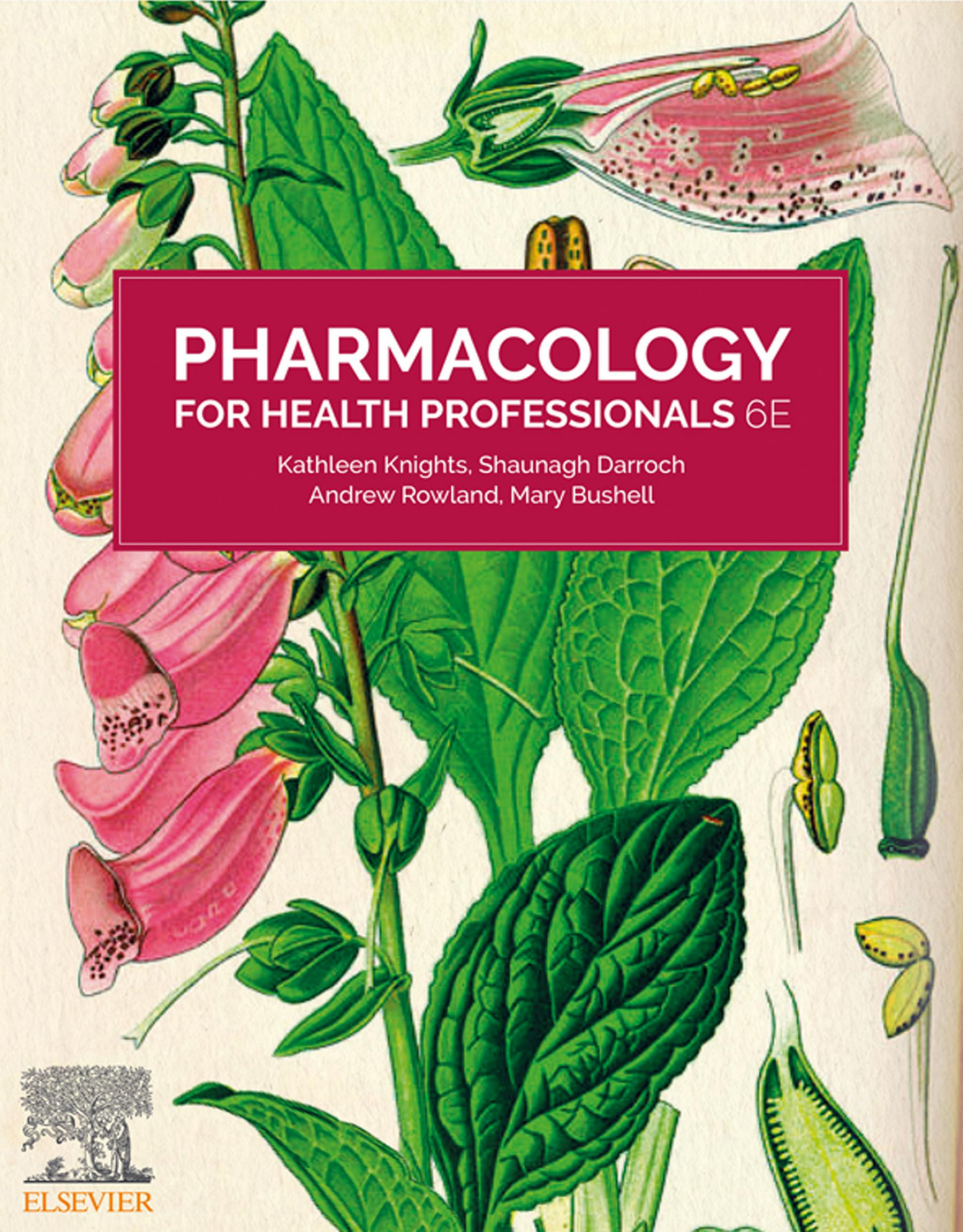

PHARMACOLOGY
FOR HEALTH PROFESSIONALS 6E

Kathleen Knights, Shaunagh Darroch
Andrew Rowland, Mary Bushell

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PHARMACOLOGY
FOR HEALTH PROFESSIONALS

6th Edition

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PHARMACOLOGY
FOR HEALTH PROFESSIONALS

6th Edition

Kathleen Knights, Shaunagh Darroch,
Andrew Rowland, Mary Bushell

ELSEVIER

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UNIT 10

UNIT 11

UNIT 12

UNIT 13

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 new chapters on drugs in aged care, vaccines and complementary therapies.

To enhance learning, chapters begin 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 new humanoid models and the comprehensive Drugs at a Glance tables. Application to the clinical situation is enhanced through new 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.
- Dysrhythmia: although the terms 'arrhythmia' and 'antiarrhythmic drugs' occur frequently in the literature, we have chosen to use the terms 'dysrhythmia' and 'antidysrhythmic drugs'. The prefix 'a' means 'without' and, in that regard, the only arrhythmia is asystole.
- We have now 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 (see Ch 4).

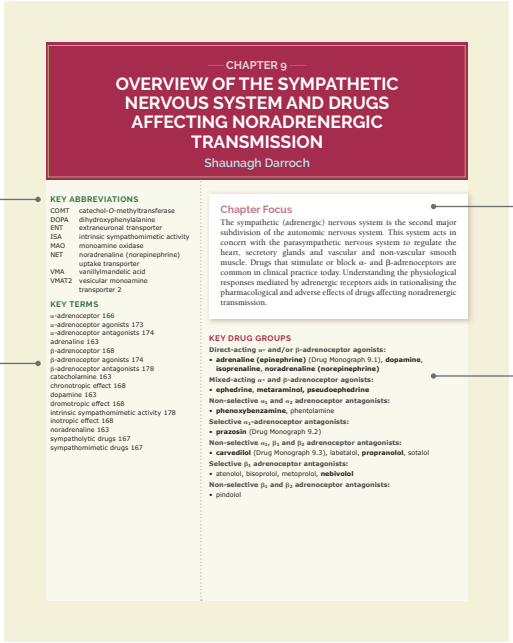
- 5-hydroxytryptamine: in line with accepted terminology, the term '5-hydroxytryptamine', abbreviated as 5-HT, is used throughout this book. Use of the term 'serotonin' is restricted to the first mention of 5-HT in a chapter (as a reminder that this is synonymous with 5-HT) and in reference to specific drug groups – for example, selective serotonin reuptake inhibitors.

GUIDE TO TEXT

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

Chapter Opening Features

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



CHAPTER 9

OVERVIEW OF THE SYMPATHETIC NERVOUS SYSTEM AND DRUGS AFFECTING NORADRENERGIC TRANSMISSION

Shaunagh Darroch

KEY ABBREVIATIONS

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

KEY TERMS

α-adrenoceptor 166
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Chapter Focus

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

KEY DRUG GROUPS

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

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

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

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

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

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

Non-selective β_1 and β_2 adrenoceptor antagonists:
- pindolol

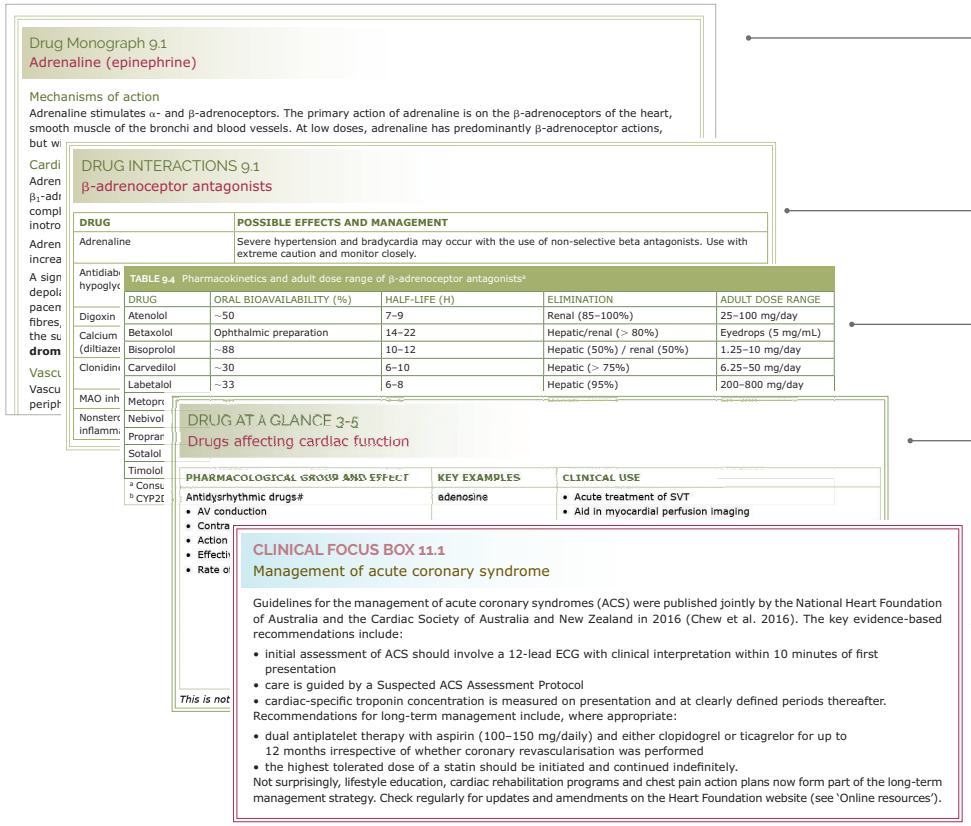
KEY ABBREVIATIONS introduces the abbreviations and acronyms that will be used, and provides a quick reference point.

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

CHAPTER FOCUS highlights what you will learn in the chapter.

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

Tables and Boxes



Drug Monograph 9.1
Adrenaline (epinephrine)

Mechanisms of action

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

DRUG INTERACTIONS 9.1
β-adrenoceptor antagonists

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

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

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

DRUG AT A GLANCE 3-5
Drugs affecting cardiac function

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

CLINICAL FOCUS BOX 11.1
Management of acute coronary syndrome

Guidelines for the management of acute coronary syndromes (ACS) were published jointly by the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand in 2016 (Chew et al. 2016). The key evidence-based recommendations include:

- initial assessment of ACS should involve a 12-lead ECG with clinical interpretation within 10 minutes of first presentation
- care is guided by a Suspected ACS Assessment Protocol
- cardiac-specific troponin concentration is measured on presentation and at clearly defined periods thereafter.

Recommendations for long-term management include, where appropriate:

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

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

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

DRUG INTERACTIONS TABLES highlight drug interactions of clinical relevance.

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

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

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

CRITICAL THINKING SCENARIO

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

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

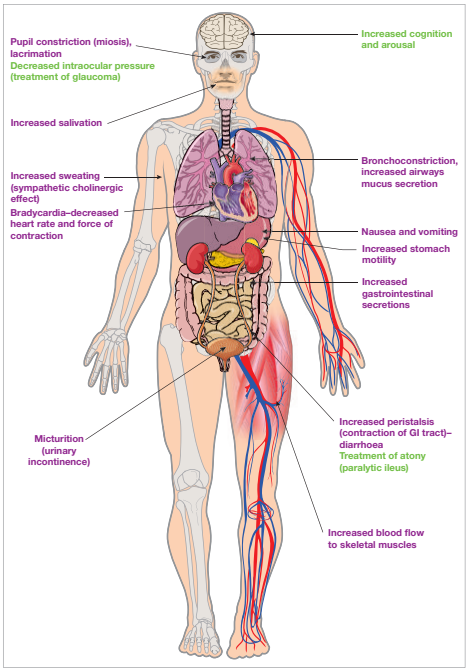


FIGURE 8.5 Pharmacological effects of muscarinic receptor agonists

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

KEY POINTS

Pharmacodynamics

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

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

REVIEW EXERCISES

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

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

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

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

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

ONLINE RESOURCES

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

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

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

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

PREFACE

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

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

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

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

ACKNOWLEDGEMENTS

The authors of the 6th edition of *Pharmacology for Health Professionals* would like to express their gratitude to Bronwen Bryant for the integral role she played in the first five editions. As one of the original authors, her drive, enthusiasm and passion for pharmacology helped to lay the foundations of the hybrid physiology/pharmacology/clinical pharmacology focus of the text. The 6th edition continues her legacy.

The authors thank all readers (students, academics and colleagues) who have provided helpful and constructive comments, which we have addressed in this edition.

The authors also thank and acknowledge the invaluable assistance of the following people, whose time and expertise contributed to the accuracy and clarity of the information:

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The authors acknowledge use of information from the *New Zealand Universal List of Medicines*, which uses information from Medsafe, PHARMAC and the Pharmacy Guild of New Zealand.

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Colleagues and Editors

We would like to acknowledge the support of our colleagues at Flinders University (KK, AR), Victoria University (SD), University of Canberra (MB) and the authors who previously kindly gave permission to use or adapt their work for our purposes, in particular Professors John Murtagh, George Sweeney and the late Bill Bowman.

Our role as authors has again been challenging, and we record our thanks to staff and associates of Elsevier, especially Melinda McEvoy (Senior Content Strategist) and Shruti Raj (Content Project Manager) for their stimulus, guidance and patience; editor Matt Davies for his editorial rigour; and pharmacists Jerry Perkins and Lynne Mackinnon for their careful technical checking. It is inevitable that recommendations for drug indications, availability, scheduling and dosage will change, and current evidence-based drug information sources should always be consulted prior to drug administration. We apologise for any errors and welcome comments and feedback on the 6th edition of *Pharmacology for Health Professionals*.

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Kathie completed a Bachelor of Science (Honours) degree at North East London Polytechnic, majoring in pharmacology, while working as a research assistant at Guy's Hospital, London. On returning home to Adelaide, she accepted a research position in the Department of Anaesthesia and Intensive Care in the School of Medicine at Flinders University, where she also completed a PhD investigating the hepatotoxicity of the inhalational anaesthetic agent halothane.

Kathie's academic career developed throughout her time at Flinders, progressing from her initial appointment as Lecturer to Professor in Clinical Pharmacology. Her teaching crossed discipline boundaries, covering medicine, nursing, nutrition and dietetics, optometry and paramedic sciences. She was a recipient of a Carrick Award in 2007 and the ASCEPT Teaching Excellence Award in 2010, both awards recognising her outstanding contribution to student learning. Her research interests centred on drug metabolism, specifically the metabolism of non-steroidal anti-inflammatory drugs and their mechanisms of renal toxicity. An invited speaker at national and international conferences, Kathie has published extensively in peer-reviewed international journals and books.

Kathie retired in 2014 and is now an Emeritus Professor in the Department of Clinical Pharmacology in the College of Medicine and Public Health, Flinders University. In 2020 she was awarded a Fellowship of ASCEPT, which recognised her significant contribution to the discipline and to the society. She remains a passionate advocate of the discipline of pharmacology.

Shaunagh Darroch

Shaunagh completed a Bachelor of Science degree at Monash University, majoring in pharmacology and physiology. She subsequently moved to the Victorian College of Pharmacy (now Monash University), where she completed a Master of Pharmacy degree in the field of cholinergic pharmacology.

Shaunagh's academic career has involved lecturing and tutoring positions, including at Monash University, La Trobe University and Victoria University within the disciplines of pharmacy, paramedicine, nursing and midwifery, podiatry, physiotherapy, and health and biomedical sciences. She has been involved in course and curriculum development, as well as face-to-face and online teaching of basic, advanced and clinical pharmacology, physiology and pathophysiology. She has been a visiting lecturer at the University of Hong Kong (School of Professional and Continuing Education) and the Fiji School of Medicine.

Alongside her many research publications and communications, Shaunagh has been a contributor to several Australian and international textbooks including the previous editions of *Pharmacology for Health Professionals*. Her research interests have ranged from G protein-coupled receptors through to paramedic clinical practice.

Shaunagh continues to be an enthusiastic educator and communicator. She is currently involved in curriculum design and development across several universities, in addition to writing and editing consultancies in various disciplines.

Andrew Rowland

Andrew completed a PhD investigating better ways to use in vitro models to predict drug metabolism in humans in 2009. He then spent two years as a post-doctoral researcher before taking up an academic position in the School of Medicine at Flinders University. Now Associate Professor, Andrew contributes to the teaching of pharmacology and therapeutics within a range of medical and health degrees including the Doctor of Medicine, Bachelor of Paramedic Science, Bachelor of Medical Science and Master of Advanced Clinical Practice degrees.

Andrew has a highly active research profile, with a primary interest in translating pharmacokinetics into clinical practice through optimising drug dosing, specifically focusing on precision dosing of anticancer drugs. He has published more than 120 research articles and reviews in peer-reviewed international journals and has received numerous research awards including the prestigious Certara New Investigator Award from the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists and a Vice Chancellor's Award for Early Career Researchers.

Mary Bushell

Mary completed her Bachelor of Pharmacy (Honors) degree at Charles Sturt University and later worked in the Northern Territory, providing care as a practising

pharmacist in some of the most remote communities in Australia. Mary's academic career began in 2011 at Charles Darwin University, where she advanced to a Senior Lecturer position coordinating and teaching pharmacology and pharmacy practice units. In 2016 Mary completed her PhD, which developed and validated a vaccination training program for pharmacy students. Now a Clinical Assistant Professor in Pharmacy at the University of Canberra, Mary enjoys coordinating and teaching pharmacology and evidence-based medicine to a range of health courses including pharmacy, medicine, nursing, optometry, nutrition and health science. Mary takes great pride in the honour of fostering the next generation of health professionals.

DEDICATION

To the discipline of pharmacology, which provided the foundation of my academic career, and to those who enrich my life – my husband, John, and my family and friends.

Kathleen Knights

To my family and friends for their continuous encouragement and humour, to my colleagues for their support and guidance, and to my students for challenging and inspiring me.

Shaunagh Darroch

It is with gratitude and love that we dedicate this work to my wonderful wife, Angela, and amazing sons Aidan and Archer. Your kindness and love enrich every element of my life.

Andrew Rowland

To my greatest teachers – my parents, Penny and Tony. Thank you for inspiring my curiosity to learn science with nectarines, tennis balls and sheep's eyes. Forever grateful.

