



PHARMACOLOGY

FOR HEALTH PROFESSIONALS 7E

Mary Bushell, Voula Tsoutsikos, Shaunagh Darroch, Andrew Rowland



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FOR HEALTH PROFESSIONALS

— 7th Edition —

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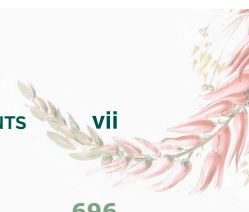
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ORGANISATION OF CONTENT

BOOK STRUCTURE

As with previous editions, this book is divided into units. Units 1 and 2 introduce general aspects of the clinical use of drugs and the principles of pharmacology; Units 3–10 consider drugs acting on the major systems of the body, from the autonomic nervous system through to the reproductive system; Units 11–13 cover drugs affecting general pathological conditions, including neoplasia, infections and inflammations; and Unit 14 includes a range of special topics including drugs affecting the skin, eye and ear, pharmacotherapy of obesity as well as chapters on drugs in aged care, vaccines and complementary therapies.

To enhance learning, each chapter begins with a Critical Thinking Scenario that lays the foundation for applying the key physiological, biochemical and pathological processes that underpin the subsequent discussions of pharmacology. We consider that this integrated approach facilitates an understanding of the cellular and molecular aspects of drug action, the rationales for the clinical use of drugs in particular disease processes, and their therapeutic and adverse effects and drug interactions. Throughout each chapter, snapshots of key information are provided in the Key Points boxes, the humanoid models and the comprehensive Drugs at a Glance tables. Application to the clinical situation is enhanced through the Clinical Focus boxes.

In some chapters, information is based on drug groups, with relevant details of the diseases for which they may be indicated, whereas in others the flow of information starts with the diseases or conditions and leads on to a discussion of the drug groups relevant to treatment. Drug Monographs give detailed information on commonly used drugs. It should be noted that specific pharmacokinetic data, drug dosage and formulation, individual adverse effects and drug interactions vary between drugs in the same group; current evidence-based drug information resources should always be consulted before administering any drug.

Terms and spelling

It is inevitable that with harmonisation many spellings and terminologies about which people feel strongly will change. We have agreed on the following usages, and apologise to those we offend:

- ♦ Although the terms ‘adverse effect’, ‘adverse reaction’ and ‘adverse event’ are often used (mistakenly) interchangeably, we have standardised the use of these terms throughout the book. Simply stated, a drug causes an *adverse effect*, a person suffers an *adverse reaction* to a drug, and an *adverse event* occurs while a

person is taking a drug, but it is not necessarily due to the drug (see Ch 7 for full explanations).

- ♦ Drugs affecting (a system): we have used this term purposely at times – for example, in ‘Drugs affecting the skin’ (Ch 39) – to include not only drugs used to treat conditions of the organ or system but also drugs that may have adverse effects particularly in that system or may be administered to that tissue to have an action elsewhere in the body.
- ♦ Drug names: throughout the text, Australian-approved (generic) drug names are used. However, in line with recommendations from the Therapeutic Goods Administration (2016), drug names have been updated consistent with International Non-Proprietary Names (INNs). When these are markedly different from American and/or Canadian names, this may be noted for clarity, such as ‘paracetamol, known as acetaminophen in the United States’. As drugs may be marketed under multiple trade names that are subject to frequent changes or deletions, we have not included trade names except in instances where readers may be so familiar with a trade name as to identify most readily with it – for example, diazepam, marketed as Valium; paracetamol, marketed as Panadol; or sildenafil, marketed as Viagra.
- ♦ We have adopted the generally accepted spelling ‘fetus’ rather than ‘foetus’ and ‘estrogen’ instead of ‘oestrogen’.
- ♦ Gonadotrophin (for example): the suffix ‘trophic’ means bringing nourishment, whereas ‘tropic’ means turning or moving in response to a stimulus; they appear to have become interchangeable in words such as gonadotrophin. There is an understanding that the English term is ‘-trophin’, whereas ‘-tropin’ is American usage. We have standardised on the form -trophin except where the approved name for a hormone or drug is otherwise, as in somatropin and follitropin.
- ♦ Receptor: because many drugs interact with molecular targets (e.g. enzymes, ion channels and receptors), we have chosen to standardise use of the term ‘receptor’ in accordance with the IUPHAR Committee on Receptor Nomenclature and Drug Classification 2003.
- ♦ 5-hydroxytryptamine: in line with accepted terminology, the term ‘5-hydroxytryptamine’, abbreviated as 5-HT, is used throughout this book. Use of the term ‘serotonin’ is restricted to the first mention of 5-HT in a chapter (as a reminder that this is synonymous with 5-HT) and in reference to specific drug groups – for example, selective serotonin reuptake inhibitors.



GUIDE TO THE 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.



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

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

CHAPTER FOCUS highlights what you will learn in the chapter.

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

TABLES AND BOXES

DRUG MONOGRAPH 9.1 • Adrenaline (epinephrine)					
Mechanism of action		response is often, however, vasodilation; for example, during situations of high sympathetic demand, the release of adrenaline from the adrenal medulla constricts blood vessels in the skin and sphincter muscle but dilates those of skeletal muscles, thus shunting blood to the areas needed for 'fight-or-flight'-type responses.			
DRUG INTERACTIONS 9.1 β-adrenoceptor antagonists					
Cardiac Adrenaline contracts adrenoceptor The strong emptying oxygen effect pre	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.			
Adrenaline of a fall oxygen effect A significant depolarising during cardiac pacemaker	Antidiabetic agents, oral hypoglycaemic agents, insulin	May mask symptoms of hypoglycaemia such as increased heart rate and lowered blood pressure, and may prolong hypoglycaemic episodes, making monitoring difficult. Monitoring of blood glucose levels and			
	Digoxin	TABLE 9.4 Pharmacokinetics and adult dose range of β-adrenoceptor antagonists*			
Calcium channel blockers Clonidine					
MAO inhibitors Labetalol	DRUG	ORAL BIOAVAILABILITY (%)	HALF-LIFE (H)	ELIMINATION	ADULT DOSE RANGE
	Atenolol	~50	7–9	Renal (85–100%)	25–100 mg/day
Non-steroid inflammation	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
DRUGS AT A GLANCE: Drugs acting on the adrenal cortex					
Corticosteroids • Regulate receptor • Increase protein synthesis	PHARMACOLOGICAL GROUP AND EFFECT		KEY EXAMPLES	CLINICAL USE	
	Corticosteroid analogue • Increases synthesis and release of corticosteroids		Tetracosactide ^{4,5,6}	• Diagnosis of adrenal insufficiency • Hypsarrhythmia and/or infantile spasms	
Corticosteroids • Promote excretion • Hydration	Corticosteroids (glucocorticoids)		Belamethasone	• Wide range of conditions requiring	
	CLINICAL FOCUS BOX 11.1 Management of acute coronary syndrome				
Guidelines for the management of acute coronary syndrome (ACS) have been updated from the previous 2016 guidelines and were published jointly by the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand in 2025 (Brieger 2025).					
The key evidence-based recommendations include the following:					
• Initial ECG assessment of ACS should involve a 12-lead ECG with clinical interpretation within 10 minutes of first clinical contact.					
• Biomarker testing is recommended in people with suspected ACS using high-sensitivity cardiac troponin tests (hs-cTn).					
• Recommended initial therapeutic management of suspected or confirmed ACS includes aspirin 300 mg orally, sublingual glyceryl trinitrate (GTN) for ongoing chest pain, and IV opioids (e.g. fentanyl or morphine) if needed.					
Recommendations for long-term management include, where appropriate:					
• early initiation of dual antiplatelet therapy with aspirin (100–150 mg/daily) and either clopidogrel or ticagrelor for up to 12 months, even in patients who do not undergo coronary revascularisation, unless contraindicated					
• commencement of the highest tolerated dose of a statin should be initiated and continued indefinitely.					

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.

CHAPTER FEATURES

Critical Thinking Scenario

Freya, a 25-year-old female, was recently diagnosed with attention-deficit/hyperactivity disorder (ADHD) and prescribed lisdexamfetamine. She tells you, the health professional, that she does not like taking medicines. Until now, she has only used simple analgesia and occasional courses of antibiotics.

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.

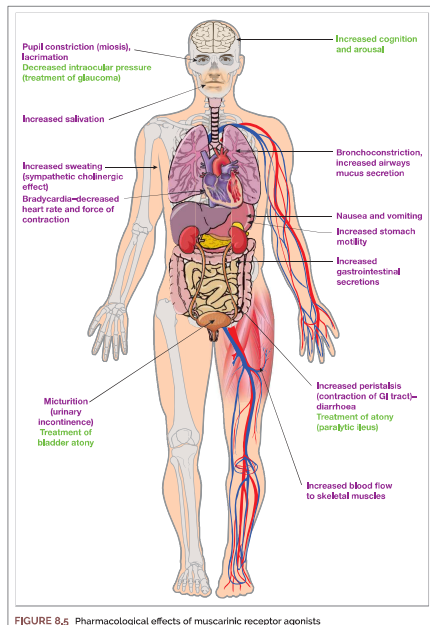


FIGURE 8.5 Pharmacological effects of muscarinic receptor agonists

HUMANOID MODEL illustrations use selected organs, tissues, body parts etc. to explain pharmacological/adverse effects of various drugs or drug groups.

KEY POINTS - Molecular drug targets

- There are four main types of regulatory proteins that drugs act on: transporters, enzymes, ion channels and receptors.
- A large group of proteins that are targets for drugs are receptors, which are cellular macromolecules directly concerned with chemical signalling that initiates a change in cell function.
- Receptors can lose responsiveness (tachyphylaxis), become desensitised or be downregulated or upregulated.

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

Review exercises

1. Mr TP presents to his GP having experienced shortness of breath while playing basketball. He is diagnosed with exercise-induced asthma and prescribed salbutamol, a short-acting β_2 -adrenoceptor agonist, to manage his symptoms. Exacerbations of asthma may also be treated with ipratropium, an acetylcholine receptor antagonist. Considering the pathways that these two drugs work on, explain how both a receptor agonist or a receptor antagonist could be used to treat the same disease state.
2. Ms SM is being treated in hospital for an exacerbation of congestive heart failure (CHF). At home Ms SM manages her CHF with a diuretic called hydrochlorothiazide, but in hospital she is treated with a different diuretic called furosemide, which has 1/10th the potency, but double the efficacy of hydrochlorothiazide. Using this comparison of drugs from the same broad therapeutic class to support your answer, discuss the clinical value of knowledge of the concentration-response relationship of different drugs.
3. Mr TS presents to the emergency department of a local hospital with a broken ankle and you need to manage his pain. There are many drug options that are available to you for managing pain. As a health professional, discuss the practical importance of maximal drug efficacy.

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

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Online resources

IUPHAR database of receptors and ion channels: <https://www.guidetopharmacology.org/> (accessed 26 May 2025)

More weblinks at: <http://evolve.elsevier.com/AU/Bushell/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 7th 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 this 7th edition.

As much of pharmacology is predicated on an understanding of physiology and biochemistry, this 7th 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.

This edition also features:

- ◆ 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
- ◆ updated 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*, *Medical Journal of Australia*, *Australian Journal of General Practice* and *Australian Prescriber*.

We are confident that this 7th 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 42 —

PHARMACOTHERAPY OF OBESITY

Voula Tsoutsikos

Key Drug Groups

Drugs inhibiting nutrient absorption:

- ♦ **Orlistat** (Drug Monograph 42.1)

Glucagon-like peptide 1 analogue:

- ♦ **Liraglutide, semaglutide**

Glucose-like peptide analogue and glucagon-like peptide-1 analogue (combination):

- ♦ **Tirzepatide (new)**

Noradrenergic drug:

- ♦ **Phentermine**

Anorexiant:

- ♦ **Naltrexone/bupropion**

Key Terms

body mass index 929

cholecystokinin 932

glucagon-like peptide-1 932

incretins 935

leptin 932

pancreatic lipase 935

waist:hip ratio 930

Chapter Focus

The incidence of obesity is increasing in the Australian and New Zealand populations. Individuals who are overweight (body mass index [BMI] of $\geq 25.0 \text{ kg/m}^2$) or obese (BMI $\geq 30.0 \text{ kg/m}^2$) have a higher long-term risk of morbidity and mortality.

Obesity is now understood to be a complex, chronic condition influenced by a wide range of interacting biological, neurobehavioural, psychological, social and environmental factors rather than a single cause. Lifestyle measures – including alterations in diet, increased physical activity and behaviour modification – remain central to the prevention and management of obesity. Continued advances in understanding the pathophysiology of obesity have driven the development of newer, more effective pharmacological options to complement lifestyle approaches.

