through to ATODS for clinical advice
South Australia	<i>Controlled Substances Act 1984</i> <a href="http://www.legislation.sa.gov.au/lz/c/a/controlled%20substances%20act%201984.aspx">www.legislation.sa.gov. au/lz/c/a/controlled%20 substances%20act%20 1984.aspx</a>	Medicines and Technology Policy and Programs <a href="http://www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/about+us/departments+of+health/public+health+and+clinical+systems/medicines+and+technology+policy+and+programs">http://www.sahealth.sa.gov.au/ wps/wcm/connect/public+content/ sa+health+internet/about+us/ department+of+health/public+health+ and+clinical+systems/medicines+and +technology+policy+and+programs</a>	Drugs of Dependence Unit, Department for Health 1300 652 584	DACAS – South Australia 08 8363 8633
Tasmania	<i>Poisons Act 1971</i>	Pharmaceutical Services Branch <a href="http://www.dhhs.tas.gov.au/psbtas/welcome">http://www.dhhs.tas.gov.au/ psbtas/welcome</a>	Pharmaceutical Services Branch, Department of Health and Human Services 03 6166 0400	DACAS – Tasmania 1800 630 093
Victoria	<i>Drugs, Poisons and Controlled Substances Act 1981</i> <a href="http://www.austlii.edu.au/au/legis/vic/consol_act/dpacsa1981422">www.austlii.edu.au/au/ legis/vic/consol_act/ dpacsa1981422</a>	Drugs and Poisons Regulation <a href="http://www.health.vic.gov.au/dpcs/index.htm">http://www.health.vic.gov.au/dpcs/ index.htm</a>	Drugs and Poisons Unit, Department of Human Services 1300 364 545	DACAS – Victoria 1800 812 804
Western Australia	<i>Poisons Act 1964</i> <a href="http://www.austlii.edu.au/au/legis/wa/consol_act/pa1964121">www.austlii.edu.au/au/ legis/wa/consol_act/ pa1964121</a>	Pharmaceutical Services Branch <a href="http://www.public.health.wa.gov.au/1/872/2/pharmaceutical_services.pm">http://www.public.health.wa.gov. au/1/872/2/pharmaceutical_ services.pm</a>	Pharmaceutical Services Branch, Department of Health 08 9222 6883	CAS 08 9442 5042

DACAS – Drug and alcohol clinical advisory service; DASAS – Drug and alcohol specialist advisory service; ADIS – Alcohol and drug information service; CAS – Clinical advisory service; ATODS – Alcohol, tobacco and other drugs

## Additional resources for Schedule 4 and Schedule 8 drug information

<b>New South Wales</b>	<i>Summary of Controls on the Prescribing and Handling of Drugs of Dependence</i> , <a href="http://www.health.nsw.gov.au/pharmaceutical/Documents/drugsofdependence-controls.pdf">www.health.nsw.gov.au/pharmaceutical/Documents/drugsofdependence-controls.pdf</a>
<b>Northern Territory</b>	<i>Remote Health Atlas; Restricted S4 Medicines</i> , <a href="http://remotehealthatlas.nt.gov.au/restricted_schedule_4_medicines.pdf">http://remotehealthatlas.nt.gov.au/restricted_schedule_4_medicines.pdf</a>
<b>Queensland</b>	<i>Regulatory requirements and resources</i> , <a href="http://www.health.qld.gov.au/clinical-practice/guidelines-procedures/medicines/drugs-of-dependence/regulation/default.asp">www.health.qld.gov.au/clinical-practice/guidelines-procedures/medicines/drugs-of-dependence/regulation/default.asp</a>
<b>South Australia</b>	<i>Drugs of Dependence</i> , <a href="http://www.sahealth.sa.gov.au/wps/wcm/connect/Public+Content/SA+Health+Internet/Clinical+resources/Clinical+topics/Medicines+and+drugs/Drugs+of+dependence/">www.sahealth.sa.gov.au/wps/wcm/connect/Public+Content/SA+Health+Internet/Clinical+resources/Clinical+topics/Medicines+and+drugs/Drugs+of+dependence/</a>
<b>Victoria</b>	<i>Things medical practitioners need to know – key prescribing requirements</i> , <a href="http://docs.health.vic.gov.au/docs/doc/Things-medical-practitioners-need-to-know--key-prescribing-requirements">http://docs.health.vic.gov.au/docs/doc/Things-medical-practitioners-need-to-know--key-prescribing-requirements</a>
<b>Western Australia</b>	<i>Requirements for the prescribing of S4 and S8 Medicines in Western Australia</i> , <a href="http://www.public.health.wa.gov.au/cproot/3565/2/Prescribing_S4_S8_080825.pdf">www.public.health.wa.gov.au/cproot/3565/2/Prescribing_S4_S8_080825.pdf</a>

## Resource D. Communication with patients

### D.1 Benzodiazepine fact sheet for patients\*

#### What are benzodiazepines?

Benzodiazepines are a group of prescription-only medicines that have a sedating and calming effect on the brain and nervous system. They are also known as sedatives or tranquillisers. Examples of benzodiazepines include medicines containing one of the following active ingredients: diazepam, lorazepam, oxazepam, temazepam and alprazolam.

They come in tablet and capsule form, and some are available for intravenous use in hospital settings.

#### How do benzodiazepines work?

Benzodiazepines differ in how quickly the active ingredient starts to work and how long the effect lasts. The effect of the medicine also depends on the prescribed dose, and on the individual (eg height, weight, health status and previous experience with benzodiazepines), which can impact on how the medication will work.

Benzodiazepines can help treat symptoms of anxiety and sleeping problems (eg insomnia). As non-medicine therapies have proven benefit in these conditions, benzodiazepines are generally considered only if these options are inappropriate or have failed.

If you have been diagnosed with an anxiety disorder, benzodiazepines can make you feel calmer. If you have insomnia, benzodiazepines may help you fall asleep. They are sometimes used for other reasons, such as a medication before an operation to alleviate nervousness.

After taking benzodiazepines, people can describe feeling drowsy, relaxed, confused/fuzzy and having a heavy sensation in their arms and legs. Coordination and reflexes can be effected too, which means you should not take benzodiazepines if you need to be focused and coordinated (eg drive a car or operate heavy machinery).

Benzodiazepines are usually taken for a set period until the intended therapeutic effect is achieved. Then, the dose is reduced and plans to stop it are made.

If you take benzodiazepines for a prolonged time, the body may adapt and get used to the effects of the medication. Stopping the medication can lead to withdrawal symptoms that includes anxiety and restlessness. Withdrawal symptoms are often mild, but can be severe if you are on high doses of a benzodiazepine. Serious side effects, including seizures, can occur if you stop taking high doses suddenly.

#### Can benzodiazepines be addictive?

Although addiction (cravings, abuse, misuse, compulsive or uncontrollable benzodiazepine-seeking behaviour) is possible with benzodiazepines, it is rare in people who are taking therapeutic doses for a specific reason over a short period as prescribed by their doctor.

You may be at a greater risk of developing an addiction to benzodiazepines if you have a history of drug dependence, or if you are currently misusing any substance including alcohol or strong pain killers (opioid drugs).

Before prescribing a benzodiazepine, your doctor will ask you questions about these sorts of things to help prevent addiction.

## What are the possible side effects of benzodiazepines?

Benzodiazepines are associated with a number of side effects including:

- drowsiness and unsteadiness, potentially increasing the risk of a fall
- impairment in judgement and dexterity, making tasks such as driving or using heavy machinery more difficult
- forgetfulness, confusion, irritability
- paradoxical aggression and excitability (although this is rare, it is the opposite effect to what is expected with these medicines).

Taking benzodiazepines in combination with other drugs or alcohol can be very dangerous, and in some cases fatal.

## Can I take benzodiazepines for a long time?

Benzodiazepines are usually taken for a short length of time. In rare instances, some patients will require long-term therapy with benzodiazepines. This is after a serious consideration of risks and benefits of long-term therapy between you and your doctor. If you and your doctor have decided that benzodiazepines are an important part of your long-term treatment, then you should continue to take them as prescribed and keep checking in with your doctor for review.

If you have been taking benzodiazepines regularly for longer than 4 weeks and wish to stop them, your doctor would be happy to advise you on how to do this. Do not stop or significantly alter the dose abruptly. Many people can stop taking benzodiazepines without difficulty. For others, gradual reduction helps prevent or reduce any withdrawal symptoms.