Mary Bushell

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CHAPTER 1

DRUGS AND MEDICINES

Mary Bushell

KEY ABBREVIATIONS

AMH	*Australian Medicines Handbook*
APF	*Australian Pharmaceutical Formulary and Handbook*
BP	British Pharmacopoeia
CFB	Clinical Focus Box
CMI	consumer medicine information
CTN	Clinical Trial Notification
DM	Drug Monograph
INN	International Non-proprietary Name
NZF	*New Zealand Formulary*
OTC	over-the-counter
RCCT	randomised controlled clinical trial
TGA	Therapeutic Goods Administration
WHO	World Health Organization

Chapter Focus

This chapter focuses on the origin, development and scope of pharmacology. It describes the physical and chemical characteristics of drugs, how drugs are named and classified and how drug information can be sourced. The stages of drug discovery and development, including the phases and important elements in clinical trials of investigational drugs, are outlined. Understanding basic pharmacology is integral for health professionals because it helps promote quality use of medicines, which subsequently improves health outcomes for their patients.

KEY TERMS

active ingredient 13
approved name 25
assay 13
chemical name 23
clinical trial 13
contraindications 2
dose 2
dose form/formulation 3
drug 2
drug development 15
formulary 28
generic name 23
indication 2
key, or prototype, drug 26
medication 2
medicine 2
over-the-counter drug 2
parenteral administration 23
pharmaceutical 2
pharmaceutics 2
pharmacist 13
pharmacodynamics 2
pharmacokinetics 2
pharmacy 2
pharmacology/pharmacologist 2
pharmacopoeia 2
pharmacy/pharmacist 13
potency 3
Prescription-Only drug 26
proprietary, or trade, name 25
randomised controlled clinical trial 5
receptors 3
route 2
selectivity 3
specificity 3
standardisation 13
structure–activity studies 9
tablet 22

CRITICAL THINKING SCENARIO

Billy, a 28-year-old male, was recently diagnosed with depression and prescribed the antidepressant sertraline. Billy tells you, the health professional, that he does not like taking medicines. Up till now, Billy has only taken simple analgesia and the odd course of antibiotics.

Billy would like to learn more about the drug development stages and the phases of clinical trials that help promote safe and effective medicines.

1. Explain the stages of drug development.
2. Explain each of the phases of the clinical trial process.
3. Explain as a health professional how you would report a suspected adverse reaction to a medicine or vaccine.

Billy has looked at many online resources, blogs, tweets and relevant Facebook posts to search for information about the safety and effectiveness of sertraline. He tells you that a lot of information he has read is conflicting and, the more he reads, the more confused he gets. Billy read one online article that suggests that 'natural' medicines made from plants are safer than 'unnatural' synthetic medicines, like the one he has been prescribed.

4. Describe drug information sources that Billy can read to get evidence-based information about his new medicine.
5. Discuss if 'natural' drugs are safer than synthetic drugs.

Introduction

Pharmacology is the study of drugs, including their sources, nature, actions, effects in living systems and uses. The word '**drug**' is defined by the World Health Organization (WHO 2007) as 'any substance or product that is used or intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient'. The prefix 'pharmaco-' is derived from the Greek word *pharmakon*, meaning 'drug' or 'medicine'. Hence, we have related terms such as **pharmacy**, **pharmacodynamics**, **pharmacokinetics**, **pharmaceutics** and **pharmacopoeia** (Table 1.1).

Pharmacologists may study the origins, isolation, purification, chemical structure/synthesis, assay (measurement), actions/mechanisms, economics, genetic aspects and toxicity of drugs, as well as their fate in the body and medical uses. Pharmacologists work in hospitals, clinics, research institutions, drug companies, government departments of health, medical publishing and universities. In other words, wherever drugs are developed, studied and used.

Pharmacology deals with all drugs used in society – legal and illegal, prescription and '**over-the-counter**' (OTC) medications, endogenous substances (those produced within the body) and natural and synthetic products – with beneficial or potentially toxic effects. The pharmacological agents available today have controlled, prevented, cured, diagnosed and, in some instances, eradicated diseases, and have improved the quality of life of billions of people.

Medicines also have the potential to cause harm. (The ancient Greek word for 'drug' was also the word for 'poison'.) To administer a drug safely, one must know the appropriate **dose**, frequency, **route** of administration, **indications**, **contraindications**, significant adverse reactions, major drug interactions, dietary implications (if applicable) and appropriate monitoring techniques and interventions, and apply this knowledge to the particular patient and situation.

Drugs and medicines

Unfortunately, the word 'drug' has come to have connotations of illicit street drugs. However, it has a much simpler and wider meaning: a drug is a substance that usefully affects living tissues. The terms '**medication**', 'medicine' and '**pharmaceutical**' usually refer to drugs

TABLE 1.1 Some common pharmacological terms[a]

TERM	DEFINITION
Adverse drug reaction	An unintended and undesirable response to a drug
Clinical pharmacology	Pharmacology applied to the treatment of human patients; the study of drugs 'at the bedside'
Dose	The quantity of a drug to be administered at one time, determined by experience as likely to be safe and effective in most people
Dose form/formulation	The form in which the drug is administered – for example, as a tablet, injection, eyedrops or ointment
Drug	A substance used to modify or explore the physiological system or pathological state for the benefit of the recipient
Indication	An illness or disorder for which a drug has a documented specific usefulness
Medicine	Drug(s) given for therapeutic purposes; possibly a mixture of drug(s) plus other substances to provide stability in the formulation; also, the branch of science devoted to the study, prevention and treatment of disease
Pharmaceutics	The science of the preparation and dispensing of drugs
Pharmacist[b]	A person licensed to store, prepare, dispense and provide drugs, and to make up prescriptions
Pharmacodynamics	What drugs do to the body and how they do it; refers to the interaction of drug molecules with their target receptors or cells, and their biochemical, physiological and possibly adverse effects
Pharmacokinetics	How the body affects a specific drug after administration; that is, how a drug is altered as it travels through the body (by absorption, distribution, metabolism and excretion)
Pharmacologist[b]	A person who studies drugs: their source, nature, actions/mechanisms, uses, fate in the body, medical uses and toxicity
Pharmacology	The study of drugs, including their actions and effects in living systems
Pharmacopoeia	A reference book listing standards for drugs approved in a particular country; may also include details of standard formulations and prescribing guidelines (a formulary)
Pharmacy	The branch of science dealing with preparing and dispensing drugs; also the place where a pharmacist carries out these roles
Receptor	Protein structure on or within a cell or membrane that is capable of binding to a specific substance (e.g. a transmitter, hormone or drug), initiating chemical signalling and causing altered function in the cell
Route	The pathway by which a drug is administered to the body; for example, in the oral route, the drug is taken by mouth and swallowed
Side effect	A drug's effect that is not necessarily the primary purpose for giving the drug in the particular condition; side effects may be desirable or undesirable. This term has been virtually superseded by the term 'adverse drug reaction', which is used throughout this book
Toxicology	The study of the nature, properties, identification, effects and treatment of poisons, including the study of adverse drug reactions

[a] See the Glossary (Appendix 2) for a more complete listing of pharmacological terms.
[b] The roles of these and many other health professionals are described in greater detail in Chapter 2.

mixed in a formulation with other ingredients to improve their stability, taste or physical form, in order to allow appropriate administration of the active drug.

Characteristics of drugs

Potency, selectivity and specificity

By our broad definition of a drug as a chemical having useful action on living tissue, many substances could be classed as drugs: even oxygen, sugar, salt and water usefully affect the body but can be toxic in overdose. However, useful drugs usually have other important attributes: potency, selectivity and specificity.

Potency relates to the amount of chemical required to produce an effect; it is an *inverse* relationship – the more potent the drug, the lower the dose required for a given effect (Fig 4.6, in Ch 4). One of the most potent chemicals known is the natural bacterial product botulinum toxin (commonly known as Botox), for which the estimated human median lethal dose (LD_{50}) is about $1–1.5 \times 10^{-7}$ g IV for a 70 kg adult. It is used to treat spasm of eye muscles and spasticity, and in neurological disorders and cosmetic surgery (DM 40.3).

Selectivity refers to the narrowness of a drug's range of actions on **receptors**, cellular processes or tissues. The antidepressant drugs known as selective serotonin reuptake inhibitors such as fluoxetine (Prozac – see DM 22.3) have fewer adverse effects than older antidepressants because of their more selective actions.

The term **specificity** may be used loosely like 'selectivity' – for example, cardiospecific or cardioselective β-blocking agents. Specificity may also refer to the relationship between the chemical structure of a drug and its pharmacological actions; for example, the effects of salbutamol and similar bronchodilators in asthma are due to their chemical similarity to the neurotransmitter noradrenaline (Fig 1.4, later), and hence their specificity for the β-adrenoceptor.

The ideal drug

In designing a new drug, a research pharmacologist might aim for it to be: easily administered (preferably orally) and fully absorbed from the gastrointestinal tract; not

highly protein-bound in the blood plasma; potent; highly specific; selective, with rapid onset and useful duration of action; of high therapeutic index (no adverse drug reactions, no interference with body functions); unlikely to interact with any other drugs or foodstuffs; spontaneously eliminated; stable chemically and microbiologically; readily formulated into an easily taken form; and inexpensive.

Sadly, there is no *ideal drug*, whether natural product or synthetic. It has been said that any substance powerful enough to be useful is also powerful enough to do some harm. The decision to prescribe, administer or take a drug requires a risk–benefit analysis based on the best information available: Do the likely therapeutic benefits (efficacy) outweigh the possible harmful effects (toxicity)?

Physical aspects of drugs

In terms of their physical state, drugs may be solids, liquids or gases. Most are solids at room temperature, but some are liquids in the pure state, such as nicotine, halothane (a general anaesthetic) and ethanol, and some are gases, especially general anaesthetics such as nitrous oxide.

Chemical aspects of drugs

Inorganic/organic

Whether found naturally in plants, animals, minerals or microorganisms, or synthesised in a laboratory, all drugs are chemicals of one sort or another. They may be inorganic (do not contain carbon) molecules such as calcium salts used to prevent and treat osteoporosis, or iodine and iron used to prevent mineral deficiencies. Most drugs, however, are organic molecules; that is, they contain carbon in their structures. All the major classes of organic compounds, including hydrocarbons, proteins, lipids, carbohydrates, nucleic acids and steroids, are represented in pharmacopoeias (Fig 1.3, later). Many drug molecules are acids or bases, which is important not only for their taste and irritant effects but also for how the drugs move across membranes and are affected by metabolism and excretion (pharmacokinetics – see Ch 5).

Molecular size

The sizes of drug molecules can also vary enormously, ranging from tiny lithium, the third-lightest element with an atomic mass of about 7, used as a specific antimanic agent, through to proteins such as insulin (molecular mass 5808 daltons) and erythropoietin (molecular mass 34 kilodaltons). Most drugs are in a more intermediate size range, with molecular weights (relative molecular masses) of between 100 and 1000. For example, aspirin has a molecular weight of 180, testosterone (a steroid hormone) 288, digoxin (a cardiac glycoside) 781 and ciclosporin (an immunosuppressant with a cyclic polypeptide structure) 1203. The size and nature of the molecule have important implications: proteins taken orally would be digested in the gut, so they must be administered by injection; large molecules generally will not readily pass through cell membranes and may need to be administered directly to their site of action.

A brief history of pharmacology

Medicines in antiquity and pre-scientific eras

For many thousands of years and in all civilisations, people have searched for substances to prevent, treat and cure disease. Discovery of safe drugs presumably developed by trial and error, with many fatalities and adverse effects. Archaeological diggings show that Stone Age people used opium poppies (Ch 12) and Inca civilisations used cocaine (Ch 11). Artefacts discovered in the ruins of Pompeii indicate that first-century Romans used pills and potions, including plant materials (poppy, henbane, *Artemisia*, cannabis) and minerals. The timeline in Table 1.2 summarises the history of medicine and major drug discoveries, and Fig 1.1 shows portraits of four famous people from medical history.

TABLE 1.2 Timeline of medical history and major drug discoveries

TIME PERIOD	COMMENTS
3000–1500 BC	Sumerian civilisation: prescriptions inscribed on clay tablets; vegetable and mineral drugs prepared in milk, beer and wine; supernatural healing rituals carried out by healers and shamans. Egyptian period: diseases believed caused by evil spirits in the body; Imhotep, the god of medicine, and Isis and Horus, gods of pharmacy, worshipped. The Ebers Papyrus, from about 1500 BC, described formulations of more than 700 drugs from plant, mineral and animal sources. Chinese medicine dating back beyond 2000 BC included use of poisons and antidotes, acupuncture, diets and moxibustion (burning of incense herbs for heating skin); medicines included ephedra (ephedrine) for asthma and seaweeds (iodine) for goitre. Ancient Indian (Ayurvedic) medicine described many surgical practices and more than 1000 natural drugs, including wine (alcohol) and hemp (marijuana) for pain relief.
1100–146 BC	Ancient Greek civilisation: the god Asclepius considered the principal god of healing, with his wife Epione soothing pain, and daughters Hygeia helping prevent disease and Panacea representing treatment (hence the phrase 'a panacea for all ills'). Hippocrates, a Greek physician, is 'the father of medicine': emphasis on humours and doctrine of opposites.

TABLE 1.2 Timeline of medical history and major drug discoveries—cont'd

100 BC – AD 400	Roman Empire: medicine based on Greek traditions of herbal remedies and healing gods. Excellent public health measures introduced: safe water supplies and sanitation. Folk remedies included wound dressings of wine, vinegar, eggs, honey, worms and pig dung. Ephedra (ephedrine, a sympathomimetic agent) was used for asthma, cough and haemorrhage. Dioscorides' textbook *De Materia Medica* documented use of more than 600 medicinal plants and minerals including analgesics, antiseptics, emetics and laxatives; translated into Latin, Arabic and Persian. Indian surgeon wrote the *Sushruta Samhita*, the classic text of Ayurvedic medicine. Celsus described four cardinal signs of inflammation and stressed the importance of moderation, exercise, knowledge of anatomy and prevention of infection and haemorrhage.
2nd century	Galen, Greek physician/surgeon/druggist: pharmacy based on 'simples' and complex mixtures now called galenicals (see prescription A in Fig 2.4).
5th–11th centuries	Dark Ages in Europe: herbal medicine, folklore, magic, religion, bleeding, surgery and cosmology interwoven and practised in monasteries. Learning carried out in Latin; libraries held Greek, Roman and Arabic medical texts. In some countries, women allowed to practise medicine and midwifery. Meanwhile in Arabia, China and India, medicine and herbal pharmacy developed.
3rd–15th centuries	Golden Age of Islamic medicine: folk medicines included camphor, henna, syrup, aloes, amber and musk; first set of drug standards formulated. Classic Greek medical works translated into Arabic; an extensive library collected in Baghdad. Persian physician Avicenna now revered as 'the father of clinical pharmacology'. Great contribution of Islamic medicine: establishment of teaching hospitals and medical libraries such as in Baghdad, Cairo and Damascus; medical education has depended ever since on this style of training.
12th–14th centuries	Mediaeval period: in Europe, medical schools developed in Salerno, Bologna and Montpellier; pharmacy declared to be separate from medicine; apothecaries documented uses of herbs and spices; alchemists pursued the 'elixir of life'. The Black Death (plague) killed more than 25 million people in Europe. Victims of battle wounds usually succumbed to infection, haemorrhage and shock or pain. Hypnotic (sleep-inducing) and analgesic (pain-relieving) effects of the herbs poppy, henbane and mandrake known and valued.
14th–17th centuries	Renaissance in Europe: rebirth of interest in arts, sciences, politics, economics and medicine. Vesalius (anatomist), Gerard and Culpepper (herbalists) revolutionised medical knowledge. In the Ming dynasty in China, Li Shizhen documented Chinese medical knowledge in his compendium *Bencao Gangmu*, still the basis for traditional Chinese medicine. Paracelsus (1493–1541), Swiss alchemist and pharmacologist, denounced 'humoral pathology', substituted theory that diseases could be combated with specific remedies, and reduced prevalent overdosing. Infectious diseases, including measles and smallpox, spread from Europe to the 'New World'. Important pharmacological discoveries included: ♦ treating gout with colchicum (colchicine) and restriction of wine intake ♦ treating malaria with 'Jesuit's bark' (cinchona, containing quinine) ♦ preventing scurvy (vitamin C deficiency) with oranges and lemons ♦ using willow bark (salicylates) to treat fever, and foxglove (digitalis) to treat 'dropsy' (oedema) ♦ using extracts of opium, mandrake and hemlock in wine to relieve pain and to allow surgical procedures, and henbane (hyoscyamus, containing hyoscine) for inducing forgetfulness. Valerius Cordus (a German physician; 1515–1544) compiled the first pharmacopoeia (reference text with standard formulae and recipes); followed by the London Pharmacopoeia (1618), the French Codex (1818), and the pharmacopoeias of the United States (1820), Britain (1864) and Germany (1872).
18th–19th centuries	Rational medicine replacing trial-and-error empiricism. Deliberate clinical testing of drugs for their actions was carried out; studies of dose–response relationships led to safer use of drugs. Active constituents of plants isolated: first morphine (1804), followed by quinine, atropine and codeine; digitalis plant shown to be source of cardiac glycosides (digoxin, digitoxin); coca bark shown to contain a useful local anaesthetic, cocaine, purified and used in eye surgery; safer synthetic analogues soon developed. Anaesthetic gas nitrous oxide and volatile liquids ether and chloroform used in surgery, dentistry and obstetrics, providing first safe, painless surgery. Vaccinations developed for smallpox, diphtheria and rabies. Public health measures and quarantines imposed. Nursing developed as a profession. X-rays discovered. Advances in chemistry, especially coal-tar (organic) chemistry, allowed development of hypnotics and sedatives such as chloral hydrate, analgesics (including aspirin) and antiseptics such as carbolic acid.
20th century	Application of organic and synthetic chemistry, and biostatistics, to drug discovery; the first 'magic bullet': salvarsan against syphilis; receptor theories developed.
1920s	Insulin isolated (first protein to have chemical structure identified), the most important discovery for treatment of diabetes mellitus; penicillin discovered.
1930s–1940s	First safe oral antimicrobials: sulfonamides, penicillins and streptomycin developed. Use of muscle relaxants with general anaesthetics, making major surgery safer. Chemical warfare agents such as mustard gas led to 'nitrogen mustard' anticancer drugs. Cortisone, the hormone from the adrenal cortex, identified and synthetically prepared.
1940s–1950s	Autonomic pharmacology studies, structure–activity relationships on α- and β-receptors. DNA shown to be carrier of genetic information. First (modern) **randomised controlled clinical trial** (RCCT) (streptomycin against tuberculosis). World Health Organization (WHO) set up.
1950s	Chlorpromazine becomes the first effective antipsychotic drug to specifically treat schizophrenia. Structure of DNA determined, and understanding of molecular genetics expanded rapidly. Oral contraceptives developed – similar to natural estrogen and progesterone hormones, revolutionising family planning. Poliovirus vaccines eliminate deaths and paralysis from polio epidemics. First successful organ transplant.
1960s	Declaration of Helsinki prescribed ethical conduct of human medical research. Levodopa used to treat Parkinson's disease; immunosuppressants made organ transplantation feasible; treatment of hypertension with thiazide diuretics and β-blockers helped prevent strokes; cytotoxic agents (alkylating agents, antimetabolites and antibiotics) developed to treat cancers. Thalidomide disaster, with thousands of infants born with severe malformations, led to tightening of regulations for testing new drugs.