Key Abbreviations

BMI	body mass index
CCK	cholecystokinin
FTO	fat mass and obesity-associated gene
GLP-1	glucagon-like peptide-1
WHR	waist:hip ratio

Critical Thinking Scenario

Jared, a 37-year-old accountant, presents to his GP expressing frustration with his weight. His BMI is 34.8 kg/m², and he has a family history of type 2 diabetes. He has attempted multiple lifestyle changes, including reducing portion sizes, attending the gym and following structured diet programs, but he has not achieved sustained weight loss. His waist circumference is 108 cm, giving him a waist-to-height ratio above 0.5, indicating excess central adiposity. He has no history of cardiovascular disease, pancreatitis or gallbladder disease. His HbA_{1c} is 5.8%, and he is not taking any regular medications.

Jared has read online about 'weekly injections that help you lose weight' and asks whether you could prescribe one of these medicines to support him in achieving a healthy weight. He is particularly interested in Ozempic after hearing about its success from a friend.

- 1 What is the mechanism of action of semaglutide in weight management?
- 2 Why must GLP-1 receptor agonists be prescribed appropriately, used cautiously or avoided in certain individuals?
- 3 What is the difference between Ozempic and Wegovy, and why is this distinction clinically important?

INTRODUCTION

The prevalence of obesity has reached epidemic proportions across the globe, bringing with it increased risks of cancer, cardiovascular disease, type 2 diabetes mellitus, dyslipidaemia, hypertension and obstructive sleep apnoea. Despite intense public interest in diet, fitness and body image, fuelled by a billion-dollar industry, rates of obesity continue to rise. In Australia, 66% of adults are living with overweight or obesity, and around 32% are classified as obese (Australian Institute of Health and Welfare 2024). In New Zealand, the 2024–25 Health Survey reported that 34.2% of adults were living with obesity, with prevalence approaching one in two adults in the most disadvantaged communities. Earlier ethnicity-specific data from the 2019–20 Health Survey show substantial variation, with higher rates among Pacific peoples (63.4%) and Māori (47.9%) compared with European/other (29.3%) and Asian (15.9%) groups.

How do we define underweight, normal weight, overweight and obesity?

It is recognised that body weight alone does not indicate fat distribution or associated cardiometabolic risk. The measurement most frequently relied on is the **body mass index** (BMI), but this has notable limitations: it does not distinguish between fat mass and muscle mass and may

TABLE 42.1 Body mass index: international classification

CLASSIFICATION	BMI (KG/M ²)
Underweight	< 18.5
Normal weight	18.5–24.9
Overweight (pre-obese)	25.0–29.9
Obese Class I	30.0–34.9
Obese Class II	35.0–39.9
Obese Class III	≥ 40.0

Note: In 2025, an international expert panel recommended revising how obesity is diagnosed, arguing that BMI alone is insufficient. The proposed framework incorporates additional measures to confirm excess adiposity, such as at least one of waist circumference, waist-to-hip ratio or waist-to-height ratio to better identify excess adiposity. Where BMI is > 40 kg/m² this is not needed as excess adiposity is assumed, and assessment of clinical obesity is also recommended. This reflects longstanding limitations of BMI, which cannot distinguish between fat and lean mass or capture variations in fat distribution (Rubino et al. 2025).

Source: World Health Organization – see www.who.int

misclassify individuals with high muscularity; it is less reliable in young people and the elderly; and it correlates poorly with visceral fat, which is closely associated with metabolic syndrome and cardiovascular disease.

BMI is calculated from the following equation:

$$\text{BMI (kg/m}^2\text{)} = \text{weight (kg)} \div \text{height}^2 \text{ (m}^2\text{)}$$

For example, for a 120 kg person who is 1.67 m tall, their BMI is $120 \div 1.67^2 = 120 \div 2.79 = 43.0 \text{ kg/m}^2$, corresponding to Class III obesity according to World Health Organization definitions (Table 42.1).

Although BMI is widely used for population-level reporting, obesity is a global health challenge extending beyond Australasia. Globally, in 2022 an estimated 2.5 billion adults aged 18 years and over were overweight, including approximately 890 million adults living with obesity. The global prevalence of overweight adults increased from 25% in 1990 to 43% in 2022 (WHO 2022).

HEALTH RISKS ASSOCIATED WITH OBESITY

Obesity is well recognised as a chronic disease in its own right. The associated health risks are numerous, and individuals living with overweight or obesity have a higher mortality rate than those with a normal BMI. According to the World Health Organization, in 2021, higher-than-optimal BMI was responsible for an estimated 3.7 million deaths worldwide from non-communicable diseases. It is well documented that individuals living with obesity have an increased likelihood of developing the conditions outlined in Clinical Focus Box 42.1.

CLINICAL FOCUS BOX 42.1

Diseases associated with obesity

Metabolic and endocrine	Cardiovascular
Type 2 diabetes mellitus Insulin resistance Hyperinsulinaemia Dyslipidaemia (hypercholesterolaemia, hypertriglyceridaemia) Hypertension Hyperuricaemia (gout) Hypogonadism Infertility	Cardiovascular disease Ischaemic heart disease Stroke Heart failure
Respiratory	Cancer*
Obstructive sleep apnoea Obesity hypoventilation syndrome	Oesophageal adenocarcinoma Colorectal cancer Endometrial cancer Pancreatic cancer Kidney cancer (renal cell carcinoma) Postmenopausal breast cancer Liver cancer (hepatocellular carcinoma) Gallbladder cancer Advanced prostate cancer Ovarian cancer
Gastrointestinal and hepatobiliary	Musculoskeletal/other
Non-alcoholic fatty liver disease (NAFLD/MASH) Gallstones	Osteoarthritis Hirsutism (typically in the context of PCOS)

PCOS = polycystic ovary syndrome. *See <https://www.cancer.gov.au/resources/position-statements/lifestyle-risk-factors-and-primary-prevention-cancer/lifestyle-risk-0#overweight-and-obesity-and-cancer>

The distribution of fat is an important determinant of disease risk. A high proportion of visceral (abdominal) fat carries a greater risk of morbidity and mortality than does peripheral fat distribution. Although large-scale studies measuring body weight, glucose and insulin concentrations simultaneously are rare, a strong association exists linking abdominal adiposity with elevated blood glucose concentration, insulin resistance and the development of type 2 diabetes. In Australia, the rising prevalence of obesity has been identified as a major contributing factor to the increasing incidence of type 2 diabetes.

A simple measure of central adiposity is the **waist:hip ratio** (WHR), which is calculated from the following equation:

$$\text{WHR} = \frac{\text{waist circumference (cm)}}{\text{hip circumference (cm)}}$$

A WHR of < 0.9 in men and < 0.85 in women is generally recommended when assessing for abdominal adiposity. Although there is no standard cutoff for waist circumference that provides an indication of greater risk, the World Health Organization suggests that a waist circumference > 94 cm in

men and > 80 cm in women indicates increased risk, while a waist circumference > 102 cm in men and > 88 cm in women indicates a substantially increased risk of health problems. These waist circumference measurement guidelines were developed primarily using data from European populations, and evidence remains insufficient to establish equivalent cutoffs for many other ethnic groups.

The need for effective prevention and intervention to reduce obesity has been recognised in both Australia and New Zealand. A range of public health strategies have been developed and implemented, including guidelines for food and nutrition in schools and national initiatives promoting regular physical activity. Both the National Health and Medical Research Council of Australia (2013) and the Ministry of Health, New Zealand (2017) have developed clinical guidelines to assist health professionals in managing overweight and obesity. Understanding the pathophysiology of obesity is essential for guiding the development of effective and sustainable management strategies.

PATHOPHYSIOLOGY OF OBESITY

Obesity is a complex multifactorial chronic disease involving dysregulation of energy balance (intake and expenditure), genetic factors, environmental factors (diet and physical activity) and psychosocial factors (Fig 42.1). The complexity of these interacting factors has made the management of obesity challenging, and some individuals now require medical or surgical interventions, including procedures such as sleeve gastrectomy, Roux-en-Y gastric bypass (often called 'gastric bypass') and adjusted gastric band surgery.

Primary obesity (arising from the complex interactions stated above) rarely results from secondary causes such as endocrine disorders (e.g. Cushing's syndrome, hypothyroidism or hypogonadism), neurological disorders or medication-induced weight gain. From the simplest viewpoint, obesity, which is manifest by increased fat storage, reflects the consequence of an imbalance between energy (food) intake and energy expenditure. Although on the surface this is a simple relationship, numerous biological and environmental factors influence this balance, contributing to weight gain and making obesity far more complex than it initially seems.

ENERGY BALANCE: INTEGRATION INVOLVING THE PERIPHERY AND THE HYPOTHALAMUS

The regulation of food intake is complex and not yet fully understood. It involves multiple interacting monoamine and peptide neurotransmitters and depends on both peripheral signals and central hypothalamic pathways that either stimulate or suppress food intake. It has been well documented scientifically that the sympathetic nervous

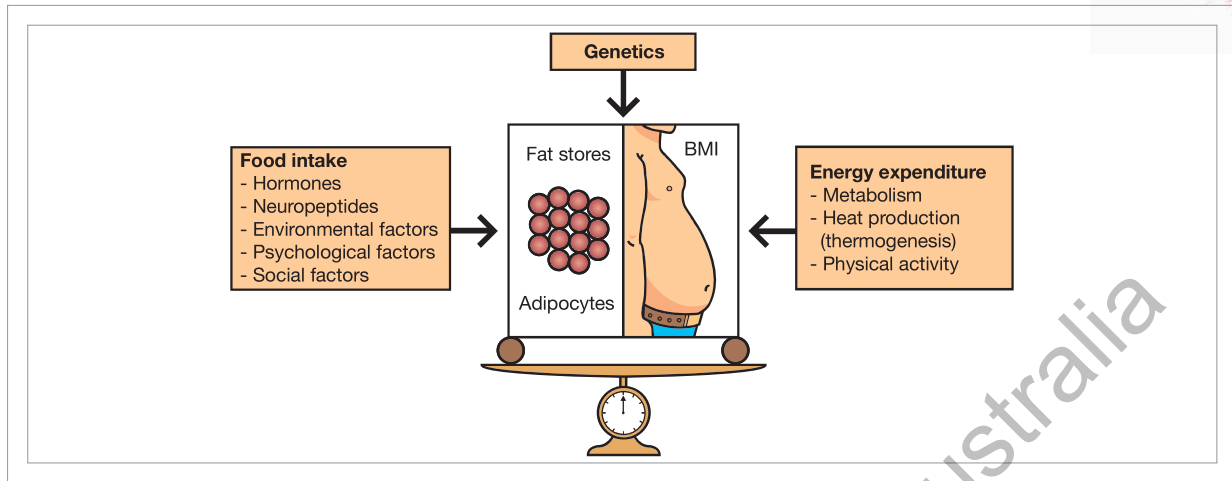


FIGURE 42.1 Energy balance: factors influencing energy intake and energy expenditure