## Where can I get more information?

- Reconnexion, [www.reconnexion.org.au](http://www.reconnexion.org.au), an Australian not-for-profit organisation that offers programs, counselling, telephone information and support for people with anxiety, stress, depression and benzodiazepine dependence and related conditions.
- The Victorian Government's Better Health Channel website, [www.betterhealth.vic.gov.au](http://www.betterhealth.vic.gov.au)
- The Australian Drug Foundation's help and support page, [www.druginfo.adf.org.au/contact-numbers/help-and-support](http://www.druginfo.adf.org.au/contact-numbers/help-and-support), lists sources of information and advice.

\* Kenny T, Harding M. Benzodiazepines and Z Drugs [Internet]. London: patient.co.uk; 2014 [updated October 2014]. Available at <http://patient.info/health/benzodiazepines-and-z-drugs> [Accessed 11 June 2015].

## D.2 Benzodiazepine reduction in the practice population

### D.2A Practice letter to patients about benzodiazepine reduction

[Insert practice name]

Address

Date

Dear [Patient name]

We are currently undertaking a review of prescriptions for medications collectively known as benzodiazepines and sleeping tablets. I am writing to you because our records show that you have received a number of prescriptions for one or more of these types of medications in the past 12 months.

A growing body of evidence suggests that if these medications are used for long periods, they can have harmful side effects, including anxiety symptoms, memory and sleep problems, and they can be addictive. We do not recommend long-term use.

We are writing to ask you to consider cutting down your dose of tablets and perhaps stopping them completely at some time in the future. As each person is different, we would like to discuss this with you in person within the next 3 months.

The best way to cut down your tablets is to take them only when you feel they are absolutely necessary. It is best to cut down gradually; otherwise you may have some withdrawal side effects. You should not stop your tablets suddenly. Once you start to reduce your dose you may start to notice that you feel a lot better and you may be able to think about stopping altogether.

Please make an appointment with your GP to discuss this further. If you have not attended to discuss this within the next 3 months, we may not be able to continue to prescribe this medicine for you. If you have already discussed this with your doctor, or have stopped your medications, this letter does not apply to you.

Yours sincerely,

[Dr name]

### D.2B Practice guide to reduction and withdrawal of benzodiazepines (and Z drugs) in the practice population

- Print a list of patients on repeat prescriptions for benzodiazepines (and Z drugs).
- Identify patients who have repeat prescriptions (including repeat acute prescriptions) of hypnotics and anxiolytics. In agreement with the general practitioner (GP), remove drug repeats for patients who have not ordered a prescription within the last 6 months.
- Agree on exclusion criteria (with GP) to identify patients not suitable for withdrawal, for example:
  - drug or alcohol problems, unless GP advises otherwise
  - terminal illness
  - acute crisis
  - risk of suicide
  - severe mental illness (liaise with psychiatrist)
  - organic brain disease
  - epilepsy requiring benzodiazepines as part of anticonvulsant therapy
  - benzodiazepine prescriptions for muscle spasm.
- The GP(s) should agree on the final list of patients to be included in the scheme.



- Invite the patient to discuss a supported withdrawal regime. If the withdrawal is to be managed by a GP, then it would be beneficial for the patient to see the same doctor throughout the process.
- Prior to the consultation, use computer records and/or paper notes to gather the required information to complete the patient clinical summary. Send the patient self-help information on sleep and relaxation.
- In the initial consultation with the patient, reiterate the benefits of withdrawing from benzodiazepines and explain the possible treatment withdrawal regimes.
- Find out how often the patient takes the hypnotic/anxiolytic, as some patients stockpile these medicines and never take them, some only take them occasionally, whereas others may give them to someone else. The anxiolytic/hypnotic can be stopped in these patients.
- If the patient agrees to participate in the scheme, agree on a treatment regime and arrange a follow-up appointment.
- Record the agreed plan in the patient-held record sheet. Provide the patient with information leaflets regarding non-drug alternatives to reduce anxiety and sleep problems.
- Following the consultation, document the outcome on the patient's electronic record and in the paper notes. Print out a prescription if one is required (leave the prescription for the GP to sign with the clinical summary sheet).
- In the patient's clinical summary sheet, complete the outcome box and pass it to the responsible GP. Once the GP has read it, they should initial it and pass it to the receptionist for filing in the patient's notes.
- Explain the intervention to local pharmacies to ensure a consistent message is conveyed to patients.
- Ensure the patient fully understands how prescriptions will be issued and that all practice staff are briefed on this.
- Offer patients general support if they call the practice for advice. If the patient wishes, arrange for an appointment to explain the program.
- If the patient is not suitable for withdrawal, consider whether no action should be taken, or to refer to the substance misuse services or psychiatric services.
- Classify your patient on your computer system in order to make identification easier. Everyone withdrawing from hypnotics/anxiolytics should have this added to their record.

### Reduction protocols to support the withdrawal from hypnotics

Different withdrawal plans are given for guidance only. The rate of withdrawal should be individualised according to the drug, dose and duration of treatment. Patient factors such as personality, lifestyle, previous experiences and specific vulnerabilities should also be taken into account.

- Throughout the process, it is important to provide advice on good sleep hygiene and basic measures to reduce anxiety.
- At each stage, enquire about general progress and withdrawal symptoms.
- If patients experience difficulties with a dose reduction, encourage them to persevere and suggest delaying the next step down. Do not revert to a higher dose.
- Offer information leaflets to help with the withdrawal program.
- Reassure patients that if they are experiencing any difficulties with the withdrawal schedule, they can contact the practice for advice.
- A copy of the protocol should be given to the patient and the patient's pharmacy. A copy should be also kept in the practice's records.

## Examples of hypnotic withdrawal schedules

To be adapted and adjusted according to individual patient needs.

### Nitrazepam

Start from the most relevant point of the schedule based on the patient's current dose.

Note that the dosage reduction withdrawal schedule is flexible and should be tailored to individual patients.

**Table D.2.1. Sample nitrazepam withdrawal schedule**

	Dose of nitrazepam	Number of 5 mg tablets/day	Number of 5 mg tablets/week
Starting dose	20 mg	4	28
Stage 1 (1–2 weeks)	15 mg	3	21
Stage 2 (1–2 weeks)	12.5 mg	2½	18
Stage 3 (1–2 weeks)	10 mg	2	14
Stage 4 (1–2 weeks)	7.5 mg	1½	11
Stage 5 (1–2 weeks)	5 mg	1	7
Stage 6 (1–2 weeks)	2.5 mg	½	4
Stage 7 (1–2 weeks)	2.5 mg <i>alternate nights</i>	½	2
Stage 8	Stop nitrazepam		

### Temazepam

Start from the most relevant point of the schedule based on the patient's current dose.

Note that the dosage reduction withdrawal schedule is flexible and should be tailored to each individual patient.

**Table D.2.2. Sample temazepam withdrawal schedule**

	Dose of temazepam	Number of 10 mg tablets/day	Number of 10 mg tablets/week
Starting dose	30 mg	3	21
Stage 1 (1–2 weeks)	25 mg	2½	18
Stage 2 (1–2 weeks)	20 mg	2	14
Stage 3 (1–2 weeks)	15 mg	1½	11
Stage 4 (1–2 weeks)	10 mg	1	7
Stage 5 (1–2 weeks)	5 mg	½	4
Stage 6 (1–2 weeks)	5 mg <i>alternate nights</i>	½	2
Stage 7	Stop temazepam		

## Zopiclone

Start from the most relevant point of the schedule based on the patient's current dose.

Note that the dosage reduction withdrawal schedule is flexible and should be tailored to each individual patient.

**Table D.2.3. Sample zopiclone withdrawal schedule**

	Dose of zopiclone	Number of tablets/ day	Number of tablets/ week
Starting dose	15 mg	2 x 7.5 mg	14 x 7.5 mg
Stage 1 (1–2 weeks)	11.25 mg	1 x 7.5 mg 1 x 3.75 mg	7 x 7.5 mg 7 x 3.75 mg
Stage 2 (1–2 weeks)	7.5 mg	1 x 7.5 mg	7 x 7.5 mg
Stage 3 (1–2 weeks)	3.75 mg	1 x 3.75 mg	7 x 3.75 mg
Stage 4 (1–2 weeks)	3.75 mg <i>alternate nights</i>	1 x 3.75 mg	4 x 3.75 mg
Stage 5	Stop zopiclone		

## Zolpidem

Start from the most relevant point of the schedule based on the patient's current dose.

Note that the dosage reduction withdrawal schedule is flexible and should be tailored to each individual patient.