Continued

TABLE 1.2 Timeline of medical history and major drug discoveries—cont'd	
1970s	Recombinant DNA technologies and monoclonal antibodies developed. Antivirals developed for prophylaxis and treatment of viral diseases. Childhood leukaemia treated successfully with cytotoxics and steroids. Ovulatory stimulants used in in-vitro fertilisation. Drug delivery methods and prodrug strategies improved.
1980s–1990s	HIV identified as the cause of AIDS. New drugs for thrombolysis, reduction of cholesterol levels, inhibition of synthesis of angiotensin or prostaglandins, antiretroviral therapy of AIDS, and treatment of impotence; new antineoplastic agents for chemotherapy of cancers, inhaled corticosteroids for asthma, atypical antipsychotics for schizophrenia; refinement of treatment protocols. Smallpox eradicated worldwide. The Human Genome Project successfully determined sequence of nucleotide base pairs in human DNA; all the genes of the human genome identified and mapped (2003).
2000–present	Stem cell therapy developed. Application of combinatorial chemistry and high-throughput screening allows rapid testing of millions of possible drug molecules. Recent innovations include chiral versions of optically active drugs (e.g. levobupivacaine, escitalopram), genetically engineered molecules (insulin glargine), prostaglandin analogues for glaucoma (latanoprost, travoprost), thiazolidinediones and incretin enhancers for type 2 diabetes; and tyrosine kinase inhibitors (imatinib, sorafenib), monoclonal antibodies (trastuzumab, ipilimumab) and BRAF inhibitors (vemurafenib) in cancer chemotherapy.

FIGURE 1.1 Famous people from medical history: **A** Hippocrates; **B** Galen; **C** Hildegard of Bingen; **D** Avicenna
A: Hippocrates (5th century BC, 'the father of medicine') taught that disease can be understood through careful diagnosis. He believed health was due to a balance of four 'humours' ebbing and flowing in the body (blood, phlegm, black bile and yellow bile); hence the related terms 'sanguine', 'phlegmatic', 'bilious', 'choleric' and 'melancholic'. His doctrine that opposites cure (cold treats fever, bleeding treats excess humours) was the basis of medicine for hundreds of years but eventually held up advances. Hippocrates still influences the practice of medicine, as in versions of the Hippocratic Oath proclaimed at many medical graduation ceremonies (CFB 2.9). **B:** Galen of Pergamon (2nd century) wrote voluminously on medical, scientific, philosophical, ethical and religious issues; he considered that bleeding (removal of large volumes of blood) was appropriate treatment for virtually all disorders. Galen was famous for his knowledge of drugs, both 'simples' (i.e. simple herbal or mineral remedies) and complex mixtures known as 'galenicals', including exotic herbs, amulets, excrement and antidotes. **C:** Hildegard of Bingen was a remarkable writer, composer, prophet, healer and abbess during the Middle Ages. Her books described the causes of many diseases and the medical and toxic properties of herbal, animal and mineral preparations. **D:** Avicenna (Abu-Ali Sina; Ibn Sina), the most famous ancient Persian physician, lived in central Asia and Persia around AD 980–1037. He was a 'man for all seasons' – physician, philosopher, astronomer, chemist, mathematician, poet, teacher. His most famous works, *The Book of Healing* and *The Canon of Medicine,* were standard medical textbooks for centuries, even in French medical schools. Avicenna is considered to be 'the father of clinical pharmacology', as he introduced systematic experimentation, quantification, randomised clinical trials and efficacy tests into the study of physiology and infectious diseases.
B *Lithograph by Pierre Roche Vigneron,* **C&D***: Wellcome Library no. 4213i, CC BY 4.0.*

Into the 20th and 21st centuries: 'magic bullets'

Early in the 20th century, drugs commonly used in medicine were: morphine and codeine as analgesics; sodium bicarbonate and glycerine for gastrointestinal problems; sodium bromide as a sedative; sodium salicylate as an anti-inflammatory and antipyretic analgesic; and strychnine as a 'tonic'. During the 20th century, medicine made enormous advances, leading to therapeutic revolutions in all areas of medicine. Of 36 major events identified as the most significant in modern medicine from 1935 to 1999, at least half are directly due to developing effective drugs to treat previously life-threatening diseases (Le Fanu 2011).

As knowledge of chemistry, physiology, medicine and pharmacology developed, it was applied to the problem

of finding drugs to treat specific conditions. The German chemist Paul Ehrlich, 'the father of chemotherapy', realised when working with synthetic dyes that the biological effect of a compound depends on its chemical composition. A major development was the production of safe, orally active synthetic antimicrobials (sulfonamides). In 1928, penicillin was discovered (by Alexander Fleming), and in the 1940s it was isolated and purified (by Howard Florey and Ernst Chain), revolutionising the treatment of microbial infections and leading to other antibiotics, such as streptomycin for tuberculosis.

These successes led to a search for the 'magic bullet' – the mythical goal of finding a specific drug to target a diseased tissue or cell while leaving all other tissues intact.

Advances in synthetic organic chemistry led to the establishment of large-scale chemical manufacturing plants to produce drugs. Structure–activity studies identified series of molecules with agonist or antagonist actions on many types of receptors. The importance of using a control group when testing drugs or other treatments was recognised, and the RCCT became the expected standard.

It is interesting to note that early in the 21st century most of the 'top 10 drugs' prescribed in developed countries are for lifestyle diseases, including statins for high cholesterol levels and calcium channel blockers and angiotensin-converting enzyme inhibitors for cardiovascular diseases (Tables 1.6 and 1.7, later).

The scientific revolution brought about by molecular biology techniques has enabled the identification and cloning of genes that code for therapeutically useful proteins, including monoclonal antibodies and receptors. Biochemical pathways in cell division are being elucidated, leading to new anticancer agents (Chs 32 and 33). Meta-analysis techniques have been developed (notably by Cochrane) to pool together and analyse results of clinical trials and medical research, and to evaluate scientific data in order to encourage implementation of evidence-based medicine.

KEY POINTS

Introduction to pharmacology

- Pharmacology is the study of drugs, which are substances used for their beneficial effects on living systems.
- People have searched for, been fascinated by, used and abused drugs throughout recorded history.
- Initially, useful natural compounds were discovered by trial and error; they were then studied for their medical actions and adverse effects.
- Drugs may be solids (most commonly), liquids or gases. Most are organic (carbon-containing) chemicals.

Drug discovery and development

The goal of the drug discovery and development process is to produce safe and effective therapeutic drugs. There are several ways in which potential therapeutic uses of chemicals – natural or synthetic – are determined, summarised as three steps: (1) understand the science, (2) unravel the story and (3) apply the technology. Drug discovery has been likened to the processes of evolution: a selection process with a high level of attrition and many influences affecting survival of the fittest. Recently, drug discovery has become more reliant on computational and artificial intelligence, accelerating the drug discovery process (Hinkson et al. 2020).

Where drugs come from

Drugs and biological products are derived from several main sources:

- microorganisms – for example, fungi used as sources of antibiotics (Fig 1.2A) and bacteria and yeasts genetically engineered to produce drugs such as human insulin
- plants – for example, *Atropa belladonna* (source of atropine), *Cannabis sativa* (marijuana), *Coffea arabica* (Fig 1.2B; coffee, caffeine), *Digitalis purpurea* (Fig 1.2C; digitalis), *Duboisia* species (hyoscine, nornicotine), *Eucalyptus* spp. (eucalyptus oil), *Papaver somniferum* (Fig 1.2D; opium, morphine[1])
- humans and other animals, from which drugs such as bovine insulin, human chorionic gonadotrophin and erythropoietin were or are obtained, sometimes by recombinant techniques
- minerals or mineral products – for example, iron, iodine and Epsom salts
- laboratories in which substances are synthesised, such as sulfonamides, β-blockers and antidepressants. Drugs may also be classed as semisynthetic when the starting material is a natural product, such as a plant steroid or microbial metabolite, which is then chemically altered to produce the desired drug molecule.

Development from natural or traditional remedies

For thousands of years, people have been trying natural products – animal, vegetable and mineral – to see if they are useful as foods or in treating disease (Table 1.3).

1 The isolation of the pure alkaloid morphine as the active pain-relieving constituent of opium poppies (in 1804) has been described as 'the single most important discovery in medicine', as it demonstrated that pharmacological activities of plants are due to the chemicals they contain.

FIGURE 1.2 Natural sources of important drugs
A *Penicillium notatum* mould, source of penicillin; **B** *Coffea arabica*, source of caffeine (and coffee); **C** *Digitalis purpurea*, source of digoxin; **D** *Papaver somniferum*, source of morphine and codeine.
A–D: *iStockphoto/habari1; iStockphoto/kannika2013; iStockphoto/Petegar; iStockphoto/AtWaG*

TABLE 1.3 Some drugs from plants

DRUG	SOURCE	MAIN PHARMACOLOGICAL ACTIONS
Aromatic oils	For example, from eucalyptus, pine, mint	Decongestant, Rx common cold, mild antiseptics
Artemisinins	*Artemisia annua* (sagewort)	Antimalarial
Atropine	*Atropa belladonna* (deadly nightshade)	Antimuscarinic, premedication, Rx asthma
Bran	Indigestible vegetable fibre	Laxative, Rx constipation
Caffeine	*Coffea arabica* (coffee)	CNS stimulant, diuretic
Cocaine	*Erythroxylum coca*	CNS stimulant, local anaesthetic, addictive
Colchicine	*Colchicum autumnale* (crocus)	Anti-inflammatory, Rx gout
Coumarins	Sweet clover	Anticoagulants, prevent thrombosis
Digoxin	*Digitalis lanata* (woolly foxglove)	Cardiac glycoside, Rx heart failure
Ephedrine	*Ephedra sinica*	Sympathomimetic, Rx asthma
Ergot alkaloids (e.g. ergometrine)	Mould on *Claviceps* spp.	Oxytocic, Rx postpartum bleeding
Galantamine	*Galanthus nivalis* (snowdrop)	Anticholinesterase, used in neurological disorders and Alzheimer's disease
Hypericin	*Hypericum perforatum* (St John's wort)	Monoamine reuptake inhibitor, Rx depression
Ipecacuanha	Cephaelis root	Expectorant, emetic, Rx poisoning
Morphine	*Papaver somniferum* (opium poppy)	Analgesic, sedative, antidiarrhoeal, cough suppressant, addictive
Nicotine	*Nicotiana tabacum* (tobacco)	Vasoconstrictor, CNS stimulant, addictive
Paclitaxel	Yew tree bark	Antineoplastic, Rx cancer
Phytoestrogens	Clover, soybeans	Estrogenic, Rx menopausal symptoms
Pilocarpine	*Pilocarpus microphyllus*	Muscarinic agonist, Rx glaucoma
Quinine, quinidine	Cinchona bark	Antimalarial, Rx cardiac arrhythmias
Salicylates, including aspirin	*Salix* spp. (willow)	Anti-inflammatory, analgesic, antipyretic
Strychnine	*Strychnos nux-vomica*	CNS stimulant, convulsant
Vincristine	*Catharanthus roseus* (periwinkle plant)	Antineoplastic, Rx cancer

CNS = central nervous system; Rx = treatment of
Source: Evans (2009), Trease and Evans' Pharmacognosy, 16th edn [ch 6].

Natural products may be used as crude extracts, such as raw opium, tobacco leaves or herbal teas, or purified and/or synthesised and then formulated as pharmaceutical preparations, such as tablets, ointments and injections.

This is called the 'reefs and rainforests' route to new drugs, recognising that there are millions of natural chemicals in the environment to be identified and tested. As biodiversity is lost worldwide, we are losing the chance to discover novel drugs such as anticancer or antibiotic agents. (For example, the recent extinction of Australia's gastric-brooding frogs means we will now never know how the frog's eggs avoided digestion in the mother frog's stomach or being moved on into her small intestine – actions potentially useful in treating gastrointestinal tract disorders. Research into threatened bear species could elucidate their mechanisms for surviving months of hibernation without losing bone mass or dying of uraemia.) The Wellcome Trust in London has established the Millennium Seed Bank project at Kew Gardens to conserve and screen plants for possible future cures.[2]

Natural products not necessarily safer

There is a widely held belief that 'natural' products are safer than synthetic drugs, a belief encouraged by health-food and alternative therapy practitioners. A quick scan of naturally occurring substances such as arsenic, botulinum toxin, cantharidin, cocaine, cyanide, deadly nightshade, ipecacuanha, mercury, methanol, physostigmine, strychnine, thallium, tobacco and uranium shows that natural is not always good. It would be foolish to expect all natural products to be automatically safer than those synthesised in laboratories – or vice versa. Any drug's safety and quality must be tested and proved before it is approved for clinical use.

Active constituents of plant drugs

The leaves, roots, seeds and other parts of some plants may be dried, crushed, boiled and extracted or otherwise processed for use as medicine and, as such, are known as crude drugs or herbal remedies (Ch 3). Their therapeutic effects are produced by the chemical substances they contain. When the pharmacologically active constituents are separated, purified and quantified, the resulting substances usually have similar pharmacological actions to the crude drugs but are more potent (weight-for-weight), produce effects more reliably and are less likely to be affected by other constituents or contaminants in the crude preparations. Indeed, the herbal antidepressant St John's wort has been shown to have a similar mechanism of action – and hence similar therapeutic and adverse effects – as the synthetic selective serotonin reuptake inhibitors such as fluoxetine.

Some types of pharmacologically active molecules found in plants, grouped according to their chemical properties, are alkaloids, glycosides, steroids, hydrocarbons, alcohols/phenols, proteins, gums and oils (Table 1.4). Note that the groups are not mutually exclusive – there can be phenolic alkaloids, glycoproteins and phenolic glycosides. Fig 1.3 shows the chemical formulae of some drugs that are extracted from plant sources.

Serendipity (sheer good luck)

Although luck plays a part in some drug discoveries – such as Fleming's bacterial culture plate becoming contaminated with a growth of the fungus *Penicillium notatum*, which inhibited bacterial growth – it usually takes lateral thinking (e.g. questioning why bacteria were inhibited near the fungus), intelligence and years of hard work (extracting the natural antibacterial agent, determining its structure and developing methods of producing enough penicillin to treat people with bacterial infections) to exploit the lucky find.

Other examples of serendipity in pharmacological discovery are the findings that people treated with the first safe synthetic oral antibacterial agents, sulfonamides, had a lowering in their blood glucose levels, which led to sulfonylurea oral hypoglycaemic agents; and that hypertensive people treated with the vasodilator minoxidil tended to grow more hair. The drug is now used mainly as a hair restorer.

Chemical plus pharmacological studies

As chemical techniques developed in the 19th and 20th centuries, the structures of pharmacologically active substances could be determined and similar substances synthesised, then tested for activity. These **structure–activity studies** led to many drug groups:

- The second- and third-generation penicillins were modelled on the first penicillin.
- All the sympathomimetic amines were initially noradrenaline 'look-alikes': studies of *Ephedra sinica*, long known in traditional Chinese medicine to be useful in respiratory conditions (asthma), led to the purification of the active ingredient ephedrine, then to synthesis of the related β-receptor-activating antiasthma drugs isoprenaline and salbutamol (with fewer cardiovascular adverse reactions).
- β-blockers, such as propranolol and later atenolol, were designed to act as ligands at the receptor without activating it, and proved useful in cardiovascular diseases. (Chemical structures of β-receptor ligands are shown in Fig 1.4.)

2 There are many wonderful pharmaceutical gardens worth visiting, including the Jardin des Plantes de Montpellier in southern France, established in 1593, and the Chelsea Physic Garden (Garden of Medicinal Plants) in London, founded in 1673 as the Apothecaries' Garden.