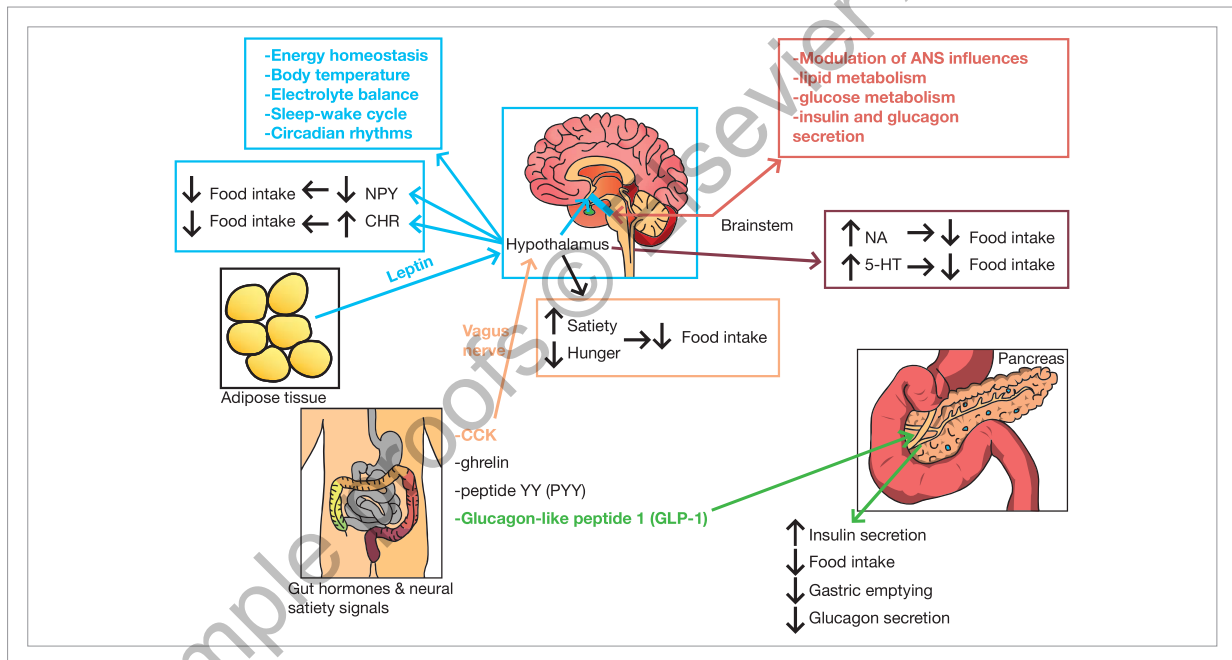


FIGURE 42.2 Schematic representation of food-regulating pathways

The hypothalamus regulates a number of key body processes, including energy homeostasis. The long-term regulation of food intake involves the leptin system, which causes a reduction in food intake by decreasing hypothalamic neuropeptide Y (NPY) synthesis and release and increasing the release of corticotrophin-releasing hormone (CRH). Short-term control involves cholecystokinin (CCK) released from the duodenum; CCK stimulates receptors on the vagus nerve to signal the hypothalamus of reduced feelings of hunger and satiety. Signals are also received by the hypothalamus from the peripheral nervous system and various gut hormones. GLP-1 stimulates insulin secretion and decreases food intake, gastric emptying and glucagon secretion. Specialised nuclei in the hypothalamus integrate the various signals and modulate the release of neurotransmitters (e.g. noradrenaline and 5-HT) that affect food intake. Additionally, the hypothalamus activates neurons in the brainstem that modulate the autonomic nervous system and energy expenditure.

system (and its neurotransmitter noradrenaline) contributes to the regulation of energy expenditure, although the popular belief that individuals with obesity simply have 'slow metabolism' and lean people have 'high metabolism' is an oversimplification of a much more complex and nuanced physiological process. Stimulation of central α -adrenoceptors

by noradrenaline can decrease food intake via actions in the feeding centre of the hypothalamus, while stimulation of peripheral β -adrenoceptors increases energy expenditure. Similarly, activation of central 5-hydroxytryptamine (5-HT, serotonin) receptors by an excess of 5-HT suppresses food intake (Fig 42.2).

In addition to these monoamine transmitters, many central and peripheral peptide neurotransmitters are involved. These are classed as orexigenic (promoting food intake) such as neuropeptide Y, while others are anorexigenic (suppressing food intake) such as cholecystokinin (CCK). Peripheral hormones including leptin, insulin, ghrelin and glucagon-like peptide-1 (GLP-1) also provide key signals to the hypothalamus that influence appetite, energy expenditure and nutritional status.

With advances in understanding these gut-brain pathways, the focus of pharmacotherapy for obesity has shifted away from targets such as leptin and CCK towards therapies that act on incretin and related signalling systems. This includes the GLP-1 receptor agonists and emerging multi-agonist compounds that combine actions on GLP-1, glucose-dependent insulintropic polypeptide (GIP) or glucagon receptors and are now progressing through clinical trials (Fig 42.3), although because these therapies are still in the development pipeline, data are mainly from animal studies.

LEPTIN

Leptin (from the Greek word *leptos*, meaning 'thin') is the protein product of the obesity (*ob*) gene. This protein is released from adipocytes (fat cells) and acts on leptin receptors within hypothalamic neurons to signal the brain about the body's fat stores. It is also a gut peptide that stimulates leptin receptors on vagal afferents. Production of leptin is increased by estrogen, glucocorticoids and possibly by insulin, and is reduced by β -adrenoceptor agonists.

On reaching the brain, leptin reduces the production of neuropeptide Y, an orexigenic peptide, which normally promotes food intake and reduces energy expenditure. In contrast, fasting or weight loss results in a decrease in leptin concentration that triggers an increase in hunger and a drive to restore energy balance. Leptin also stimulates the production of corticotrophin-releasing hormone, which contributes to appetite suppression (Fig 42.2). In a small proportion of obese people, alterations in leptin synthesis, secretion and/or signalling may be associated with an intense desire to overeat (van der Klaauw and Farooqi 2015). Additionally, leptin influences energy balance through modulation of melanocortin-dependent and -independent pathways in the hypothalamus.

CHOLECYSTOKININ

Cholecystokinin is a hormone secreted from the duodenum in the presence of food. It inhibits gastric emptying, pyloric sphincter contraction and stimulation of pancreatic exocrine secretions, and significantly reduces feelings of hunger and increases satiety (feeling of fullness) (Fig 42.2). Stimulation of CCK-A receptors on the vagus nerve sends signals to the hypothalamus, and evidence suggests an interaction between leptin and CCK that may contribute to both short- and long-term regulation of body weight. Additional peripheral and central pathways also participate in the regulation of food

intake and energy storage, and understanding of these mechanisms continues to evolve (Page et al. 2012).

GLUCAGON-LIKE PEPTIDE-1 (GLP-1)

Glucagon-like peptide-1 is an incretin hormone released from intestinal L-cells in response to nutrient exposure, particularly fats and carbohydrates. It slows gastric emptying, enhances glucose-dependent insulin secretion, reduces glucagon release and promotes satiety through actions on vagal afferents and appetite-regulating centres in the hypothalamus. GLP-1 acts via the GLP-1 receptor, a G protein-coupled receptor that shares structural features with similar receptors for GLP-2, glucagon, GIP, secretin and growth hormone-releasing hormone. Each receptor is highly selective for its corresponding endogenous peptide, with little physiological cross-reactivity.

Although native GLP-1 is rapidly degraded by dipeptidyl peptidase 4 and has a short half-life, its metabolic and appetite-regulating actions have guided the development of longer-acting GLP-1 receptor agonists for the treatment of obesity and type 2 diabetes.

GENETIC FACTORS

There is now widespread acceptance that genetics contributes substantially to obesity risk. Studies of adopted children show that their body weight is related to that of their biological parents and not to that of their adopted parents. Estimates of a contribution of genetic effects to obesity range from 40% to 70%, and these findings have undoubtedly given credibility to the widely held perception that children with overweight or obese parents are at higher risk of developing obesity themselves.

Obesity is strongly associated with insulin resistance and type 2 diabetes, and although the mechanisms linking these conditions were once unclear, they are now understood to reflect complex hormonal, inflammatory and genetic interactions. In a landmark study using mice, a team of researchers showed a link between diabetes and a protein called resistin, which is produced in adipocytes. Their studies established that diabetic mice have higher resistin levels, and these are linked to both diet-induced and genetic obesity (Steppan et al. 2001).

More recent human studies have focused on genetic linkage with obesity-related traits from the fat mass and obesity-associated (FTO) gene. A number of variant alleles of FTO have been demonstrated, and people who are homozygous for the high-risk alleles weigh, on average, 3 kg more than those with the low-risk allele. This gene encodes for an enzyme in the hypothalamic nuclei that is involved in regulating energy balance (Gerken et al. 2007). Further research has identified mutations in melanocortin-4 receptors (MC4-R), which are associated with hypothalamic neural circuits involved in energy balance (Heymsfield and Wadden 2017).

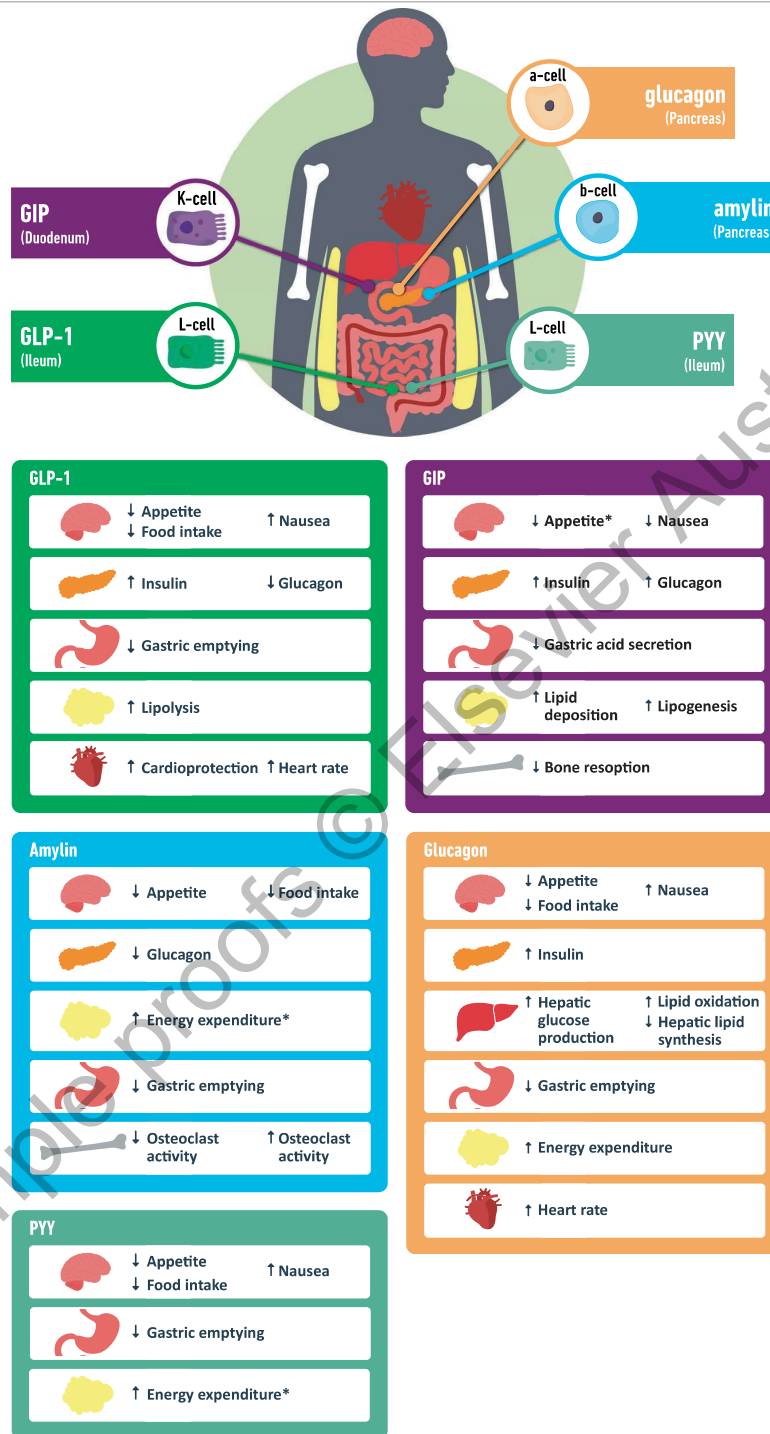


FIGURE 42.3 Hormonal regulation of appetite and energy balance through gut–brain–pancreas hormones used in the pipeline obesity therapies

Includes glucagon-like peptide-1 (GLP-1), which underpins the development of many current and emerging treatments, together with other gut hormones such as glucose-dependent insulinotropic polypeptide (GIP) and peptide YY (PYY).

Source: Melson et al. (2025).

ENVIRONMENTAL FACTORS

Environmental influences play a major role in the development of obesity. The widespread availability of energy-dense, highly processed fast foods, combined with increased portion sizes, aggressive marketing and increasing sedentary lifestyle, has contributed significantly to excess energy intake. These dietary patterns, combined with changes in daily routines, including greater reliance on motorised transport, increased screen time and reduced physical activity, have created an environment that promotes weight gain.

Public health strategies to address the obesity pandemic are aimed at supporting healthier choices by encouraging the consumption of vegetables, fruit, whole grains and minimally processed foods while reducing intake of energy-dense items high in added sugars, fats and refined carbohydrates. Increasing opportunities for physical activity is also key to addressing the modern lifestyle imbalance between high caloric intake and low energy expenditure.

KEY POINTS - Obesity

- ◆ Obesity is a complex multifactorial chronic disease involving dysregulation of energy balance and is influenced by genetic, environmental, behavioural and psychosocial factors.
- ◆ Genetic factors contribute to an estimated 40% to 70% of an individual's susceptibility to obesity.
- ◆ BMI is widely used as an indicator of excess body fat and is calculated by dividing a person's body mass (kg) by the square of their height in metres (m^2), although it does not distinguish between fat mass and lean mass.
- ◆ Adults with a BMI $\geq 25 \text{ kg/m}^2$ are considered overweight, and those with a BMI $\geq 30 \text{ kg/m}^2$ are classified as obese under World Health Organization definitions.
- ◆ A waist-to-hip ratio (WHR) > 0.9 in men and > 0.85 in women indicates significant visceral fat distribution, which is associated with a greater risk of cardiometabolic complications and increased morbidity and mortality.
- ◆ Food intake is regulated by a complex system of interacting central and peripheral pathways including monoamine neurotransmitters, hypothalamic circuits and gut-derived hormones.
- ◆ Leptin and CCK remain physiologically important modulators of appetite, although they have not translated into effective pharmacotherapies for common obesity.
- ◆ Current pharmacotherapy focuses on incretin-based pathways, particularly GLP-1 receptor agonists and emerging multi-agonists (e.g. GLP-1/GIP, GLP-1/glucagon).