**Table D.2.4. Sample zolpidem withdrawal schedule**

	Dose of zolpidem	Number of 5 mg tablets/day	Number of 5 mg tablets/week
Starting dose	10 mg	2	14
Stage 1 (1–2 weeks)	7.5 mg	1½	11
Stage 2 (1–2 weeks)	5 mg	1	7
Stage 3 (1–2 weeks)	2.5 mg	½	4
Stage 4 (1–2 weeks)	2.5 mg <i>alternate nights</i>	½	2
Stage 5	Stop zolpidem		

**Reduction protocols for anxiolytics**

Different withdrawal plans are given for guidance only. The rate of withdrawal should be individualised according to the drug, dose and duration of treatment. Patient factors such as personality, lifestyle, previous experiences and specific vulnerabilities should also be taken into account.

- Throughout the process, it is important to provide advice on good sleep hygiene and basic measures to reduce anxiety.
- At each stage, enquire about general progress and withdrawal symptoms.
- If patients experience difficulties with a dose reduction, encourage them to persevere and suggest delaying the next step down. Do not revert to a higher dosage.
- Offer information leaflets to help with the withdrawal program.
- Reassure patients that if they are experiencing any difficulties with the withdrawal schedule, they can contact the practice for advice.
- Give the patient and the patient's pharmacy a copy of the protocol. Keep a copy in the practice's records.
- If a patient has complex needs, refer to appropriate specialist services for further advice.
- Lorazepam and oxazepam have short half-lives making withdrawal effects more pronounced. Patients treated with these drugs may need to be converted to diazepam during the withdrawal process. Initial dose reductions should be made using their current medication, followed by conversion to diazepam, and subsequent reduction of the diazepam dose according to the following schedules.

Note: Some patients will prefer to remain on the original drug for the duration of the withdrawal.

**Table D.2.5. Diazepam equivalent doses**

Approximate equivalent doses to diazepam 5 mg	
Lorazepam	0.5 mg
Oxazepam	15 mg
Clonazepam	0.25 mg

Resource D.2B is adapted with permission from Educational pack – Material to support appropriate prescribing of hypnotics and anxiolytics across Wales – Welsh Medicines Partnership, April 2011. For more information visit: [http://awttc.org/about\\_wmp.html](http://awttc.org/about_wmp.html)

## D.3 Stopping benzodiazepines (benzodiazepine withdrawal) fact sheet for patients

### How would I benefit by stopping benzodiazepines?

People who have been on long-term benzodiazepines often feel like they need to stay on them. This may be because of fears about returning symptoms of anxiety or sleeplessness, or due to withdrawal symptoms or needing the medication to feel normal.

While you might feel 'normal' when you take benzodiazepines, studies have found people who stopped taking them have:

- improved memory and reaction times
- increased levels of alertness
- improved quality of life (more vitality, better ability to function).

Stopping benzodiazepines also reduces your risk of falls, accidents, fractures and other injuries.

### How should I stop taking benzodiazepines?

The best place to start is by talking to your general practitioner (GP). Some people can stop quickly and easily; others need a more gradual approach with additional support. Your GP can advise you on the rate at which you should reduce the dose and help you to consider other ways of dealing with your worries or sleeping problems. Sometimes your GP will change your prescription to a different benzodiazepine before withdrawing.

If you are taking other addictive medicines, in addition to benzodiazepines, you may need specialist help to come off the various medicines. Your GP will be able to advise you or refer you to local services that can help.

Some tips for withdrawing from benzodiazepines:

- **Choose when to start reducing** – If you have been taking benzodiazepines to help you cope with a personal crisis, it may be advisable to wait until things settle down before starting to reduce the dose. Consider starting while on holiday, when you have less pressure from work, fewer family commitments or less stress.
- **Do not try to stop suddenly** – Unless your GP has advised you to do so. You should reduce your medication in a slow, gradual process, as this often gives a better chance of long-term success. You can go as slowly as you need to.
- **Do not increase the dose** – It is common to have a bad patch at some time during the withdrawal. You might be tempted to go back to the higher dose, but it is best to stick with the current dose. Don't consider a further reduction until you feel ready; this may take several weeks.
- **Get help and support** – Consider asking family or friends for encouragement and support, or consider joining a self-help group. Advice and support from other people in similar circumstances, or those who have come off a benzodiazepine, can be very encouraging.
- **Keep a record** – Keeping a diary can help as it records your progress and achievements. This in itself will give you more confidence and encouragement to carry on.

## How do I cope with withdrawal symptoms?

Not everyone experiences the same degree or type of symptoms when withdrawing from benzodiazepines. The best way to cope is to go slowly to minimise the withdrawal symptoms. It can also help to know what to expect and know that these will pass.

- Panic attacks commonly occur due to the effects of adrenaline and rapid, shallow breathing (hyperventilation). When this happens, you may experience palpitations, sweating, unsteady legs and trembling. Regaining control of your breathing can help to alleviate the symptoms.
- Anxiety is also common upon withdrawal, especially if dose reduction is not gradual enough.
- Agoraphobia can present in a range of forms from a reluctance to go out in public to feeling completely unable to do so. However agoraphobic feelings usually lessen as withdrawal continues.
- Aches and pains are very common during withdrawal.
- Problems with sleeping can occur during withdrawal. Strategies such as ensuring enough exercise during the day, resolving concerns before bedtime and not trying to force sleep can help.
- Stomach and bowel problems such as diarrhoea and irritable bowel syndrome are very common during withdrawal and can be very distressing. Your GP may be able to recommend a diet and indigestion remedies that can improve these symptoms, which usually disappear after withdrawal is complete.
- Hot flushes and shivering are also common.
- Sinus problems are experienced by many people as they withdraw.
- Vivid dreams and nightmares are another common occurrence during withdrawal. However this may in fact be a good sign, as it can indicate your sleep and your body are re-adjusting to normal.

## Where can I get some more information and help?

Reconnexion, [www.reconnexion.org.au](http://www.reconnexion.org.au), an Australian not-for-profit organisation that offers programs, counselling, telephone information and support for people with anxiety, stress, depression and benzodiazepine dependence and related conditions.

\* Kenny T, Harding M. Stopping Benzodiazepines and Z Drugs [Internet]. London: patient.co.uk; 2014 [updated October 2014]. Available at [www.patient.co.uk/health/stopping-benzodiazepines-and-z-drugs](http://www.patient.co.uk/health/stopping-benzodiazepines-and-z-drugs) [Accessed 11 June 2015].  
Welsh Medicines Partnership. Educational pack – Material to support appropriate prescribing of hypnotics and anxiolytics across Wales. Wales: Welsh Medicines Partnership; 2011. Available at [www.awmsg.org/docs/awmsg/medman/Educational%20Resource%20Pack%20-%20Material%20to%20support%20appropriate%20prescribing%20of%20hypnotics%20and%20anxiolytics%20across%20Wales.pdf](http://www.awmsg.org/docs/awmsg/medman/Educational%20Resource%20Pack%20-%20Material%20to%20support%20appropriate%20prescribing%20of%20hypnotics%20and%20anxiolytics%20across%20Wales.pdf) [Accessed 12 June 2015].

## D.4 Sleep hygiene and stimulus control fact sheet for patients

### Sleep hygiene

Good sleep hygiene refers to actions you can take to improve and maintain good sleep. These actions include:

- Sleep as long as necessary to feel rested (usually 7–8 hours for adults), then get out of bed.
- Maintain a regular sleep schedule.
- Try not to force sleep.
- Avoid caffeinated beverages after lunch.
- Avoid alcohol near bedtime (late afternoon and evening).
- Avoid smoking or other nicotine intake, particularly during the evening.
- Adjust the bedroom environment as needed to decrease stimuli (eg reduce ambient light, turn off the television or radio).
- Resolve concerns or worries before bedtime.
- Exercise regularly for at least 20 minutes, preferably more than 4–5 hours prior to bedtime.
- Avoid daytime naps, especially if they are longer than 20–30 minutes or occur late in the day.
- Avoid going to bed until you are drowsy and ready to sleep.
- If you are not asleep within 15–20 minutes, get out of bed and return only when drowsy.

### Stimulus control

People with insomnia may associate their bed and bedroom with the stress of not sleeping, rather than the more pleasurable anticipation of sleep. The longer you stay in bed trying to sleep, the stronger the association becomes. This perpetuates the difficulty of falling asleep.

Stimulus control therapy is designed to disrupt this association by enhancing the likelihood of sleep. Your sleep may not improve immediately. However, sticking with this should improve your ability to get to sleep.

