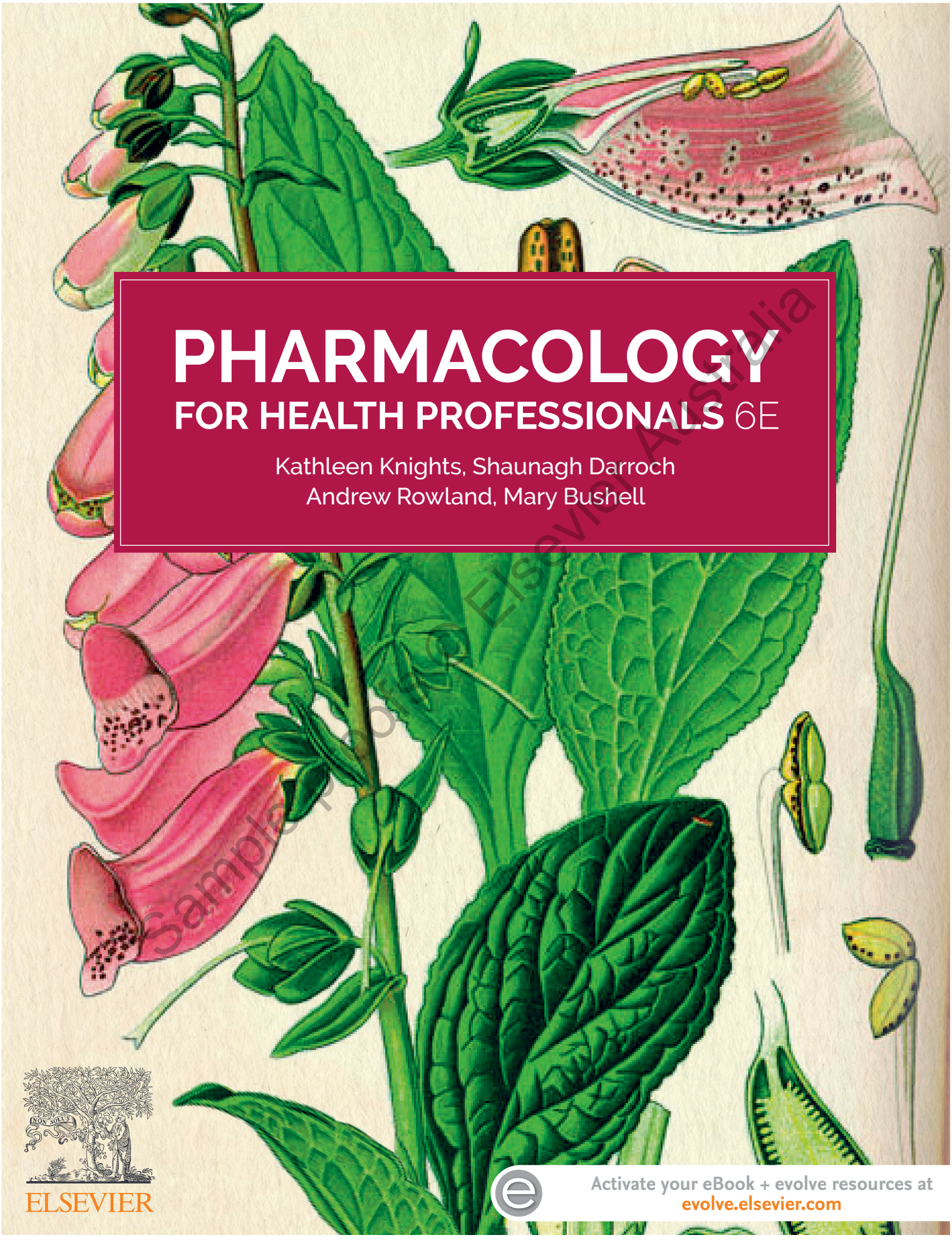

PHARMACOLOGY
FOR HEALTH PROFESSIONALS 6E

Kathleen Knights, Shaunagh Darroch
Andrew Rowland, Mary Bushell

ELSEVIER

PHARMACOLOGY
FOR HEALTH PROFESSIONALS

6th Edition

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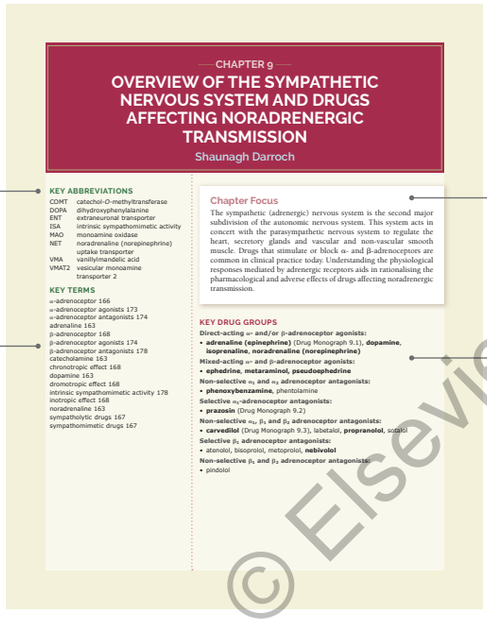
GUIDE TO TEXT

Get the most out of your textbook by familiarising yourself with the key features of this new edition of *Pharmacology for Health Professionals*.

Chapter Opening Features

Chapters have been carefully structured to aid learning. Chapter openings are designed to help you focus and mentally organise content.


CHAPTER 9

OVERVIEW OF THE SYMPATHETIC NERVOUS SYSTEM AND DRUGS AFFECTING NORADRENERGIC TRANSMISSION

Shaunagh Darroch

KEY ABBREVIATIONS

COMT	catechol-O-methyltransferase
DOPA	dihydroxyphenylalanine
ENT	extraneuronal transporter
ISA	intrinsic sympathomimetic activity
MAO	monoamine oxidase
NET	noradrenaline (norepinephrine) uptake transporter
VMA	vanillylmandelic acid
VMAT2	vesicular monoamine transporter 2

KEY TERMS

α-adrenoceptor 166
α-adrenoceptor agonists 173
α-adrenoceptor antagonists 174
adrenaline 163
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Chapter Focus

The sympathetic (adrenergic) nervous system is the second major subdivision of the autonomic nervous system. This system acts in concert with the parasympathetic nervous system to regulate the heart, secretory glands and vascular and non-vascular smooth muscle. Drugs that stimulate or block α- and β-adrenoceptors are common in clinical practice today. Understanding the physiological responses mediated by adrenergic receptors aids in rationalising the pharmacological and adverse effects of drugs affecting noradrenergic transmission.

KEY DRUG GROUPS

Direct-acting α_1 and/or β-adrenoceptor agonists:
- **adrenaline (epinephrine)** (Drug Monograph 9.1), **dopamine, isoprenaline, noradrenaline (norepinephrine)**

Mixed-acting α_1 and β-adrenoceptor agonists:
- **ephedrine, metaraminol, pseudoephedrine**

Non-selective α_1 and α_2 adrenoceptor antagonists:
- **phenoxybenzamine**, phentolamine

Selective α_1-adrenoceptor antagonists:
- **prazosin** (Drug Monograph 9.2)

Non-selective α_1, β_1 and β_2 adrenoceptor antagonists:
- **carvedilol** (Drug Monograph 9.3), labetalol, **propranolol**, sotalol

Selective β_1 adrenoceptor antagonists:
- atenolol, bisoprolol, metoprolol, **nebivolol**

Non-selective β_1 and β_2 adrenoceptor antagonists:
- pindolol

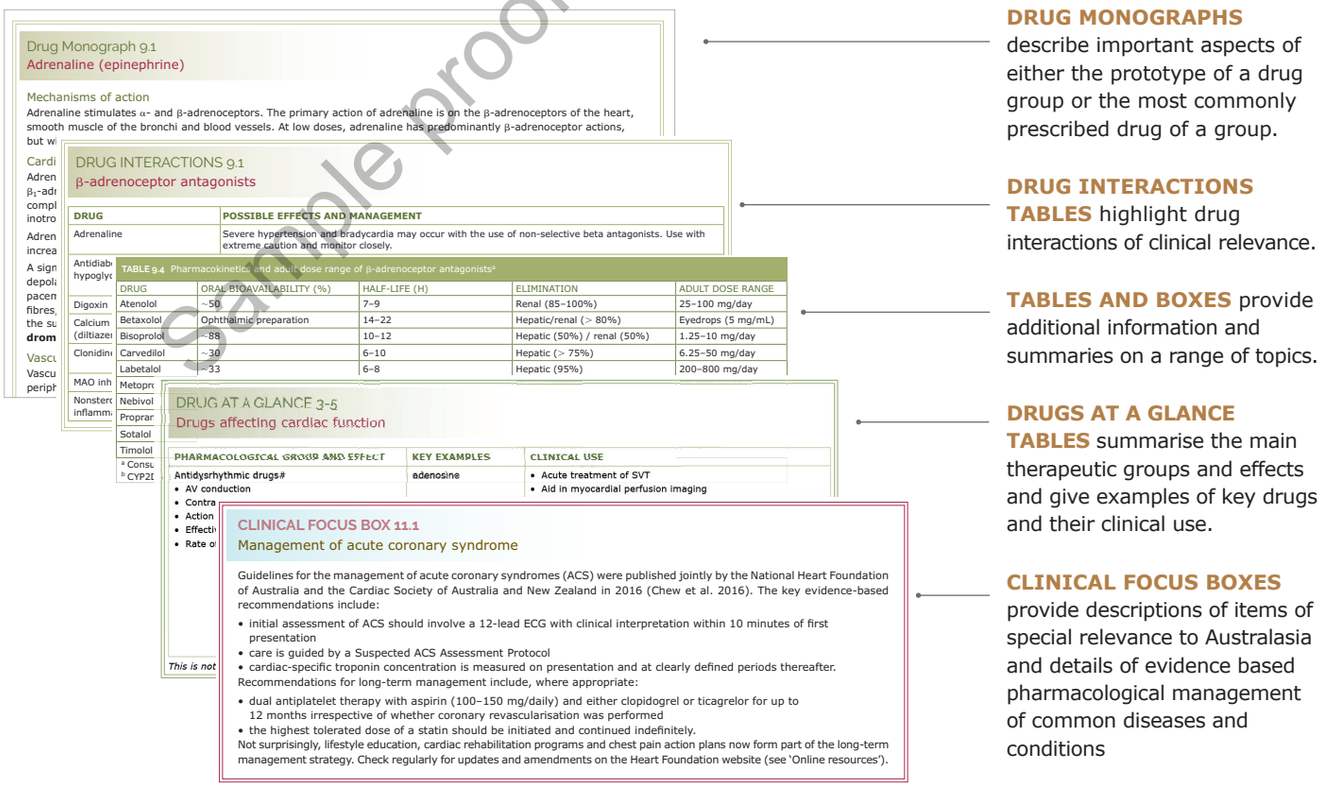
KEY ABBREVIATIONS introduces the abbreviations and acronyms that will be used, and provides a quick reference point.

KEY TERMS lists the essential terminology that is bold-faced in the text.

CHAPTER FOCUS highlights what you will learn in the chapter.

KEY DRUG GROUPS lists the drug groups addressed in that chapter.

Tables and Boxes


Drug Monograph 9.1
Adrenaline (epinephrine)

Mechanisms of action

Adrenaline stimulates α- and β-adrenoceptors. The primary action of adrenaline is on the β-adrenoceptors of the heart, smooth muscle of the bronchi and blood vessels. At low doses, adrenaline has predominantly β-adrenoceptor actions,

DRUG INTERACTIONS 9.1
β-adrenoceptor antagonists

DRUG	POSSIBLE EFFECTS AND MANAGEMENT
Adrenaline	Severe hypertension and bradycardia may occur with the use of non-selective beta antagonists. Use with extreme caution and monitor closely.