MANAGEMENT OF OBESITY

Obesity is a complex chronic disease, and a complete understanding of all the interacting factors that contribute to its development is still evolving. Management can be challenging, and compliance with one or all aspects of a program, diet, physical activity and behavioural strategies varies widely between individuals. While weight regulation and the adoption of healthy lifestyle patterns remain foundational for all individuals, including those with a strong genetic predisposition, many people experience difficulty not only in losing weight but also in maintaining weight loss over time. Strategies include dietary modification (low-fat diet), increased physical activity, and behaviour modification and support tailored to the individual. Obesity is often a lifelong condition, and people living with obesity frequently experience stigma, which can undermine compliance with treatment.

Pharmacological therapy may play an important role, particularly as understanding of the biochemical and genetic factors contributing to obesity advances. However, although drugs may produce an initial weight loss, long-term weight maintenance remains challenging, and many earlier anti-obesity drugs have been withdrawn from clinical practice because of severe and unacceptable psychiatric and/or cardiovascular effects. Newer pharmacological options such as GLP-1 receptor agonists (liraglutide and semaglutide), combined GIP and GLP-1 agents such as tirzepatide, and emerging triple receptor agonist therapies still under investigation (e.g. retatrutide, which uniquely targets the GLP-1, GIP and glucagon receptors) have demonstrated greater effectiveness and improved tolerability compared with earlier medicines in clinical trials.

DRUG THERAPY

Safe and effective medicines free of adverse effects for treating obesity are not yet available, although several agents targeted at specific physiological pathways are under active development. Historically, the main drugs used for treating obesity were the centrally-acting appetite suppressants that mimic the actions of noradrenaline, but many of these were withdrawn due to safety concerns.

Pharmacological options for managing excess body weight remain limited. Medicines currently used include semaglutide, liraglutide, orlistat, phentermine and the combination of naltrexone with bupropion and tirzepatide; none of the medicines used for weight management are subsidised under the Pharmaceutical Benefits Scheme, and all require private funding when prescribed for obesity.

Noradrenergic drugs

Dexamphetamine was introduced during the 1930s to treat narcolepsy (desire to sleep) and was found to produce weight loss. It was later established that the anorectic effect of amphetamine is mediated via release of noradrenaline

DRUG MONOGRAPH 42.1 • Orlistat

Mechanism of action

Orlistat is a reversible inhibitor of gastric and pancreatic lipase. By binding to the active site of these enzymes, it inhibits the action of the lipases and prevents the breakdown of dietary triglycerides (fat) into absorbable free fatty acids and monoglycerides. As a result, orlistat decreases the absorption of dietary fat by approximately 30% and promotes a modest reduction in weight and plasma cholesterol.

Pharmacokinetics

Orlistat undergoes minimal systemic absorption and is essentially retained within the gastrointestinal tract. Plasma concentrations of the drug are either not detectable or exceedingly low (<2 micrograms/L). Most metabolism occurs within the gastrointestinal wall, producing five major metabolites. Less than 2% of orlistat is excreted in urine; most of the drug is eliminated in faeces (> 96%), with unchanged drug accounting for 83% of the total dose excreted.

Drug interactions

Orlistat may reduce absorption of the fat-soluble vitamins (A, D, E and K). A decrease in vitamin K uptake may affect anticoagulation control in people taking warfarin, and regular monitoring of coagulation parameters is recommended.

Co-administration of orlistat and ciclosporin should be avoided as it may result in reduced plasma concentration of ciclosporin. Similarly, concomitant use with thyroid hormone replacement may lead to hypothyroidism due to decreased thyroxine absorption.

Additional contraceptive precautions are recommended when taking combined oral contraceptives and orlistat concurrently because of reports of breakthrough bleeding and contraceptive failure.

Adverse reactions

Adverse effects are mainly gastrointestinal and reflect the presence of unabsorbed fat in the stool. Common effects include fatty or oily stools, flatulence, liquid stools, abdominal pain, faecal incontinence and urgency, and headache and nausea. Gastrointestinal effects improve if dietary fat intake is reduced.

Warnings and contraindications

Current drug information sources should be consulted regarding warnings and contraindications. Orlistat should be used with caution in people with active peptic ulcer disease or significant cardiac, gastrointestinal, renal, hepatic or endocrine disorders.

Use is contraindicated in people with cholestasis, chronic pancreatitis or pancreatic enzyme deficiency or chronic malabsorption syndrome.

Its safety in pregnant women has not been established and, generally, use of weight-loss drugs during pregnancy is inappropriate.

Dosage and administration

The recommended dose is 120 mg, taken with fat-containing meals up to three times daily; no advantage has been observed with higher doses. Orlistat should be taken during a meal or shortly afterwards. A dose should be omitted if a meal is missed or contains negligible fat.

Orlistat 120 mg is available as a Schedule 4 (Prescription Only) drug, while the 60 mg tablets are available through a pharmacy (Schedule 3, Pharmacist Only) in both Australia and New Zealand. Over-the-counter availability was based on the outcome of clinical trials that indicated reasonable efficacy for weight reduction and a low incidence of adverse effects. It also recognised the role of pharmacists in providing high-quality advice on managing obesity.

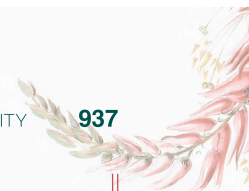
cessation. Although its mechanism of action is not fully understood, it is thought to be a non-selective inhibitor of transporters involved in the reuptake of dopamine and noradrenaline. When used alone, it produces very modest weight loss. Naltrexone (Ch 19), an opioid receptor antagonist, is used as an adjunct in the management of alcohol dependence and to support abstinence following opioid detoxification, and it is devoid of weight-loss properties.

Both drugs when used as monotherapy produce little in the way of weight loss. However, when used together, the combination produces an anorectic response thought to be mediated by pro-opiomelanocortin neurons in the brain that release a melanocyte-stimulating hormone that decreases hunger and induces satiety. The most common adverse effects include nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth and diarrhoea.

In clinical studies the combination is effective in sustaining weight loss and improving cardiometabolic parameters, including a reduction in waist measurement and an improvement in lipid profiles. The combination drug was approved for use in Australia in 2019 and in New Zealand in 2020 (Clinical Focus Box 42.2).

CLINICAL FOCUS BOX 42.2
Naltrexone with bupropion

- ◆ Used in adults with a BMI > 30 kg/m², or > 27 kg/m² plus cardiovascular risk factors, and as an adjunct to lifestyle modifications.
- ◆ If weight loss is less than 5% of initial body weight, treatment is ceased after 16 weeks.
- ◆ Contraindicated in adults receiving chronic opiate therapy (e.g. for chronic pain or opioid dependence) due to the naltrexone component (i.e. risk of inadequate analgesia or withdrawal syndrome, respectively).
- ◆ Has potential for multiple drug interactions, and relevant and current drug information sources should be consulted before prescribing.
- ◆ Blood pressure and pulse should be monitored regularly (may increase blood pressure).
- ◆ Long-term efficacy and safety beyond 1 year have not been established.
- ◆ Due to its modified-release formulation, tablets should be taken whole and not chewed, cut or crushed, and should be taken with food.



Tirzepatide

Tirzepatide is an agonist of two incretins, the GLP-1 and GIP receptors, and enhances glucose-dependent insulin secretion, reduces glucagon release, slows gastric emptying and decreases appetite. It is approved for weight management in adults with obesity or who are overweight with weight-related comorbidities. In clinical trials, tirzepatide produced substantially greater weight loss than single incretin receptor agonists, with average reductions up to approximately 20% of initial body weight (Sokary and Bawadi 2025).

Adverse effects commonly involve the gastrointestinal tract (i.e. nausea, vomiting, abdominal pain), and the medicine should be used cautiously in people with gallbladder disease, renal impairment, a history of pancreatitis or severe gastrointestinal disorders. Use in pregnancy should be avoided due to limited safety data. Treatment is initiated at 2.5 mg once weekly by subcutaneous injection. After 4 weeks, the dose is increased to 5 mg weekly and may be further titrated in 2.5 mg increments at intervals of no less than 4 weeks, according to response and tolerability, to a maximum weekly dose of 15 mg.

weight loss is less than 5% of the person's initial weight.

- ♦ Naltrexone with bupropion is an anorexiant with mixed opioid receptor antagonist and noradrenaline dopamine reuptake inhibitor properties (i.e. acts on hypothalamic appetite control pathways and reward circuits). Treatment is ceased after 16 weeks if weight loss is less than 5% of the person's initial weight. It is contraindicated in individuals receiving opioid therapy.
- ♦ Tirzepatide is a dual GLP-1 and GIP receptor agonist that produces greater weight loss than monotherapy with single incretin analogues. It is approved for use in Australia and available on private prescription; it is not PBS subsidised for weight loss.

KEY POINTS - Drugs for obesity

- ♦ Pharmacological options for treating obesity remain limited, although a growing pipeline of new therapies is in development and progressing through clinical trials.
- ♦ Phentermine, orlistat, liraglutide, semaglutide and naltrexone with bupropion are indicated for weight management in adults meeting BMI criteria: BMI > 30 kg/m², or BMI > 27 kg/m² plus at least one weight-related comorbidity, for example cardiovascular risk factors.
- ♦ Phentermine is a centrally-acting noradrenergic drug used as an appetite suppressant. It is indicated only for short-term use due to the development of tolerance and its potential for misuse. It is contraindicated in people with cardiovascular and cerebrovascular disease due to its stimulant effects, which can raise blood pressure and heart rate and increase the risk of arrhythmias, ischaemia and stroke in susceptible individuals.
- ♦ Orlistat inhibits gastric and pancreatic lipases within the gastrointestinal tract which prevents the absorption of dietary fat. Weight loss is modest (typically an additional 2–3 kg over several years beyond dietary changes alone) and adverse gastrointestinal effects may limit adherence.
- ♦ Liraglutide and semaglutide are GLP-1 receptor agonists and exert insulinotropic effects. They slow gastric emptying, decrease appetite and increase satiety. Treatment is stopped after 12 weeks if

THE FUTURE

Maintaining weight loss after stopping medication remains a major challenge, and most people regain weight once treatment stops. The therapeutic landscape has shifted markedly in recent years. Orlistat was once the only drug available for the long-term treatment of obesity; however, incretin-based therapies have transformed pharmacological management of obesity. GLP-1 receptor agonists such as liraglutide and semaglutide, and dual agonists such as tirzepatide targeting both GLP-1 and GIP pathways, consistently achieve greater weight loss than earlier agents.

Multi agonists are now progressing through development, including triple agonist retatrutide which activates GLP-1, GIP and glucagon receptors. These have produced some of the largest weight reductions seen in clinical trials. Other emerging approaches include amylin analogues (e.g. cagrilintide), combined amylin GLP-1 agonists (e.g. cagrilintide semaglutide combinations) and selective melanocortin-4 receptor agonists, which aim to more precisely target central appetite regulatory pathways.

At the same time, several previously explored drugs are no longer progressing. Lorcaserin, a selective 5-HT_{2C} agonist with 15–100-fold greater selectivity for 5-HT_{2C} receptors than 5-HT_{2A} and 5-HT_{2B}, was approved by the FDA in June 2012 for treating select populations of obese people; however, it was withdrawn in 2020 because of a possible association with malignancy. In 2012, the FDA also approved a combination of phentermine and topiramate (an antiepileptic drug that is known to induce weight loss) for obese people (BMI ≥ 30 kg/m²) with at least one weight-related comorbidity; however the European Medicines Agency has twice rejected marketing approval for the drug because of ongoing concerns over cardiovascular toxicity, teratogenicity, and psychiatric and cognitive effects, and the potential for misuse by recipients.

The search for safe and effective drugs continues, but it is unlikely that there will ever be a drug that produces weight loss if a person's increased food intake and reduced physical activity persist. Current research in obesity pharmacotherapy focuses on improving long-term

tolerability, reducing adverse effects, developing agents that prevent weight regain after treatment cessation and refining therapies that safely and effectively target the interconnected biological pathways that regulate appetite, satiety, energy use and metabolic adaptation.