TABLE 1.4 Pharmacologically active constituents of plant drugs

CHEMICAL CLASS AND STRUCTURE	CHARACTERISTICS	EXAMPLES
Alkaloids ♦ Organic nitrogen-containing compounds that are alkaline and usually bitter-tasting ♦ The nitrogen atom is usually in a heterocyclic ring of carbon atoms (Fig 1.3A)	♦ Many alkaloid drugs are amines, so their names often end in the suffix '-ine' ♦ Combined as salts to make them more soluble (e.g. morphine sulfate) ♦ Plants may have evolved the ability to synthesise bitter alkaloids as a defence against herbivorous animals	♦ Analgesics morphine (Fig 1.3A),* cocaine and codeine ♦ Antiasthma drugs ephedrine, theophylline and atropine ♦ Vinca alkaloids (anticancer) ♦ Alkaloids used in gout (colchicine), malaria (quinine) and obstetrics (ergot alkaloids) ♦ 'Social' drugs: nicotine and caffeine
Carbohydrates ♦ Organic compounds of carbon, hydrogen and oxygen	♦ Sugars are a source of energy ♦ Gums and mucilages are carbohydrate plant exudates; when water is added, some will swell and form a gelatinous mass, a useful laxative effect ♦ Gums are also used to soothe irritated skin and mucous membranes and may be a rich source of starch	♦ Sugars such as glucose ♦ Starches and fibres such as cellulose and inulin, a fructose–furanose polysaccharide (Fig 1.3B) used in kidney function tests (not to be confused with insulin, a protein from the pancreas) ♦ Gelling agents such as agar, and gums such as tragacanth and *Aloe vera* products (CFB 41.2)
Glycosides ♦ Particular type of carbohydrate that, on hydrolysis, yields a sugar plus one or more additional active substances	♦ The sugar part is believed to increase the solubility, absorption, permeability and cellular distribution of the glycoside	♦ Digoxin (Fig 1.3C), found in *Digitalis* (foxglove) plants; known as a cardiac glycoside because of its stimulant actions on the heart ♦ Glycosides present in oleanders and some other Australian plants are responsible for their poisonous nature ♦ Cane toads also contain cardioactive glycosides
Hydrocarbons ♦ Organic molecules consisting entirely of hydrogen and carbon ♦ May be straight-chain or aromatic (containing benzene rings)	♦ Derivatives such as organic alcohols and esters contribute the fragrances to many plants and perfumes ♦ Commonly used by drug companies and pharmacies when preparing topical formulations of drugs, especially creams and ointments	♦ Fats and waxes ♦ Oils such as castor, olive and coconut oil ♦ Fatty acids, prostaglandins and balsams
Oils ♦ A subgroup of hydrocarbons ♦ May be terpene-type compounds ♦ May contain many types of functional groups including ketones, phenols, alcohols, esters and aldehydes	♦ Viscous liquids high in hydrocarbon content ♦ Often flammable and immiscible with water and aqueous solvents ♦ Frequently used as flavouring agents, in perfumery, in chemical industries and as antiseptics ♦ A fixed oil dropped onto filter paper will leave a greasy stain, whereas a volatile oil (which evaporates) will not	♦ Eucalyptus, peppermint and clove oils are volatile oils used in medicine ♦ Castor oil (mainly composed of ricinoleic acid, Fig 1.3D) and olive oil are fixed oils ♦ Australian Myrtaceae family and *Melaleuca* genus plants contain many fragrant and useful oils, including eucalyptus and tea-tree oils
Phenols ♦ Phenols contain a benzene ring with a hydroxyl substituent	♦ Phenols are a specialised type of alcohol, a compound containing a hydroxyl group, –OH	♦ Salicylates, including aspirin-like compounds and flavouring agents (e.g. vanillin) ♦ Isoflavones, including phytoestrogens ♦ Coumarins, including the anticoagulant dicoumarol (Fig 1.3E) ♦ Cannabinols from marijuana ♦ Hypericin, from St John's wort, used in depression (Fig 1.3E)
Tannins ♦ A specialised type of phenol	♦ Astringent plant phenolics have the ability to tan hides (animal skins) by precipitating proteins ♦ Common plant constituents, especially in bark, accounting for some of the brown colour in swamps and rivers and in cups of tea	♦ In Australian native medicine, kino, the gum exuded from eucalyptus trees, was an important source of tannins, which were used to treat diarrhoea, haemorrhages and throat infections
Isoprenes, terpenes and steroids ♦ Terpenes are 10-carbon molecules built up from small 5-carbon building blocks called isoprenes ♦ Plant steroids are also synthesised naturally from isoprene sub-units	♦ Plant steroids, with their characteristic 4-ring structures, are used as the starting material for the production of many hormone drugs (Fig 28.2) ♦ The plant sterol diosgenin, from the *Dioscorea* species, has been used in the synthesis of estrogenic hormones	♦ Carotenoids such as β-carotene and vitamin A ♦ Salicylate analgesics including aspirin (acetylsalicylic acid) ♦ Pyrethrins (insecticides) ♦ Menthol (Fig 1.3F), camphor and thymol, aromatic compounds used in respiratory medicine ♦ Gossypol, a Chinese male contraceptive agent (Fig 1.3F)

* In Tasmania and Victoria, the opium poppy *Papaver somniferum* is grown and harvested for production of opium alkaloids, including morphine and codeine.

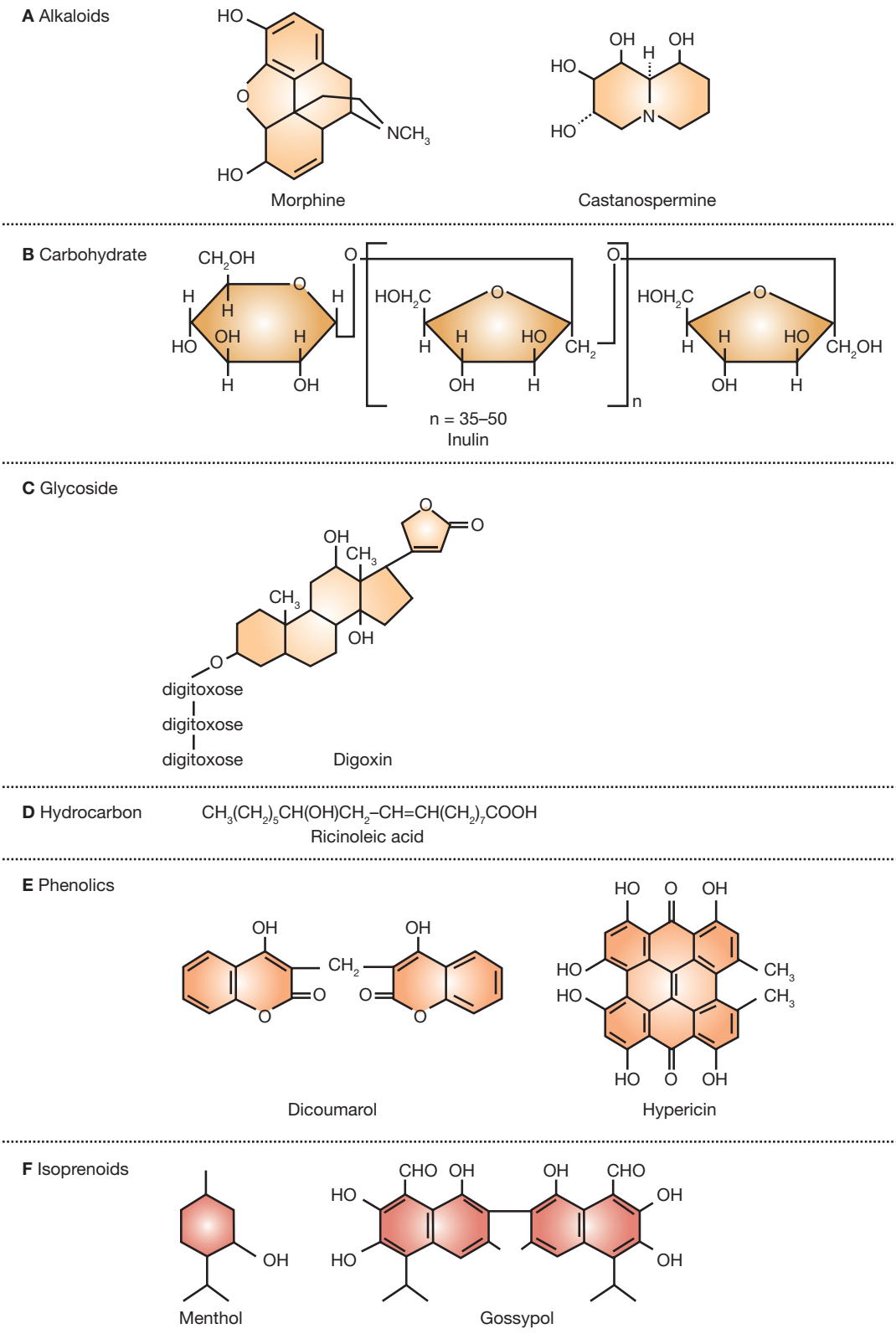


FIGURE 1.3 Chemical structures of some active drugs derived from plant sources
A Alkaloids: morphine and castanospermine. **B** A carbohydrate: inulin. **C** A glycoside: digoxin. **D** A hydrocarbon: ricinoleic acid. **E** Phenolics: dicoumarol and hypericin.* **F** Isoprenoids: menthol and gossypol.

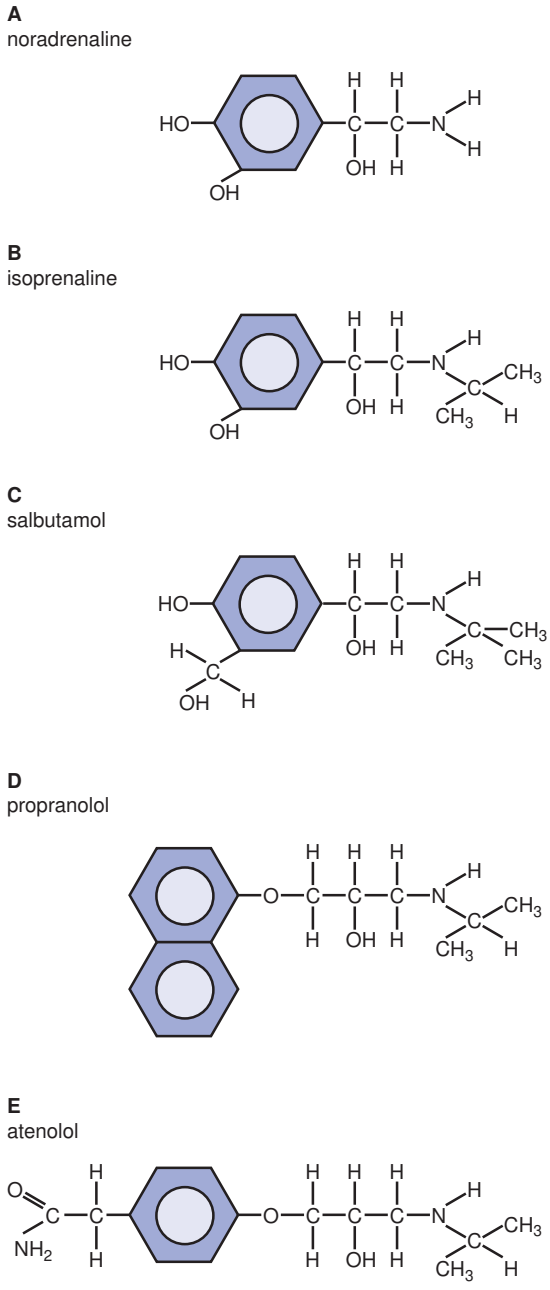


FIGURE 1.4 Structure–activity relationships for some drugs binding to adrenoceptors

A The sympathetic neurotransmitter noradrenaline. **B** Isoprenaline, a non-selective β-adrenoceptor agonist. **C** Salbutamol, a selective β_2-adrenoceptor agonist. **D** Propranolol, a non-selective β-adrenoceptor antagonist. **E** Atenolol, a selective β_1-adrenoceptor antagonist with less likelihood of causing asthma. Increasing the 'bulkiness' of the substituents at the catechol end (two adjacent –OH groups) or the amine end ($-NH_2$) may select for ligand-binding affinity or agonist/antagonist activity at specific receptors.

Research carried out by pharmacologists, biochemists and chemists in universities and research institutes may lead to the discovery of new drugs. The pharmaceutical industry monitors such research via the scientific literature, patent applications and scientific conferences.

Active metabolites of existing drugs

Sometimes drugs are found to be more active after metabolism in the body and so the metabolites are tested. Paracetamol is one of the metabolites of phenacetin, an early antipyretic analgesic agent, and is much safer than phenacetin. Many of the benzodiazepine antianxiety agents have pharmacologically active metabolites, some of which are drugs in their own right.

Rational molecular design

Structure–activity studies can predict the shape of the active site of a receptor and lead to the design of drugs that may be agonists or antagonists at that receptor. The early antihistamines were modelled on the histamine molecule. Subsequent brilliant pharmacology by Sir James Black[3] led to the discovery of histamine H_2-receptors and the development of specific H_2-antagonists, revolutionising the treatment of peptic ulcer (Fig 27.3).

Computer-aided design

Drug receptors, enzymes, ion channels and transporters are no longer simply 'black boxes' referred to by pharmacologists wishing to explain (or pretend that they understand) drug mechanisms; many are proteins with known amino acid sequences and tertiary structures (three-dimensional shapes), able to be cloned. Computer modelling of their active sites allows testing of chemicals for virtual binding affinity. Using such techniques, angiotensin-converting enzyme (ACE) inhibitors were designed for use in hypertension, dopa-decarboxylase inhibitors for administration with levodopa in Parkinson's disease, the anti-flu drug zanamivir to inactivate the flu virus and potential anticancer drugs to inhibit steps in the pathways of macromolecular synthesis.

Combinatorial chemistry ('combichem') techniques make it possible for millions of new molecules to be synthesised, either actually or virtually. This may involve systematic and repetitive use of commercially available chemical reagents to synthesise 'libraries' of new chemical compounds, preferably small molecules, which are then screened for activities on proteins, receptors, enzymes and transporters.

3 Black, a Scottish pharmacologist, was awarded the Nobel Prize in Medicine in 1988 for his work on 'important principles of drug treatment', discovering β-blockers and H_2-antagonists; when surprised to hear of his award, he quipped: 'I wish I had my beta-blockers handy!'

Standardisation of drugs

Formulations of drugs obtained from natural sources may fluctuate in strength, depending on how extracts are harvested and purified. Because accurate dosage and the reliability of drug effects depend on uniformity of strength and purity, **standardisation** (bringing the preparation to a specified concentration or quality, like the model) and publication of standards are necessary.

Drug standards in Australia and New Zealand

The main standards for drugs in Australia are those published in the *Martindale*, *British Pharmacopoeia*[4] and the *Australian Pharmaceutical Formulary* (APF; see later under 'Drug information sources'). The BP gives detailed, legally accepted standards for hundreds of drugs and herbal products, with chemical information and the approved formulations containing the substance. It lists criteria for purity; chemical methods for identification and assay (measurement); tests and maximum levels allowed for impurities; and storage conditions. Preparations meeting these standards are referred to as the BP preparation.

The APF is a reference book for **pharmacists** that helps promote quality use of medicines. It contains evidence-based information on medicine and pharmacy-specific topics – for example, dispensing, counselling and therapeutic management. It also contains key 'recipes' for commonly made formulations by pharmacists (i.e. extemporaneously prepared medicines). For example, Calamine Lotion APF is one 'recipe'. It lists the required quantity of individual ingredients (active and excipient), gives the method for preparation of the lotion and describes the use of the formulation. The New Zealand Formulary (NZF) is more like the Australian Medicines Handbook (AMH), with detailed information about drugs (see later under 'Drug information sources').

Assays

The technique, either chemical or biological, by which the strength and purity of a drug are measured is known as an **assay**; if available, a chemical method is used. For some drugs, either the **active ingredients** have not been completely identified or there are no available chemical methods. The pharmacological activity of such tissue extracts or pharmaceutical formulations may be standardised by biological methods, or **bioassay**.

Bioassays

Bioassays are typically performed by determining the amount of a preparation required to produce a defined effect on a suitable living tissue (or animal, cell suspension, enzyme, microorganism, etc.) and then comparing the response to that produced by a standard preparation in the same bioassay system. Examples of early bioassays were for the potency of a sample of insulin measured by its ability to lower the blood glucose levels of rabbits, or for the strength of digoxin preparations assayed by their effects on contractions of isolated cardiac muscle tissue.

Bioassays are especially applicable to:

- substances that are poorly defined chemically
- mixtures containing chemically very similar substances (e.g. optical isomers, of which only one is active)
- highly active substances, especially endogenous mediators, present in very small amounts
- testing drugs in animals to predict effects in humans.

The bioassay method may be in vitro (in glass) – for example, using a suspension of an enzyme, cell or tissue culture, a microbiological culture, a standard preparation of an antibody or an isolated organ or tissue; or in vivo (in the living organism) – for example, testing the effect of a drug on blood pressure or behaviour.[5] Some drug actions are virtually impossible to test in animals either in vitro or in vivo, particularly the effects of CNS-active agents on mood, perception and thought processes. **Clinical trials** (see 'Clinical trials of drugs', later) are essentially bioassays in humans: the new drug (unknown) is tested against the best currently available therapy (standard drug or placebo) and compared for safety and efficacy.

The design of bioassays usually involves comparing two preparations and constructing log dose–response curves. If the substances act by similar mechanisms, the curves will be roughly parallel in their mid-sections and so the potency ratio can be determined, allowing the strength of the unknown to be calculated compared to the known standard (Fig 4.7). Because of biological variability, there may be variations in results quoting the absolute amount of biologically active material. Bioassays are not used as frequently as previously because techniques such as radioimmunoassay (itself a type of bioassay) and high-performance liquid chromatography have allowed very low levels of chemicals to be measured accurately without using animals.

4 The 'BP', as it is fondly known by generations of pharmacy students and pharmacists.

5 There is currently a worldwide dearth of pharmacologists with the skills necessary to carry out many experimental methods in medical research or to train new generations of students in these techniques. This has come about largely because of the decrease in the number of practical classes held in pharmacology courses and the replacement of animal experiments with computer-modelled 'practicals'. In-vivo testing, however, is vital for the analysis of drug actions and development of new drugs–see discussion in Chapter 2 under 'Ethical aspects of pharmacotherapy'.

Bioassays in the BP

The *BP 2020* still gives several standard methods for bioassays, including for blood pressure–lowering substances, blood coagulation factors, anticoagulants, interferons, vaccines, antibiotics, endotoxins and pyrogens (substances that cause fever), plus tests for acute toxicity, microbiological sterility or contamination, including examination of herbal products.

Isolated organ experiments

In these pharmacological experiments, a small piece of animal tissue (e.g. a length of intestinal smooth muscle) or an entire organ (e.g. a heart) is 'isolated' from the animal's body and kept alive in warmed, oxygenated physiological saline solution in an organ bath, set up so that responses of the tissue (e.g. contractions of muscle, beats of the heart) can be monitored following administration of a drug solution into the organ bath. The classic experiment is the isolated guinea pig ileum preparation, in which a short strip of gastrointestinal tract smooth muscle responds (contracts) to stimulation by various neurotransmitters and other endogenous mediators; a great deal of classical pharmacology can be demonstrated and understood using this simple technique.