TABLE 9.4 Pharmacokinetics and adult dose range of β-adrenoceptor antagonists[a]

DRUG	ORAL BIOAVAILABILITY (%)	HALF-LIFE (H)	ELIMINATION	ADULT DOSE RANGE
Atenolol	~50	7–9	Renal (85–100%)	25–100 mg/day
Betaxolol	Ophthalmic preparation	14–22	Hepatic/renal (> 80%)	Eyedrops (5 mg/mL)
Bisoprolol	~88	10–12	Hepatic (50%) / renal (50%)	1.25–10 mg/day
Carvedilol	~30	6–10	Hepatic (> 75%)	6.25–50 mg/day
Labetalol	~33	6–8	Hepatic (95%)	200–800 mg/day

DRUG AT A GLANCE 3-5
Drugs affecting cardiac function

PHARMACOLOGICAL GROUP AND EFFECT	KEY EXAMPLES	CLINICAL USE
Antidysrhythmic drugs#	adenosine	• Acute treatment of SVT
• AV conduction		• Aid in myocardial perfusion imaging

CLINICAL FOCUS BOX 11.1
Management of acute coronary syndrome

Guidelines for the management of acute coronary syndromes (ACS) were published jointly by the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand in 2016 (Chew et al. 2016). The key evidence-based recommendations include:
- initial assessment of ACS should involve a 12-lead ECG with clinical interpretation within 10 minutes of first presentation
- care is guided by a Suspected ACS Assessment Protocol
- cardiac-specific troponin concentration is measured on presentation and at clearly defined periods thereafter.

Recommendations for long-term management include, where appropriate:
- dual antiplatelet therapy with aspirin (100–150 mg/daily) and either clopidogrel or ticagrelor for up to 12 months irrespective of whether coronary revascularisation was performed
- the highest tolerated dose of a statin should be initiated and continued indefinitely.

Not surprisingly, lifestyle education, cardiac rehabilitation programs and chest pain action plans now form part of the long-term management strategy. Check regularly for updates and amendments on the Heart Foundation website (see 'Online resources').

DRUG MONOGRAPHS describe important aspects of either the prototype of a drug group or the most commonly prescribed drug of a group.

DRUG INTERACTIONS TABLES highlight drug interactions of clinical relevance.

TABLES AND BOXES provide additional information and summaries on a range of topics.

DRUGS AT A GLANCE TABLES summarise the main therapeutic groups and effects and give examples of key drugs and their clinical use.

CLINICAL FOCUS BOXES provide descriptions of items of special relevance to Australasia and details of evidence based pharmacological management of common diseases and conditions

CRITICAL THINKING SCENARIO

Terry, a 61-year-old male, was diagnosed with renal cell cancer 2 years ago and has been taking 50 mg of sunitinib (a cancer medicine) daily without any complications ever since. Last week Terry contracted COVID-19. Fearing that he is quite frail, Terry's doctor prescribed a 5-day course of Paxlovid (nirmatrelvir/ritonavir) to help minimise his symptoms. What, if any, impact is Paxlovid likely to have on Terry's cancer medicine and how might this be addressed?

CRITICAL THINKING SCENARIO for each chapter allows application of the key physiological, biochemical and pathological processes that underpin the pharmacological use of a particular drug.

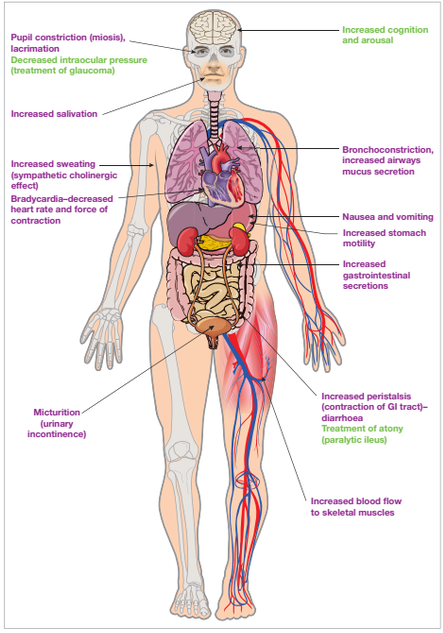


FIGURE 8.5 Pharmacological effects of muscarinic receptor agonists

HUMANOID MODEL are a new addition to the book. For illustrative purposes these models use selected organs, tissues, body parts etc. to explain pharmacological/adverse effects of various drugs or drug groups.

KEY POINTS

Pharmacodynamics

- An agonist binds to the orthosteric site of the receptor (governed by affinity) and activates the receptor (governed by efficacy) to produce the same response as the endogenous ligand.
- Partial agonists produce less than the maximal effect caused by the endogenous ligand, even when all receptors are occupied.
- An antagonist binds to a receptor and blocks access of the endogenous ligand, diminishing the normal response.
- When a drug is administered, the response usually increases in proportion to the dose until the receptors

KEY POINTS reinforce your learning and help you to review material.

REVIEW EXERCISES

1 Ms FG, a 14-year-old, presents to the emergency department after an allergic reaction after eating peanuts at a party. She first experienced breathing difficulties and swelling of her lips and hands. As she is being triaged, she collapses. She is administered adrenaline 1:1000 IM injection into her thigh. Explain the effect of adrenaline on the cardiovascular and respiratory systems. Explain why this drug is useful in treating anaphylactic shock.

2 Ms MC has recently been diagnosed with moderate heart failure. She has been prescribed an ACE inhibitor to reduce fluid load and now her cardiologist has prescribed the beta-blocker nebivolol. She has now titrated her dose from 1.25 mg to a 5 mg dose. She returns to the clinic in 2 weeks complaining of tiredness, insomnia and vivid dreams. What is your explanation as to why these symptoms have occurred? Should she stop taking nebivolol immediately?

REVIEW EXERCISES are given for every chapter to help you master the material in manageable parts.

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Schena G, Caplan MJ. Everything You Always Wanted to Know about β3-AR * (* But Were Afraid to Ask). Cells. 2019 Apr 16;8(4):357. doi: 10.3390/cells8040357. PMID: 30995798; PMCID: PMC6523418.

Therapeutic Goods Administration 2021. Changes to adrenaline and noradrenaline labels [online] Available at: <https://www.tga.gov.au/changes-adrenaline-and-noradrenaline-labels [Accessed 9 Oct 2021].

ONLINE RESOURCES

Australasian Society of Clinical Immunology and Allergy: https://www.allergy.org.au/ (accessed 24 February 2022)

Australian Resuscitation Council: https://www.resus.org.au/ (accessed 24 February 2022)

More weblinks at: http://evolve.elsevier.com/AU/Knights/pharmacology/.

REFERENCES is an up-to-date bibliography at the end of each chapter, with references relevant to all health professionals.

ONLINE RESOURCES lists key websites where you can find additional information. Further web links are also supplied on the Evolve site for this text.

PREFACE

Pharmacology is a universal discipline, but the availability of drugs and the patterns of their use differ between countries. Most pharmacology texts are written for health professionals and students in the northern hemisphere; this 6th edition continues to be ideally suited to the needs of all health professionals practising in Australia and New Zealand. The discussion of drugs reflects the names used and their availability and clinical use within the Australasian region, and the material on drug legislation and ethical principles focuses on regional aspects. To complement and enhance this regional flavour, information on traditional medicinal plants and patterns of use of medicines by Indigenous peoples is interspersed in relevant chapters. We acknowledge that paramedics and practitioners of some other professions, such as nursing, midwifery, podiatry, physiotherapy, optometry and orthoptics, are increasingly being granted limited prescribing rights, and additional information relevant to these emerging roles has been incorporated throughout the 6th edition.

As much of pharmacology is predicated on an understanding of physiology and biochemistry, the 6th edition showcases fully updated, revised and condensed chapters that reduce the overlap of material. The content is more concise and reflects recent epidemiological data, research findings, the introduction of new drugs, withdrawals of old drugs and changes in recommendations and guidelines from learned bodies on the pharmacological management of disease conditions. Many of the figures have been redrawn and new figures (e.g. humanoid models) included to enhance understanding and interest. This edition also features:

- new chapters on vaccines and drugs in aged care
- Key Points boxes that provide a snapshot of important information
- new and updated Drug Monographs using either the prototype of a drug group or the most commonly prescribed drug of a group, or drugs that have gained 'drug of first choice' status
- tables containing more details of drug interactions occurring with major drug groups
- new comprehensive Drugs at a Glance tables
- information on recent changes in the pharmacological management of major conditions, including asthma, cardiac failure, cancers, stroke, dementia, diabetes mellitus, epilepsy, HIV, hypertension, osteoporosis, rheumatoid arthritis, macular degeneration, otitis media, endometriosis, common complications of pregnancy and childbirth, and on anaesthesia in surgery and analgesia and sedation for children
- new Clinical Focus Boxes, including descriptions of items of special interest specific to Australasia and of typical pharmacological treatment of common diseases and conditions
- enhanced information on the use of complementary and alternative medicine modalities and on interactions between drugs and these therapies
- a full-colour treatment to distinguish the text elements and make navigating the text easy.

With advances in drug development, drugs in clinical use continue to have a high rate of obsolescence. The facts learned for a particular drug may therefore become irrelevant when each year brings new drugs with differing modes of action. With an emphasis on personalised or precision medicine, the challenge for health professionals is to stay up to date with advances in the field of pharmacology and their impact on the quality use of medicines. We have retained both a scientific and a clinical approach, founded on evidence-based medicine and always emphasising the clinical use and therapeutic/adverse effects of drugs. Information on the clinical use of drugs is based especially on data in the *Australian Medicines Handbook*, the *Therapeutic Guidelines* series and reviews in *Drugs*, the *Medical Journal of Australia*, *Australian Family Physician* and *Australian Prescriber*. We are confident that this 6th edition will continue to fulfil the needs of students and academics in all health professions and will make the study of pharmacology logical, enjoyable, easy and, above all, interesting.

CHAPTER 20

ANTIANXIETY, SEDATIVE AND HYPNOTIC DRUGS

Shaunagh Darroch

KEY ABBREVIATIONS

CAM	complementary and alternative medicine
CNS	central nervous system
EEG	electroencephalograph
GABA	gamma-aminobutyric acid
REM	rapid eye movement
SNRIs	serotonin noradrenaline reuptake inhibitors
SSRIs	selective serotonin reuptake inhibitors
TCA	tricyclic antidepressant

KEY TERMS

anterograde amnesic effect 452
antianxiety (anxiolytic) agents 445
anxiety 444
benzodiazepines 448
gamma-aminobutyric acid 444
hypnotics 446
insomnia 444
melatonin 457
non–rapid eye movement (non-REM) sleep 443
orexin 458
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rapid eye movement (REM) sleep 443
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sleep hygiene 446
Z-drugs 456

Chapter Focus

Anxiety and insomnia are common health problems that occur across the life span. When anxiety or fear is in response to a threat or danger, this is a normal physiological response to a threatening situation. However, excessive anxiety or panic that interferes with daily functioning and sleep is counterproductive and usually requires medical intervention and treatment. Insomnia is a common sleep disorder and is often a concern in the elderly. This chapter reviews the antianxiety, sedative and hypnotic drugs available to treat these disorders. Barbiturates were previously used extensively as sedative–hypnotic agents, but because of their low therapeutic index and relative non-selectivity they have largely been replaced by the safer benzodiazepines and newer related agents that have specific anxiolytic (antianxiety) actions. Antidepressants (Ch 22) are now recommended as first-line treatment for anxiety disorders.

KEY DRUG GROUPS

Barbiturates:

- Phenobarbital (phenobarbitone)

Benzodiazepines:

- **Diazepam** (Drug Monograph 20.1), **lorazepam**, **midazolam** (Drug Monograph 20.2)

Benzodiazepine antagonists:

- **Flumazenil**

Other sedatives/hypnotics:

- Buspirone, **chloral hydrate**, **melatonin**, **promethazine**, suvorexant

Z-drugs:

- **Zolpidem**, **zopiclone**

CRITICAL THINKING SCENARIO

Millie, aged 3 years, is attending a remote health service clinic with her two parents in preparation for upcoming cleft palate surgery. A specialist clinic appointment and CT scan has been scheduled at the nearest regional hospital. This appointment will require a 4-hour road trip and an overnight stay for the family.