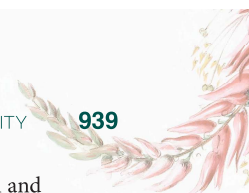
DRUGS AT A GLANCE: Anti-obesity drugs

PHARMACOLOGICAL GROUP AND EFFECT	KEY EXAMPLES	CLINICAL USE
Sympathomimetic anorexiant ◆ Increase release of noradrenaline in hypothalamus ◆ Increase sympathetic transmission ◆ Decrease appetite ◆ Increase energy expenditure	Phentermine	◆ Adjunct to lifestyle modifications in obese adults with BMI > 30 kg/m ² or in adults with BMI > 27 kg/m ² with cardiovascular risk factors
Lipase inhibitors ◆ Reversible inhibitor of gastric and pancreatic lipase ◆ Decrease breakdown of dietary triglycerides ◆ Inhibit absorption of cholesterol and lipid-soluble vitamins	Orlistat	◆ Adjunct to lifestyle modifications in obese adults with BMI > 30 kg/m ² or in adults with BMI > 27 kg/m ² with cardiovascular risk factors
GLP-1 analogues ◆ Bind GLP-1 receptors on pancreatic β-cells ◆ Stimulate insulin secretion ◆ Decrease food intake ◆ Suppress glucagon secretion	Liraglutide/ semaglutide	◆ Adjunct to lifestyle modifications in obese adults with BMI > 30 kg/m ² or in adults with BMI > 27 kg/m ² with one or more weight-related comorbidity
Dual GLP-1 and GIP agonist ◆ Enhances insulin secretion and insulin sensitivity ◆ Suppresses glucagon secretion ◆ Delays gastric emptying and reduces appetite	Tirzepatide	◆ Adjunct to lifestyle modifications in adults with BMI > 30 kg/m ² , or BMI > 27 kg/m ² with at least one weight-related comorbidity
Anorexiant (mixed action) ◆ Act in the appetite regulatory centre in the hypothalamus ◆ Combined opioid receptor antagonist with inhibitor of dopamine and noradrenaline transporters	Naltrexone with bupropion	◆ Adjunct to lifestyle modifications in obese adults with BMI > 30 kg/m ² or in adults with BMI > 27 kg/m ² with cardiovascular risk factors

Review exercises

- 1 Ms BG, a 28-year-old office worker, has been overweight since childhood and is classified as having Class III obesity (BMI 42.4 kg/m²). She has sought your advice regarding any drug that could help her to lose weight. On a previous visit her blood pressure reading was 139/85 mmHg. She admits that she loves food and hates exercise and feels that she has no time to do anything about her weight. Considering her lifestyle factors, discuss your approach to initiating and supporting a weight reduction program for her. At this stage, which drug therapy, if any, would you consider?
- 2 Mr BD, a 31-year-old builder, presented to his local GP practice complaining of intense dyspepsia,

loose oily stools and persistent flatulence. You asked his height while weighing him and a quick calculation indicated he had a BMI of 43 kg/m². He told you that he was getting married in a month and his fiancée was keen on him losing some weight before the wedding. During the consultation, he mentioned that he has been taking six capsules daily for the past week of 'Alli' (orlistat 60 mg), which he bought over the counter from his local pharmacy because he wanted to lose weight quickly. Discuss the pharmacological relationship between his gastrointestinal symptoms and the excessive dose of orlistat he has been taking.



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UNIT 4 DRUGS AFFECTING THE HEART AND VASCULAR SYSTEM

— CHAPTER 10 —

DRUGS AFFECTING CARDIAC FUNCTION

Voula Tsoutsikos

Key Drug Groups

Antiarrhythmic drugs:

- ♦ **adenosine** (Drug Monograph 10.4), **amiodarone** (Drug Monograph 10.3), digoxin (a cardiac glycoside), **disopyramide** (Drug Monograph 10.1), esmolol, **flecainide** (Drug Monograph 10.2), lidocaine (see Ch 11), **sotalol**

Drugs for heart failure:

- ♦ **milrinone**, **sacubitril/valsartan**

Antianginal drug:

- ♦ **ivabradine**

Key Terms

afterload 189
arrhythmia 196
automaticity 184
chronotropic effect 190
diastole 184
dromotropic effect 190
heart failure 190
inotropic effect 190
pacemaker cells 185
preload 189
proarrhythmogenic 198
refractoriness 186
stroke volume 189
systole 184

Chapter Focus

Knowledge of the anatomy and physiology of the heart and vascular system is essential for understanding the action and use of drugs in the treatment of hypertension, cardiac failure, angina and thromboembolic disorders. Numerous drugs affect the heart both directly and indirectly and include the autonomic transmitter adrenaline (epinephrine) and related drugs, antiarrhythmic drugs, the cardiac glycoside digoxin and the calcium channel blockers (Ch 11). The drugs used to treat arrhythmias are very potent, with the potential to cause sudden cardiac death. Careful drug selection, along with close monitoring of a person's clinical condition, is crucial to achieving the goal of safe and effective antiarrhythmic therapy.

Key Abbreviations

ANP	atrial natriuretic peptide
ATP	adenosine triphosphate
AV	atrioventricular
BNP	B-type natriuretic peptide
CNP	C-type natriuretic peptide
CO	cardiac output
HR	heart rate
LAD	left anterior descending
mV	millivolts
NA	noradrenaline
SA	sinoatrial
SV	stroke volume

Critical Thinking Scenario

Mavis is 65 years old and newly diagnosed with atrial fibrillation (AF). She has been on digoxin therapy (62.5 micrograms once daily) for the last 2 weeks. She has presented to the clinic with symptoms of nausea, vomiting and diarrhoea that have progressively worsened. Additionally, she complained that her vision has become 'funny', describing it as blurry.

- 1 What explanations can you think of for her symptoms? Consider drug dosage, concurrent conditions and drug interactions.
- 2 What laboratory tests would you recommend?
- 3 A digoxin plasma drug concentration is measured, and the result is 2.9 micrograms/L. Discuss what further laboratory tests would be undertaken to help explain why her plasma digoxin concentration is high and recommend a plan to monitor and support Mavis to manage her treatment.

INTRODUCTION: THE HEART

The heart, which lies in the mediastinum slightly to the left of the midline of the thoracic cavity, consists of four chambers – the upper right and left atria and the lower right and left ventricles (Fig 10.1A). The heart wall consists of the external smooth epicardium, the middle layer of myocardium (or muscle tissue) and the inner endocardium, which lines the chambers of the heart and the valves (Fig 10.1B). The pumping action of the heart depends on the ability of the cardiac muscle to contract. Contractility of the heart is energy-dependent, and the heart derives most of its energy from oxidative metabolism of fatty acids and lactate, which occurs in mitochondria and cardiac muscle cells.

The myocardium is composed of interconnected branching muscle fibres, or cells, that form the walls of the atria and the ventricles. The thickness of the myocardium of the atria and ventricles varies. The atrial walls tend to be thinner because the atria act more as delivery containers, whereas the ventricular walls tend to be thicker because the ventricles forcibly contract and pump blood against a resistance. The resistance of the pulmonary bed is low, so the wall of the right ventricle is not as thick as that of the left ventricle, which has to pump blood to all parts of the body against total systemic vascular resistance.

CORONARY VASCULAR SUPPLY OF THE HEART

Blood supply to the myocardium is provided by the left and right coronary arteries, which arise from the base of the aorta (Fig 10.1C). The left coronary artery divides into the left anterior descending (LAD) artery and the circumflex

artery and supplies blood to the left atrium and ventricle. Similarly, the right atrium and ventricle are supplied with blood from the right coronary artery which divides into many branches.

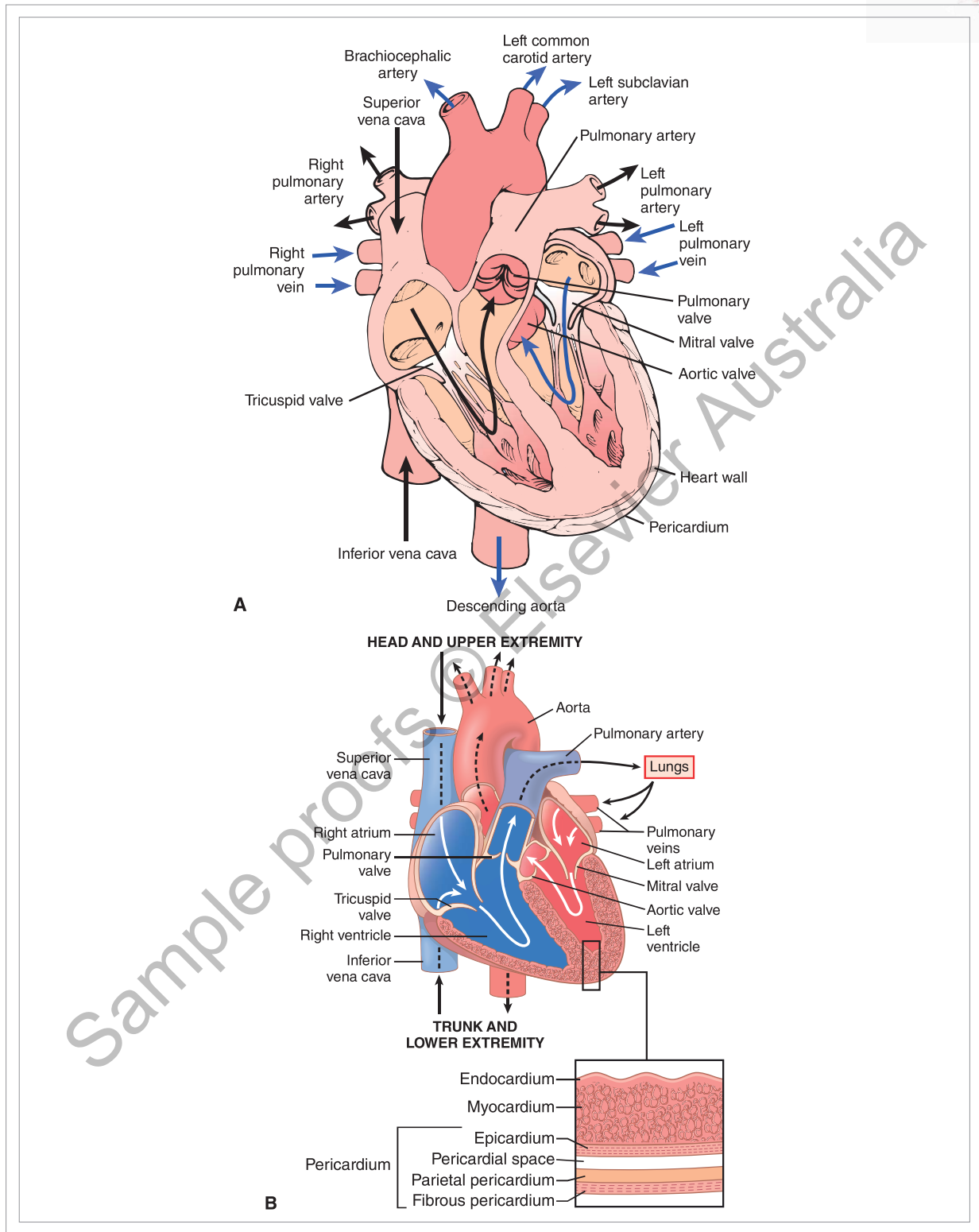
These main coronary vessels continue to divide, forming numerous branches, resulting in a profuse network of coronary vessels. The major arterial vessels supplying the heart are located on the external surface of the ventricles (epicardium) and are known as epicardial arteries. Branches penetrate the myocardium towards the endocardial (inner) surface. Venous coronary blood drains via the coronary sinus into the right atrium. Coronary perfusion is well-timed, and occurs as a result of the high pressure of blood in the aorta, primarily when the ventricles have relaxed and there is minimal compression of coronary arteries, allowing blood to flow into them.

Increased oxygen delivery to the myocardium is supported almost exclusively by the increased coronary blood flow. When the demand for oxygen and nutrients by body tissues increases, cardiac output (CO) must increase. At the same time, the heart muscle itself must be supplied with enough oxygen and nutrients to replace the energy it expends. In other words, a balance must be maintained between energy expenditure and energy restoration. The increase in heart rate (HR) increases the metabolic needs of the heart and, normally, coronary dilation occurs to meet the higher metabolic demand and to overcome restricted blood inflow.

Whenever the delivery of oxygen to the myocardium is inadequate to meet the increased oxygen consumption by the heart, myocardial ischaemia occurs. Atheroma formation is one of the main causes of ischaemia, which manifests in the signs and symptoms of angina (Ch 11), while rupture of a plaque may cause a myocardial infarction.