### Stimulus control instructions

- Go to bed only when sleepy.
- Get out of bed if unable to sleep after 15–20 minutes, leave the bedroom and do something relaxing (eg reading or listening to soothing music). Avoid stimulating activities such as eating or watching TV. Return to bed only when sleepy. (Repeat as necessary.)
- Use the bed/bedroom only for sleep (not reading, watching TV or worrying).
- Arise at the same time each day (including weekends).
- Do not take naps during the day.

## Sleep restriction therapy

Some people with insomnia stay in bed longer to try to make up for lost sleep. This causes a shift in your day/night cycle. It makes sleep onset the following night more difficult and results in the need to stay in bed even longer.

Sleep restriction therapy limits the total time allowed in bed, including naps and other sleep periods outside of bed, in order to increase your drive to sleep and improve the efficiency of your sleep.

Sleep restriction therapy begins by decreasing the time you spend in bed to the same amount of time that you actually sleep (usually this is determined from a sleep diaries or logs), but not less than 5 hours per night.

On a daily basis, you record the amount of sleep obtained the previous night and the amount of time spent in bed. Once you are spending more than 85% of the time in bed asleep, you increase the time spent in bed (by 15–30 minutes).

You repeat this process until you achieve improved sleep without residual daytime sleepiness.

Naps are not permitted.

## Relaxation

You may implement relaxation therapy before going to sleep. There are two common techniques for relaxation therapy:

- **Progressive relaxation** is based upon the theory that you can learn to relax one muscle at a time until the entire body is relaxed. Beginning with the muscles in your face, you contract the muscles gently for 1–2 seconds and then relax. You repeat this several times. Use the same technique for other muscle groups, usually in the following sequence: jaw and neck, upper arms, lower arms, fingers, chest, abdomen, buttocks, thighs, calves and then feet. Repeat this cycle for approximately 45 minutes, if necessary.
- **The relaxation response** begins by lying or sitting comfortably. Close your eyes and allow relaxation to spread throughout your body. Use relaxed, abdominal breathing and redirect your thoughts away from everyday worries and toward a something like a peaceful word or image.<sup>108</sup>



## Resource E. Practice policies and forms

### E.1 Practice policy example for repeat prescriptions

#### Purpose

To inform patients about practice policies regarding repeat prescriptions for benzodiazepines.

#### Example policy

*[Insert practice name]*

Date effective:

Review date:

#### **REQUESTS FOR REPEAT DRUG OF DEPENDENCE PRESCRIPTIONS – BENZODIAZEPINES**

Patients should be aware of their responsibilities in requesting prescriptions for drugs of dependence, including benzodiazepines.

Patients should note the following:

- All requests for repeat scripts for drugs of dependence will go to your usual doctor.
- All requests require a clinical review by your doctor. If it appears to your doctor that there is no improvement in your daily function or quality of life from the controlled substance, your medication may be discontinued.
- As a patient, you agree to and understand that your usual doctor reserves the right to perform random or unannounced urine drug testing. This is a safety issue.
- Patients are responsible for their prescriptions. Lost prescriptions will not be replaced.
- Repeat prescriptions are generally written for a maximum of 1 month supply and will be filled at the same pharmacy.
- Patients have the responsibility to schedule appointments for the next benzodiazepine prescription before leaving the clinic or within 3 days of the last clinic visit.
- Patients have the responsibility for keeping medications in a safe and secure place, such as a locked cabinet or safe. If medications are lost, misplaced or stolen your doctor may choose not to replace the medications or to taper and discontinue the medications.
- Patients have the responsibility for taking medications as directed and understand that increasing the dose without the close supervision of your doctor could lead to cessation of prescribing. Early requests for repeat scripts will not be performed.
- Patients have the responsibility to set appointments to review ongoing therapy. This should be monthly and made at the last clinic appointment. No walk-in appointments for medication refills will be granted.

## E.2 Prescription plan/agreement for a trial of longer term treatment

### Purpose

To inform patients of their responsibilities and expected behaviours regarding benzodiazepines.

### Example agreement

*This example is based on the Blaustein Pain Treatment Center – Johns Hopkins Medicine therapy agreement and should be modified by the practice to suit local circumstances.*

*[Insert practice name]*

Date effective:

Review date:

#### PATIENT AGREEMENT FOR BENZODIAZEPINE THERAPY

Benzodiazepines are drugs of dependence. People who take them long term can risk adverse effects including becoming dependent (addicted). Therefore, benzodiazepine prescription is highly regulated. These drugs also have a high potential for misuse and are therefore closely controlled by the local, state and Federal government.

Generally, benzodiazepines are used in the short term for reduction of distressing symptoms (eg anxiety and insomnia). A trial of long-term benzodiazepine therapy may be considered for severe or resistant mental illness.

The purpose of this agreement is to give you information about the benzodiazepine medications prescribed at this practice, and to assure that you and your general practitioner (GP) comply with all relevant regulations.

Your GP's goal is for you to have the best quality of life possible given the reality of your clinical condition. The success of treatment depends on the mutual trust and honesty in the doctor–patient relationship, and full agreement and understanding of the risks and benefits of using potentially addictive drugs to manage your condition.

In signing this agreement, you have agreed to a trial of long-term use of potentially addictive medications as part of your treatment. Because your doctor is prescribing such medication to help manage your condition, it is considered good practice to agree to the conditions outlined below.

#### My responsibilities as a patient

- I agree to see one doctor at one practice for all my health needs and prescriptions.
- I will have all my medications dispensed at one pharmacy.
- I agree that this medication is prescribed as a trial. If it appears to my doctor that there is no improvement in my daily function or quality of life from the controlled substance, my medication may be discontinued. I will gradually taper my medication as prescribed by my doctor.
- I will inform my doctor of all medications I am taking, including herbal remedies and illicit medication. Medications can interact with drugs of dependence and produce serious side effects.
- I will fully communicate with my doctor to the best of my ability at the initial and all follow-up visits my pain level and functional activity along with any side effects of the medications. This information allows my doctor to adjust my treatment plan accordingly.
- I will not request or accept drugs of dependence from any other doctor or individual while I am receiving such medication from my doctor at the *[insert practice name]*.
- I understand the use of alcohol together with benzodiazepines is contraindicated.
- I will not use any illicit substances (eg cocaine, amphetamines or marijuana) while taking these medications. Use of these substances may result in a change to my treatment plan, including safe discontinuation of my benzodiazepine medications when applicable or complete termination of the doctor–patient relationship.
- If I have a history of alcohol or drug misuse/addiction, I must notify my doctor of such history since treatment with benzodiazepines may increase the possibility of relapse.

... Continues on page 69

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- I agree and understand that my doctor reserves the right to perform random or unannounced urine drug testing. If requested to provide a urine sample, I agree to cooperate. If I decide not to provide a urine sample, I understand that my doctor may change my treatment plan, including safe discontinuation of my benzodiazepine medications when applicable or complete termination of the doctor–patient relationship. The presence of a non-prescribed drug(s) or illicit drug(s) in the urine can be grounds for termination of the doctor–patient relationship. Urine drug testing is not forensic testing, but is done for my benefit as a diagnostic tool and in accordance with certain legal and regulatory materials on the use of controlled substances to treat pain.
- I agree to allow my doctor/healthcare provider to contact any healthcare professional, family member, pharmacy, legal authority or regulatory agency to obtain or provide information about my care or actions, if my doctor feels it is necessary.
- I understand my capacity to drive may be affected and I may be asked to cease driving.

#### My prescriptions

- I am responsible for my prescriptions. I understand that lost prescriptions will not be replaced.
- I understand that benzodiazepine prescriptions **will not** be mailed if I am unable to obtain my prescriptions monthly.
- Repeat prescriptions can be written for a maximum of 1 month supply and will be filled at the same pharmacy.

Pharmacy: \_\_\_\_\_ Phone number: \_\_\_\_\_

- It is my responsibility to schedule appointments for the next benzodiazepine prescription before I leave the clinic or within 3 days of the last clinic visit.

#### Taking my medications

- I understand that the medication is strictly for my own use. My medication should never be given or sold to others because it may endanger that person's health and is against the law.
- I am responsible for keeping my medication in a safe and secure place, such as a locked cabinet or safe. I am expected to protect my medications from loss or theft. If my medication is stolen, I will report this to my local police department and obtain a stolen item report. I will then report the stolen medication to my doctor. If my medications are lost, misplaced or stolen my doctor may choose not to replace the medications or to taper and discontinue the medications.
- I am responsible for taking my medications as directed. I agree to take the medication only as prescribed.
- I understand increasing my dose without the close supervision of my doctor could lead to drug overdose, causing severe sedation and respiratory depression and death.
- I understand that decreasing or stopping my medication without the close supervision of my doctor can lead to withdrawal. Withdrawal symptoms can include yawning, sweating, watery eyes, runny nose, anxiety, tremors, aching muscles, hot and cold flashes, 'goose flesh', abdominal cramps and diarrhoea. These symptoms can occur 24–48 hours after the last dose and can last up to 3 weeks.
- Any evidence of drug hoarding, acquisition of any benzodiazepine medication or additional drugs of dependence from other doctors (which includes emergency rooms), uncontrolled dose escalation or reduction, loss of prescriptions, or failure to follow the agreement may result in termination of the doctor–patient relationship.