Her parents are reminded that, to facilitate the scan, Millie may need to be still for 20–30 minutes, and short-term sedation using a drug named chloral hydrate may be required. The parents mention that their daughter becomes distressed during her frequent medical procedures and that the long road trips are also a cause of agitation. They have heard that a drug named Phenergan™ could be used to calm their daughter during the road trip.

1. What is the mechanism of action of chloral hydrate?
2. What is the recommended clinical use for chloral hydrate? Note potential adverse reactions, contraindications and special precautions.
3. What advice would you give about using Phenergan™ for the road trip?
4. What is Phenergan's generic name and mechanism of action?
5. What are potential adverse reactions, contraindications and special precautions for use as a sedative in paediatrics?
6. What are other clinical uses for this drug?

Introduction: Sleep and anxiety

Sleep: Physiology and purposes

Sleep is a recurrent, natural, reversible condition of inertia, reduced consciousness and reduced metabolism, during which a person is no longer in sensory contact with the immediate environment, and stimuli no longer attract attention or exert a controlling influence over voluntary and involuntary movements or functions. Some of the proposed purposes of sleep are to regulate glucose homeostasis and appetite, consolidate synaptic circuits to maintain memory and regulate hormone levels and circadian rhythms. A person's normal sleep pattern can vary from night to night and is influenced by their emotional and physical state. The sleep pattern is controlled from the ascending reticular activating system in the brainstem, as noted in Chapter 18. The main neurotransmitters involved in sleep are histamine, noradrenaline (norepinephrine), serotonin and the orexins.

Stages of sleep

The stages of sleep are based on electrical activity that can be observed in the brain by means of an electroencephalograph (EEG). The EEG is also used to detect abnormal brainwaves in epilepsy, for example (Fig 21.1, in Ch 21). Sleep consists of two fundamental states that occur cyclically: non–rapid eye movement (non-REM) sleep and rapid eye movement (REM) sleep. Periods of REM and non-REM sleep alternate throughout the night. The individual moves through three stages of **non-REM sleep** (stage 1, stage 2 and combined stages 3 and 4) into progressively deeper stages of sleep during which brainwaves are seen to be of high amplitude and low frequency (Fig 20.1). The individual then passes into **REM sleep**, which is characterised by rapid eye movements, dreaming and low-amplitude, high-frequency waves on an EEG (similar to the awake state).

REM sleep is not synonymous with light sleep: it takes a more powerful stimulus to arouse a person from REM sleep than from synchronous slow-wave sleep.

The sleep–wake cycle varies with age: infants spend more time asleep, and a much greater proportion of sleep time in REM sleep, than do adults. Adolescents usually prefer to go to sleep later, whereas elderly people tend to go to sleep earlier, and spend more time

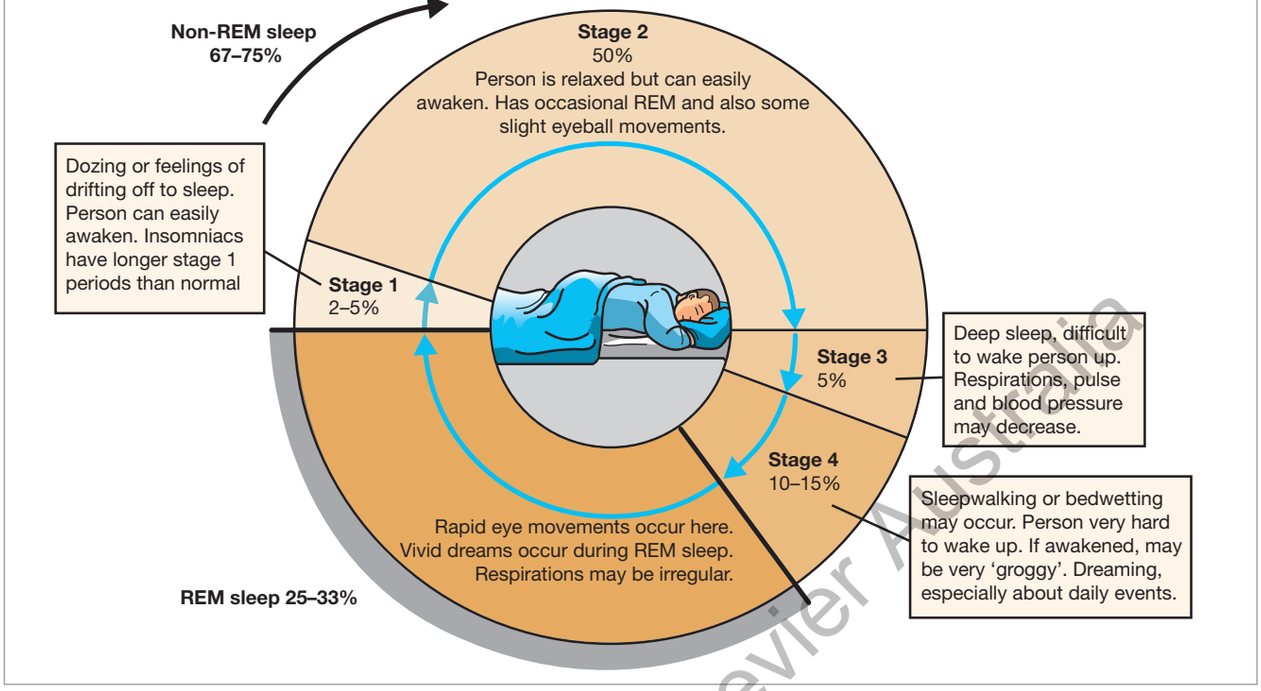

FIGURE 20.1 Stages of sleep

Source: Adapted from Salerno 1999; used with permission.

in stages 1 and 2 of non-REM sleep with frequent arousals.

Sleep disorders

A person's sleep patterns can be affected by their emotional and physical states and can vary from night to night. There are various sleep disorders caused by neurological disorders or lifestyle factors. Sleep-related respiratory disorders include obstructive sleep apnoea and Cheyne-Stokes respiration associated with congestive cardiac failure. Shift workers whose regular circadian rhythms are often disrupted may suffer from adverse effects on hormonal and metabolic patterns. Narcolepsy is an uncommon neurological disorder that affects sleep–wake cycles and causes episodes of unpreventable sleep throughout the day.

Insomnia

Insomnia is the inability to obtain adequate sleep, whether from difficulty in falling asleep, frequent nocturnal waking or early awakening. It can be classified as a standalone disorder or associated with other disorders (e.g. depression). Excessive intake of central nervous system (CNS) stimulants such as caffeine-containing drinks can cause insomnia, as can anxiety disorders, depression, alcohol abuse, environmental factors (heat, cold and noise), pain, cardiac or respiratory disorders and jet lag. Furthermore, shift workers often suffer adverse effects on hormonal and metabolic patterns. It is important to treat the causes of insomnia individually.

Disorders of excessive daytime sleepiness may be due to inadequate sleep at night, excessive use of CNS depressants (including antidepressants, antihistamines and alcohol), and narcolepsy (sudden sleep attacks) or sleep apnoea causing disturbed sleep at night. Clinical Focus Box 20.1 lists some drugs that can cause insomnia or sedation.

Anxiety

Anxiety is a state of apprehension, agitation, uncertainty and fear resulting from the experience or anticipation of some stress or danger. It may impact on sleep cycles and may interfere with day-to-day activities. Anxiety is thought to be mediated in the limbic system (Fig 20.2); neurotransmitters particularly involved are noradrenaline, 5-hydroxytryptamine (5-HT [serotonin]) and **gamma-aminobutyric acid** (GABA), while the neuropeptide cholecystokinin appears to be a modulator in panic disorder. The orexin neuropeptides are

CLINICAL FOCUS BOX 20.1

Drugs associated with inducing insomnia or causing sedation

Drugs liable to induce insomnia or sleep disturbances

- ACE inhibitors (e.g. perindopril)
- Alcohol
- β-adrenoceptor antagonists (e.g. propranolol)
- CNS stimulants (amphetamines, caffeine)
- Corticosteroids
- Levodopa
- Methyldopa
- Metoclopramide
- Monoamine oxidase inhibitors
- Nicotine (cigarettes, gum, patches)
- Phenytoin
- Thyroid hormones
- Xanthines (caffeine, theophylline)

Withdrawal from CNS depressants can induce insomnia; these depressants include alcohol, barbiturates, benzodiazepines, tricyclic antidepressants, hypnotics and opioids.

Drugs liable to induce sedation or CNS depression

- Alcohol
- All CNS depressants (e.g. benzodiazepines, barbiturates, antiepileptics, general anaesthetics)
- Antihistamines
- Antipsychotics (phenothiazines)
- Cannabis (marijuana)
- Clonidine
- Melatonin
- Methyldopa
- Opioids
- Tricyclic antidepressants (high doses)

Effects of alcohol

It is notable that alcohol can induce insomnia or sleep disturbances and sedation. Alcohol is a CNS depressant; hence, it acts as a hypnotic, and is taken by many people as a 'nightcap'. However, it also disrupts sleep, delaying and reducing time spent in REM sleep, suppressing breathing and increasing snoring due to its muscle relaxant and nasal congestant effects (from additives in red wines, especially). It is recommended that alcohol not be drunk within about 2 hours of bedtime.

produced in discrete groups of neurons in the hypothalamus and are involved in regulation of the sleep–wake and activity cycles, feeding and reward-seeking, as well as anxiety and depressive behaviours. Orexin receptor antagonists are being investigated for their role in reducing panic/anxiety and promoting sleep (see under 'Miscellaneous Anxiolytics, Sedatives and Hypnotics' later).

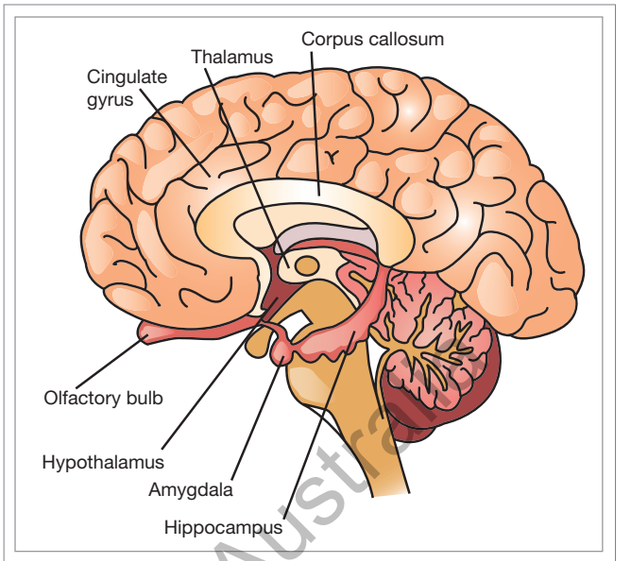

FIGURE 20.2 Sagittal section of the human brain, showing components of the limbic system

Anxiety is usually a natural psychological and physiological response to a personally threatening situation such as a threat to one's health, loved ones, job or lifestyle. Generally, this anxiety effectively stimulates the person to take constructive actions to counteract the perceived threats. In its extreme form, anxiety can be characterised by autonomic nervous system responses including rapid heart rate, dry mouth, sweaty palms, insomnia, loss of appetite, muscle tremor, diarrhoea and dyspnoea.

When excessive anxiety interferes with daily functioning, it may be necessary to seek help. Many non-pharmacological treatments such as counselling and behaviour modification therapies are available, while **anxiolytic** drugs (**antianxiety agents**) are commonly prescribed for the short-term treatment of anxiety. These drugs reduce feelings of excessive anxiety, such as apprehension, fear and panic, and reduce the physiological responses, such as dyspnoea and insomnia, thus improving sleep patterns. Hence, both directly and indirectly, anxiolytic drugs are also sedatives/hypnotics. The drug classes to be discussed in this context include benzodiazepines as well as antidepressants and atypical antipsychotics.