CONTROL BY THE AUTONOMIC NERVOUS SYSTEM

The cardiac conduction system inherently possesses the ability to spontaneously generate electrical impulses that are responsible for setting the pace of the rhythmic myocardial contractions. Regulation of the rate, rhythm and force of myocardial contraction, required at times to adapt to the body's requirements, is extrinsically modulated by the autonomic nervous system. Postganglionic fibres of the sympathetic nervous system, which release noradrenaline (NA), innervate the sinoatrial (SA) node, atria and ventricles. Action of NA on β_1 receptors located in both nodes and atrial/ventricular muscles increases HR, automaticity, conduction velocity and force of contraction. Circulating adrenaline from the adrenal medulla also elicits cardiac responses – for example, tachycardia. Clinically, high doses of administered adrenaline (epinephrine) may exert a direct effect on the electrophysiological properties of cardiac tissue, causing cardiac arrhythmias.

**FIGURE 10.1** Schematic diagrams of the heart

A Schematic diagram of the heart, valves, major blood vessels and blood flow. Black arrows indicate the direction of flow of deoxygenated blood, and blue arrows the flow of oxygenated blood. **B** Layers of the heart, including the pericardium, myocardium and endocardium.

Source: A, Guyton and Hall (2020).

Continues

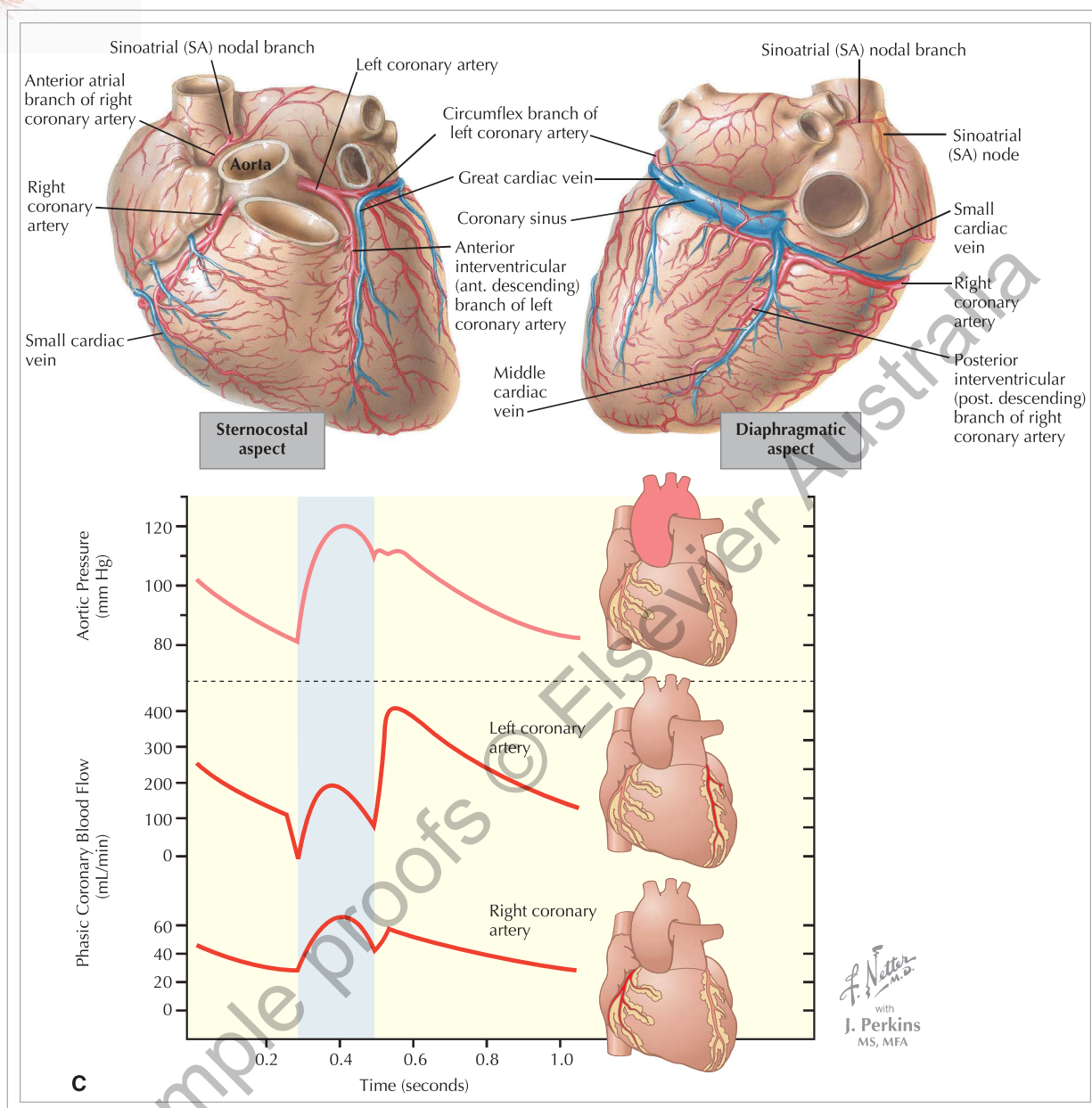


FIGURE 10.1 Schematic diagrams of the heart—cont'd

C Coronary blood supply to the heart. Dark-shaded vessels are those located on the external surface of the ventricles; light-shaded vessels show penetration of arterial branches towards the endocardial surface.

Source: C. Netter Images; used with permission.

Vagal nerve fibres of the parasympathetic branch, which release acetylcholine, are found primarily in the SA and atrioventricular (AV) nodes and atrial muscle. Acetylcholine acts on muscarinic (M_2) receptors of the SA node to decrease HR, on the AV node to decrease conduction velocity and, to a limited extent, on the M_2

receptors on cardiac myocytes to reduce cardiac contractility. Control by the vagus nerve ensures the HR is slowed to typical resting values (~60–80 beats/minute) (Fig 10.2).

In the absence of input from the parasympathetic nervous system the heart would contract at about 90–100 beats/minute, which is the normal automatic firing

SACUBITRIL/VALSARTAN, A NEPRILYSIN/ANGIOTENSIN (AT₁) RECEPTOR INHIBITOR

Sacubitril/valsartan is a fixed-dose combination used to treat chronic HFrEF, in patients with NYHA class II–IV symptoms who remain symptomatic despite standard therapy. It combines sacubitril, a neprilysin inhibitor that increases levels of beneficial natriuretic peptides, and valsartan, an angiotensin II receptor blocker. Together, they improve cardiac outcomes by promoting vasodilation and reducing fluid retention and cardiac fibrosis. Current clinical data support a role for this drug combination in the treatment of heart failure, notably PARADIGM-HF, which shows that sacubitril/valsartan reduces cardiovascular death and heart failure hospitalisations more effectively than enalapril.

Mechanism of action

Sacubitril is a prodrug that is metabolised within approximately 3.5 hours after oral dosing to its active form, LBQ657, which inhibits neprilysin – a membrane-bound enzyme responsible for breaking down vasoactive peptides such as natriuretic peptides. Inhibiting neprilysin increases the concentration of these peptides, leading to an array of advantageous cardiovascular effects (see previous section ‘Cardiac natriuretic peptides’) such as vasodilation and natriuresis. Valsartan blocks angiotensin II (AT₁) receptors, counteracting the renin-angiotensin-aldosterone system (RAAS) activation that may result from neprilysin inhibition. Combined, sacubitril and valsartan produce vasodilation, increase the glomerular filtration rate, and reduce blood pressure, sympathetic tone and aldosterone release, improving cardiac function in heart failure.

Pharmacokinetics

After oral administration, sacubitril/valsartan dissociates into sacubitril and valsartan. Peak plasma concentrations occur within 1.5–2 hours for sacubitril and 0.5–1 hour for valsartan. Sacubitril is rapidly converted to its active metabolite LBQ657. Approximately 85% of LBQ657 is excreted via urine and faeces. While valsartan undergoes minimal metabolism and is primarily excreted unchanged, there is limited knowledge of the metabolism of both sacubitril and LBQ657.

Adverse reactions

Common adverse reactions of sacubitril/valsartan include hypotension, dizziness and fainting due to the vasodilatory action. Additionally, patients may experience hyperkalaemia and renal impairment, requiring regular monitoring of electrolytes and kidney function during treatment.

KEY POINTS - Drugs affecting cardiac function

- ◆ Numerous drugs that affect the heart and vascular system are used to treat heart failure, arrhythmias, hypertension and ischaemic heart disease.
- ◆ Many drugs exert a direct effect on the heart or vasculature; others indirectly affect cardiac function as a consequence of actions on vascular tissue.
- ◆ Drugs acting directly on the heart include the catecholamines (e.g. adrenaline, noradrenaline; Ch 9), ivabradine, milrinone, cardiac glycosides (such as digoxin) and antiarrhythmic drugs.
- ◆ SGLT2 inhibitors (e.g. dapagliflozin, empagliflozin) are oral antihyperglycaemic agents used to treat chronic HFrEF, with or without diabetes, by promoting osmotic diuresis and natriuresis, thereby reducing preload and afterload and offering cardiovascular and renal benefits.
- ◆ Ivabradine is the first selective inhibitor of the I_f (‘funny’) current in the SA node. It reduces the slope of the spontaneous diastolic depolarisation of the SA node, hence lowering HR at rest and during exercise. It does not affect myocardial contractility or AV conduction, and the beneficial effect in angina occurs from the reduction in cardiac work and myocardial oxygen demand.
- ◆ Milrinone, at low doses, is a selective inhibitor of PDE3, and improves myocardial contractility and vasodilation without increasing myocardial oxygen consumption and HR. It is indicated for short-term treatment (~48 hours) of severe heart failure refractory to other drugs, and for low-cardiac-output states.
- ◆ Sacubitril/valsartan is a fixed dose combination comprising sacubitril, a neprilysin inhibitor, and valsartan, an AT₁ receptor inhibitor, used to treat heart failure. The active metabolite of sacubitril increases natriuretic peptides (e.g. ANP, BNP), which then produce an array of advantageous cardiovascular effects. The combination with valsartan prevents angiotensin II binding and counteracts the adverse effects of angiotensin II accumulation due to neprilysin inhibition alone.

ARRHYTHMIAS AND ANTIARRHYTHMIC DRUGS

ARRHYTHMIAS

A cardiac **arrhythmia** is defined as any deviation from the normal rhythm of the heartbeat (Table 10.1). Disorders of cardiac rhythm arise because of abnormality in spontaneous initiation of an impulse (i.e. in automaticity) or abnormality in impulse conduction (i.e. in conductivity). In some circumstances, a combination of both processes occurs.

Abnormality in automaticity

A disturbance in automaticity can alter the heart's rate or rhythm or the site where the electrical impulse originates. When automaticity of the SA node decreases, it results in sinus bradycardia (a condition characterised by a regular but abnormally slow HR of < 60 beats/minute). An increase in automaticity of the SA node results in sinus tachycardia

(a condition where the heart contracts regularly but at a rate > 100 beats/minute).

A shift in the site of origin of impulse formation can generate an abnormal pacemaker or an ectopic focus, causing the heart to activate from a location other than the SA node. This is called an ectopic pacemaker, and it may discharge at either a regular or an irregular rhythm. It occurs because the cardiac fibres depolarise more frequently than the SA node. Abnormal automaticity can develop in cardiac cells that usually do not initiate impulses (e.g. atrial or ventricular muscle cells).

Clinical conditions such as hypoxia and ischaemia can cause impulse disturbances in automaticity and in conductivity, contributing to the development of ectopic beats. Ectopic beats are classified into escape beats, premature beats (also called extrasystoles) and ectopic tachyarrhythmias.