#### Monitoring effects of treatment

- I accept that drug of dependence therapy is only part of my care, and that I must be fully compliant with additional care interventions deemed appropriate for my health.
- I accept that set appointments must be made to review ongoing therapy. This should be monthly and made at the last clinic appointment. No walk-in appointments for medication refills will be granted.
- If an appointment is missed, another appointment will be made as soon as possible. Immediate or emergency appointments will not be granted.
- I will be seen on a regular basis and given prescriptions for enough medication to last from appointment to appointment, and sometimes 2–3 days extra **if** the prescription ends on a weekend or holiday. This extra medication is **not** to be used without the explicit permission of the prescribing doctor unless an emergency requires your appointment to be deferred 1 or 2 days.

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- It is my responsibility to notify my doctor of any side effects that continue or are severe (eg sedation, confusion). I am also responsible for notifying my doctor immediately if I need to visit another healthcare provider or need to visit an emergency room, or if I become pregnant.
- I understand that during the time that my dose is being adjusted, I will be expected to return to the clinic as instructed by my clinic doctor. After I have been placed on a stable dose, I may receive longer-term therapy from my doctor, but will return to the medical centre for a medical evaluation at least once every 3 months.
- I understand that a reduction of medication will occur if I have deterioration at home or work, or reduction of social activities because of medication, or due to medication side effects.
- I understand that while physical dependence is to be expected after the long-term use of benzodiazepines, any signs of addiction, abuse or misuse shall prompt the need for substance dependence treatment as well as weaning and detoxification from the benzodiazepines.

### My behaviour

I understand that cessation of the medication trial, or cessation of the doctor–patient relationship may occur if I display any of the following behaviours:

- presenting to the clinic intoxicated, as assessed by clinical staff
- making any physical threat to any member of staff or other patients
- aggressively complaining about a need for medication
- persistently requesting to have my medication dose increased despite clinical advice
- taking a few extra, unauthorised doses on occasion
- visiting multiple doctors for controlled substances (doctor shopping)
- hoarding medication
- using my medication for non-medical purposes (ie in any other way than prescribed)
- starting frequent unscheduled clinic visits for early refills
- using consistently disruptive behaviour when arriving at the clinic
- obtaining drugs of dependence from family members (including stealing from older relatives)
- having a pattern of lost or stolen prescriptions
- displaying anger or irritability when questioned closely about my symptoms
- being unwilling to consider other medications or non-pharmacologic treatments
- escalating my dose without authorisation
- testing positive for a non-prescribed drug(s) or illicit drug(s) in my urine
- injecting an oral formulation
- forging prescriptions
- selling medications
- refusing diagnostic workup or investigation
- obtaining controlled substance analgesics from illicit sources.

I understand that non-compliance with the above conditions may result in a re-evaluation of my treatment plan and discontinuation of benzodiazepine therapy. I may be gradually taken off these medications, or even discharged from the clinic.

I \_\_\_\_\_ have read the above information or it has been read to me and all my questions regarding treatment with benzodiazepines have been answered to my satisfaction. I hereby give my consent to participate in trial benzodiazepine therapy and acknowledge receipt of this document.

Patient's signature \_\_\_\_\_

Date \_\_\_\_\_

Doctor's signature \_\_\_\_\_

Date \_\_\_\_\_

## Resource F. Drug and alcohol assessment tool

### Alcohol Use Disorders Identification Test

#### AUDIT questionnaire: Screen for alcohol misuse

The Alcohol Use Disorders Identification Test (AUDIT) was developed by the World Health Organization as a questionnaire to identify persons whose alcohol consumption has become hazardous or harmful to their health.

The AUDIT tool and its *Guidelines for use in primary care* are available at [www.who.int/substance\\_abuse/activities/sbi/en](http://www.who.int/substance_abuse/activities/sbi/en)

The Department of Veterans Affairs has an easy-to-use AUDIT tool that can be printed to work through with your patients. It is available at <http://at-ease.dva.gov.au/therightmix/resources/for-health-professionals>

The AUDIT-C tool is a modified version of the 10-question AUDIT instrument. It is printed below and is available at [www.racgp.org.au/your-practice/guidelines/redbook/appendices/appendix-3-audit-c](http://www.racgp.org.au/your-practice/guidelines/redbook/appendices/appendix-3-audit-c)

Each AUDIT-C question has a choice of five answers. It is scored on a scale of 0–12.

In men, a score of 4 or more, and in women, a score of 3 or more, is considered positive, optimal for identifying hazardous drinking or active alcohol use disorders. However, when the points are all from Question 1 alone (questions 2 and 3 are zero), it can be assumed that the patient is drinking below recommended limits and it is suggested the provider review the patient's alcohol intake over recent months to confirm accuracy.\* Generally, the higher the score, the more likely it is that the patient's drinking is affecting their safety.

\* Bradley KA, Bush KR, Epler AJ, et al. Two brief alcohol-screening tests From the Alcohol Use Disorders Identification Test (AUDIT): validation in a female Veterans Affairs patient population. *Arch Intern Med* 2003;163(7):821–9.

#### Audit-C questionnaire

Patient name:

Date of visit:

##### 1. How often do you have a drink containing alcohol?

- a. Never
- b. Monthly or less
- c. 2–4 times a month
- d. 2–3 times a week
- e. 4 or more times a week

##### 2. How many standard drinks containing alcohol do you have on a typical day?

- a. 1 or 2
- b. 3 or 4
- c. 5 or 6
- d. 7 to 9
- e. 10 or more

##### 3. How often do you have six or more drinks on one occasion?

- a. Never
- b. Less than monthly
- c. Monthly
- d. Weekly
- e. Daily or almost daily

a = 0 points; b = 1 point; c = 2 points; d = 3 points; e = 4 points

AUDIT-C is based on The Alcohol Use Disorders Identification Test. Reproduced, with the permission of the publisher, from The Alcohol Use Disorders Identification Test: guidelines for use in primary care, AUDIT, second edition. Geneva: World Health Organization; 2000. P 17. Available at [http://whqlibdoc.who.int/hq/2001/WHO\\_MSD\\_MSB\\_01.6a.pdf](http://whqlibdoc.who.int/hq/2001/WHO_MSD_MSB_01.6a.pdf) [Accessed 22 January 2015].

## Resource G. GP guide to behavioural therapy for insomnia

### Behavioural therapy for insomnia – Information for GPs

Behavioural therapies for insomnia include sleep hygiene education, stimulus control, relaxation and sleep restriction therapy.<sup>108</sup>

#### Sleep hygiene

Sleep hygiene refers to actions that tend to improve and maintain good sleep.<sup>108,195,196</sup>

- Sleep as long as necessary to feel rested (usually 7–8 hours for adults), then get out of bed.
- Maintain a regular sleep schedule.
- Try not to force sleep.
- Avoid caffeinated beverages after lunch.
- Avoid alcohol near bedtime (late afternoon and evening).
- Avoid smoking or other nicotine intake, particularly during the evening.
- Adjust the bedroom environment as needed to decrease stimuli (eg reduce ambient light, turn off the television or radio).
- Resolve concerns or worries before bedtime
- Exercise regularly for at least 20 minutes, preferably more than 4–5 hours prior to bedtime.
- Avoid daytime naps, especially if they are longer than 20–30 minutes or occur late in the day.
- Avoid going to bed until you are drowsy and ready to sleep.
- If you are not asleep within 15–20 minutes, get out of bed and return only when drowsy.