Generalised anxiety disorder

Generalised anxiety disorder exists when a person has symptoms of excessive anxiety, uncontrollable worry, irritability, muscle tension and sleep disturbances for a

KEY POINTS

Sleep and anxiety

- Sleep is a recurrent, natural, reversible condition of inertia, reduced consciousness and reduced metabolism.
- A person's sleep pattern is influenced by their emotional and physical state and is controlled from the ascending reticular activating system in the brainstem. The main neurotransmitters involved are histamine, noradrenaline (norepinephrine), serotonin and the orexins.
- The stages of sleep are monitored via an EEG and consist of two fundamental states that occur cyclically: non-REM and REM sleep.
- Sleep disorders, including insomnia, disorders of excessive daytime sleepiness, narcolepsy and sleep apnoea, cause many physiological dysfunctions. They are common, particularly in elderly people.
- Anxiety is a state of apprehension, agitation, uncertainty and fear resulting from the experience or anticipation of some stress or danger. It can impact on sleep cycles and may interfere with day-to-day activities.
- Anxiety is thought to be mediated in the limbic system. The neurotransmitters particularly involved are noradrenaline, 5-HT and GABA.
- Anxiety disorders include generalised anxiety, panic, obsessive–compulsive, phobic and post-traumatic stress disorders.
- Anxiolytic drugs (antianxiety agents) are commonly prescribed for the short-term treatment of anxiety. Drugs used for anxiety include benzodiazepines (sedatives and hypnotics), antidepressants and antipsychotics.
- Treatment of sleep disorders includes the sedatives and hypnotics; all are CNS depressants.
- Sedatives, including the benzodiazepines, reduce alertness, consciousness, nervousness or excitability. Hypnotics induce sleep.
- Non-pharmacological treatments for sleep disorders include promotion of good sleep patterns (sleep hygiene).
  - Owing to the risk of dependence, sedative/hypnotic drugs should be used only for limited periods.
  - In paediatric clients, caution is advised in using anxiolytics, sedatives or hypnotics, due to their CNS-depressant effects.
  - In geriatric clients, sleep disturbance is one of the most frequent concerns. Hypnotic/sedative drugs are used, although drug interactions, altered pharmacokinetics and increased sensitivity to CNS effects combine to cause frequent problems.

Sedatives, hypnotics and anxiolytics

A psychoactive drug that acts on the central nervous system and has a sedating effect is named **psycholeptic**. Psycholeptics include benzodiazepines, barbiturates, phenothiazines and opioids.

Benzodiazepines

The **benzodiazepines** are among the most widely prescribed drugs in clinical medicine, primarily because of their advantages over older sedative/hypnotic agents such as barbiturates, chloral hydrate and alcohol, and their action as anxiolytics. These advantages include:

- specific dose-related anxiolytic action
- lower fatality rates following acute toxicity and overdose
- lower potential for abuse
- more favourable adverse effect profiles
- fewer potentially serious drug interactions when administered with other medications
- the availability of a specific antidote (flumazenil).

Diazepam (well known as Valium; see Drug Monograph 20.1) is the prototype benzodiazepine. It was the most prescribed for many years until newer and safer (shorter acting) benzodiazepines such as temazepam and alprazolam were released. As the various benzodiazepines have similar pharmacodynamic effects, they will be discussed as a group; pharmacokinetic differences are summarised in Table 20.1.

Pharmacological effects

Benzodiazepines are not general CNS-depressants: specific actions include sedative, hypnotic, antianxiety, muscle-relaxant, antiepileptic and memory-impairing effects.

Mechanism of action

Benzodiazepines act via effects on receptors for the inhibitory CNS neurotransmitter GABA. This is the main inhibitory transmitter in the brain, at about 30% of all CNS synapses, in many pathways and brain areas (Table 18.1, in Ch 18). There are 11 different confirmed subtypes of $GABA_A$ receptors; all are ligand-gated chloride channels, composed of five sub-units, in the membranes of postsynaptic cells, and they mediate fast inhibition: when activated by GABA, there is an increase in chloride permeability and influx of chloride into the cell causing hyperpolarisation and decreased excitability of the neuron.

$GABA_A$ receptors have several modulatory sites at which drugs can act; particular sites have been identified as involved with different actions – for example, sedative, anxiolytic, muscle relaxant or affecting cognition. The natural endogenous ligand is (obviously) GABA, but other

Drug Monograph 20.1
Diazepam

Diazepam is the prototype benzodiazepine and, as such, has anxiolytic, sedative–hypnotic, muscle relaxant and antiepileptic actions.

Mechanism of action

Diazepam acts as an agonist at an allosteric modulatory site (sometimes confusingly referred to as the benzodiazepine receptor) to facilitate GABA binding to the $GABA_A$ receptors, changing conformation of the active site and thus enhancing the frequency of chloride channel opening, leading to more neuronal inhibition. This results in anxiolytic, sedative, hypnotic, muscle relaxant as well as antiepileptic effects.

Indications

Diazepam is indicated for short-term (a few days) management of anxiety, acute withdrawal from alcohol or benzodiazepines, acute behavioural disturbance, muscle spasm and spasticity, premedication and conscious sedation, and febrile seizures and epilepsy (as adjunctive treatment or for acute treatment of seizures such as in status epilepticus).

Pharmacokinetics

Diazepam is one of the longest-acting benzodiazepines because it is very lipid-soluble and has active metabolites, some of which themselves are administered as benzodiazepines (Table 20.1). However, owing to its metabolism to active derivatives and hence very long duration of action, other benzodiazepines may be indicated when short-acting sedatives are required or for the elderly.

Adverse reactions

All benzodiazepines can cause excessive CNS depression, dependence and neurological dysfunction.

Diazepam is likely to cause fatigue, drowsiness and muscle weakness. Less common adverse effects include disturbances of memory, gastrointestinal tract function, genitourinary functions and vision and skin reactions.

Paradoxical CNS stimulation can occur. Tolerance and dependence develop readily.

Drug interactions

Diazepam has additive CNS-depressant effects with all other CNS depressants, including alcohol, other sedative–hypnotics, antihistamines, anaesthetics, antidepressants and antiepileptic agents.

Many drugs can inhibit the metabolism of diazepam and hence prolong its effects; examples are cimetidine and fluconazole (see also Drug Interactions 20.1).

Warnings and contraindications

Diazepam is contraindicated in people with chronic obstructive airways disease, severe respiratory or liver disease, sleep apnoea, myasthenia gravis and dependence on other substances or hypersensitivity to benzodiazepines.

It should be prescribed only for short periods. Dependence develops readily and a long withdrawal period may be necessary to avoid withdrawal seizures.

Diazepam should be used only with caution in people with glaucoma, impaired kidney or liver function, depression or other psychosis, elderly or very young people, or during pregnancy or lactation. In pregnancy consider the use of shorter acting benzodiazepines.

Dosage and administration

Dosage should be individualised depending on the person's liver and kidney functions, age and the indication for which the drug is prescribed

- agitation and anxiety: diazepam is normally given orally, the adult dose being 2–5 mg up to a maximum of 10 mg daily; it can also be administered IV or by rectal solution
- premedication: IV, 0.1–0.2 mg/kg
- acute severe anxiety, agitation, behaviour disturbance: IV, 5–10 mg, repeated if necessary every 5–10 minutes to a maximum of 30 mg.

endogenous ligands have been identified, including some neuropeptides and steroid metabolites. These could be considered the body's 'natural diazepam', by analogy with endorphins being named as the body's endogenous morphine.

Benzodiazepines do not act as agonists by occupying the entire $GABA_A$ receptor or at the active site but act at an allosteric modulatory site (sometimes confusingly referred to as the benzodiazepine receptor) to facilitate GABA binding to the $GABA_A$ receptors, changing conformation of the active site and thus enhancing the frequency of chloride channel opening, leading to more neuronal inhibition. The limbic system (Fig 20.2),

TABLE 20.1 Pharmacokinetic overview: benzodiazepines

NAME	DURATION OF ACTION	HALF-LIFE (h)	ACTIVE METABOLITES (HALF-LIFE [h])	MAIN INDICATIONS
Midazolam	VS	1–3	1-hydroxymidazolam (1–3)	Sedation, premedication, induction anaesthetic, status epilepticus
Alprazolam	S	11–16	4-hydroxyalprazolam and α-hydroxyalprazolam (10–15)	Anxiety, panic
Oxazepam	S	5–15	None	Anxiety, alcohol withdrawal
Temazepam	S	5–15	None	Insomnia
Bromazepam	M	12–24	3-hydroxybromazepam (20)	Anxiety
Lorazepam	M	10–20	None	Anxiety, insomnia, premedication
Clobazam	L	18–48	N-desmethyl-clobazam (2–5 days)	Anxiety, insomnia, epilepsy
Clonazepam	L	18–50	None	Epilepsy
Diazepam	L	20–70	Desmethyldiazepam (30–100) Temazepam (8–15) Oxazepam (5–15)	Anxiety, alcohol withdrawal, agitation, muscle spasm, premedication, sedation, status epilepticus
Flunitrazepam	L	20–30	7-amino-flunitrazepam and *N*-desmethyl-flunitrazepam (10–16, 23–33)	Insomnia
Nitrazepam	L	25	None	Insomnia, infantile spasms, myoclonic epilepsy

L = long-acting; M = medium-acting; S = short-acting; VS = very short-acting

associated with the regulation of emotional behaviour, contains a highly dense area of GABA binding sites in the amygdala, suggesting that the antianxiety effects occur there. People with pathological anxiety have reduced numbers of GABA–benzodiazepine receptor complexes.

Other drugs also can bind to $GABA_A$ receptors; these include the Z-drugs (more selective at the alpha sub-unit) and the barbiturates, which have hypnotic/antiepileptic actions by acting as channel modulators. Barbiturates increase the duration of channel opening. Flumazenil (see later discussion) is an antagonist at the benzodiazepine binding site on the $GABA_A$ receptor, where it decreases the binding of GABA so the chloride channels remain closed. Flumazenil is anxiogenic and is used to treat benzodiazepine overdoses.

Indications for clinical use

The most common indications for benzodiazepines include anxiety disorders, panic disorders, insomnia and sleep disturbances, seizure disorders, alcohol withdrawal, muscle spasm, preoperative medication and to calm aggressive patients (see Fig 20.3, later). They are also used to induce amnesia during cardioversion and endoscopic procedures. The choice of benzodiazepine depends on pharmacokinetic characteristics (Table 20.1), with longer-acting (long half-life) agents such as diazepam preferred for treating anxiety and epilepsy and short-acting agents such as temazepam and midazolam (Drug Monograph 20.2) preferred for induction of anaesthesia or sleep and for treating insomnia. Medium-acting sedative drugs are useful for ensuring early-morning wakefulness.

Anxiety disorders

Diazepam or medium-acting (lorazepam) or long-acting benzodiazepines (clonazepam and flunitrazepam) are commonly used as antianxiety agents. There is overuse and abuse of these drugs (known previously as 'mother's little helpers') when preferably the causes of anxiety should be addressed, and long-term coping methods encouraged. Antidepressants are also effective in generalised anxiety disorders but have significant unwanted adverse effects.

Panic disorders

First-line treatment for panic attacks and panic disorder is non-pharmacological: many people respond to cognitive behaviour therapy and lifestyle changes, particularly control of caffeine and alcohol use. Benzodiazepines are effective, but the requirement for chronic administration (6–12 months) and the likelihood of dependence and sedation limit their usefulness. Various types of antidepressant drugs are also effective.