The use of isolated tissues for assaying responses reached a sophisticated level in the classic experiments of Sir John Vane at the Royal College of Surgeons in London in the 1960s. A set of five organ baths was set up in vertical series such that the physiological saline solution (or blood from an anaesthetised animal) from the top bath superfused (flowed down over) the next bath, and so on down the cascade. Small samples of gastrointestinal tract smooth muscle from four different species were set up in the baths, and the pattern of contraction or relaxation responses to seven endogenous mediators, including noradrenaline, bradykinin, prostaglandins and antidiuretic hormone, was studied. Vane discovered the mechanism of action of aspirin and other non-steroidal anti-inflammatory drugs, namely inhibition of the synthesis of prostaglandins; for this he was subsequently awarded the 1982 Nobel Prize for Medicine (and knighted by the Queen).

International units of activity

The strength of extracts of natural substances for which the purity is not 100% cannot be expressed in absolute terms such as grams or milligrams because the whole weight is not due to a single active ingredient. Such preparations are assayed biologically, and a unit of pharmacological activity is defined. A particular preparation – for example, of a hormone, enzyme, vitamin, vaccine, blood product or plant alkaloid – is designated by the WHO Expert Committee on Biological Standardization as the International Standard preparation, against which other national standard preparations are assayed. In Australia, for example, the Commonwealth Serum Laboratories (CSL) in Melbourne maintained the national standard for insulin, and all CSL insulin preparations were compared to it. The strengths of preparations are expressed in terms of International Units of Activity (IU)[6] measured in the particular bioassay (CFB 30.4), allowing comparison of preparations in terms of their biological efficacies.

Statistical methods in bioassays

It is well recognised that biological parameters, such as heights of adults, vary within a wide range, and the mean can be calculated as an average value. Consequently, biological experiments need to be repeated many times to get a mean result, and statistical tests can be applied to determine how likely this is to be the 'true value'. Values may be found to be normally distributed, and when plotted as a frequency distribution will assume a 'normal' bell-shaped curve.

Similarly, it can be expected that responses to a dose of a drug will also vary about a mean value. Variations may be due to many causes, especially errors in measurement and inherent biological variability both within and between individuals. In bioassays the same dose (or concentration) repeated several times may therefore give differing responses; likewise, the dose required to give the same response varies. Variability can be partly reduced by refining methods and using a very homogeneous population of animals or very similar subjects; however, this reduces the wide applicability of the results.

Statistical methods must then be applied to deal with random variations and to extrapolate from the sample mean to the population; such techniques are the province of biostatistics, rather than pharmacology. In the pharmacological context, statistical methods[7] are typically applied to bioassays studying dose–response relationships, cause–effect correlations, differences between groups of subjects treated differently and the results of clinical trials. Usually a 'null hypothesis' is defined (i.e. that there is no statistically significant difference between the groups being studied), and when results are analysed the null hypothesis is either accepted or rejected. The probability level (p) at which the results are accepted as being due to a real difference rather than occurring by chance is

6 The abbreviation IU may become confusing because the U may be misread as a V (IV: intravenous); some authorities recommend that the term 'unit' be written in full.

7 The first medical statistician credited with applying rigorous mathematical methods in the study of responses to drugs, and developing standard clinical trial methodologies, was Professor Austin Bradford Hill in the Medical Statistics Department of the London School of Hygiene and Tropical Medicine in the 1950s. Hill proved that two drugs together, streptomycin and para-aminosalicylic acid, given over a period of several months, markedly improved patients with tuberculosis and reduced development of microbial resistance to the antibiotic. And in an epidemiological study of lung cancer, by separating subjects into groups based on their smoking habits, Hill demonstrated conclusively that the more cigarettes people smoked, the greater their risk of lung cancer.

usually set at 0.05; that is, there is only a 5% likelihood (1 in 20 chance) that the results could have occurred by chance.

Typical statistical tests employed are either parametric (assuming a normal distribution of results), such as independent or paired *t*-test, analysis of variance; or non-parametric (when normal distribution cannot be assumed, i.e. the data is skewed) – for example, Mann–Whitney U test, or a chi-squared test.

Drug development

Development of new drugs is regulated by government legislation and administered by government authorities such as the Therapeutic Goods Administration (TGA) in Australia, the Ministry of Health and Medsafe in New Zealand and the Food and Drug Administration in the United States (Ch 2). Regulation protects consumers so that only safe and effective drugs are approved and protects sponsoring drug companies for their investment in terms of intellectual property and patents.

The pharmaceutical industry

The pharmaceutical industry is constantly searching for potential new drugs. The major markets are the United States, Europe, Japan, China and India; Australia accounts for only 1–2% of world sales of pharmaceuticals.

Stages of drug development

Drug development has traditionally been described as occurring in several clearly defined phases, involving multidisciplinary teams:

- the new idea or hypothesis – routes to drug discovery include selection of a target, new hypothesis for disease causation, ideas for new molecules, discovery of new natural products, optimisation of lead compounds, and research with new molecular biology, genetic engineering and formulation technologies
- design, purification or synthesis of the new molecule, from various sources (described above under 'Where drugs come from')
- screening new compounds for useful pharmacological activities or possible toxic effects – screening may be broad, to detect all actions, or specific, for affinity for a particular receptor, transporter or enzyme; high-throughput screening allows millions of compounds to be run through automated initial screens; these three stages may take between 2 and 5 years
- preclinical pharmacology – this includes in-vitro and in-vivo studies: pharmacodynamic actions and pharmacokinetic aspects (the fate of the molecule or compound in the body, including susceptibility to phases of metabolism) are studied usually in at least three mammalian species, including non-human primate species
- toxicology studies (adverse effects) – these include acute toxicity, long-term toxicity (chronic effects and effects on reproduction) and tests for mutagenicity and carcinogenicity; requirements depend on anticipated exposure and clinical use, whether acute or chronic
- pharmaceutical formulation and manufacturing – scale-up of the synthetic pathway, including stability tests and assay methods; these stages may take 1–2 years
- an application to drug-regulating authorities for approval to undertake a trial in humans, details of the molecule and its formulation, manufacturing information – all results of non-clinical studies, proposed clinical protocols, the sites for conduct of the study, names of personnel in the clinical trial team and approval from an ethics committee are submitted (note that in Australia many clinical trials are undertaken with approval from an ethics committee and notification to the TGA)
- clinical trials – if the drug appears to be safe, effective and worth testing, it will go to clinical trial while being closely monitored by the investigators and by the sponsor company or a clinical research organisation contracted by the sponsor (progress must be reported regularly to the national regulatory authority, which may sometimes undertake inspections; the first three phases of a clinical trial may take 5–7 years)
- registration – depending on the results of the full clinical trial program, the sponsors may apply for registration of the drug and approval to market it for clinical use
- ongoing post-marketing studies – these follow up the drug, monitoring its effects and interactions in the wider community for longer periods.

The costs in time, money and effort

The development of a drug takes a prodigious amount of money, effort and time, and it is a high-stakes, long-term, risky business. Drug development from idea to market typically takes 10–15 years. Once the idea, chemical or process is patented (to protect the developers from other companies stealing their ideas), the clock starts ticking! In most countries, the duration of a patent is 15–17 years, with a possible short extension. When the patent expires, other companies can manufacture and market the drug under their own trade names and as a 'generic' drug.[8]

8 Companies also try to extend their patent protection period when it is running out and maintain monopoly market share for blockbuster drugs by a process known as 'evergreening'–for example, by patenting an optical isomer of the drug, or a modified formulation.

It is estimated that every new drug costs around A$1 billion for basic and clinical studies and for the costs of application and promotion (a figure of US$2.6 billion has even been quoted), and that a drug company needs one to two new drugs every 3–4 years to remain financially viable. ('Me-too' drugs are significantly cheaper to develop because much of the expensive, time-consuming work has already been carried out for the original drug.) High costs are attributed to:

- the need for evidence of safety and cost-effectiveness
- increasing emphasis on 'lifestyle drugs', which require studies of long-term safety
- need for evidence about possible effects of concomitant medicines and the prevalence of polypharmacy, with inherent risks of drug interactions
- increasingly ageing populations, requiring drug testing in many chronic degenerative conditions
- the high attrition rate: drug development may be abandoned (or drugs withdrawn from use) at any stage because of problems with safety, efficacy, changes in fashion or a better competitor drug.

To achieve economies of scale, many drug company mergers have taken place, leaving only a few major research drug companies worldwide. Companies are trying to streamline testing procedures and get early information on toxicity or pharmacokinetic problems so as to waste as little time and money as possible.

Clinical trials of drugs

A clinical trial is a prospective study involving human participants that measures the effectiveness and safety of an intervention (e.g. diet, procedure, medical device) or treatment (e.g. drug, vaccine) (CFB 1.1). The intervention or treatment can be investigational (new and innovative) or established. Clinical trials report data on both safety (adverse reactions) and efficacy. The 'gold standard' of clinical trials is the **randomised controlled clinical trial** (RCCT), also known as the randomised controlled trial. In this type of study participants are randomly allocated to treatment groups; that is, they have an equal chance of being allocated to the new treatment (or the treatment undergoing investigation) or the control group. The control group will receive the current standard therapy (usually the best) treatment for the condition or a placebo treatment (if there is currently no available standard treatment). Placebo treatments contain no active ingredients. The outcomes of interest (e.g. reduction in blood pressure, blood glucose level or cholesterol) are measured in both groups and then compared. All clinical studies in humans must be approved by a local human research ethics committee.

Clinical trials are generally required for all new drugs and for new uses (new indications) or new formulations of old drugs; however, there are exceptions:

- Potentially toxic drugs (e.g. anticancer drugs) may go straight to phase II studies (see below) in a small number of people with the disease so volunteers without the disease are not subjected to adverse effects.
- The rules may be bent for orphan drugs (non-patentable, or for rare diseases; see Ch 2).
- There is public pressure for fast-tracking drugs potentially useful in otherwise fatal diseases such as cancers.

CLINICAL FOCUS BOX 1.1
The clinical trial process and the COVID-19 vaccines

In 2020 the world was waiting on a COVID-19 vaccine to mitigate the spread of the deadly SARS-CoV-2 virus. Once potential COVID-19 vaccines were developed, they had to undergo the rigorous clinical trial process to determine if the vaccines were safe and effective in humans before widespread use. Unfortunately, many vaccines did not progress through the clinical trial process. For example, the University of Queensland COVID-19 vaccine entered phase I human trials; however, after finding the vaccine induced false-positive HIV results, the vaccine did not progress to phase II.

The Pfizer/Biontech BNT162b2 mRNA vaccine (Ch 43) was one of several COVID-19 vaccines used in Australia and New Zealand. Prior to being approved, the vaccine went through a large (43,548 participants) randomised, observer-blind, placebo-controlled Phase II/III clinical trial. The trial was multicentre and multinational, with 152 sites worldwide. To ensure participants were 'blinded' to their treatment allocation, both groups received two injections, 21 days apart, delivered into the deltoid muscle.

The main outcome under examination in this RCCT was the efficacy of the COVID-19 vaccine against a COVID-19 diagnosis. The results showed eight cases of COVID-19 in the intervention and 162 in the placebo (control) group, equalling a vaccine efficacy of 95%. Results also showed the vaccine was safe. Although 27% of participants given the COVID-19 vaccine had local adverse reactions (indicative of an immune response), only four developed serious adverse effects, one of which was related to poor administration technique (Ch 43). The outcomes were then published in the *New England Journal of Medicine*. Following their own assessment, regulatory bodies across countries, including the TGA (Australia) and Pharmac (New Zealand), approved the vaccine for use. At the time of writing, this vaccine was still in phase IV of the clinical trial process (i.e. post-marketing surveillance). All health professionals play a role in reporting adverse drug reactions when they are available on the market – this is called pharmacovigilance.

The objectives of RCCTs need to be realistic, valid and specific, yet allow for the results to be applied for the population at large (generalisation). Statisticians, researchers and clinicians are involved to optimise internal and external validity of the study. Clinical trials are a staged process, with few subjects in the early phases and stepwise decision making so that trials can be stopped if clear differences or toxicities become apparent; they are prolonged and expensive to run.

It is now customary for a Data Safety Monitoring Board to be appointed for a trial. Such a board is composed of a small number of independent experts who periodically review the emerging safety information from a trial.

Phase I: The first tests in humans using healthy volunteers

After extensive testing in vitro and in animals, the drug is administered initially in very low and increasing doses to small numbers of healthy volunteers, usually in a research centre or institution, under close medical and scientific supervision. The objectives are to determine in humans the pharmacological activities, pharmacokinetic parameters including bioavailability, tolerable dosage range and acute toxicity of the drug.

Phase II: The first administration to people with the condition the intervention or treatment is designed to treat

In phase II, the first studies on efficacy are conducted. To do this a small number of people with the condition that the intervention is designed to treat are given either the new investigational drug/intervention or the standard/placebo. There are approximately 50 subjects in each treatment group. The subjects are closely monitored, usually in major teaching hospitals. The tests may be 'single-blind'; that is, subjects do not know which treatment they are getting, but the investigators do, or 'double-blind'. Usually the investigators are specialists in the appropriate field, such as oncologists, psychiatrists or rheumatologists. Phase II studies indicate the pharmacokinetic and pharmacodynamic properties, therapeutic range of doses, maximum tolerated dose and common adverse reactions in those with the disease. They act as 'pilot studies' to optimise the protocol and determine dosing and sample sizes in the phase III trial.

Phase III: The full-scale randomised controlled clinical trial

This is 'the clinical trial', as commonly understood, in which the drug is administered to numerous (from several hundred to thousands) subjects under the guidance of experienced clinical investigators to ascertain whether, under defined conditions, the drug shows clinical benefit for the disease state, with an acceptably low rate of adverse drug reactions. The trial is usually 'multicentre', carried out simultaneously in different institutions or countries, to increase the number of subjects and investigators and achieve quicker results; many are partly carried out in Australia. A typical RCCT may cost up to AU$7 million, so it must be designed carefully to ensure statistically significant results can be extrapolated back to the target population. Important elements of the RCCT are as follows:

- Investigators must initially believe that the new treatment is at least as good as the old.
- Subjects must be randomised to ensure groups are initially similar in gender, age range, weight range and severity of disease.
- Participants must give informed consent. The 'informed consent' form for participants should contain detailed information about the study, potential benefits and adverse reactions and the option to withdraw at any stage.
- Double-blinding is usual, with coded packs of drugs so that neither investigators nor subjects know who received the new drug. After the trial has concluded, results are analysed and the code is revealed.
- The institution's ethics committee must have given approval to an application to run the trial (discussed in Ch 2).

Advance planning determines parameters such as: the study design (paired, crossover, parallel); criteria for those to be included or excluded (inclusions are generally wider than those in phase II trials); maximum length; outcome criteria (whether by changes in biomarkers or patient-improvement outcome); justification (who benefits?); information given to patients; protocols; sample sizes required for valid results; monitoring for adverse events; database management and statistical analysis methods; withdrawal procedures and follow-up schedules; regular auditing for safety; and quality control.

Usually the statistical basis for the trial is the null hypothesis – that there is in fact no difference between the two treatments; in other words, the new drug is just as good as the current therapy. If it becomes apparent that one group is benefiting statistically significantly more than the other, or suffering more adverse reactions, the trial is halted. Historically, results have been analysed for statistical equivalence and the null hypothesis is accepted or rejected. Increasingly, however, studies termed 'non-inferiority' studies are conducted. The study design allows that the new treatment may have a small degree of inferiority of efficacy. Prior to the study, an acceptable difference between the new treatment and

the comparator for the new treatment to be regarded as equivalent is decided by expert clinicians. Provided the new treatment does not exceed the acceptable difference, it may be judged as non-inferior. It is important that raw data from clinical trials be published (even negative results) so conclusions can be examined by outsiders not involved with the researchers, drug companies or funding bodies.

If the new drug is shown to be safe, efficacious and cost-effective, it may be approved for market by the government's regulatory body – the TGA in Australia and Medsafe in New Zealand. In both countries, advice is usually taken from the national advisory committee – the Advisory Committee on Medicines in Australia or the Medicines Assessment Advisory Committee in New Zealand.

Phase IV: Post-marketing studies

If the new drug is shown to be safe, efficacious and cost-effective, it may be approved for marketing. However, there are limitations in the testing and trialling processes: the number of people studied and the time allotted to the study have been limited (Fig 1.5); and certain types of subjects may have been excluded, such as children, pregnant women, the elderly and people with multiple disease states or taking other drugs.

Once marketed, the drug is used in many more people and for longer periods; extended monitoring of safety and efficacy (pharmacovigilance) is then possible. Inevitably, events will surface that were not seen during the trial such as rare adverse reactions, effects in subgroups of the population and drug interactions. Studies in older people are especially important because they may have comorbidities and require many drugs for prolonged periods.

Later, a meta-analysis may be conducted. A meta-analysis pools together all the results from similar clinical trials with the same or similar research question. Pooling the data increases the statistical power, making significant results more likely; however, meta-analyses suffer inevitably from 'publication bias' because negative results are less likely to be published than positive results. (Some regulating authorities and journals require authors to advise in advance when trials are to be carried out, and publish a study protocol, to ensure that results of all trials are published.) Sometimes, different trials will produce conflicting results; the choice to prescribe the drug is then based on clinical judgement.

As part of its post-market vigilance, the TGA encourages drug companies to share their large quantities of information about new drugs; it then rates companies' responses with a T-score for transparency. The TGA publishes detailed 'Australian Public Assessment Reports for new medicines and extended indications of prescription medicines' on its website. The *Australian Prescriber* publishes notes in a 'New Drugs' section of each issue. The TGA also carries out laboratory investigations of products on the market and ongoing monitoring to ensure compliance with legislation. The TGA publishes details about Australian reports of suspected adverse reactions in an online database called DAEN (Drug Adverse Event Notifications). Consumers are advised to discuss any concerns with a health professional. In New Zealand, Medsafe regulates clinical trials and carries out similar pharmacovigilance.