#### Stimulus control

Patients with insomnia may associate their bed and bedroom with the fear of not sleeping or other arousing events, rather than the more pleasurable anticipation of sleep. The longer you stay in bed trying to sleep, the stronger the association becomes. This perpetuates the difficulty of falling asleep.<sup>108</sup>

Stimulus control therapy is designed to disrupt this association by enhancing the likelihood of sleep.<sup>197</sup> Patients should not go to bed until they are sleepy and should use the bed primarily for sleep (and not for reading, watching television, eating or worrying). They should not spend more than 20 minutes in bed awake. If they are awake after 20 minutes, they should leave the bedroom and engage in a relaxing activity, such as reading or listening to soothing music. Patients should not engage in activities that stimulate them or reward them for being awake in the middle of the night, such as eating or watching television. In addition, they should not return to bed until they are tired and feel ready to sleep. If they return to bed and still cannot sleep within 20 minutes, the process should be repeated. An alarm clock should be set to wake the patient at the same time every morning, including weekends. Daytime naps are not allowed. Patients may not improve immediately. However, accumulating sleepiness will facilitate sleep during successive nights.<sup>108</sup>

#### Stimulus control instructions

- Go to bed only when sleepy.
- Get out of bed if unable to sleep after 15–20 minutes, leave the bedroom and do something relaxing (eg reading or listening to soothing music). Avoid stimulating activities such as eating or watching TV. Return to bed only when sleepy. (Repeat as necessary.)
- Use the bed/bedroom only for sleep (not reading, watching TV or worrying).
- Arise at the same time each day (including weekends).
- Do not take naps during the day.<sup>108</sup>

## Sleep restriction therapy

Some patients with insomnia stay in bed longer to try to make up for lost sleep. This causes a circadian shift and a reduction in the homeostatic drive that makes sleep onset the following night more difficult and results in the need to stay in bed even longer.<sup>108</sup>

Sleep restriction therapy counteracts this tendency by limiting the total time allowed in bed, including naps and other sleep periods outside of bed, in order to increase the drive to sleep.<sup>198</sup> This consolidates sleep and improves sleep efficiency (the percentage of time in bed that the patient is asleep).<sup>108</sup>

Sleep restriction therapy begins by decreasing the time spent in bed to the same amount of time that the patient reports sleeping (usually determined from sleep diaries or logs completed by the patient), but not less than 5 hours per night. On a daily basis, the patient reports the amount of sleep obtained the previous night and the amount of time spent in bed. The clinician then computes the sleep efficiency, which is the reported time asleep divided by the time in bed. The time in bed is increased by 15–30 minutes once the sleep efficiency exceeds 85%. This process is repeated until the patient reports improved sleep without residual daytime sleepiness.<sup>108</sup>

Naps are not permitted.

To improve compliance, the rationale for the therapy needs to be carefully explained to patients. Some care needs to be used to determine and schedule the time in bed in a manner that maximises the ability to sleep that is acceptable to the patient. Older patients tend to have more difficulty maintaining sleep even when restricted; therefore, they are given more lenient criteria.<sup>108</sup>

## Relaxation

Relaxation therapy may be implemented before each sleep period. There are two common techniques for relaxation therapy: progressive muscle relaxation and the relaxation response.<sup>108</sup>

Progressive relaxation is based on the theory that an individual can learn to relax one muscle at a time until the entire body is relaxed. Beginning with the muscles in the face, the patient contracts the muscles gently for 1–2 seconds and then relaxes. This is repeated several times. The same technique is used for other muscle groups, usually in the following sequence: jaw and neck, upper arms, lower arms, fingers, chest, abdomen, buttocks, thighs, calves and then feet. This cycle is repeated for approximately 45 minutes, if necessary.<sup>108</sup>

The relaxation response begins by lying or sitting comfortably. The eyes are closed and relaxation is allowed to spread throughout the body. A relaxed, abdominal breathing pattern is established. Thoughts are redirected away from everyday thoughts and toward a neutral mental focusing device, such as a peaceful word or image.<sup>108</sup>

## Cognitive therapies

Patients who are awake at night commonly become concerned that they will perform poorly the next day if they do not obtain adequate sleep. This worry can exacerbate their difficulty falling asleep, creating a vicious cycle of wakefulness and concern. A person may begin to blame all negative events in their life on poor sleep. During cognitive therapy, a person works with a therapist to deal with anxiety and catastrophic thinking, while establishing realistic expectations related to insomnia and the need for sleep.<sup>108</sup>

Cognitive behavioural therapy (CBT) is a strategy that combines several of the previously described approaches over several weeks.<sup>199</sup> A sample, 8-session CBT program may include an introductory sleep education session, followed by two sessions that focus on stimulus control and sleep restriction. These may be followed by two sessions that focus on cognitive therapy and then a session on sleep hygiene. Finally, there may be a session that reviews and integrates the previous session and a session that addresses future problems, such as stress and relapse.<sup>200</sup>

Patients are encouraged to complete sleep logs as they learn and apply the various strategies. This allows improvement to be measured. The advantage of the educational nature of CBT is that it provides patients with the tools to apply it in the future. Disadvantages of CBT include the duration of therapy, and the relatively few clinicians who are skilled at all of its components.<sup>108</sup>

The benefit of CBT may be reduced when it is administered by less experienced clinicians.<sup>108,201</sup>

## Appendix A. Key terms and definitions

### A.1 Drugs of addiction and drugs of dependence

Legal definitions of drugs of dependence and drugs of addiction vary between states/territories. Refer to RACGP's *Prescribing drugs of dependence in general practice, Part A – Clinical governance framework*.

This guide uses the following definitions:

**Drugs of addiction** refer to all Schedule 8 (S8) drugs. These have strict legislative controls regarding their manufacture, supply, distribution, possession and use to reduce abuse, misuse, and physical and psychological dependence. Examples of S8 drugs include morphine, oxycodone, dexamphetamine, flunitrazepam (Rohypnol) and, as of February 2014, alprazolam.\*

**Drugs of dependence** describe all S8 drugs plus specified Schedule 4 (S4) drugs that are subject to misuse, abuse and trafficking. All S4 drugs are restricted substances, but only some (eg benzodiazepines) can form dependence (these are called S4D drugs in New South Wales). Some other drugs, like anabolic steroids and amphetamines, are restricted and can only be prescribed by authority.

Each state and territory has its own legislative requirements. Refer to RACGP's *Prescribing drugs of dependence in general practice, Part A – Clinical governance framework*.

*\*Xanax (Pfizer) has been withdrawn from the Australian market, however generic alprazolam is still currently available.*

### A.2 Tolerance, dependence, substance use disorder and withdrawal

The two commonly used classification systems for data collection are the International Statistical Classification of Diseases and Related Health Problems, 10th revision, (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, (DSM-5). Some of the terminology adapts poorly to the situation where prescription drugs are used to treat conditions, such as chronic non-malignant pain.

**Tolerance** is a decrease in response to a drug dose. It occurs with all chronically used drugs of dependence, including opioids and benzodiazepines. Increased doses are required to achieve the effects originally produced by lower doses.<sup>31</sup>

**Dependence**, in strict pharmacological terms, is a state that develops during chronic drug treatment in which drug cessation elicits an abstinence reaction (withdrawal).

Dependence can be associated with a whole range of psychoactive drugs or chemicals (eg caffeine, alcohol, opioid, cannabis or stimulant dependence). As awareness of problematic drug use grew, the definition of dependence changed to include addiction and abuse. Various definitions of dependence evolved with DSM-4, ICD-10, World Health Organization (WHO) and leading authors describing it as a cluster of behavioural, cognitive and physiological phenomena that may develop after repeated substance use. Now people link dependence with 'addiction' when in fact dependence can be a normal body response to a substance. While drug dependence can be part of addiction, is not the same thing.

To reduce confusion, the new DSM-5 (2013) criteria has replaced drug dependence with DSM-5 substance use disorder measured on a continuum from mild to severe. Refer to *Appendix A.3 Misuse, non-medical use and abuse*.

**Note:** There are legal implications involving the term dependence (eg restrictions around prescribing to drug-dependent persons). Characteristics of person who is drug dependent include having a history of substance misuse and being identified as a 'doctor shopper' or 'prescription shopper'.<sup>202</sup> Refer to *Appendix A.4, Drug-seeking behaviour*.



**Substance use disorder** has been introduced in DSM-5<sup>40</sup> to replace dependence (or dependence syndrome) as used to refer to complex symptoms beyond tolerance and withdrawal. The essential feature of SUD is a cluster of cognitive, behavioral and physiological symptoms indicating the individual continues using the substance despite significant substance-related problems.<sup>40</sup> Diagnosis of SUD requires the presence of at least two of 11 criteria, across four categories: impaired control, social impairment, risky use and pharmacology.

**Note:** In DSM-5, substance **dependence** and substance **abuse** have been combined into a single category of **SUDs** (eg 'benzodiazepines dependence' would be included within sedative, hypnotic, or anxiolytic use disorder).<sup>40</sup> Each SUD is divided into mild, moderate and severe subtypes, with the number of criteria present determining the severity. (Refer to *Table 3* for DSM-5 criteria and *Table A.1* for ICD-10 criteria.)