Sleep disorders

Generally, sedative drugs are indicated only for short-term treatment of insomnia (2–4 weeks), after sleep hygiene is addressed, owing to the risk of dependence developing and broken sleep after withdrawal. The preferred hypnotics

DRUG INTERACTIONS 20.1
Benzodiazepines

DRUG OR DRUG GROUP	LIKELY EFFECTS AND MANAGEMENT
CNS depressants such as alcohol, antihistamines, antianxiety agents, opioids, other sedatives/hypnotics, psychotropic agents (especially clozapine) and antidepressants	Enhanced CNS-depressant effects, sedation and respiratory depression; monitoring is necessary because the dosage of one or both drugs may need adjustment
Many drugs can inhibit the metabolism of benzodiazepines (especially drugs that inhibit CYP3A4); examples are azole antifungals (itraconazole), cimetidine, verapamil, omeprazole, macrolide antibiotics (erythromycin, clarithromycin), fluoxetine and some antivirals used against HIV infection	CNS depression and respiratory depression effects of benzodiazepines are prolonged; reduce dose or substitute a non-interacting drug
Drugs can increase benzodiazepine metabolism (carbamazepine, phenytoin, rifampicin, St John's wort)	Higher dose of benzodiazepine may be required
Stimulant drugs such as theophylline may reduce the sedative effects of benzodiazepines	Increase benzodiazepine dose if necessary
Drugs that lower the seizure threshold, including many antipsychotics, antivirals and antimicrobials	Benzodiazepines used cautiously, if at all

(Ch 18). They can also produce a useful **anterograde amnesic effect**; that is, they minimise the person's memory of the procedure.

Muscular spasms

Benzodiazepines, especially diazepam, are useful as adjunct medications for treating skeletal muscle spasms, caused by muscle or joint inflammation, or spasticity resulting from upper motor neuron dysfunction, such as cerebral palsy and paraplegia.

Withdrawal from CNS depressants

Acute withdrawal from regular use of CNS depressants such as alcohol, barbiturates or benzodiazepines can lead to acute agitation, anxiety, tremors and headache, and may require treatment with more CNS depressants. The withdrawal should be gradual. Withdrawal symptoms can include anxiety, dysphoria, irritability, insomnia, nightmares, sweating, memory impairment, hallucinations, tachycardia, psychosis, tremors and seizures. The benzodiazepines most often used to treat alcohol withdrawal syndromes are diazepam and oxazepam.

Pharmacokinetics

The pharmacokinetic properties of the benzodiazepines vary widely and determine the choice between the drugs in this group. For example, half-lives range from about 2 to 70 hours, and there are many metabolic interconversions to active metabolites with long half-lives (Table 20.1). The injectable benzodiazepines include diazepam and midazolam. The onset of sedative, anticonvulsant, antianxiety and muscle-relaxant effects of these agents after intravenous administration occurs at 1–5 minutes.

Absorption and distribution

Most benzodiazepines are lipid-soluble and readily absorbed from the gastrointestinal tract; diazepam and flunitrazepam are the most rapidly absorbed and produce a prompt and intense onset of action. The benzodiazepines become widely distributed in the body and brain. Redistribution from the CNS to peripheral tissues can reduce the duration of action; for example, although diazepam has a long half-life, it has only a short duration of antiepileptic action after IV administration. Midazolam is water-soluble, so is readily formulated for injection. It has a short action because its (active) metabolite has a shorter half-life than the parent drug.

After multiple doses, benzodiazepines accumulate in the body's fluids and tissues, which act as storage depots and account for the prolonged sedative actions even after the drugs have been discontinued. These drugs are mostly highly protein-bound (> 85%); protein binding is reduced in newborns, in those with alcoholism and in those with cirrhosis or impaired liver function.

Elimination

The gastrointestinal tract and the liver are the sites of metabolism. Benzodiazepines are often hydroxylated or demethylated to active derivatives, including desmethyldiazepam, a long-acting metabolite (30–100 hours). The long-acting benzodiazepines such as diazepam with active metabolites oxazepam and temazepam are more apt to accumulate, especially in the elderly, resulting in higher risk of falls and hip fractures (Clinical Focus Box 20.3). Oxazepam and lorazepam are metabolised to inactive metabolites and are preferred agents in elderly people and people with liver disease. Metabolites are generally excreted by the kidneys.

CLINICAL FOCUS BOX 20.3
Falls and fractures in the elderly

Studies have shown that each year about 30% of people aged over 65 have a major fall, with the rate even higher in nursing homes; many falls lead to fractures, particularly hip fractures with severe associated morbidity and mortality (Westaway et al. 2019). Tracing links between medications and falls reveals:

- a twofold increased risk of falls and fractures in elderly people taking psychotropic drugs, especially antidepressants and benzodiazepines
- other drugs commonly taken by elderly people that increase risk of falls include cardiovascular drugs, non-steroidal anti-inflammatory drugs, antiepileptics, antiparkinson drugs, opioids and diuretics
- antipsychotic drugs are more commonly prescribed in nursing homes than for elderly people in other locations
- the greater the use of CNS depressants such as benzodiazepines, antidepressants, antipsychotics and opioids, the worse is the decline in cognitive function over 5 years
- higher doses and increased number of CNS medications increase the risk of falls, with an extra two falls per year likely
- in middle-aged and older adults, polypharmacy, including antidepressant or benzodiazepine use, is associated with injurious falls and a greater number of falls.

It is recommended that hypnotics should be reserved to treat acute insomnia and, when prescribed, limited to short-term or intermittent use to avoid the development of tolerance and dependence. Further, psychotropic drug use in the elderly should be minimised and monitored, especially in nursing home residents. Refer to Chapter 41 for drugs in aged care.

Drug interactions

Significant drug interactions can occur when benzodiazepines are used in combination with other CNS depressants or with drugs that affect their metabolism (Drug Interactions 20.1, earlier). Effects are often unpredictable, so patients should be monitored closely. Drug metabolism interactions occur particularly with alprazolam, diazepam and midazolam; there are relatively fewer metabolic interactions with lorazepam, oxazepam and temazepam. (Reference sources such as *Australian Medicines Handbook* should be consulted for interactions with specific benzodiazepines.)

Adverse drug reactions

Excessive CNS depression

As a group, the benzodiazepines commonly cause excess CNS depression: drowsiness, ataxia, diplopia, vertigo, lassitude, memory loss, slurred speech and loss of dexterity. Less frequently, headaches, decreased libido, anterograde amnesia, muscle weakness and hypotension can occur, as well as increased behavioural problems (anger and impaired ability to concentrate), seen mostly with children. Neurological reactions include paradoxical insomnia, increased excitability, hallucinations and apprehension (Fig 20.3). There is a greater risk of falls and motor vehicle crashes, particularly in the elderly.

General points

Because elderly people are more sensitive to these agents than younger adults and are at risk of accumulating active drugs and of falls, non-pharmacological approaches are recommended to treat their sleep disturbances. Both paediatric and geriatric patients are at risk of paradoxical-type reactions (CNS stimulation, rather than depression) from sedative drugs. It is recommended that prescriptions for these agents be limited in these groups, with close monitoring.

Many other drugs can cause sedation and CNS depression, including anaesthetics, alcohol, antipsychotics and antidepressants, opioid analgesics, melatonin and antihistamines. Insomnia can also be an adverse effect of drugs, especially CNS stimulants such as the amphetamines and caffeine-containing drinks.

Management of benzodiazepine overdose

Benzodiazepine overdose is manifest as CNS depression, ranging from confusion and drowsiness through to coma, hypotonia, hypotension and respiratory depression.

Overdose is not usually life-threatening unless multiple other CNS depressant drugs have been taken. Supportive treatment is necessary, and may include maintaining an adequate airway with oxygen for depressed respiration, monitoring vital signs and promoting diuresis by administering IV fluids. Hypotension must be monitored and might require vasopressors such as noradrenaline (norepinephrine) or dopamine. Dialysis is of limited value in treating a benzodiazepine overdose.

Flumazenil

Intravenous administration of flumazenil, a specific benzodiazepine antagonist, is sometimes required to treat a benzodiazepine overdose or reverse the sedative effects of benzodiazepines after surgical or diagnostic procedures to avoid intubation and intensive care admission. It may precipitate withdrawal symptoms and seizures in people taking benzodiazepines to control epilepsy, or in mixed overdoses with benzodiazepines and proconvulsant drugs such as antidepressants or CNS stimulants.

Flumazenil is administered IV, with antagonistic effects (reversal of sedation) occurring within 2 minutes and duration of action of 1–3 hours. Because most

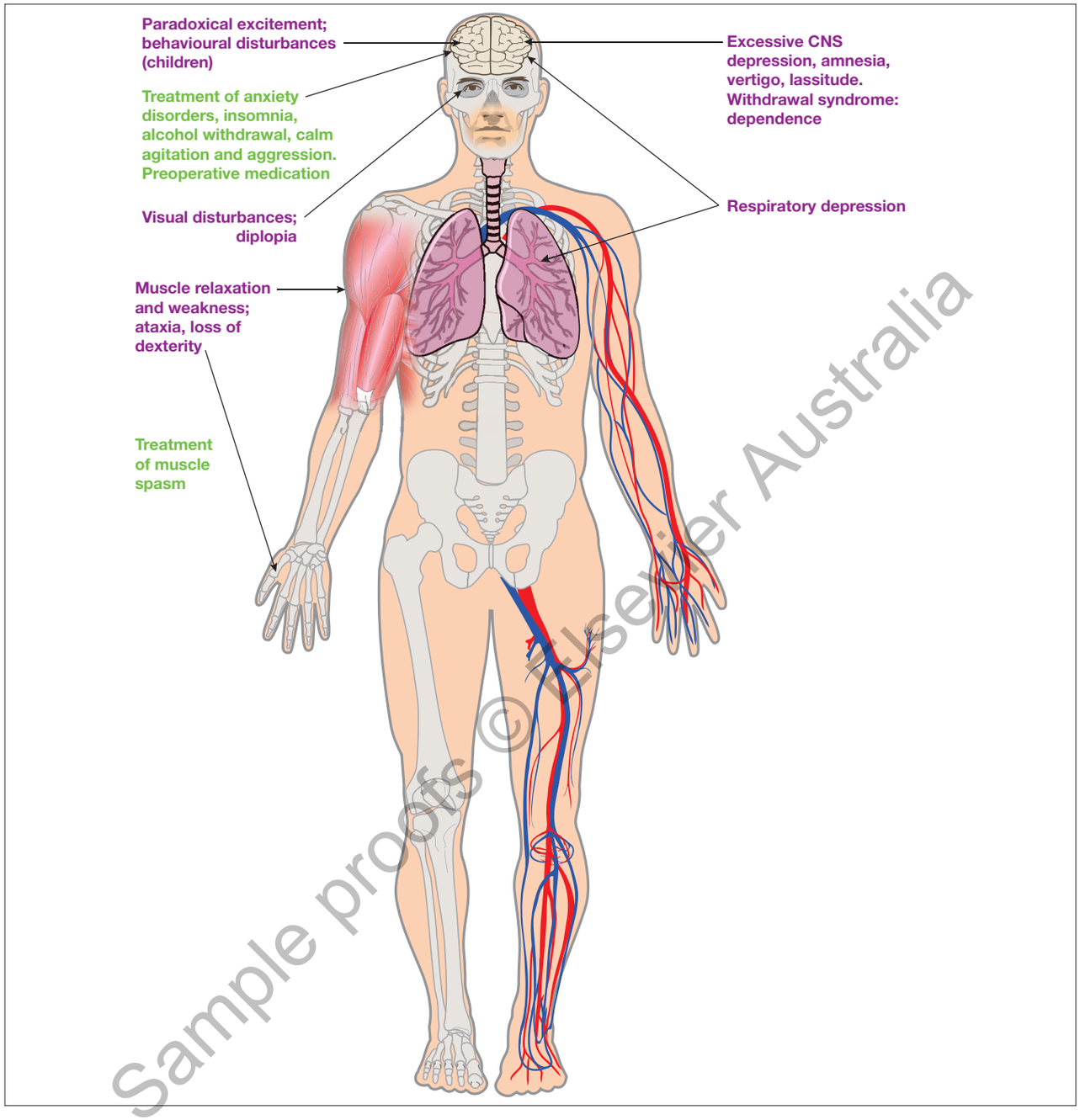

FIGURE 20.3 Pharmacological effects of benzodiazepines

benzodiazepines have a half-life longer than an hour, repeated injections of flumazenil are necessary. The drug is metabolised in the liver and excreted by the kidneys. Adverse reactions reported with this drug include headache, visual disturbance, increased anxiety, nausea and light-headedness.