Pharmacovigilance: the 'blue card'

Through its Advisory Committee on Medicines, the TGA encourages and facilitates the reporting by consumers and health professionals of adverse events they suspect are related to medications and medical devices. Historically,

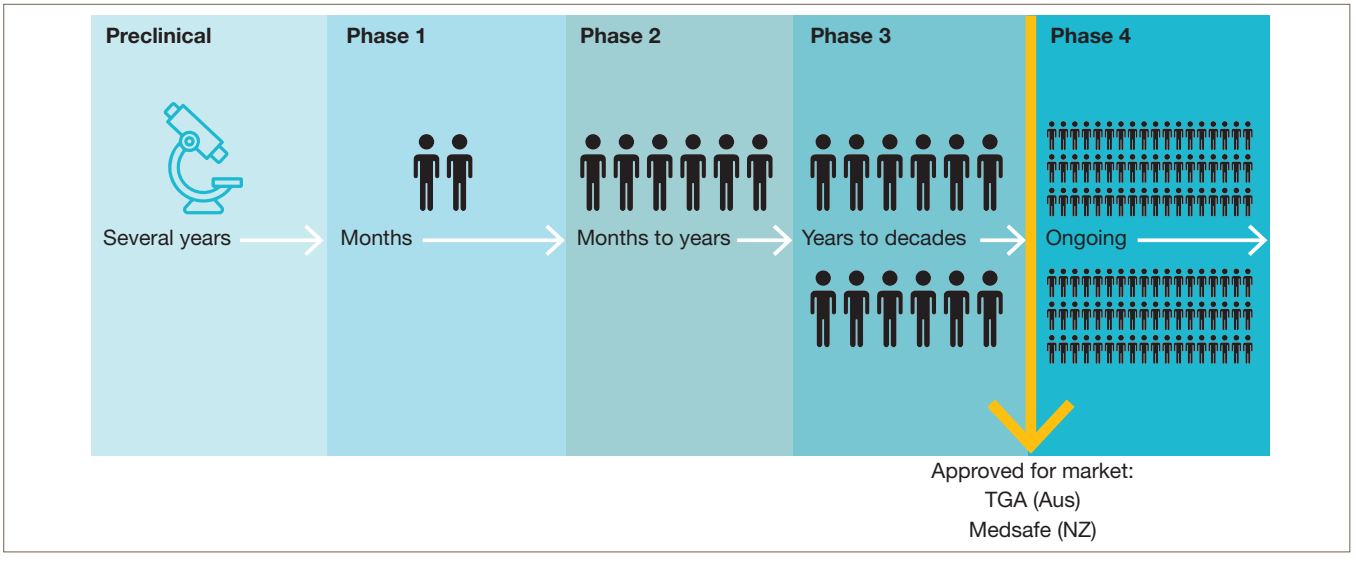


FIGURE 1.5 Overview of the clinical trial process

reporting has been by use of a one-page form (the 'blue card' – see Fig 1.6) that is readily available and can be completed. Online reporting is now also possible. Confidentiality is maintained. Consumers can also report their own adverse reactions via a 1300 telephone number designated as the Adverse Medicine Events Line (1300 134 237).

Reports of adverse reactions are reviewed, entered into DAEN and analysed for patterns. The Advisory Committee on Medicines informs health professionals about adverse events and can recommend actions ranging from no action required, to change of aspects of prescribing or dispensing, through to withdrawal of a drug from the

Australian Government
Department of Health
Therapeutic Goods Administration

TGA use only

Report of suspected adverse reaction to medicines or vaccines

See statement about the collection and use of personal information overleaf, and please attach any additional data to this form

Patient initials or medical record number:	Sex: M ☐ F ☐ Weight (kg):	Date of birth or age:

Suspected medicine(s)/vaccine(s)

Medicine/vaccine (please use trade names; include batch number and AUST R or AUST L number if known)	**Dosage** (Dose number for vaccines eg 1st DTP)	Date begun	Date stopped	Reason for use

Other medicine(s)/vaccine(s) taken at the time of the reaction

Medicine/vaccine	**Dosage**	Date begun	Date stopped	Reason for use

Reaction(s): Date of onset of reaction (for vaccines time after administration): / /

Describe: (please provide as much detail as possible and include any results of relevant laboratory data and other investigations)

Seriousness: Life threatening ☐ Hospitalised ☐ Required a visit to doctor ☐

Treatment of reaction:

Outcome: Recovered ☐ Date: / / | Not yet recovered ☐ | Fatal ☐ Date: / / | Unknown ☐

Sequelae? No ☐ Yes ☐ Describe:

Reporting: Doctor ☐ Pharmacist ☐ Other ☐

Name:

Address:

Postcode:

Contact details (email or phone)

Signature:

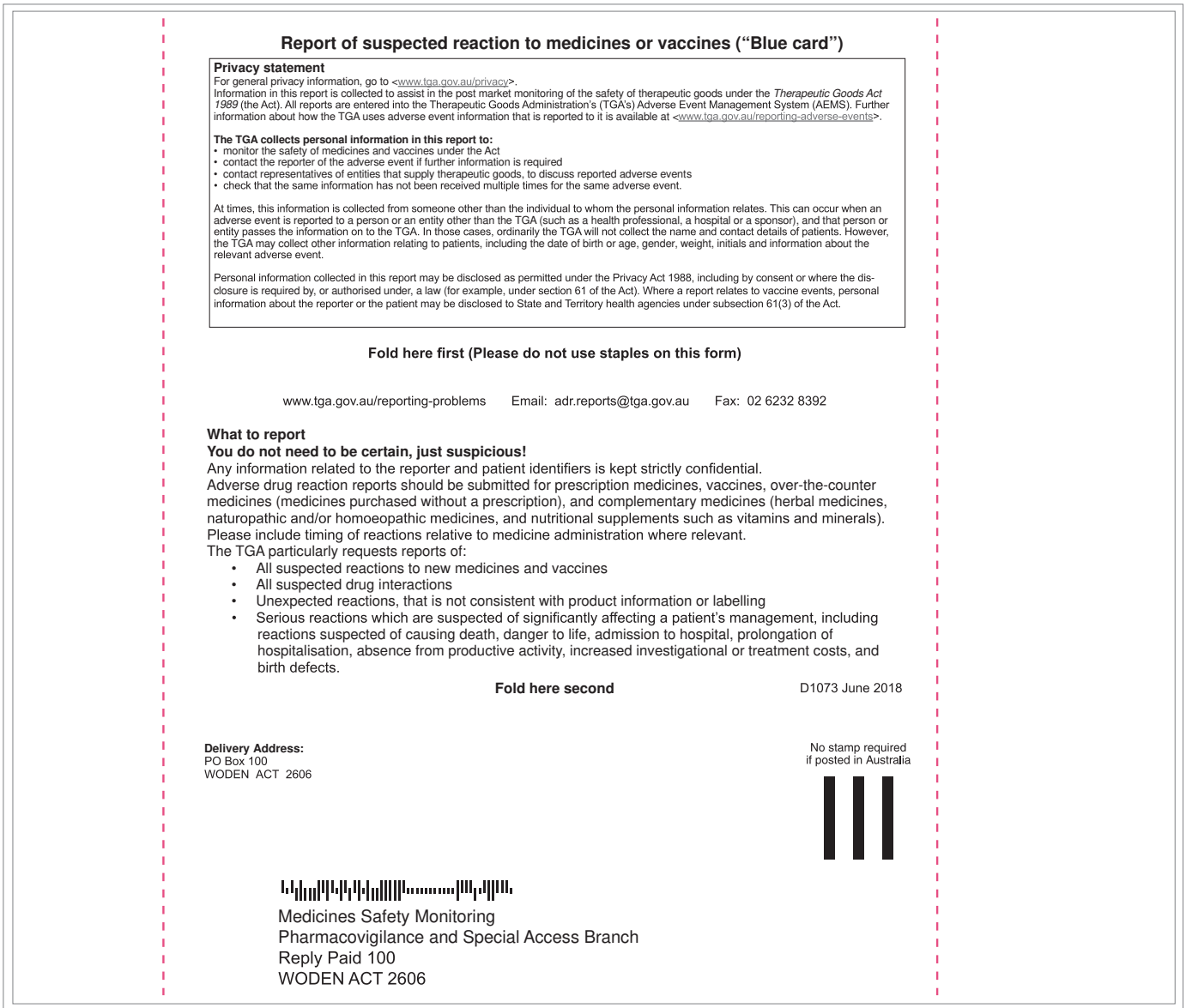
Date: / /

Thank you for taking the time to complete this form PTO

FIGURE 1.6 The 'blue card', used by health professionals to report suspected adverse reactions to drugs and vaccines

Source: Adapted from Therapeutic Goods Administration <https://www.tga.gov.au/sites/default/files/blue-card-adverse-reaction-reporting-form.pdf>

Continued



Report of suspected reaction to medicines or vaccines ("Blue card")

Privacy statement

For general privacy information, go to <www.tga.gov.au/privacy>.
Information in this report is collected to assist in the post market monitoring of the safety of therapeutic goods under the *Therapeutic Goods Act 1989* (the Act). All reports are entered into the Therapeutic Goods Administration's (TGA's) Adverse Event Management System (AEMS). Further information about how the TGA uses adverse event information that is reported to it is available at <www.tga.gov.au/reporting-adverse-events>.

The TGA collects personal information in this report to:

- monitor the safety of medicines and vaccines under the Act
- contact the reporter of the adverse event if further information is required
- contact representatives of entities that supply therapeutic goods, to discuss reported adverse events
- check that the same information has not been received multiple times for the same adverse event.

At times, this information is collected from someone other than the individual to whom the personal information relates. This can occur when an adverse event is reported to a person or an entity other than the TGA (such as a health professional, a hospital or a sponsor), and that person or entity passes the information on to the TGA. In those cases, ordinarily the TGA will not collect the name and contact details of patients. However, the TGA may collect other information relating to patients, including the date of birth or age, gender, weight, initials and information about the relevant adverse event.

Personal information collected in this report may be disclosed as permitted under the Privacy Act 1988, including by consent or where the disclosure is required by, or authorised under, a law (for example, under section 61 of the Act). Where a report relates to vaccine events, personal information about the reporter or the patient may be disclosed to State and Territory health agencies under subsection 61(3) of the Act.

Fold here first (Please do not use staples on this form)

www.tga.gov.au/reporting-problems Email: adr.reports@tga.gov.au Fax: 02 6232 8392

What to report
You do not need to be certain, just suspicious!
Any information related to the reporter and patient identifiers is kept strictly confidential.
Adverse drug reaction reports should be submitted for prescription medicines, vaccines, over-the-counter medicines (medicines purchased without a prescription), and complementary medicines (herbal medicines, naturopathic and/or homoeopathic medicines, and nutritional supplements such as vitamins and minerals).
Please include timing of reactions relative to medicine administration where relevant.
The TGA particularly requests reports of:

- All suspected reactions to new medicines and vaccines
- All suspected drug interactions
- Unexpected reactions, that is not consistent with product information or labelling
- Serious reactions which are suspected of significantly affecting a patient's management, including reactions suspected of causing death, danger to life, admission to hospital, prolongation of hospitalisation, absence from productive activity, increased investigational or treatment costs, and birth defects.

Fold here second D1073 June 2018

Delivery Address:
PO Box 100
WODEN ACT 2606

No stamp required
if posted in Australia

Medicines Safety Monitoring
Pharmacovigilance and Special Access Branch
Reply Paid 100
WODEN ACT 2606

FIGURE 1.6, cont'd

market. For example, the COX-2 inhibitor lumiracoxib was included in the Pharmaceutical Benefits Scheme in 2006 and became widely used; however, by late 2007 the TGA had received eight reports of serious liver damage (including two deaths), so the drug was deregistered. The TGA publishes (since 2010) Medicines Safety Updates. Sponsors of newly registered medicines must obtain TGA approval of a Medicines Risk Management Plan based on the European Medicines Agency's good-pharmacovigilance-practice (GVP) guideline.

Drug development in Australia

There is little basic research carried out by 'big pharma' drug companies in Australia or New Zealand, where most companies are offshoots of multinationals based overseas. Scientific work in Australian companies is mainly on formulations suitable for local conditions or preparation of submissions for the marketing of drugs developed overseas. Australia's share of global research and development is only about 1.3%, so Australia relies on the rest of the world to develop most advances in knowledge.

Australian medical schools and medical research institutes have an enviable reputation worldwide for medical and healthcare research; new compounds of interest may be discovered, and researchers collaborate with drug companies in developing drugs, after which commercial exploitation and 'value-adding' of the research usually happen overseas.

CSL (formerly Commonwealth Serum Laboratories) was established in Australia more than 100 years ago (1916) to develop 'immune sera' (vaccines). It is now a major international producer of blood products,

antivenoms and influenza and Q-fever vaccines, and markets many pharmaceutical drugs produced by other companies. CSL's subsidiary company Sequirus is the major manufacturer of the Oxford/AstraZeneca COVID-19 vaccine for Australia during the global pandemic. CSL employs more than 10,000 people in 27 countries.

Clinical trials in Australia and New Zealand

In Australia the TGA has overall control of therapeutic goods by regulating: pre-market evaluation and approval of products; clinical trials; roles of Human Research Ethics Committees (HRECs); trials involving gene therapy and related therapies; preventing or stopping a trial; indemnity and compensation; licensing of manufacturers; and post-market surveillance. Details of the relevant regulations and guidelines are covered in the TGA booklet *Australian Clinical Trial Handbook 2020* (see details in 'Online resources'). Use of a registered or listed product in a clinical trial beyond the conditions for which registration/listing has already been granted also requires approval. Overseas drug companies favour carrying out trials in Australia because our regulatory authority (the TGA) is respected, and data generated here is likely to be accepted in the United States and Europe. All clinical trials should be registered in advance at the Australian New Zealand Clinical Trials Registry, based at the National Health and Medical Research Council's Clinical Trials Centre in Sydney; thus, Australian and New Zealand researchers contribute to a worldwide initiative to make public the details of all clinical trials.

There are two main schemes under which drugs (and medical devices) may be trialled. The first is application for approval under the Clinical Trial Approval (CTA) scheme. An application to conduct a trial is submitted to the TGA, whose delegate reviews the data and may object to the trial or comment on the proposal. When any objections have been satisfactorily met and the local HREC has approved it, the trial may go ahead without further assessment from the TGA. Early phase I and II studies and trials of medical devices most commonly come under the CTA scheme. The scheme is complex, and few trials now come under these rules.

The second approach is notification under the Clinical Trial Notification (CTN) scheme, under which data are submitted to the local HREC, which reviews the data and the trial design and advises the institution if it approves the trial, or can refer the application to the CTA scheme. A CTN form must be submitted to notify the TGA of the trial. Phase III and IV trials and bioequivalence studies are best suited to the CTN scheme.

Principles of good clinical practice must be followed, such as those promulgated by the European Forum for Good Clinical Practice. These principles cover aspects such as: responsibilities of the investigators and the drug company; drug product handling, storage and accounting; reporting of adverse effects; and keeping and archiving of records. There are potential problems relating to lack of transparency about procedures, delaying or withholding of negative results, applying 'spin' to make drugs look better or participating doctors accepting funding or gifts from sponsoring drug companies.

In New Zealand, approval to trial a new drug not yet approved is submitted to the Standing Committee on Therapeutic Trials, a committee of the Health Research Council of New Zealand. Quite a few clinical trials are carried out in New Zealand because it is a small, closed, not too mixed population. Medsafe publishes *Guidelines on the Regulation of Therapeutic Products in New Zealand*; Part 11 concerns regulatory approval and good clinical practice requirements. Pharmaceutical companies conducting clinical research must comply with the principles contained in the guidelines; and participating doctors must be familiar with good clinical research practice requirements and assess the proposed research for compliance (see 'Online resources').

Future drug development

The new genetics

The discovery of the double-helical structure of DNA (published by Francis Crick and James Watson in 1953) and the determination of the sequence of nucleotide base pairs that make up the human genome[9] and mapping all its genes (declared complete in 2003) were arguably the most important scientific events of the 20th century. Although drugs are still being discovered by the old methods, there has been great interest in searching for new drugs using 'the new genetics' – application of molecular biology techniques to biochemistry and pathology. This has led to the discovery of genes associated with cancers, arthritis, cystic fibrosis, type 1 diabetes and various anaemias.

The human genome is estimated to encode from 20,000 to 25,000 gene products, of which many hundreds (especially proteins and receptors) are targets for existing drugs and thousands may be usefully exploited in the future (Oprea et al. 2018). The terms 'pharmacogenetics' and 'pharmacogenomics', and their relevance to expression of specific genes in diseases, related phenotypes, effects on drug responses and genetic differences in drug-metabolising enzymes or receptors, are discussed in more detail in Chapters 5 and 32.

Nanomedicines

The term 'nanotechnology' refers to the study of controlling matter at the nanometre (nm) level; a nanometre is one-billionth of a metre, or 10^{-9} m. Different

9 The suffix '-ome' has taken off. Originally used in 'genome' to imply a combination of gene and chromosome, it now seems to be added to almost any prefix to denote molecular biology technology applied to genetic information; thus, we now read about transcriptomics, proteomics, chemogenomics, metabolomics, glycomics, interactomics, even fluxomics. A paper given at the 2016 meeting of the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists in Melbourne included in its title the keyword 'Drugomics'!

pharmacokinetic and toxicity issues can be expected from administering drugs in such tiny forms. Nanomedicines currently developed include polymeric particles, micelles, UV-blockers, particles of silver and gold, liposomes, magnetic particles enhancing selectivity of gene therapy delivery to cancer cells and multifunctional carriers.

KEY POINTS

How drugs are discovered and developed

- Drugs and biological products have been derived from several main sources:
  - microorganisms (e.g. antibiotics from fungi)
  - plants (e.g. morphine from the poppy *Papaver somniferum*; active plant constituents include alkaloids, carbohydrates, hydrocarbons, phenols and isoprenoid structures)
  - humans and other animals (e.g. human chorionic gonadotrophin)
  - minerals or mineral products (e.g. iron and iodine)
  - laboratories, in which substances such as β-blockers and antidepressants are synthesised chemically, or made by genetically engineered microorganisms (e.g. human insulin).

  New technologies, including those of combinatorial chemistry, high-throughput screening and genetic engineering are applied in the discovery of new drugs and diagnostic methods.
- Drug development takes place in various stages over many years:
  - design and synthesis of a new molecule
  - screening for useful and adverse biological activities
  - pharmaceutical formulation and manufacturing scale-up
  - clinical trials:
    - phase I: first in-human tests, for pharmacokinetics and safety
    - phase II: efficacy studies in a small cohort of people, for dose range
    - phase III: the randomised controlled clinical trial, double-blinded, statistically valid
    - if approved and marketed: ongoing post-marketing studies and pharmacovigilance.