Abnormality in conductivity

Altered conduction of cardiac impulses is likely responsible for more arrhythmias than changes in automaticity. A

TABLE 10.1 Examples of arrhythmias

TYPE	DESCRIPTION	POSSIBLE CAUSES
Bradyarrhythmias		
Atrioventricular block	Intermittent or absent conduction between atria and ventricles. Commonly occurs at AV node or within bundle branch system.	Drug induced (e.g. β -blockers, digoxin, diltiazem, verapamil), infection, myocardial infarction
Sick sinus syndrome	Associated with SA node dysfunction, usually SA block or inadequate SA node conduction. Characterised by severe sinus bradycardia and symptoms of weakness, dizziness, lethargy and syncope. Treatment usually requires a pacemaker.	Various cardiomyopathies, inflammatory myocardial disease, myocardial ischaemia, digoxin toxicity
Tachyarrhythmias		
Atrial tachyarrhythmias		
Atrial fibrillation	Common sustained arrhythmia characterised by disordered electrical activity in atria resulting in a fast, irregular ventricular response. High risk of stroke and heart failure.	Acute myocardial infarction, can be idiopathic, cardiac surgery, mitral stenosis, rheumatic disease, advanced age (> 65 years)
Atrial flutter	Atrial tachycardia characterised by contraction rate 230–380/minute with ventricular contractions in 1:2, 1:3, 1:4 or variable ratio.	Cause often unknown, heart disease, AV node dysfunction, chronic hypertension, overactive thyroid
Supraventricular tachycardia	Atrial tachycardia and arrhythmias arising from AV junction.	Hypoxia, electrolyte and acid–base abnormalities, enlarged atria, digoxin toxicity
Ventricular tachyarrhythmias		
Premature ventricular ectopics	Ectopics	Alcohol, caffeine, stress
Ventricular tachycardia	> 100 beats/minute	Acute myocardial infarction
Torsades de pointes	Characterised by a prolonged ventricular action potential (prolonged QT interval). Can be congenital (mutations in the cardiac sodium or potassium channels) or acquired.	Acquired: electrolyte disturbances or from a number of drugs and drug classes, such as antiarrhythmic drugs (e.g. amiodarone, disopyramide, sotalol), antipsychotics, antimicrobial drugs, methadone, tacrolimus, tricyclic antidepressants

ANTIARRHYTHMIC DRUGS

The rationale for use of antiarrhythmic drugs includes restoring haemodynamic stability, preventing life-threatening arrhythmias, preventing sudden cardiac death, controlling ventricular rate and preventing thromboembolism in AF. Despite their use for the treatment of arrhythmias, these drugs all possess **proarrhythmogenic** potential and can worsen the arrhythmia and cause sudden death. Use of these drugs requires careful consideration of other treatment options and, following institution of therapy, careful monitoring of the person's clinical condition.

Although various classification systems exist, the Vaughan Williams classification, first proposed in 1970, remains the most commonly used framework for categorising antiarrhythmic drugs in clinical practice. It groups agents based on their effects on cardiac electrophysiology and is useful for predicting therapeutic efficacy; however, drugs within the same class may not share identical actions. The pharmacokinetics and classification of currently available antiarrhythmic drugs are shown in Table 10.2 and Figure 10.10, but there are several drugs not classified in the Vaughan Williams system.

TABLE 10.2 Pharmacokinetics of selected antiarrhythmic drugs

DRUG	ONSET OF ACTION (h)	HALF-LIFE (h)	THERAPEUTIC RANGE ^a
Class Ia drug			
Disopyramide	0.5–3	4–10	2–4 mg/L (6–12 micromol/L)
Class Ib drugs			
Lidocaine	IV: 1 min IM: 3–15 min	1.6	
Class Ic drug			
Flecainide	1–6	Varies (12–27)	0.2–0.9 mg/L
Class II drugs – β -adrenoceptor antagonists (Ch 9)			
Class III drugs			
Amiodarone	3–7	14–59 days (metabolite 60–90 days)	1–2.5 mg/L (1.6–4 micromol/L)
Sotalol	2–3	12–14	
Class IV drugs – calcium channel blockers (Ch 11)			
^a Local or regional laboratories should be consulted. Sources: Australian Medicines Handbook (2021); Thummel et al. (2018).			

Classification of antiarrhythmic drugs

Antiarrhythmic drugs are classified into classes I–IV. The Vaughan Williams classification, while still widely used, has limitations. Many antiarrhythmic drugs have multiple

mechanisms of action that span across classes, leading to inconsistencies in classification (e.g. amiodarone, a class III drug, additionally has class I, II and IV properties). Patel and Goyal (2025) is a good reference for understanding some of the antiarrhythmic agents used and the classification system.

Class I

Class I drugs block voltage-sensitive sodium channels interfering with sodium influx during phase 0 of the action potential. In general, class I drugs bind to the sodium channel when it is in the open or refractory state and less so during the resting state. Thus, the more frequently the channel is activated, the greater the degree of block by the class I drugs. Although they all share the same basic mechanism, there are differences between the drugs based on their binding to either the resting, open or refractory states of the sodium channel. These minor differences give rise to the following subclasses:

- ♦ **Class Ia** drugs (e.g. disopyramide, Drug Monograph 10.1) are the oldest antiarrhythmics and previously included quinidine and procainamide. Quinidine is not registered for use in Australia and New Zealand because of evidence of increased mortality with chronic use. Disopyramide binding properties lie between the Ib and Ic drugs, but in addition it prolongs the repolarisation phase but not to the same extent as the class III drugs. It is not marketed in Australia, but may be accessed via the Special Access Scheme (SAS).
- ♦ The **class Ib** drug lidocaine (Ch 18) differs from class Ia drugs because, in general, it does not affect conduction velocity. Lidocaine binds to the open sodium channels during phase 0 such that many of the channels are blocked when the action potential peaks. The drug dissociates from the channel rapidly, leaving it available for the next action potential if cardiac rhythm is normal. However, conduction of premature beats is blocked while the channel remains occupied. Additionally, lidocaine binds to refractory channels and is particularly effective in ischaemic myocardium when the cells are depolarised. Lidocaine is useful for acute ventricular arrhythmias. Like the class Ia drugs, lidocaine can worsen arrhythmias, and a high incidence of adverse effects has limited its usefulness.
- ♦ The **class Ic** drug flecainide (Drug Monograph 10.2) is used to treat AF and flutter and serious ventricular arrhythmias. It binds to and dissociates from the sodium channels slowly, effectively maintaining the block throughout the cardiac cycle. As binding to refractory channels is marginal, this drug does not have greater efficacy in ischaemic/damaged myocardium. It also inhibits conduction in the His–Purkinje system. The potential for proarrhythmic effect is of special concern, especially in people with poor left ventricular function or sustained ventricular arrhythmias. The class Ic drugs can also aggravate congestive heart failure.

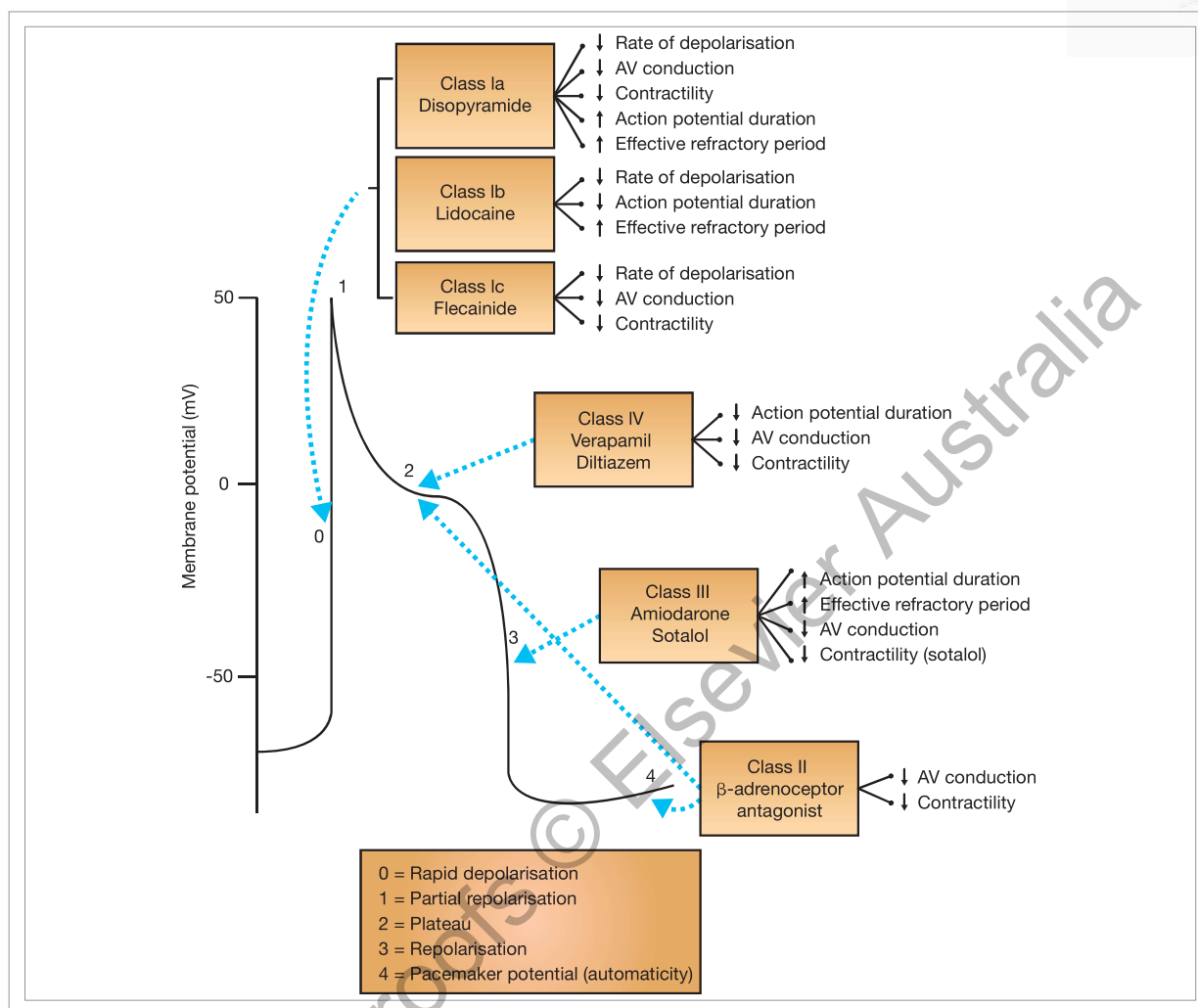


FIGURE 10.10 Phases of the cardiac action potential and the effects produced by the various classes of antiarrhythmic drugs

DRUG MONOGRAPH 10.1 • Disopyramide

Mechanism of action

Disopyramide prevents the movement of sodium and potassium across cell membranes. The inhibition of cation exchange results in a decrease in the rate of diastolic depolarisation from the resting potential during phase 4 and an increase in the threshold potential (the voltage shifts towards 0 mV) causing decreased impulse conduction and delayed repolarisation in the atria, ventricles and Purkinje fibres. The delay repolarisation probably exerts an important antiarrhythmic action. The tissue remains refractory for a period after full restoration of the resting membrane potential. This property is believed to influence the conversion of unidirectional block to bidirectional block, thereby abolishing the re-entry type of arrhythmia (Fig 10.9C).

Additionally, by decreasing impulse generation at ectopic sites, disopyramide suppresses or abolishes arrhythmias. Abnormal or ectopic pacemaker tissue appears to be more sensitive to

disopyramide than the SA node, thus permitting the SA node to re-establish control over impulse formation in the heart.

Disopyramide also exerts an anticholinergic effect, resulting in inhibition of vagal action on the SA node and AV junction. This effect permits the sinus node to accelerate and can often provoke a dangerous sinus tachycardia. The latter is the reason why a drug that slows AV conduction may be administered with disopyramide when it is used in the treatment of atrial flutter or AF.

Pharmacokinetics

Disopyramide is well absorbed and is metabolised by the liver to the weakly active metabolite mono-*N*-dealkylated disopyramide, which has both antiarrhythmic and anticholinergic effects. The half-life of disopyramide is about 4 hours, and about 50% is excreted as unchanged drug in urine. The therapeutic plasma concentration range for disopyramide is 2–4 mg/L (Table 10.2).

Continues

Drug interactions

The following drug interactions may occur with disopyramide:

- ◆ Azole antifungals: Increase disopyramide plasma concentration. Avoid combined use.
- ◆ Erythromycin: Increases disopyramide plasma concentration. Avoid combined use.
- ◆ Other antiarrhythmic agents, such as diltiazem, flecainide, lidocaine, verapamil and β -adrenergic blocking agents: Require close monitoring for evidence of negative chronotropic (bradyarrhythmia) and inotropic effects (heart failure). β -adrenergic blocking agents may exacerbate heart failure, especially in individuals with compromised ventricular function. Avoid combined use, or potentially serious drug interactions may occur.
- ◆ Phenytoin: Promotes induction of hepatic drug-metabolising enzymes, which reduces disopyramide plasma concentration. Monitor plasma concentration and increase dose if required.
- ◆ Drugs that prolong the QT interval (e.g. tricyclic antidepressants): Should not be co-administered, as prolongation of the QT interval increases the risk of proarrhythmic activity.

Adverse reactions

Common adverse reactions include:

- ◆ blurred vision, constipation, urinary retention and dry mouth (due to anticholinergic effects)
- ◆ hypersensitivity reactions
- ◆ severe disturbances of cardiac rhythm and exacerbation of heart failure.