Tolerance and dependence associated with benzodiazepine use

With chronic administration, tolerance develops to the sedative effects but less often to the anxiolytic effects. Dependence is common and leads to craving, overuse and abuse of these drugs, and drug-seeking behaviours.

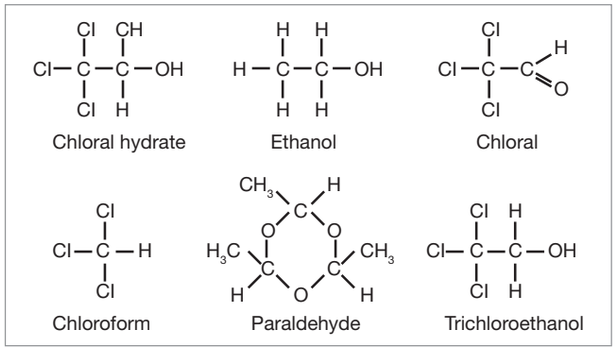

FIGURE 20.4 Chemical structures of some simple sedative drugs showing close structural relationships between the sedative chloral hydrate, anaesthetic chloroform, depressant ethanol (alcohol) and sedative paraldehyde, which can be visualised as three molecules of ethanol joined in a cyclical ether formation.

CNS-depressant effects additive but trichloroethanol also inhibits the metabolism of alcohol and prolongs its actions.

Orexin antagonists

Orexin neuropeptides are produced in discrete groups of neurons in the hypothalamus; they are involved in regulation of the sleep–wake and activity cycles, feeding and reward-seeking. They activate two G-protein-coupled receptors (OX_1R and OX_2R), the relative roles of which are still being established. Orexin receptor antagonists are being investigated for their role in reducing panic/anxiety and promoting sleep (Han et al. 2019).

These antagonists inhibit the action of the wakefulness-promoting orexin neurons of the arousal system reducing activity and promoting sleep; OX_2R antagonists mainly increase non-REM sleep and may be useful in treating insomnia, while dual antagonists such as suvorexant increase REM sleep.

Older drugs

Bromides

Bromide salts such as potassium bromide were used in medicine as antiepileptic agents and as sedative–hypnotics from the mid-1850s to the mid-20th century (Lampe 2013). Bromide ion is absorbed in the body and replaces chloride (biologically the more common halide ion) in extracellular fluids. Bromide acts in the CNS as a depressant and sedative, and in (not much) larger doses it depresses motor activity and reflexes. At toxic levels it causes ataxia, delirium, coma and death and is particularly toxic as a cumulative poison, so it has been replaced by safer drugs.

Paraldehyde

Paraldehyde is a polymer of acetaldehyde (Fig 20.4); it is a colourless liquid with a strong odour and taste. The CNS-depressant effects of paraldehyde are similar to those of alcohol, barbiturates and chloral hydrate; it depresses various levels of the CNS, including the ascending reticular activating system. It is used when other agents are inappropriate or ineffective. It may also be used to treat convulsive episodes arising from tetanus, status epilepticus and poisoning by convulsive drugs, and in reducing the anxiety associated with withdrawal from drugs such as narcotics or barbiturates, or delirium tremens due to alcohol withdrawal. Paraldehyde was used in the past as a sedative–hypnotic agent but has been superseded by safer and more effective drugs.

Complementary and alternative sedatives and anxiolytics

Many natural products and techniques from complementary and alternative medicine (CAM) have been used to attain sleep or relieve stress and anxiety. For treating insomnia, the natural products melatonin, valerian, kava kava, lavender, lemon balm, passionflower, hops, withania and L-tryptophan have been shown to be clinically effective.

In the treatment of anxiety, music therapy, massage, acupuncture, selenium and many herbs (Baical skullcap, ginger, *Ginkgo biloba*, ginseng, licorice and St John's wort) as well as the Chinese herb *Suan Zao Ren Tang* have been shown to be effective.

KEY POINTS

Miscellaneous anxiolytics, sedatives and hypnotics

- Miscellaneous anxiolytics, sedatives and hypnotics include the following:
  - Buspirone is indicated for treating generalised anxiety disorders (only available in Australia under the special access scheme). Its exact mechanism of action is unknown.
  - Dexmedetomidine is used for procedural sedation. It is related to the α_2-adrenoceptor agonists such as clonidine, and exhibits similar pharmacological profiles.
  - Melatonin (*N*-acetyl-5-methoxytryptamine) is chemically related to 5-HT and is a hormone secreted by the pineal gland in darkness hours. It acts on melatonin receptors in the hypothalamus and may help reset the body's circadian rhythm 'clocks'.
  - The older antihistamines (histamine H_1-antagonists, e.g. promethazine) have significant sedative effects, as well as being useful in suppressing allergic reactions (and as antiemetics). These are non-prescription medications, and antihistamine mixtures are sometimes used as mild sedatives for children.

- Chloral hydrate is related structurally to both chloroform and ethanol and is now used mainly as a mild hypnotic or preoperative sedative. Its use as a sedative has been superseded by less toxic agents.
- Orexin receptor antagonists promote sleep; mainly increasing non-REM sleep. Suvorexant is an example of a dual antagonist.
- Older drugs include the bromides and paraldehyde. Although bromides are no longer used, paraldehyde is used when other agents are inappropriate or ineffective.
- Many natural products and techniques from CAM have been used to attain sleep or relieve stress and anxiety.

DRUGS AT A GLANCE
Antianxiety, sedative and hypnotic drugs

PHARMACOLOGICAL GROUP AND EFFECT	KEY EXAMPLES	CLINICAL USE
Antianxiety/sedative agents		
Benzodiazepines • Act at an allosteric modulatory site to facilitate GABA binding to the $GABA_A$ receptors, changing conformation of the active site and enhancing the frequency of chloride channel opening, leading to more neuronal inhibition		
• Long acting	Diazepam	Sedation, anxiety
• Short acting	Alprazolam	Insomnia, anxiety
• Very short acting	Midazolam	Insomnia
Other sedative/hypnotics		
Barbiturates • Act at an allosteric modulatory site (distinct from benzodiazepine site) to facilitate GABA binding to the $GABA_A$ receptors, changing conformation of the active site and increasing the duration of chloride channel opening, leading to more neuronal inhibition	Phenobarbital (phenobarbitone)	Sedation
Z drugs • Agonists at the $GABA_A$ receptors and more selective at the alpha sub-unit than the benzodiazepines (see benzodiazepine actions above)	Zopiclone[NZ, AUS]	Insomnia
Miscellaneous sedatives, anxiolytics, hypnotics		
• High affinity for and partial agonist activity at 5-HT_{1A} (serotonin) receptors and a moderate affinity for agonist activity at dopamine D_2 receptors in the CNS	Buspirone	Generalised anxiety disorders
• Related to α_2-adrenoceptor agonists; acts in CNS to stimulate imidazoline –1 receptors (I_1) resulting in a central hypotensive and antiarrhythmic	Dexmedetomidine	Procedural sedation
Acts on melatonin MT_1 and MT_2 receptors, in the anterior hypothalamus and promotes sleepiness; it may help re-set the body's circadian rhythm	Melatonin	Jet lag, insomnia
• Histamine 1 receptor antagonists; significant sedative effects by blocking histamine (as well as muscarinic and other receptors) in the CNS	Diphenhydramine, doxylamine, promethazine	Sedation
• Exact mechanism of action is unknown. It has a general CNS-depressant effect similar to that of alcohol.	Chloral hydrate	Mild hypnotic or preoperative sedative (paediatric)
Orexin antagonists • OX_1R and OX_2R antagonists inhibit wakefulness, promoting orexin neurons of the arousal system	Suvorexant[AUS]	Insomnia
Benzodiazepine antagonists		
• Antagonism of action of GABA and benzodiazepines at the GABA receptor complex	Flumazenil	Benzodiazepine overdose

[AUS] = Australia only
[NZ] = New Zealand only

CHAPTER 41

DRUGS IN AGED CARE

Kathleen Knights

KEY ABBREVIATIONS

ADRs	adverse drug reactions
DBI	drug burden index
FRIDs	fall risk-increasing drugs
PIMS	potentially inappropriate medications
QUM	quality use of medicines
RACF	residential aged care facility
RMMR	Residential Medication Management Review

KEY TERMS

Beers Criteria 909
deprescribing 912
Drug Burden Index 909
polypharmacy 907

Chapter Focus

A significant proportion of the Australasian population are aged 65 years or older. Although many live independently and lead healthy and productive lives, increasing disease burden and/or physical/cognitive impairment often results in a move to residential aged care facilities. Those living in aged care in general have a greater number of comorbidities and experience a higher incidence of polypharmacy and drug-related harms. The latter often results in increasing risk of falls, hospitalisation and/or death. Multiple drug groups are implicated in increasing falls risk. Residential Medication Management Review and the process of deprescribing play a role in addressing/reducing inappropriate polypharmacy and the harms associated with multiple drug use in older adults.

KEY DRUG GROUPS

Anticholinergics

Antipsychotics

Benzodiazepines

CRITICAL THINKING SCENARIO

Kitty, an 84-year-old, lives in a residential aged care facility and has multiple health issues including hypertension, diabetes and Parkinson's disease. Staff at the facility have asked for a Residential Medication Management Review because they have noticed a deterioration in Kitty's health including episodes of dizziness, confusion, memory impairment and increasing drowsiness. For her Parkinson's disease Kitty has been taking benzatropine 5 mg daily for the past 2 years.

1. Discuss the relationship between benzatropine and her current clinical symptoms.
2. What age-related factors may have contributed to developing her current symptoms?
3. What actions could be taken at this stage to improve her clinical condition?

Introduction

'Population ageing is a human success story, a reason to celebrate the triumph of public health, medical advancements, and economic and social development over diseases, injuries and early deaths that have limited human life spans throughout history.'

United Nations 2019

In 2019 approximately 10% (703 million) of the world's population were aged 65 years or older. This is expected to double to 1.5 billion people by 2050, which equates to one in every six people being older adults (65 years or older) (Australian Bureau of Statistics 2017). In Australia, one in seven people were aged 65 years or older in 2011, and one in six in 2016. This is expected to rise to one in five by 2031. With a total population of 5,122,600 15.9% of the New Zealand population (June 2021; 819,100 people) were aged 65 years or older, and the proportion of people aged 85 years or older is projected to double by 2063 (Stats NZ 2021). Australians and New Zealanders can, on average, expect to live long (80–85 years) and relatively healthy lives. However, the continued rise in the proportion of aged people in the population has placed, and will continue to place, increased pressure on support systems. This is not limited to just the support provided by the family but more broadly the vast array of aged-care services funded by government and private providers. The long-term goal for any ageing person should be the ability to balance age-related changes in their physical and psychological health with a healthy, productive and socially inclusive lifestyle. However, for many people a decline in their physical and/or mental health necessitates a change to their living environment.

In 2020, 189,954 people, of which 50% were aged between 80 and 89 years, lived in residential aged care facilities (RACFs) in Australia (Australian Institute of Health and Welfare 2021). In 2017–18, 31,600 New Zealanders lived in RACFs, of which about 25% were aged 85 years or older. The need for cultural inclusivity in New Zealand RACFs is evident from the fact that around 5% of residents identified as Māori and 2% as Pacific Islanders (Stats NZ 2021). Throughout Australasia, RACFs are divided into three categories:

- self-care retirement villages (low-level care)
- hostels (intermediate-level care)
- nursing homes (high-level care).

Clearly many factors will impact on both the quality of life of and the level of care of an aged person in an RACF. Not surprisingly these factors include long-term health conditions (Clinical Focus Box 41.1), physical limitations/disabilities (e.g. incomplete use of arms or legs), cognitive issues and medication use. It is estimated that about 75% of aged care residents have between five and 10 long-term health conditions. In addition, 53% of residents in Australian RACFs have dementia including Alzheimer's disease (Australian Institute of Health and Welfare 2020).