  During the process of testing drugs, chemical and biological assays are carried out to determine their strength and purity. Bioassays may be of various types: in vitro, in vivo or in silico; drugs need to be tested in animals and humans before being approved as safe and effective.

  Legal requirements for drug regulation are implemented to remove unsafe or ineffective drugs.

Drug formulations

Drug formulations (pharmaceutics)

Depending on the route by which a drug is administered, different dosage forms are appropriate. **Pharmaceutics** is the science of formulating drugs – for example, into tablets, ointments, parenteral solutions, metered-dose inhalers or eyedrops; it is an important aspect of a pharmacist's work. The prescriber nominates the formulation best suited to the person and route of administration, according to whether the drug is intended to act locally or be absorbed.

A comprehensive listing of various forms of drug preparations is shown in Table 2.4; the routes of drug administration are discussed in Chapter 5. More details of formulations and routes of administration are given later for drugs administered locally to the respiratory system, eyes and ears and skin.

Formulations for oral administration

About three-quarters of all drugs prescribed are administered orally, in solid or liquid form. After swallowing, a solid **dose form** disintegrates into finer particles before dissolving into solution and becoming available for absorption.

Tablets

Of drugs taken orally, about 60% are in **tablet** form. Tablets are compressed mixtures of an active drug with other pharmacologically inert excipients: diluents (fillers), binders, adhesives, disintegrants, lubricants, flavours, colours, sweeteners or absorbents. (Supposedly inert excipients can cause adverse and hypersensitivity reactions.) Thus, the active drug may make up only a small fraction of the total tablet weight. The weight quoted for the tablet (e.g. aspirin 300 mg) refers to the average amount of *active drug* present. Tablets may appear as simple white discs or may be multilayered or coated with a film[10] to mask an unpleasant taste. Effervescent tablets fizz and dissolve in water for ease of swallowing.

The rate of release of active drug from a tablet – hence the rate of absorption and distribution to the active site – can be manipulated by pharmaceutical processing. Active

10 Brightly coloured film-coated tablets look dangerously like sweets such as 'Smarties' or 'M&Ms' and account for many cases of childhood poisoning annually–especially from iron tablets.

drug may be released slowly from a resin to delay absorption (**sustained-release** [SR] or controlled-release [CR] preparations) or a tablet may be coated to prevent nausea or to resist the digestive action of stomach contents (enteric coating, EC). SR, CR or EC tablets should not be cut.

Formulations for parenteral administration

Parenteral administration means administration of drugs by injection. The IV route, where the drug is injected directly into the circulation, avoids absorption delay. Other parenteral routes include intradermal (into the skin), intramuscular, intra-arterial and subcutaneous (into the fatty tissue under the skin); specialist techniques for local anaesthetics include the epidural (= extradural) and intrathecal routes (Ch 11).

Equipment and solutions

Because any injection is invasive with potential for irritation or infection, solutions for parenteral administration must be sterile, filtered, particle-free and preferably isotonic with body solutions (i.e. with 0.9% normal saline) and buffered to body pH. Injected solid particles can cause granulomas, ischaemia or phlebitis. If the drug to be administered parenterally is very insoluble in water, such as the general anaesthetic propofol, it can be formulated in an oily emulsion. Solutions for injection are usually presented in glass ampoules or bottles or plastic bags; typical equipment for delivery of a drug by IV infusion is shown in Figure 2.5.

Most institutions have guidelines for using IV sets, with lists of infusion solutions and possible compatible admixtures (agents added to IV fluids). The general rule is that, unless a combination is specifically approved by a hospital pharmacist or drug information centre, it should not be made. (As always, if in doubt, don't!)

Formulations for children

Formulations suitable for taking by children pose a special challenge to pharmacists and drug companies: very young children cannot swallow tablets or capsules; unpleasant tastes may need to be masked by sweeteners or flavours, but sugary mixtures encourage dental caries and impair management of diabetes. Unusual drug-delivery systems may not have been clinically trialled in children. One success story is the fentanyl 'lollipop', an applicator for self-administration of the opioid analgesic by rubbing on the inside cheek mucosa; these are manufactured in a wide range of strengths suitable for children with severe pain (DM 12.2).

Drug names and classifications

Drug names

As a drug passes through investigational stages (under a code number) before it is approved and marketed, it collects three different types of name: the **chemical name**, the approved (or generic or non-proprietary) name and the proprietary (or brand or trade) name or names. For example, the chemical name of amoxicillin, a commonly prescribed antibacterial antibiotic, is actually (2S,5R,6R)-6-{[(2R)-2-amino-2-(4-hydroxyphenyl)-acetyl]amino}-3,3-dimethyl- 7-oxo-4-thia-1-azabicyclo-[3.2.0] heptane-24-carboxylic acid, abbreviated to D(−)-α-**am**ino-p-hydr**ox**ybenzylpen**icillin**. Its approved (generic) name, amoxicillin, is clearly derived from parts of its chemical name. It is marketed under several proprietary names including Alphamox, Amoxil, Bgramin, Cilamox, Fisamox, GenRx Amoxycillin, Maxamox, Ranmoxy and Yomax; in various formulations such as injections, capsules, tablets, syrups, suspensions and paediatric drops, and in combinations with other antibacterials and proton-pump inhibitors.

It would be helpful if every drug had a name related to other drugs in the same class (Table 1.5); however, this tends to be true only of the more recent drug groups. Thus, we refer to 'the statins', 'gliptins' and 'the glitazones'. Names can be deceiving: names of most β-blockers end in '-olol', but stanozolol is an anabolic steroid, not a β-blocker; nystatin is an antifungal agent and somatostatin is a growth hormone release inhibitory factor – neither is a 'statin'; so we cannot assume that drugs whose names sound similar always have similar effects and uses. And Table 1.5 cannot be read backwards; that is, while the suffix '-vir' implies the drug is probably an antiviral, not all antiviral drugs end in -vir (think zidovudine and ribavirin).

Chemical names

The **chemical name** is a unique, precise description of the drug's chemical composition and molecular structure. It is particularly meaningful to medicinal chemists – who should be able to draw the chemical structure if given the chemical name – but may be unintelligible to others. Because chemical names are too complicated to remember, or fit on a prescription pad or bottle label, a drug likely to reach the market and to be used medically is allocated a name that is simpler and easier to spell.

Active ingredient names

The active ingredient name (sometimes referred to the approved or **generic name**) is usually suggested by the manufacturer and approved by a drug regulating authority; it becomes the official drug name. These should now be the same as the International Non-proprietary Name (INN; see below). It is shorter, often derived from the chemical name, and is the name listed in official compendia such as the AMH or the BP. The active ingredient name needs to be distinct in sound and spelling so it is not easily confused with other drugs. Names that are overly fanciful or optimistic about their beneficial effects, or that refer to medical conditions or body parts, are (supposed to be) rejected.

TABLE 1.5 Drug classes

PREFIX OR SUFFIX	DRUG GROUP	EXAMPLE GENERIC NAME
cefa/o-	Cefalosporins	Cefalexin
gli-	Sulfonylureas	Glibenclamide
-afil	Phosphodiesterase 5 inhibitors	Sildenafil
-a/oquine	Quinine antimalarials	Mefloquine
-artan	Angiotensin-II-receptor antagonists (sartans)	Candesartan
-a/ovir	Antivirals	Aciclovir
-azepam	Benzodiazepines	Diazepam
-azole	Azole antifungal agents	Fluconazole
-caine	Local anaesthetics	Lidocaine
-cillin	Penicillins	Ampicillin
-coxib	Cyclo-oxygenase-2 inhibitors (coxibs)	Celecoxib
-cycline	Tetracycline antibiotics	Doxycycline
-dipine	Calcium channel blockers (dihydropyridine-type)	Nifedipine
-dronate	Bisphosphonates	Alendronate
-eplase	Thrombolytics	Alteplase
-floxacin	Quinolone antibiotics	Ciprofloxacin
-glitazone	Thiazolidinediones (glitazones)	Pioglitazone
-i/ythromycin	Macrolide antibiotics	Azithromycin
-lutamide	Antiandrogens	Flutamide
-mab	Monoclonal antibodies	Rituximab
-olol (most)	β-blockers	Metoprolol
-onidine	Alpha$_2$-adrenoceptor agonists (α_2-agonists)	Clonidine
-oxifen(e)	Selective estrogen receptor modulators	Tamoxifen
-prazole	Proton-pump inhibitors	Omeprazole
-pril	ACE inhibitors	Captopril
-pristone	Progesterone receptor antagonists	Mifepristone
-prost	Prostaglandin analogues	Latanoprost
-rubicin	Anthracycline antineoplastic agents	Doxorubicin
-setron	5HT$_3$ antagonists	Ondansetron
-statin (some)	HMG-CoA reductase inhibitors (statins)	Simvastatin
-stim	Colony-stimulating factors	Filgrastim
-tidine	Histamine H_2-receptor antagonists (H_2-receptor antagonists)	Cimetidine
-tinib	Tyrosine kinase inhibitors	Imatinib
-triptan	5HT$_1$ agonists (triptans)	Sumatriptan
-zolamide	Carbonic anhydrase inhibitors	Acetazolamide

ACE = angiotensin-converting enzyme (converts angiotensin I to angiotensin II, which is a vasoconstrictor and hence raises blood pressure); HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A (a coenzyme involved in the early stages of cholesterol synthesis); 5HT = 5-hydroxytryptamine or serotonin.
* For a full listing of the prefixes, suffixes and other stems approved for INN drug names, see the reference under 'International Non-proprietary Names', later.

Active ingredient (generic) prescribing and bioequivalence

Because numerous brand names may exist for the same drug, prescribers are mandated to use the active ingredient name (CFB 1.2). This helps to avoid confusion between drugs with similar brand names and reduces errors and costs. With some exceptions, most generic drug products sold (assuming same dose and type of formulation) are considered therapeutically equivalent (bioequivalent), and some 'generic' products are much less expensive than a particular brand name drug.

CLINICAL FOCUS BOX 1.2
Communicate the active ingredient name

In Australia, from February 2021, it became a legal requirement for all prescribers to write scripts using the name of a medicine's active ingredient. For example, instead of writing a script for *Lipitor 20 mg*, a brand (proprietary) name, the script should be written for *atorvastatin 20 mg* (the active ingredient). Prior to this, prescribers used a mix of brand and active ingredient names when prescribing, which was confusing for patients and led to medication errors.

It is not uncommon for there be many brand names for the one active ingredient. To continue using the atorvastatin example, there are many atorvastatin brands such as Atovachol, Torvastat and Trovas to name a few. In Australia and New Zealand, generic brands must show bioequivalence to the original brand before being available to the public. Bioequivalence is when two active ingredients result in similar blood concentration levels that lead to the same physiological effect.

Prior to the legislation, unless brand substitution was not permitted by the prescriber, a prescription written using a brand name could be substituted to another bioequivalent brand. For example, a script written for Torvastat 20 mg could be substituted to Atovachol 20 mg. In fact, because it would be impossible for hospital and community pharmacies to stock all the different brands of a medicine, it was routine for substitution to occur. It is hoped that active ingredient prescribing will reduce medication errors and simplify the language around medications. For example, Mr Smith will get used to calling his cholesterol-lowering medication 'atorvastatin' and looking for the active ingredient names on his medicines.

Another step you should take to improve medicines' safety is to use the active ingredient name when communicating with your patients and other health professionals. You will also note that this textbook does not often refer to brand names but to active ingredient names.

International Non-proprietary Names

WHO has a constitutional mandate to 'develop, establish and promote international standards with respect to biological, pharmaceutical and similar products' (WHO 2022). To this end, WHO collaborates with national nomenclature committees to select a single name of worldwide acceptability for each substance that is to be marketed as a drug. The name should be (as close as possible) the same in most countries and should aid harmonisation between jurisdictions and reduce prescribing errors.

Each INN is a unique name that is globally recognised and public property. The names of more than 8000 drugs are published in lists, each in eight languages, including a modernised version of Latin.[11] The general principles used by WHO in devising and approving INNs are given on its website (see 'Online resources'). They include:

- *ph* is replaced by *f* (dexamfetamine, not dexamphetamine)
- *th* is (sometimes) replaced by *t* (beclometasone, not beclomethasone)
- *y* is replaced by *i* (amoxicillin, not amoxycillin)
- *h* and *k* are avoided.

An exception to the Australian adoption of INNs is that we can keep referring to 'adrenaline' and 'noradrenaline', rather than adopting 'epinephrine' and 'norepinephrine'. However, the latter (US) terms must be included in parentheses whenever relevant – for example: 'Noradrenaline (norepinephrine) has a high affinity for ...'

American names

Sometimes, however, other approved names are used in the United States (USAN, the US Approved Name), Canada and countries that follow their lead. Australian and New Zealand students can become confused if they do not realise, for example, that a common drug with very different names is paracetamol, known as acetaminophen in the US/Canada.

Proprietary (trade or brand) names

When a drug company markets a particular drug product, it selects and copyrights a **proprietary, or trade, name** for its drug, thereby restricting use of the name to that individual drug company and to that formulation of the drug. To avoid confusion, which could jeopardise the safety of patients, trademark names should neither be derived from INNs nor contain common stems used in INNs. Drug companies carry out extensive advertising to encourage doctors to prescribe their particular version of the drug and to promote sales of trade name drugs; this expense is eventually borne by the consumer, or by government (i.e. taxpayers) if the drug is subsidised.

In this text, we will always use generic (approved) names for drugs but may sometimes add a trade name if it is sufficiently well known (e.g. Valium, Prozac, Viagra) to help readers identify a particular drug. (We do not imply thereby any preference for that particular brand of the drug.) Note that approved/generic names use lower-case letters, whereas a trade name always begins with an upper-case letter.

Drug classifications

Classification systems

Drug classification can be approached from many perspectives. Using the example of amoxicillin again, this could be classified by:

- source: where the drug comes from (semisynthetic antibiotic from *Penicillium* spp.)
- chemical formula or structure (β-lactam, penicillanic acid derivative)
- pharmacokinetic parameters: relating to how the drug is absorbed or metabolised in the body (acid-resistant, β-lactamase-sensitive)
- activity: relating to the effects of the drug in the body (wide-spectrum antibacterial agent)
- mechanism of action: explaining how the drug works (inhibitor of bacterial cell wall synthesis)
- clinical use: conditions for which the drug is prescribed (indicated for treatment of infections by sensitive Gram-positive and Gram-negative organisms)
- body systems affected by the drug (for infections of the respiratory system; ear, nose and throat; genitourinary tract, etc.)
- drug schedule: the group into which the drug is classified for legal purposes (S4 Prescription-Only medicine)
- pregnancy safety schedule: grouping drugs depending on their safety for use in pregnancy (A: considered safe)
- popularity (one of the most commonly prescribed drugs in the world)
- whether its use is allowed in sporting competitions (yes – approved by the World Anti-Doping Agency).

Not surprisingly, students are often confused by drug classification, particularly because sometimes the same drug may be classified into various groups depending on the clinical use. For example, aspirin-like drugs may be classified as analgesics, antipyretics, anti-inflammatory agents or antithrombotics. This book uses various

11 Classical scholars will be amused to hear that paracetamol becomes paracetamolum.

approaches where appropriate. For example, the title of Chapter 15, 'Psychotropic agents', refers to drug clinical effects. Antidepressants are grouped there as 'tricyclic antidepressants' (a chemical class), or by mechanism of action: 'monoamine oxidase inhibitors' or 'selective serotonin reuptake inhibitors'. Such drug classifications can simplify understanding about individual drugs.

Prototype drugs

Pharmacology is easier to understand and learn when **key, or prototype, drugs** are studied – that is, the most important drug in a class, to which other drugs in the class can be compared. In this text, many prototype drugs are described in detail in a consistent format called a Drug Monograph (DM); thus, insulin is the prototype antidiabetic agent (DM 30.2), and estradiol the prototype estrogenic hormone. When a new, similar drug becomes available, it can be associated with its prototype, and inferences made about its basic pharmacodynamic qualities before focusing on specific properties (usually pharmacokinetic) to differentiate it from the prototype and other similar drugs.

Prescription-Only or OTC drugs

A drug may be classified into schedules as a **Prescription-Only drug**, which means that it requires a legal prescription to obtain it, or it may be a non-prescription or **OTC drug**, which means that it may be purchased without a prescription, possibly in a pharmacy or supermarket. (Drug Schedules are considered in more detail in Ch 2.)

WHO Essential Medicines List

It is recognised that, with the enormous number of drugs available, few countries or health services can subsidise or provide the whole range of drugs, and no retail or hospital pharmacy could stock them all. To assist in deciding which drugs are the most important, WHO has derived a model Essential Medicines List, now comprising about 433 core drugs for adults and children in some 30 main categories that are 'deemed essential for addressing the most important public health needs globally' (see 'Online resources'). This is useful for all countries attempting to curtail rapidly increasing expenditure on drugs, particularly for developing countries, allowing them to allocate limited resources to essential drugs, defined as 'those that satisfy the priority health care needs of a population ... They are intended to be available in functioning health systems at all times, in appropriate dosage forms, of assured quality and prices individuals and health systems can afford' (WHO 2021).

The selection of drugs is determined by an Expert Committee on the Selection and Use of Essential Medicines and is updated regularly. These drugs first require market approval based on efficacy, safety, quality and value for money. Listing 'essential' drugs inevitably raises concerns, particularly from manufacturers of drugs not on the list, which may be seen as 'non-essential' (see 'Online resources').

Médecins Sans Frontières (MSF; Doctors Without Borders), the world's leading independent organisation for medical humanitarian aid, also publishes a list based on WHO's list. The MSF (2021) medical guidance is 'a practical manual intended for health professionals, physicians, pharmacists, nurses and health auxiliaries involved in curative care and drug management', especially in developing countries and those where MSF is involved in humanitarian care.