Warnings and contraindications

Disopyramide should be used with caution in people with diabetes mellitus, glaucoma (closed-angle), hypokalaemia, myasthenia gravis, enlarged prostate or renal impairment. Avoid use in people with disopyramide hypersensitivity, AV block, cardiogenic shock, cardiac conduction abnormality, cardiomyopathy or heart failure.

Dosage and administration

Dosage and oral administration are individualised according to response and tolerance, and the dose is reduced in people with impaired renal function.

DRUG MONOGRAPH 10.2 • Flecainide

Mechanism of action

Flecainide is a sodium channel-blocking agent used to treat ventricular arrhythmias; it has minimal effects on repolarisation and no anticholinergic properties. It suppresses premature ventricular contractions, and in high doses can exacerbate arrhythmias in people with a preexisting ventricular tachyarrhythmia or with a previous myocardial infarction.

Pharmacokinetics

Flecainide is well absorbed after oral administration. It is hepatically metabolised by CYP2D6 to inactive metabolites and about 45% is renally excreted as unchanged drug. The therapeutic range for flecainide is 0.2–0.9 mg/L (Table 10.2).

Drug interactions

The administration of flecainide with other antiarrhythmic drugs (e.g. amiodarone, digoxin, β -blockers and verapamil) can result in enhanced adverse cardiac effects. In addition, concomitant use with drugs that inhibit its metabolism (e.g. paroxetine, ritonavir) may increase plasma

concentration and risk of toxicity. In people with diuretic-induced hypokalaemia, there is an increased risk of arrhythmias.

Adverse reactions

Adverse reactions include:

- ◆ blurred vision, dizziness, headaches
- ◆ constipation, nausea
- ◆ chest pain, irregular heartbeats and arrhythmias.

Warnings and contraindications

Use flecainide with caution in people with heart failure, hypokalaemia or hyperkalaemia, and renal impairment. Flecainide is contraindicated in post-myocardial infarction, in people with heart block or in situations of cardiogenic shock.

Dosage and administration

Flecainide is available as both an oral and an IV formulation. Dosage is adjusted based on clinical response and drug concentration monitoring.

Class II

Class II drugs include atenolol, esmolol and metoprolol. All three drugs are β -adrenoceptor antagonists used to control cardiac arrhythmias caused by excessive sympathetic activity. They reduce the rate of the SA node, slow conduction in the atria and AV node, and increase the functional refractory period. These drugs are the only class of antiarrhythmics to show a reduction in mortality post-myocardial infarction.

Drugs such as atenolol are used to treat atrial tachyarrhythmias and ventricular arrhythmias, whereas esmolol is indicated for short-term treatment of supraventricular tachycardia (SVT) induced by AF or atrial flutter.

Class III

Class III drugs include amiodarone (Drug Monograph 10.3) and sotalol. The electrophysiological properties of amiodarone and sotalol differ markedly from those of the other classes. Drugs in this group prolong the effective refractory period by prolonging the action potential duration.

Sotalol is a β -adrenoceptor antagonist that also blocks cardiac potassium channels, prolonging the action potential duration and increasing the effective refractory period in atrial and ventricular tissue and at the AV node. It is indicated for treatment and prevention of atrial and serious ventricular arrhythmias. Sotalol is predominantly cleared renally (around 90%) and therefore accumulates in people with renal impairment (Table 10.2). Additive depressant

CLINICAL USES OF ANTIARRHYTHMIC DRUGS – cont'd

Class Ic (e.g. flecainide)

- ◆ Paroxysmal AF or atrial flutter
- ◆ Serious ventricular arrhythmias

Class II (e.g. esmolol)

- ◆ Control of arrhythmias provoked by increased sympathetic activity
- ◆ Non-compensatory sinus tachycardia

Class III (e.g. amiodarone)

- ◆ Serious tachyarrhythmias e.g. VT, AF and SVT

Class IV (e.g. verapamil)

- ◆ SVT, AF or atrial flutter

Unclassified antiarrhythmic drugs

Drugs not classified under this scheme include adenosine (Drug Monograph 10.4), atropine (Ch 8), adrenaline (epinephrine) (Ch 9), digoxin and magnesium sulfate heptahydrate.

Digoxin

The digitalis glycosides – that is, those glycosides derived from the *Digitalis* species (e.g. digoxin and digitoxin) – are among the oldest drugs known to affect both cardiac contractility and rhythm. They increase the force of contraction (positive inotropism) and alter the electrophysiological properties of the heart by slowing the HR (negative chronotropism) and slowing conduction velocity (negative dromotropism).

DRUG MONOGRAPH 10.4 • Adenosine

Mechanism of action

Adenosine is a naturally occurring biologically active endogenous molecule in humans that arises following the breakdown of ATP. Adenosine binds to adenosine receptor types A_1 , A_{2A} , A_{2B} and A_3 , which are G-protein coupled receptors that transduce intracellular signals that modulate different cell responses.

Adenosine receptors are widespread throughout the central nervous system but are also found in peripheral tissues including the heart, liver, kidneys, adipose tissue, gastrointestinal tract, lungs and blood vessels. Examples of actions and physiological responses mediated by adenosine receptor subtypes in the cardiovascular system and kidney are shown below.

ADENOSINE RECEPTOR SUBTYPE	ACTION/PHYSIOLOGICAL RESPONSE
A_1	In cardiac tissue, binding to A_1 receptors opens potassium channels, which results in hyperpolarisation of myocytes and a decrease in cyclic adenosine monophosphate (cAMP); this inhibits L-type calcium channels and calcium entry into the cell. In the SA node, adenosine inhibits pacemaker activity, which decreases the slope of phase 4 of the action potential (Fig 10.10), decreasing the spontaneous firing rate and causing a negative chronotropic effect. Inhibition of L-type calcium channels at the AV node causes a negative dromotropic effect because of a reduction in conduction velocity.
	In the kidneys, A_1 receptor activation results in vasoconstriction, decreased glomerular filtration rate and inhibition of renin secretion.
A_{2A}	Activation of A_{2A} receptors on coronary smooth muscle cells results in stimulation of adenylyl cyclase, which increases cAMP and ultimately results in smooth muscle relaxation. Increased cAMP also causes smooth muscle relaxation by inhibiting myosin light chain kinase, which leads to decreased myosin phosphorylation and a decrease in contractile force. Upregulation of A_{2A} receptors has been reported in patients with end-stage chronic heart failure.
A_{2B}	A_{2B} receptors found in vascular endothelium and smooth muscle cells of the heart and kidneys are thought to regulate vascular tone by exerting vasodilatory effects. Activation of A_{2B} receptors is also thought to prevent cardiac remodelling after myocardial infarction.

Indications

Adenosine is used for:

- ◆ acute treatment of supraventricular tachycardia
- ◆ cardiac diagnostic procedures.

Pharmacokinetics

Adenosine has a rapid onset of action of less than 2 minutes, and action persists only for the duration of administration. It is rapidly transported into vascular cells and red blood cells (within 10 seconds) where it is phosphorylated by adenosine

kinase to form AMP and also metabolised to inosine by adenosine deaminase. Inosine is rapidly (within minutes) metabolised by nucleoside phosphorylase to hypoxanthine, which is detectable in blood. Hypoxanthine is then metabolised by xanthine oxidase to xanthine, which is further metabolised by xanthine oxidase to uric acid. Hypoxanthine, xanthine and uric acid are excreted in urine by the kidneys.

Drug interactions

As caffeine and theophylline are methylxanthines and theophylline acts at adenosine receptors, it is not unexpected that both drugs would antagonise the effects of adenosine.

Magnesium sulfate heptahydrate

Magnesium sulfate heptahydrate blocks calcium entry by inhibiting L-type calcium channels during phase 3 of the action potential, an effect that potentially could shorten the QT interval. It also blocks the outward movement of potassium via potassium channels, which could potentially prolong the QT interval. These counterbalancing cellular actions may terminate torsade de pointes independently of the QT interval. Magnesium sulfate heptahydrate also

decreases early after-depolarisations, contributing to an antiarrhythmic effect.

It is cleared renally, and hypermagnesaemia is an issue in situations of renal impairment. Adverse effects relate to hypermagnesaemia and include loss of deep tendon reflexes and respiratory depression resulting from neuromuscular blockade. The latter is potentiated in combination with aminoglycosides, and the combination should be used with extreme caution and with monitoring of respiratory function.

KEY POINTS - Arrhythmias and antiarrhythmic drugs

- ◆ Antiarrhythmic drugs are used to prevent and treat cardiac rhythm disorders.
- ◆ Cardiac arrhythmias are usually the result of an abnormality in the electrophysiology of the cells in the cardiac conduction system or cardiac muscle cells.
- ◆ The antiarrhythmic drugs are subdivided into four classes (I–IV) according to their mechanism of action.
- ◆ Class Ia, Ib and Ic drugs suppress automaticity.
- ◆ Class Ia includes disopyramide, which decreases conduction velocity and prolongs the action potential.
- ◆ Class Ib drugs (e.g. lidocaine) may increase or have no effect on conduction velocity.
- ◆ The class Ic drug flecainide is indicated for treating or preventing supraventricular tachyarrhythmias.
- ◆ Class II drugs have β -adrenergic-blocking action and are discussed in Chapter 9.
- ◆ The class III drugs are amiodarone and sotalol.
- ◆ The class IV drugs have calcium channel blocking activity and are discussed in Chapter 11.
- ◆ Unclassified antiarrhythmic agents include adenosine, digoxin and magnesium sulfate heptahydrate.
- ◆ Digoxin decreases HR and slows conduction. It is used to treat cardiac arrhythmias, especially atrial flutter and AF, and heart failure.
- ◆ Digoxin has a narrow therapeutic index, can exacerbate or worsen arrhythmias and is subject to many serious drug interactions.
- ◆ Several factors, such as hypokalaemia, hypercalcaemia and hypomagnesaemia, may predispose to digoxin toxicity.
- ◆ Ovine digoxin-specific antibody fragment is used to treat digoxin poisoning.
- ◆ All antiarrhythmic drugs are potent medications that require careful selection and close monitoring to avoid drug-induced adverse effects.

DRUGS AT A GLANCE: Drugs affecting cardiac function

PHARMACOLOGICAL GROUP AND EFFECT	KEY EXAMPLES	CLINICAL USE
Antiarrhythmic drugs ^a ◆ ↓ AV conduction ◆ ↓ contractility ◆ ↑ or ↓ action potential duration ◆ ↑ effective refractory period ◆ ↓ rate of depolarisation	Adenosine	◆ Acute treatment of SVT ◆ Aid in myocardial perfusion imaging
	Amiodarone	◆ Serious tachyarrhythmias
	Disopyramide	◆ Life-threatening ventricular tachyarrhythmias
	Flecainide	◆ Serious ventricular arrhythmias ◆ SVT ◆ Paroxysmal AF or atrial flutter
	Lidocaine	◆ Serious ventricular arrhythmias
	Propafenone ^b	◆ Supraventricular extrasystoles ◆ Supraventricular tachycardia ◆ Wolff-Parkinson-White syndrome ◆ Serious ventricular tachyarrhythmias
	Sotalol	◆ Treatment and prevention of arrhythmias

DRUGS AT A GLANCE: Drugs affecting cardiac function – cont'd

Antianginal drug ♦ I _f channel inhibitor ♦ Interferes with depolarisations of SA node ♦ ↓ HR	Ivabradine	♦ Stable angina (sinus rhythm, HR > 70 bpm); chronic stable HFrEF (sinus rhythm, HR > 77 bpm; adjunct therapy)
Cardiac glycoside ♦ ↑ myocardial contraction ♦ ↓ HR and AV nodal conduction ♦ ↑ vagal tone	Digoxin	♦ AF and atrial flutter ♦ Heart failure
Drugs for heart failure ♦ PDE3 inhibitor ♦ ↑ calcium influx into sarcoplasmic reticulum ♦ ↑ force of myocardial contraction ♦ Neprilysin inhibitor ♦ ↓ degradation of natriuretic peptides ♦ Blocks angiotensin II ♦ Vasodilator ♦ ↓ sympathetic tone	Milrinone	♦ Severe heart failure ♦ Low CO states
	Sacubitril with valsartan	♦ Heart failure

^aNot all antiarrhythmic drugs have all properties. ^bNew Zealand only.

Review exercises

- Mr BC is a 65-year-old male with a history of AF. He has been feeling unwell for several weeks and was recently admitted for observation. The admitting doctor has taken some blood to determine Mr BC's plasma digoxin concentration. The student nurse asks you to explain why digoxin is beneficial for AF and why the blood was taken before Mr BC's next digoxin dose.
- Edith, a nurse practitioner, has been explaining to you the classification of antiarrhythmic drugs. She asks you to explain the pharmacological effects of amiodarone and why it is contraindicated for use in people with second- or third-degree heart block.

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