Changes in pharmacodynamics and pharmacokinetics with ageing

Pharmacotherapy in the older population is challenging because this group in general:

- often have multiple comorbidities
- take a high proportion of prescribed drugs and over-the-counter medications
- take three times more drugs than younger people
- frequently take multiple medications (four to five prescription drugs at any one time)

CLINICAL FOCUS BOX 41.1

Examples of long-term health conditions in older adults

Anxiety
Arthritis
Atrial fibrillation
Cerebrovascular disease
Chronic obstructive pulmonary disease
Congestive heart failure
Dementia
Depression
Diabetes
Hyperlipidaemia
Hypertension
Insomnia
Migraine
Osteoporosis
Partial/complete deafness
Peripheral vascular disease
Stroke
Vision impairment

- experience drug interactions and adverse drug reactions (ADRs) more frequently than younger adults.

The pattern of drug use also varies depending on the setting; for example, in the community, use of analgesics and cardiovascular drugs (e.g. antihypertensive, statins, anticoagulants) is common, while in RACFs there is also a tendency for greater use of sedative-hypnotics and antipsychotics (see later sections). Without a doubt many drugs are beneficial (e.g. antihypertensives, oral hypoglycaemic agents, antibiotics), and appropriate prescribing in older adults is very much a balance between benefits and harms. Unfortunately, the incidence of **polypharmacy** (commonly defined as the concomitant use of five or more drugs) is high, and this can impact negatively on the quality of life of older people by increasing the incidence of ADRs. Drug interactions and ADRs may then contribute to a reduction in daily physical/social activities and increase mortality. In addition to polypharmacy, other medication-related issues that can affect the quality of life of older people are age-related alterations in pharmacodynamics and pharmacokinetics.

Pharmacodynamic changes with ageing

Changes in target-organ or receptor sensitivity in older adults may result in either a greater or a lesser drug effect than normal. The reason for this alteration is often unknown, but it may be due to either a decrease in the number of receptors at the target site or an altered receptor response (second-messenger effect) subsequent to drug binding. Older people often have a decreased response to β-adrenoceptor agonists (e.g. salbutamol) and β-adrenoceptor antagonists (e.g. propranolol), but they have a greater response (e.g. central nervous system [CNS] depression) to diazepam. It has also been reported that the muscarinic receptor density in the cortex tends to decrease with ageing, so older adults are often very sensitive to anticholinergic drugs.

Pharmacokinetic changes with ageing

It has been estimated that 70–80% of all ADRs in the older population are dose-related. As physiological changes (Fig 41.1) may alter the pharmacokinetics of a drug, this can lead to higher blood and tissue concentrations of drugs and/or their metabolites, thus increasing the incidence of ADRs.

Absorption and distribution

Pharmacokinetics of a drug may be altered in old age because of reduced gastric acid secretion and slowed gastric motility, resulting in unpredictable rates of dissolution and absorption of drugs. Changes in absorption may occur when gastric acid production decreases, altering the absorption of weakly acidic drugs such as barbiturates. However, few studies of drug absorption have shown clinically significant changes occurring with advanced age.

Changes in body composition, such as an increased proportion of body fat and decreased total body water, plasma volume and extracellular fluid, have been noted in the older population. The increased proportion of body fat increases the volume of distribution of some lipid-soluble drugs (e.g. benzodiazepines), prolonging half-life. The half-life of diazepam increases from 20 hours in a 20-year-old to 90 hours in people in their 80s because of the increase in volume of distribution in the latter. The loss in total body water and lean body mass (decreased volume of drug distribution) in many older people may require initiation of therapy at a lower adult dose or re-evaluation of dosages of polar drugs already in use because the risk of toxicity with hydrophilic (water-soluble) drugs increases as total body water decreases. Digoxin, theophylline, lithium and gentamicin are examples of hydrophilic drugs that may accumulate, causing adverse effects.

In older adults, the criterion for dosage should be shifted from age to weight, as some older people weigh no more than the average large child and some weigh a lot less, yet they are often prescribed the 'normal' adult doses.

Metabolism

Hepatic drug metabolism is also affected by ageing. For drugs with a high extraction ratio, the clearance is rate-limited by blood flow and hence, with an age-related

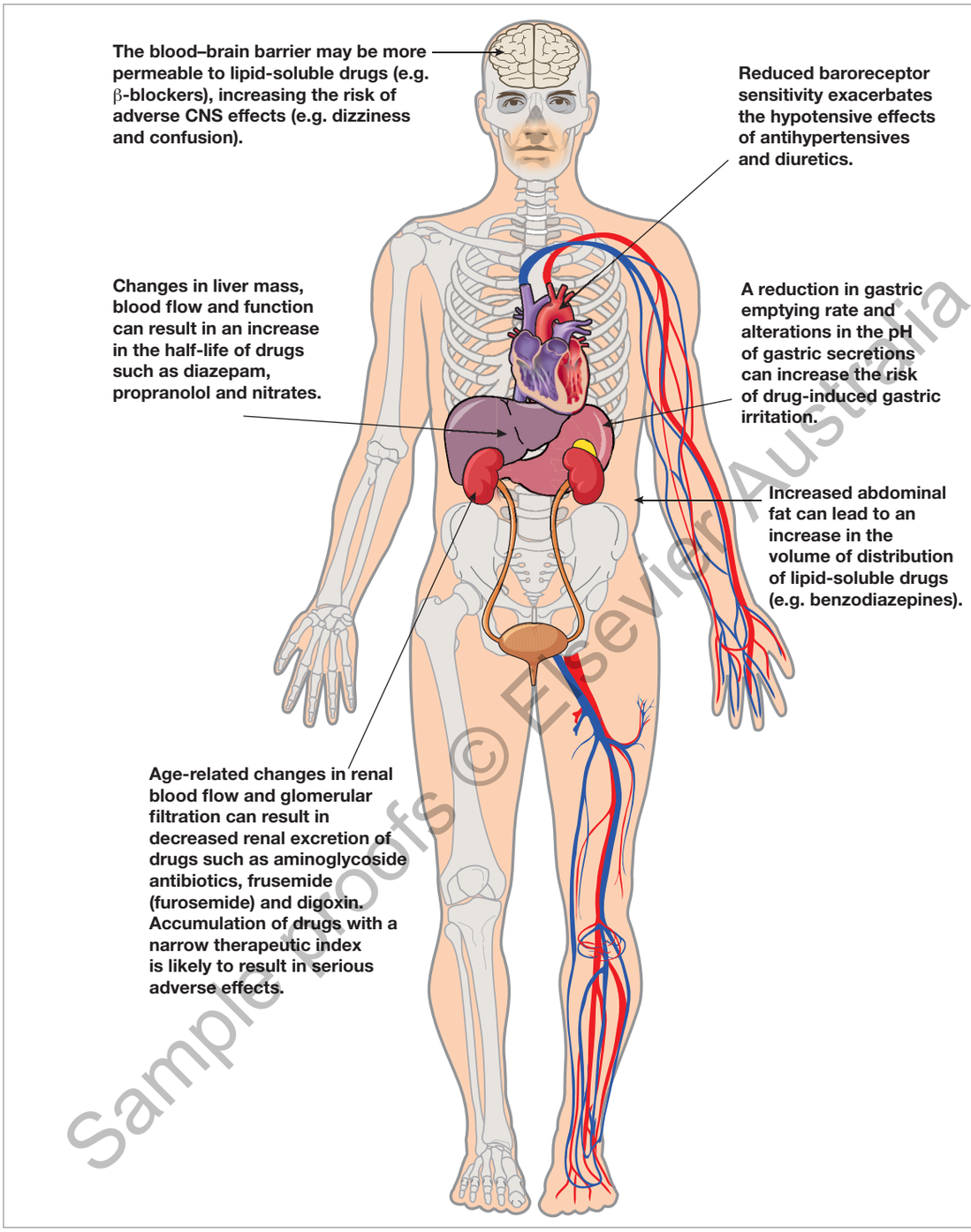

FIGURE 41.1 Physiological changes with ageing that impact on the pharmacokinetics of drugs.
Source: Figure 8.1 from the 5th edition. Goodman RM, Gorlin RJ. Atlas of the face in genetic disorders, ed 2 St louis, MO, 1977, Mosby

decrease in liver blood flow, the hepatic extraction of high clearance drugs will be affected (Ch 6). Drugs that are metabolised by functionalisation reactions (e.g. oxidation, hydroxylation or demethylation) may have a decreased metabolism, while conjugative metabolism (e.g. glucuronidation) appears not to be affected by ageing (Ch 4). Disorders common to the older population, such as congestive heart failure, may impact on liver function and decrease the metabolism of drugs, increasing the risk of drug accumulation and toxicity.

Renal excretion

For drugs primarily excreted by the kidneys, reduced renal function may result in drug accumulation and toxicity because a significant proportion of older adults have some degree of renal dysfunction. Renal function may be impaired because of loss of nephrons, decreased renal blood flow and decreased glomerular filtration rate. A reduction in renal function is also secondary to heart failure. Decreased renal clearance may cause increased plasma drug concentrations and longer half-lives of drugs and active metabolites excreted by the kidney.

A 2015 Australian study identified inappropriate prescribing of renally cleared drugs in older residents in both the community and RACFs. The drugs inappropriately prescribed included alendronate, fenofibrate, glibenclamide, olmesartan, metformin, perindopril and the gliptins (Khanal et al. 2015). When compromised renal function is suspected, determination of creatinine clearance and the use of therapeutic drug monitoring will help optimise dosing in this group.

KEY POINTS

Changes in drug disposition with ageing

- Age-related changes in target-organ or receptor sensitivity can result in enhanced or diminished drug response (e.g. increased CNS depression with diazepam but reduced response to salbutamol and propranolol).
- Pharmacokinetics of a drug in older adults can be altered by a reduction in gastric acid secretion, slowed gastric motility, changes in body composition (e.g. increased body fat and decreased total body water, plasma volume and extracellular fluid).
- Changes in body fat increases the volume of distribution of lipid-soluble drugs (e.g. benzodiazepines), increasing half-life.
- Reduction in total body water decreases the volume of distribution of hydrophilic (water-soluble) drugs, necessitating a reduction in dose.
- Weight-related changes in older adults should be taken into consideration when initiating drug therapy.

Drug treatment for older adults

Drug treatment in older adults is often a challenging process because of changes in physiology, the impact of acute and chronic disease states and alterations in drug pharmacodynamics and pharmacokinetics that occur with ageing. Some factors for consideration when considering drug treatment in this group include:

- balancing the risks and benefits for the person
- referring to evidence-based guidelines and treating comorbid diseases as appropriate
- optimising polypharmacy, using the simplest drug regimen and avoiding over/under treatment
- using the lowest dose to achieve the desired clinical outcome
- considering any new symptoms as possible drug interactions or ADRs
- providing simple written and verbal instructions to the client and all people (e.g. RACF staff, carers, family members) involved in medication management
- undertaking regular Residential Medication Management Reviews (see later section)
- deprescribing drug(s) (see later section).

Beers Criteria

Developed by Mark H Beers in 1991 (updated 2003, 2012, 2015 and 2020), the evidence-based **Beers Criteria** is a tool widely used to guide prescribers on the drugs that should be:

(1) avoided in most older people
(2) avoided in older adults with certain conditions
(3) used with caution when the benefit outweighs the risk
(4) avoided in people with cognitive impairment or dementia (American Geriatrics Society 2015; Croke 2020).

Prescribing of potentially inappropriate medications (PIMs) according to the Beers Criteria in RACFs has been shown to increase the risk of hospitalisation and death (Lau et al. 2005). Table 41.1 lists examples of potentially inappropriate drug groups used in older people (independent of diagnoses), Beers Criteria and adverse effects.