**Withdrawal** or **withdrawal syndrome** is a group of symptoms of variable clustering and degree of severity which occur on cessation or reduction of use of a psychoactive substance that has been taken repeatedly, usually for a prolonged period and/or in high doses. Signs of physiological disturbance may accompany the syndrome. A withdrawal syndrome is one of the indicators of a dependence syndrome.<sup>31</sup>

**Table A.1. ICD-10 criteria for diagnosing benzodiazepine dependence\***

Drug related criteria	<ul style="list-style-type: none"><li>• Compulsion/craving to take benzodiazepine</li><li>• Difficulties in controlling benzodiazepine use</li></ul>
Consequences of use criteria	<ul style="list-style-type: none"><li>• Progressive neglect of alternative pleasures/interests due to benzodiazepine use</li><li>• Persistent benzodiazepine use despite harmful consequences</li></ul>
Physiological criteria	<ul style="list-style-type: none"><li>• Characteristic benzodiazepine withdrawal state</li><li>• Evidence of tolerance to benzodiazepines</li></ul>

Notes: A diagnosis of dependence is made if three of six criteria listed above have been met in the last 12 months.

\* World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders – ICD-10 criteria for diagnosing benzodiazepine dependence. Geneva: WHO; 2010. Available at [http://www.who.int/substance\\_abuse/terminology/icd\\_10/en/](http://www.who.int/substance_abuse/terminology/icd_10/en/) [Accessed 12 June 2015].

## A.3 Misuse, non-medical use and abuse

**Misuse** refers to use of a substance for a purpose that is not consistent with legal or medical guidelines, and includes the non-medical use of prescription medication. Patients may inadvertently misuse prescription medication by taking them as prescribed but in response to inappropriate prescribing practices. Patients may deliberately misuse medication for non-medical purposes.<sup>31</sup>

**Non-medical use** describes use of a prescription drug, whether obtained by prescription or otherwise, for any purposes other than in the manner or for the time period prescribed, or by a person for whom the drug was not prescribed (ie diversion). Non-medical use occurs for a variety of reasons such as enjoyment of effects (especially when binge dosed), to enhance the effects of other drugs (eg benzodiazepines taken with opiates), to decrease withdrawal symptoms, to enhance confidence, to feel normal and to facilitate sexual assault (eg flunitrazepam used as 'date rape' drug).<sup>31</sup>

**Abuse** is a commonly used term with a variety of meanings. It is sometimes used disapprovingly to refer to any use at all, particularly of illicit drugs, while in other contexts abuse has referred to non-medical or unsanctioned patterns of use, irrespective of consequences.<sup>31</sup>

**Problematic drug use** may be a wider, yet clearer, more descriptive and less judgemental term than misuse or abuse.<sup>31</sup>

## A.4 Drug-seeking behaviour

**Drug-seeking behaviour** is a poorly defined term that describes a range of activities directed towards attainment of sought after medications. The most common medications sought are opioids and benzodiazepines. Behaviours include attending multiple practitioners (prescription or doctor shopping) and employing manipulating tactics.<sup>203</sup>

A comprehensive list of tactics and behaviours used to obtain medication is available in RACGP's *Prescribing drugs of dependence in general practice, Part A – Clinical governance framework*.

**Prescription or doctor shopping** is when patients unknowingly or deliberately obtain more medicines than is medically needed. This is often done by visiting many doctors, without telling them about their other consultations.<sup>204</sup> The Medicare Australia Prescription Shopping Information Service (PSIS) defines prescription shoppers as anyone, within any 3-month period, that has been supplied with PBS items prescribed by six or more different prescribers (including nurse practitioners and midwives, but excluding specialists and consultant physicians), and/or a total of 25 or more target PBS items, and/or a total of 50 or more items.<sup>204</sup> Target items are analgesics, anti-epileptics, anti-parkinson medicine, psycholeptics (including antidepressants), and all other nervous system medicine.

## A.5 Prescriber behaviour

**Appropriate prescriber behaviour** refers to prescription decisions based on evidence at the time of assessment and taking into account the patient's perspective. This is related to the term [accountable prescribing](#).

**Accountable prescribing** is defined as a commitment to evidence-based practice, the use of medicines with proven effectiveness and the avoidance of medicines when they do not help or cause harm.<sup>205</sup>

**Inappropriate prescriber behaviour** refers to persistent prescribing of drugs of dependence despite absence of sustained improvement in function, deterioration of function and/or the development of unacceptable side effects.<sup>206</sup>

## A.6 Staged supply

**Staged supply** is the process by which pharmacists supply medicine to a patient in periodic instalments of less than the originally prescribed quantity, at agreed time intervals. The balance of the medicine is held by the pharmacy to fulfil subsequent instalments. This service can be initiated by the pharmacist, the prescriber, the patient (or their carer) or another health professional involved in the patient's care.<sup>207</sup>

# Appendix B. Recommendations and grading

## B.1 Evidence-based statements and recommendations – Insomnia

Number	Recommendations	Grading and source of grade
Rec 1	Cognitive behavioural therapy based treatment packages for chronic insomnia including sleep restriction and stimulus control are effective and should therefore be offered to patients as a first-line treatment	<p>Grade A recommendation</p> <p>Source:</p> <p>Wilson SJ, Nutt DJ, Alford C, et al. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders. <i>J Psychopharmacol</i> 2010;24(11):1577–601.</p> <p>Supported by:*</p> <p>Bloom HG, Ahmed I, Alessi CA, et al. Evidence-based recommendations for the assessment and management of sleep disorders in older persons. <i>J Am Geriatr Soc</i> 2009;57(5):761–89.</p> <p>Bonnet MH, Arand DL. Treatment of insomnia. In UpToDate, Benca R (ed). UpToDate, Waltham, MA 2014. Available at <a href="http://www.uptodate.com/contents/treatment-of-insomnia">www.uptodate.com/contents/treatment-of-insomnia</a> [Accessed October 2014].</p> <p>Guideline Development Group for the management of patients with insomnia in primary care. Clinical Practice Guidelines for the management of patients with Insomnia in Primary Care. UETS No 2007/5-1. Madrid: Ministry of Health and Social Policy; 2009.</p> <p>Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. <i>J Clin Sleep Med</i> 2008;4(5):487–504.</p> <p>RACGP Handbook of non-drug interventions (HANDI). Brief behavioural therapy: Insomnia in adults. Available at <a href="http://www.racgp.org.au/your-practice/guidelines/handi/interventions/mental-health/brief-behavioural-therapy-for-insomnia-in-adults">www.racgp.org.au/your-practice/guidelines/handi/interventions/mental-health/brief-behavioural-therapy-for-insomnia-in-adults</a> [Accessed October 2014].</p> <p>Riemann D, Perlis ML. The treatments of chronic insomnia: a review of benzodiazepine receptor agonists and psychological and behavioral therapies. <i>Sleep Med Rev</i> 2009;13(3):205–14.</p>
Rec 2	Z drugs and short-acting benzodiazepines are efficacious for insomnia	<p>Grade A recommendation</p> <p>Source:</p> <p>Wilson SJ, Nutt DJ, et al. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders. <i>J Psychopharmacol</i> 2010;24(11):1577–601.</p> <p>Supported by:*</p> <p>Guideline Development Group for the management of patients with insomnia in primary care. Clinical Practice Guidelines for the management of patients with Insomnia in Primary Care. UETS No 2007/5-1. Madrid: Ministry of Health and Social Policy; 2009.</p> <p>Riemann D, Perlis ML. The treatments of chronic insomnia: a review of benzodiazepine receptor agonists and psychological and behavioral therapies. <i>Sleep Med Rev</i> 2009;13(3):205–14.</p>
Rec 3	Prescription of zolpidem and zopiclone should be treated with the same cautions as benzodiazepines	<p>Grade A recommendation</p> <p>Source:</p> <p>Ministry of Health Singapore. Prescribing of Benzodiazepines: MOH Clinical Practice Guidelines 2/2008. Singapore: MOH; 2008.</p> <p>Supported by:*</p> <p>Riemann D, Perlis ML. The treatments of chronic insomnia: a review of benzodiazepine receptor agonists and psychological and behavioural therapies. <i>Sleep Med Rev</i> 2009;13(3):205–14.</p>

Number	Recommendations	Grading and source of grade
Rec 4	Intermittent dosing may further reduce the risk of tolerance and dependence	Grade B recommendation Source: Wilson SJ, Nutt DJ, Alford C, et al. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders. <i>J Psychopharmacol</i> 2010;24(11):1577–601
Rec 5	If hypnotics are to be used for treating insomnia, it is recommended that treatment is short term (ie not more than 4 weeks) and at the lowest possible dose	Grade B recommendation Source: Guideline Development Group for the management of patients with insomnia in primary care. Clinical Practice Guidelines for the management of patients with Insomnia in Primary Care. UETS No 2007/5-1. Madrid: Ministry of Health and Social Policy; 2009.

\*Recommendation supported, however gradings (where given) may be different from source.

## B.2 Evidence-based statements and recommendations – Anxiety

Number	Recommendations	Grading and source of grade
Rec 6	Cognitive behavioural therapy is recommended as one of the treatments of choice for generalised anxiety disorder, panic disorder, and panic attacks due to its effectiveness at reducing the symptoms of anxiety in the short and long term, although patient preference must be taken into consideration	Grade A recommendation Source: Guideline Working Group for the Treatment of Patients with Anxiety Disorders in Primary Care. Clinical Practice Guideline for Treatment of Patients with Anxiety Disorders in Primary Care. UETS no 2006/10 ed. Madrid: Ministry of Health and Social Policy; 2008. Supported by:* Agency for Healthcare Research and Quality (AHRQ). Guideline Summary NGC – 7124: Practice guideline for the treatment of patients with panic disorder. Derived from: American Psychiatric Association (APA). Practice guideline for the treatment of patients with panic disorder. 2nd ed. Washington, DC: APA; 2009. Agency for Healthcare Research and Quality (AHRQ). Guideline Summary NGC –8660: Generalised anxiety disorder and Panic Disorder (with or without agoraphobia) in adults. Management in primary, secondary and community care. <sup>208</sup> Derived from: National Collaborating Centre for Mental Health, National Collaborating Centre for Primary Care. Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults. Management in primary, secondary and community care (Clinical guide no 113). London: National Institute for Health and Clinical Excellence (NICE); 2011.
Rec 7	Consider an selective serotonin reuptake inhibitor (SSRI) for first-line treatment, as SSRI are effective across the anxiety and related disorders, in both the short term and long term, and are generally well tolerated	Grade A recommendation Source: Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: A revision of the 2005 guidelines from the British Association for Psychopharmacology. <i>J Psychopharmacol</i> 2014;28(5):403–39. Supported by:* Agency for Healthcare Research and Quality (AHRQ). Guideline Summary NGC – 7124: Practice guideline for the treatment of patients with panic disorder. Derived from: American Psychiatric Association (APA). Practice guideline for the treatment of patients with panic disorder. 2nd ed. Washington, DC: APA; 2009. Agency for Healthcare Research and Quality (AHRQ). Guideline Summary NGC –8660: Generalised anxiety disorder and Panic Disorder (with or without agoraphobia) in adults. Management in primary, secondary and community care. Derived from: National Collaborating Centre for Mental Health, National Collaborating Centre for Primary Care. Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults. Management in primary, secondary and community care (Clinical guide no 113). London: National Institute for Health and Clinical Excellence (NICE); 2011. Guideline Working Group for the Treatment of Patients with Anxiety Disorders in Primary Care. Clinical Practice Guideline for Treatment of Patients with Anxiety Disorders in Primary Care. UETS no 2006/10 ed. Madrid: Ministry of Health and Social Policy; 2008.

Number	Recommendations	Grading and source of grade
Rec 8	Benzodiazepines have evidence of benefit in generalised anxiety disorder, social anxiety disorder and panic disorder, but not obsessive compulsive disorder or post-traumatic stress disorder	<p>Grade A/B recommendation</p> <p>Source: Bandelow B, Sher L, Bunevicius R, et al. Guidelines for the pharmacological treatment of anxiety disorders, obsessive-compulsive disorder and posttraumatic stress disorder in primary care. <i>Int J Psychiatry Clin Pract</i> 2012;16(2):77–84.</p> <p>Supported by:*</p> <p>Agency for Healthcare Research and Quality (AHRQ). Guideline Summary NGC – 7124: Practice guideline for the treatment of patients with panic disorder. Derived from: American Psychiatric Association (APA). Practice guideline for the treatment of patients with panic disorder. 2nd ed. Washington, DC: APA; 2009.</p> <p>Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: A revision of the 2005 guidelines from the British Association for Psychopharmacology. <i>J Psychopharmacol</i> 2014;28(5):403–39.</p> <p>Bandelow B, Boerner JR, Kasper S, Linden M, Wittchen HU, Moller HJ. The diagnosis and treatment of generalized anxiety disorder. <i>Dtsch Arztebl Int</i> 2013;110(17):300–9.</p> <p>Bandelow B, Zohar J, Hollander E, Kasper S, Moller HJ, WFSBP Task Force on Treatment Guidelines for Anxiety Obsessive-Compulsive Post-Traumatic Stress Disorders. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders – first revision. <i>World J Biol Psychiatry</i> 2008;9(4):248–312.</p> <p>Canadian Agency for Drugs and Technologies in Health (CADTH). Short- and Long-Term Use of Benzodiazepines in Patients with Generalized Anxiety Disorder: A Review of Guidelines. Ottawa: CADTH; 2014.</p> <p>Davidson JR, Feltner DE, Dugar A. Management of generalized anxiety disorder in primary care: identifying the challenges and unmet needs. <i>Prim Care Companion J Clin Psychiatry</i> 2010;12(2).</p> <p>Dell'osso B, Lader M. Do benzodiazepines still deserve a major role in the treatment of psychiatric disorders? A critical reappraisal. <i>European psychiatry: J Assoc Europ Psychiat</i> 2013;28(1):7–20.</p> <p>Guideline Working Group for the Treatment of Patients with Anxiety Disorders in Primary Care. Clinical Practice Guideline for Treatment of Patients with Anxiety Disorders in Primary Care. UETS no 2006/10 ed. Madrid: Ministry of Health and Social Policy; 2008.</p> <p>Katzman MA, Bleau P, Blier P, et al. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. <i>BMC Psychiatry</i> 2014;14 Suppl 1:S1</p>

\*Recommendation supported, however gradings (where given) may be different from source.

## B.3 Evidence-based statements and recommendations – Alcohol withdrawal

Number	Recommendations	Grade and source of grading
Rec 9	Benzodiazepines (eg diazepam, oxazepam) are the drugs of choice for treatment of acute alcohol withdrawal (including alcohol withdrawal delirium), but for a maximum of 7 days	<p>Grade A recommendation</p> <p>Source: Scottish Intercollegiate Guideline Network. The Management of Harmful Drinking and Alcohol Dependence in Primary Care. Guideline No 74. Edinburgh: SIGN; 2004</p>

## *Appendix C. Process of development*

This guide was developed in response to calls for a resource for GPs and general practice teams to manage benzodiazepine prescribing. It represents a synthesis of current scientific knowledge and rational clinical practice regarding treatment with benzodiazepines. The content broadly conforms to the highest evidence-based standards according to the principles underlying the Appraisal of Guidelines Research and Evaluation (AGREE) Instrument. It strives to be as free as possible of bias toward any theoretical approach to treatment.

The RACGP convened a GP-led advisory group, comprising GP members with expertise and experience in drugs of dependence and guideline development. A literature search was conducted and key resources were identified.

A limited literature search was conducted, using key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, international health technology agencies, in addition to a focused Internet search. Filters were applied to limit retrieval to articles in English, health technology assessments, systematic reviews, meta-analyses and guidelines. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved based on:

- national and international benzodiazepine prescribing guidelines
- national and international guidelines of specific disease state management (eg insomnia, anxiety)
- high-quality systematic reviews on benzodiazepine prescribing
- high-quality publications that address key issues with benzodiazepine pharmacology, dependence, tolerance and adverse effects.

An in-depth critical analysis of the publications was not undertaken.

This guide provides recommendations based on current evidence-based guidelines, including the Scottish Intercollegiate Guidelines Network (SIGN), the British Association of Psychopharmacology, and the Health Technology Assessment Unit of the Spanish Ministry of Health and Social Policy.

In cases where guideline recommendations specific to the indication were not available, other sources, such as systematic reviews, have been used to inform the recommendations.

The advisory group did not attempt to re-evaluate the evidence behind these recommendations or convert the recommendation grades to the Australian National Health and Medical Research Council (NHMRC) grading levels. Therefore, the recommendations tables include the reference and sources of recommendations, the recommendation grade and links to further information on the evidence grade where available (refer to [Appendix B](#)). For some recommendations, an evidence grade was not available; therefore, these recommendations should be treated as expert opinion

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