Drug Burden Index

Unlike the Beers Criteria that provides a list of inappropriate drugs the **Drug Burden Index** (DBI) 'calculates individuals' exposure to anticholinergic and sedative drugs utilising dose-response and cumulative effect parameters' (Harrison et al. 2018). Calculation of the DBI takes into account:

- the daily dose of each anticholinergic or sedative drug taken by a person
- the minimum recommended daily dose registered with the Australian Therapeutic Goods Administration that achieves 50% of the maximum anticholinergic/sedative effect of the particular drug.

DBI ranges from 0 to 1, and a value of 0.5 indicates exposure of the person at the minimum recommended

TABLE 41.1 Examples of potentially inappropriate drug groups used in the older population, Beers Criteria and adverse effects

DRUG GROUP[a,b]	BEERS CRITERIA	ADVERSE EFFECTS
Anticholinergics (first-generation antihistamines)	Avoid	Blurred vision, dry mouth, constipation, confusion, urinary retention, nausea, delirium, orthostatic hypotension
Antidepressants (tricyclics)	Avoid	Sedation, agitation, delirium, dry mouth, blurred vision, confusion, cardiac dysrhythmias, dizziness, insomnia, tachycardia
Antipsychotics	Avoid (exceptions: schizophrenia, bipolar disorder or short-term use as antiemetic)	Increased risk of stroke, orthostatic hypotension, sedation, agitation, anxiety, blurred vision, cognitive impairment, extrapyramidal effects, mortality, hospitalisation
Barbiturates	Avoid	Physical dependence, sedation, confusion, cognitive impairment, altered mood and behaviour, paradoxical insomnia
Benzodiazepines	Avoid	Older adults have increased sensitivity (oversedation), ataxia, cognitive impairment, delirium, falls
Central α-blockers	Avoid	CNS effects, bradycardia, orthostatic hypotension
Digoxin	Avoid as first-line therapy for atrial fibrillation	Nausea, vomiting, cardiac dysrhythmias, visual disorders, mental status changes, hallucinations
NSAIDs	Avoid chronic use if possible	Gastritis, gastrointestinal bleeding, ulceration

[a] Drug group independent of diagnoses
[b] See American Geriatrics Society 2015 for details of individual drugs in each group.
Sources: Gnjidic et al. 2012; Adapted from American Geriatrics Society 2015.

daily dose. It has been demonstrated that in the older population a higher DBI score is associated with impaired physical functioning (Harrison et al. 2018), a lower quality of life (Hasan et al. 2020) and frailty (Australian Medicines Handbook 2021).

The impact of drugs on functional outcomes in older adults

Antipsychotics

Of particular concern is the use of antipsychotics to manage behavioural and psychological symptoms commonly associated with dementia. These symptoms fluctuate over time, occur episodically, negatively impact on the quality of life of the affected person, and are distressing for the family and other people living/working in the RACF. The use of antipsychotics in older people is complicated; in Lewy body dementia these drugs can worsen behaviours, increase agitation and further impair cognitive and motor function (Gnjidic et al. 2012). In addition, older drugs like haloperidol can increase the risk of stroke and death in older people. In Australia, risperidone is the only drug indicated for use in Alzheimer's disease to control severe behavioural and psychological symptoms, but use is not recommended beyond 12 weeks (Gnjidic et al. 2012).

Various programs to reduce the use of antipsychotics in RACFs have been implemented. These include in-house educational programs, pharmacist-driven regular medication reviews and involvement of multidisciplinary teams (pharmacists, doctors, nurses, RACF support staff) with a view to reducing antipsychotic drug use.

In recent times an emphasis has been placed on non-pharmacological approaches including personalised interventions that focus on distraction and reassurance rather than resorting in the first instance to antipsychotics to control behavioural and psychological issues (Aged Care Quality and Safety Commission 2020).

For more on antipsychotics, see Chapter 22.

Benzodiazepines

Insomnia is a common problem in the older population, manifesting in earlier bed and rise times, difficulty falling asleep, easy arousability, brief awakenings and in general lighter and less sleep. Consequently, an older insomniac experiences increased daytime cognitive and attentional impairment that may be misconstrued as early symptoms of dementia. Chronic sleep deprivation also increases the risk of cancer, stroke, heart disease, depression, anxiety, suicide and falls (Abad & Guilleminault 2018).

Non-drug strategies should always be first-line. These include:

- avoiding daytime naps, caffeine-containing drinks and alcohol consumption late in the day
- cognitive behaviour therapy, relaxation therapy, mindfulness interventions
- combinations of psychological and behavioural therapy.

In addition, rescheduling and adjusting the dose of medications that cause CNS stimulation and insomnia to morning or early afternoon (e.g. adrenoceptor agonists,

anticholinesterases, β-blockers, glucocorticoids, selective serotonin reuptake inhibitors) is advised.

Older people are more susceptible to the effects of benzodiazepines because of the increased volume of distribution and prolonged half-life. If adhering to the Beers Criteria, benzodiazepines should not be prescribed in this group because of the increased risk of ataxia, falls/fractures, excessive sedation, delirium and impaired cognition. However, benzodiazepines are widely prescribed in old age to treat anxiety and insomnia, but long-term use is not recommended (Aged Care Quality and Safety Commission 2020). The short-acting agents (e.g. temazepam, oxazepam) are preferred, while the long-acting benzodiazepines (e.g. diazepam, nitrazepam) should be avoided. Tolerance develops rapidly, and rebound insomnia is highly variable and occurs even with intermittent dosing. In general, benzodiazepines are not the drug of choice for the routine management of insomnia in older adults.

For more on benzodiazepines, see Chapter 20.

Drugs that increase the risk of falls

Falls in general can result in soft tissue injuries, fractures and short/long-term physical impairment. In the older population, falls contribute to loss of quality of life and an increase in morbidity and mortality. Not surprisingly, many studies have reported a high risk of falls in RACF residents who are either of an advanced age, have balance disorders, are frail, have diminished cognition, have physical impairments or who are taking psychotropic drugs or drugs known to cause orthostatic hypotension (Fig 41.2). Preventing falls is paramount, and all modifiable risk factors should be addressed including, for example, removing tripping hazards (e.g. loose floor mats) and reviewing the drugs administered.

In 2010 the Swedish National Board of Health and Welfare published a list of fall risk-increasing drugs (FRIDs) classifying them into two main categories

- drugs increasing the risk of falls
- drugs implicated in causing/worsening orthostatic hypotension (Clinical Focus Box 41.2).

CLINICAL FOCUS BOX 41.2
Examples of falls risk-increasing drugs

Drugs increasing falls risk

Antiarrhythmics
Antidepressants
Antipsychotics (excluding lithium)
Anxiolytics
Cardiac glycosides
Hypnotics and sedatives
Opioids

Drugs causing/worsening orthostatic hypotension

α-Adrenoceptor antagonists
Antidepressants
Antihypertensives
Antipsychotics (excluding lithium)
β-Blockers
Calcium channel blockers
Diuretics
Dopaminergic drugs
Renin–angiotensin–aldosterone system inhibitors

Sources: Beunza-Sola et al. 2018; Wang et al. 2021.

Lower falls risk
- Walks unaided
- No gait/balance issues
- Independent lifestyle/low care
- Physically active
- No major sensory deficits
- No falls history
- No major cognitive issues
- Low disease burden
- Limited drug therapy
- No PIMs/FRIDs

Higher falls risk
- Needs assistance with walking (e.g. cane/walker)
- Gait/balance issues
- High level of care
- Limited physical activity
- Vision/hearing impairment
- Falls history
- Cognitive issues
- Multiple chronic conditions
- Polypharmacy
- ↑ likelihood of PIMs/FRIDs

FIGURE 41.2 Examples of factors that can either lower or increase the risk of falls in older adults

family and staff who must deal with the deprescribing process, the likelihood of withdrawal symptoms and possible worsening of clinical symptoms.

It is crucial that the older person taking the drug is at the centre of any decision and that all parties involved (e.g. RACF staff/carer, family, GP, community pharmacist) are involved in the decision when attempting to deprescribe a particular drug(s). Clinical evidence has indicated that initially deprescribing a drug with no noticeable withdrawal effects is a good strategy because it alleviates any perceived concerns about 'stopping' a drug. Similarly, it is essential to choose carefully which drugs are stopped, as drugs with overlapping indications may make it difficult to ascertain which drug may be causing withdrawal effects (Liacos et al. 2020). Other factors for consideration include a gradual reduction in drug dose to mitigate withdrawal effects (e.g. benzodiazepines) and trialling discontinuation with reinstatement of the drug at a lower dose if symptoms reoccur (e.g. antihypertensives).

Clearly, deprescribing is a complex process and is only one tool for managing inappropriate polypharmacy in older adults. The main aims are to reduce harm and improve quality of life. To date, there are limited data on the clinical and cost-effectiveness of deprescribing and the impact of deprescribing on quality of life (e.g. psychosocial functioning, cognitive ability or physical functioning). Similarly, there are limited guidelines to assist in the deprescribing process and to mitigate against withdrawal symptoms. Clearly comprehensive guides to assist health professionals in the deprescribing process for individual drugs would be valuable.

KEY POINTS

Medication management in older adults

- Safe and effective medication management is a cornerstone of QUM.
- Use of drugs in older adults is problematic, with numerous reports of overprescribing, inappropriate prescribing and ADRs resulting in hospitalisations.
- Regular medication reviews optimise medication use, improve clinical outcomes and ensure adherence to the tenets of QUM.
- Deprescribing is one strategy to either reduce or address inappropriate polypharmacy and the harms associated with it in the older population.
- There are limited data on the clinical and cost-effectiveness of deprescribing and the impact of deprescribing on quality of life (e.g. psychosocial functioning, cognitive ability or physical functioning).
- To date, comprehensive guidelines for individual drugs to aid in the deprescribing process are limited.

REVIEW EXERCISES

1. Mrs BC, an active 76-year-old woman, lives in an RACF and regularly enjoys social outings. She has been treated for the past 6 years with warfarin for atrial fibrillation. Although her international normalised ratio is usually 2–3, her most recent result was 1. She reluctantly advises you that she bought a 'little pick-me-up' from the local pharmacy without speaking to the pharmacist. You immediately recognise that she has bought St John's wort, which she has been taking for 3 weeks. Discuss the mechanistic interaction between warfarin and St John's wort.
2. Mr OD, an 87-year-old resident of Sunny View Aged Care, recently complained of persistent dizziness and fell while going to the bathroom. Because he has been prescribed multiple drugs to treat a variety of disorders, an RMMR was undertaken. The pharmacist in his report noted that Mr OD had been taking a combination of amlodipine (5 mg), valsartan (160 mg) and hydrochlorothiazide (12.5 mg) that had recently been increased to 10 mg/320 mg/25 mg by a visiting GP. Discuss the pharmacology of the three drugs and provide an explanation as to his recent persistent dizziness. What action should be taken to address his dizziness?
3. Mrs DP has recently celebrated her 96th birthday. Over the past 6 months her general health, both mental and physical, has deteriorated and her care team, along with her family, have decided to trial deprescribing alendronate, ibuprofen and pantoprazole. Explain why these three drugs have been selected. Is she likely to experience any withdrawal symptoms?

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ONLINE RESOURCES

Australian Government Department of Health – Medication Management Reviews: https://www1.health.gov.au/internet/main/publishing.nsf/Content/medication_management_reviews.htm (accessed 24 January 2022)

Australian Government Department of Health – Guiding principles for medication management in residential aged care facilities: https://www1.health.gov.au/internet/main/publishing.nsf/Content/EEA5B39AA0A63F18CA257BF0001DAE08/$File/Guiding%20principles%20for%20medication%20management%20in%20residential%20aged%20care%20facilities.pdf (accessed 24 January 2022)

New Zealand Ministry of Health – Medicines Management Guide for Community Residential and Facility-based Respite Services – Disability, Mental Health and Addiction: https://www.health.govt.nz/publication/medicines-management-guide-community-residential-and-facility-based-services-disability-mental (accessed 24 January 2022)

More weblinks at: http://evolve.elsevier.com/AU/Knights/pharmacology/.