Australia's top 10 drugs

The Australian Commonwealth Department of Health regularly audits the usage of prescription drugs in Australia and publishes lists of the top 10 drugs, scored by numbers of defined daily doses, by prescription counts and by cost to the government (i.e. to taxpayers). The lists for drug use in the year 2019–20 are summarised in Table 1.6.[12] Note that only some subsidised drugs are audited here; it excludes those coming under 'co-payment' or 'closing-the-gap' schemes, bought OTC or provided under private prescriptions.

New Zealand's top 10 drugs

New Zealand's Pharmaceutical Management Agency (Pharmac) also publishes lists of the most prescribed medications, as a 'top 20'. Their top 10 (reported for 2019–20) were as follows: paracetamol, atorvastatin, omeprazole, aspirin (antithrombotic dosage), amoxicillin, ibuprofen, metoprolol, salbutamol, cilazapril, cholecalciferol (Table 1.7) – very similar to their 2015–16 list (Pharmac 2020a).

12 The three most expensive drugs (to government) in this list are new antivirals to treat hepatitis C.

TABLE 1.6 The top 10 drugs by prescription counts (in millions), Australia, 2019–20

ORDER	DRUG (MAIN INDICATION)	MILLIONS OF PRESCRIPTIONS
1	Rosuvastatin (lipid-lowering)	12.7
2	Atorvastatin (lipid-lowering)	11.0
3	Pantoprazole (oesophageal reflux)	8.0
4	Esomeprazole (oesophageal reflux)	8.0
5	Perindopril (hypertension)	6.6
6	Cefalexin (antibiotic)	5.3
7	Metformin (diabetes)	5.1
8	Escitalopram (depression)	4.9
9	Amoxicillin with clavulanic acid (antibiotic)	4.7
10	Sertraline (depression)	4.6

Source: Data from the Commonwealth Department of Health 2021

TABLE 1.7 The top 10 drugs by prescription counts (in millions), New Zealand, 2019–20

ORDER	DRUG (MAIN INDICATION)	MILLIONS OF PRESCRIPTIONS
1	Paracetamol (analgesic)	2.88
2	Atorvastatin (lipid-lowering)	1.53
3	Omeprazole (oesophageal reflux)	1.48
4	Aspirin (anticoagulant)	1.14
5	Amoxicillin (antibiotic)	1.04
6	Ibuprofen (analgesic)	1.03
7	Metoprolol (cardiovascular)	0.95
8	Salbutamol (respiratory)	0.94
9	Cilazapril (hypertension)	0.84
10	Cholecalciferol (bone health)	0.46

Source: Data from the Commonwealth Department of Health 2021

The main cross-Tasman differences appear to be the slightly different statins and ACE inhibitors used in New Zealand (cilazapril is not available in Australia), the inclusion of amoxicillin and ibuprofen and the absence of an angiotensin-receptor antagonist (e.g. irbe- or candesartan), metformin (for diabetes) or pregabalin (for neuropathic pain/seizures) from the New Zealand list.

New Zealand's 10 most expensive drug groups (reported by Pharmac in 2020) were: immunosuppressants, antivirals (hepatitis C), vaccines, chemotherapeutic agents, antithrombotic agents, antidiabetic agents, long-acting β-adrenoceptor agonists, endocrine therapy, antipsychotics (Pharmac 2020b).

KEY POINTS

How drugs are named and classified

- A drug may have three main names:
  - its unique chemical name
  - an approved (generic) name, allocated by a regulating authority; in Australia and New Zealand, this now should be the official INN
  - a trade or brand name, given by the marketing company.
- Generic prescribing is encouraged, and dispensing of substituted products considered bioequivalent is sometimes permitted.
- Drugs are classified by any of a number of criteria – for example, by source, chemical group, pharmacokinetic parameters, pharmacological activity, mechanism of action, clinical use, body systems affected, legal drug schedule, pregnancy safety category, popularity, whether allowed in sporting competitions or whether considered 'essential'.
- Drug classifications help facilitate understanding of pharmacology by comparing the common characteristics of an example of a drug group or classification (the key, or prototype, drug) with those of other drugs in the same category.

Drug information

Important drug information

Our Drug Monographs summarise for selected prototype drugs the important basic information, including the drug's:

- group or category
- approved/generic name
- pharmacodynamic effects (what the drug does to the body)
- mechanisms of action
- indications for clinical use
- particular pharmacokinetic parameters (what the body does to this drug)
- common adverse effects (adverse drug reactions)
- **contraindications** (the medical conditions in which a drug should *not* be prescribed) and precautions
- significant drug interactions
- dosage and administration guidelines, optimum therapeutic plasma levels and monitoring techniques.

Information as to potential toxic effects and treatment of poisoning may also be relevant, as is safety of use in particular cohorts of people, such as infants or the elderly. The Australian Drug Evaluation Committee's Pregnancy Safety Category indicates the likely safety or risks with the use of a drug during pregnancy (see 'Online resources').

What patients want to know

There is a huge – often overwhelming – amount of information available on most drugs, especially on the internet, where its accuracy and bias cannot easily be judged. When it comes down to the basics, what patients most want to know is:

- What is the drug for?
- What will it do to me (risks and benefits)?
- How do I take it?
- What other treatment options are there?
- What might happen if I *don't* take it?

These are the questions that health professionals prescribing, recommending or administering drugs should be ready to answer.

Drug information sources

Publication of data on new drugs and new information on old drugs is an ongoing process – in scientific journals, news releases, patient information brochures, reference books and textbooks. Much information (some of it of dubious quality) is found on the internet (Ioannidis et al. 2017). No single source will meet the varied and specialised needs of clinical practice today. It is always important to read critically, beware of bias or selectivity of information and consider what credibility can be given to the author and the publication, particularly with information found on the internet.

An excellent overview 'Where to find information about drugs' (Day & Snowden 2016) can be found via the *Australian Prescribe*r website.

Official sources, pharmacopoeias and formularies

Official sources of drug information are published by government bodies such as departments of health and hospitals, and by pharmaceutical societies and medical colleges, containing legally or medically accepted standards for drugs. Pharmacopoeias are reference texts collecting together drug information relevant to a particular country, including descriptions, formulae, strengths, standards of purity and dosage forms.

Formularies are similar but may also include information on drug actions, adverse effects, general medical information, guidelines for pharmacists dispensing medicines and the 'recipes' for formulation or production of different medicines such as tablets, injections, ointments and eyedrops. A national **formulary** may also be used by government to limit the drugs available or subsidised, in order to encourage rational, cost-efficient prescribing and enhance the quality use of medicine (QUM; Ch 2).

The APF

The *Australian Pharmaceutical Formulary and Handbook: A Guide to Best Practice* is published by the Pharmaceutical Society of Australia. The APF now contains not just formulae ('recipes') for medicines but also principles of drug therapy, therapeutic management of common conditions (e.g. cough, head lice, tinea), monographs on complementary medicines, counselling guides, health information, physicochemical data on drugs, codes of ethics for pharmacists and Australian standards. It aims to underpin the expanding roles of pharmacists and encourage 'best practice' pharmacy (Pharmaceutical Society of Australia 2021).

New Zealand drug information sources

Medsafe is the New Zealand government's Medicines and Medical Devices Safety Authority. It is responsible for ensuring the regulation and safety of medicines and medical devices in New Zealand. The Medsafe website is a great source of independent information for health professionals and consumers (and students), with prescriber update articles, medicine data sheets, reporting of adverse reactions, 'patient info leaflets' and media releases, plus information about classification and regulation of medicines, medical devices, drug abuse, patient support groups, clinical trials and complementary medicines.

The New Zealand Ministry of Health and various organisations interested in medicines have developed a *New Zealand Formulary*, which provides point-of-care advice for health professionals and has a companion *New Zealand Formulary for Children*. It includes the New Zealand Universal List of Medicines, a list of all medicines prescribable in New Zealand. It is continuously updated and integrated with electronic prescribing and dispensing software packages. It provides four main components:

- preliminary general notes on use of drugs (medicines)
- practical notes on specific therapeutic categories
- datasheets (monographs) on individual drugs
- details of preparations available and relevant subsidy information.

The NZF therefore parallels much of the AMH, with the advantage that it is freely available and accessible online (in New Zealand), compared with the AMH, published annually at a cost to purchasers of approximately A$260.

Some other official sources

Other examples of official drug information sources are:

- *Martindale: The Complete Drug Reference:* monographs on drugs classified under therapeutic groups, such as analgesics, anthelmintics, vaccines; includes details of preparations, and lists of manufacturers and pharmaceutical terms (Buckingham 2020)
- *British Pharmacopoeia* (British Pharmacopoeia Commission): with official standards and monographs on thousands of drugs, formulated medicines, herbal drugs, blood products, radio-pharmaceuticals and surgical materials
- *United States Pharmacopeia* and the National Formulary (US Pharmacopeial Convention)
- *Handbook of Non-prescription Drugs: An Interactive Approach to Self-Care* (American Pharmaceutical Association): an authoritative source on 'non-prescription drug pharmacotherapy, nutritional supplements, medical foods, non-drug and preventive measures, and complementary therapies'.

Semi-official sources

Semi-official sources of drug information may be published by government bodies or other groups, such as medical and pharmacology societies, and may include drug bulletins, reference books and updates, but no drug advertisements. While not official standards, they attempt to provide up-to-date, independent and unbiased information on drugs. Information such as lists of food additives, patient support organisations, poisons information centres and prescribing guidelines may be included.

Australian Medicines Handbook

In the years since the AMH was first published (1998), it has become virtually 'the bible' as a source of peer-reviewed, independent, authoritative information on therapeutic drugs and clinical practice in Australia. It is published by three national bodies concerned with drug therapy: ASCEPT (the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists), the PSA (Pharmaceutical Society of Australia) and the RACGP (Royal Australian College of General Practitioners). It aims to fulfil a need for 'an independent and up-to-date source of drug information to foster rational prescribing in Australia', much as the British National Formulary had done in the United Kingdom. It contains three main types of information:

- treatment considerations for common diseases, with comparisons between classes of drugs
- statements about classes of drugs, with comparisons between individual drugs in the class
- monographs on individual drugs, with some trade names and formulation types.

Preliminary sections provide general prescribing information, plus details on prescribing for patient groups. Appendices provide invaluable reference information, especially on significant drug interactions (see 'Online resources').

Therapeutic Guidelines series

Therapeutic Guidelines Limited is an independent not-for-profit organisation based in Melbourne, which started with a very small booklet called *Antibiotic Guidelines* published more than 20 years ago in a determined bid to encourage rational prescribing of antibiotics at the Royal Melbourne Hospital. Its aim was to reduce the risk of antibiotic resistance developing.

There is now (2021) a series of 19 guidelines, each dedicated to a branch of medicine or major drug therapy – for example, antibiotics, cardiovascular medicine and palliative care. The guidelines, each written by an 'Expert Group', are intended principally to provide prescribers with clear, practical, succinct and up-to-date therapeutic information, categorised according to diagnosis and updated every few years. They are published in print and electronic formats suitable for computers and mobile devices (see 'Online resources').

Cochrane

Cochrane is an international organisation that publishes systematic reviews and meta-analyses of the best evidence from research on healthcare interventions, with the aim of helping people to make well-informed decisions about health care. It aims to avoid duplication of studies, minimise bias and provide relevant, up-to-date, easily accessible information. There are Cochrane databases of reviews, clinical trials, methodologies and economic evaluations, among others (see 'Online resources').

Other semi-official sources

Other examples include:

- National Prescribing Service (NPS) MedicineWise: an independent, not-for-profit, evidence-based Australian organisation that works to improve the way health technologies, medicines and medical tests are prescribed and used; it provides newsletters, websites, fact sheets, apps and public campaigns to 'deliver meaningful information for health consumers, health professionals, government, research and other businesses to enable the best decisions about medicines and health technologies' (see 'Online resources')
- *Australian Prescriber*: a free bi-monthly independent review journal, published by the NPS, that provides critical commentary on drugs and therapeutics for health professionals, including Medicines Safety Updates; it has been freely available online since 1996, and articles are now included in the PubMed Central database
- reference books such as the *Australian Prescription Products Guide* ('PP Guide'), the *Merck Index*, *Drug Interactions: Analysis and Management* and journals such as *Current Therapeutics*, *Annals of Pharmacotherapy* and *Drugs* (references for current editions of these can best be found via a search engine).

Drug or poisons information centres and pharmacists

Drug information centres, usually located in the pharmacy departments of major teaching hospitals, are set up to disseminate information about drugs, adverse reactions, drug interactions, treatment of drug overdoses and other related information, to maximise safety, efficacy and economy in drug use (see AMH, Appendix, 'Drug

Information Centres'). They are excellent sources of information for both the public and health professionals. Community and hospital pharmacists, as medicines experts, are usually available and willing to provide drug information as part of their professional role.

Other drug information sources

- *Textbooks and drug guides:* An up-to-date pharmacology textbook is a valuable source of drug information for inclusion in the health professional's library! Various 'drug guides' also exist, acting as quick reference sources of summarised information on drugs. Most are now available online. Examples are the *MIMS Abbreviated* drug reference guides, published and updated four times per year. An app that is easily accessed on a smartphone, called 'Drug Names', provides concise information on a drug's class, mechanism of action, uses and dosage.
- *Reference books:* For example, *MIMS Annual* provides photographs to assist in identifying an unknown tablet or capsule. MIMS is now also published in various electronic formats (eMIMS) for android and Apple platforms, suitable for desktops, laptops, integratable to popular dispensing programs and as MIMSonline.
- *Drug companies' information:* Companies applying for registration of their products must supply to health authorities information on all aspects of the drug to prove its safety, efficacy and cost-effectiveness. A summary of this information is available in publications such as *MIMS Annual* and the PP Guide, and in consumer medicine information (see below) sheets, advertisements and promotions. Material supplied by drug companies is likely to be less objective than information in independent sources such as the AMH or *Australian Prescriber*. (Ethical aspects of drug advertising are discussed in Ch 2 of this text.)
- Consumer medicine information (CMI) pamphlets handed out to patients help improve people's understanding and usage of drugs they are prescribed. They are particularly important when a drug is first provided, the dose or formulation is changed or the information is revised. Previously, all products had to have CMI handouts/inclusions; however, many manufacturers now rely on consumers accessing information on their website.

The internet

With the proliferation of medical sites on the internet, many search engines (e.g. PubMed, Embase, eMedicine, Medline, Ovid, AusDI, Up-To-Date and the American Society of Health-System Pharmacists' drug information site) and directories are available to provide both general and specialised drug information for everyone – health professionals and consumers/patients. Some professional journals, databases, indexes and abstracting services also provide current drug information on the internet.

It is essential to read internet sites critically when seeking drug information because there is no screening system to determine the accuracy of internet information, and incorrect, commercial or biased information may be posted (Ioannidis et al 2017).[13]

KEY POINTS

Drug information sources

- Information about drugs is available from a wide variety of sources, ranging from official government publications through semi-official sources to drug company information and websites.
- Internet sources can be evaluated on the following criteria: accuracy, appearance, authority, currency and objectivity.

13 Students tempted to use Wikipedia as a quick source of drug information for assignments or revision purposes should beware. A comparison study looking at the accuracy and completeness of Wikipedia and Micromedex compared with FDA-approved production information found that Wikipedia was less complete and accurate. The authors concluded that Wikipedia should not be used by health professionals as a reference source (Reilly et al. 2017).

REVIEW EXERCISES

1 Mr MS is prescribed two new drugs, one for his blood pressure and one for his cholesterol. Mr MS does not like taking medicines and wants to know they are safe. He asks you, the health professional, to outline and describe the process from preclinical testing to post-marketing surveillance.

2 The doctor prescribes your patient an investigational drug that is new to you. Which drug information source would you select to find evidence-based information on this drug? What credibility could you give the information?

3 Compare the advantages and disadvantages of prescribing and using active ingredient (approved or generic) names rather than brand (or trade) names when communicating with patients.

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Australian Medicines Handbook: https://shop.amh.net.au (accessed 17 May 2021)

Australian Pharmaceutical Formulary: https://www.psa.org.au/apf (accessed 17 May 2021)

Australian Prescriber: https://www.nps.org.au/australian-prescriber/ (accessed 17 May 2021)

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CHAPTER 2

CLINICAL, ETHICAL AND LEGAL FOUNDATIONS OF PHARMACOTHERAPY

Mary Bushell

KEY ABBREVIATIONS

ADR	adverse drug reaction
Ahpra	Australian Health Practitioners Regulation Agency
Cth	Commonwealth
DUE	drug use evaluation
EBM/P	evidence-based medicine/ practice
FDA	US Food and Drug Administration
Medsafe	Medicines and Medical Devices Safety Authority (NZ)
NP	nurse practitioner
NPS	National Prescribing Service
OTC	over-the-counter
PBS	Pharmaceutical Benefits Scheme
PHARMAC	Pharmaceutical Management Agency (NZ)
QUM	Quality Use of Medicines
RCCT	randomised controlled clinical trial
SUSMP	*Standard for the Uniform Scheduling of Medicines and Poisons*
TGA	Therapeutic Goods Administration
UN	United Nations

Chapter Focus

'Pharmacotherapy' refers to the use of drugs for treating or preventing disease, as distinct from theoretical or experimental pharmacology, in which drugs may be studied to understand their mechanisms of action and effects. In this chapter, we focus first on the Australian laws relating to the regulation of prescription and over-the-counter (OTC) drugs, poisons, controlled substances, proscribed substances and investigational drugs, especially the *Therapeutic Goods Act 1989* (Cth); the drugs, poisons and controlled substances Acts and Regulations; and relevant customs, crimes and narcotic drugs Acts. The regulation and scheduling of drugs and controlled substances in Australia and New Zealand are compared.

Health professionals who prescribe, formulate, dispense or administer drugs are legally accountable for their actions related to drug therapy. This chapter reviews the roles of health professionals in relation to the use of medicines, and how quality use of medicines and drug use evaluations help optimise pharmacotherapy.

Many ethical principles also apply to drug use, based on human rights and bioethics; these should always underlie decisions related to pharmacology research and clinical practice. Controversy can arise as to how ethical principles are applied in clinical situations.

KEY TERMS

adherence 37
clinical pharmacology 51
controlled drug 59
deprescribing 51
drug offence 62
drug schedule 58
drug use evaluation 35
evidence-based medicine 33
medical ethics 52
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Narcotic 56
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CRITICAL THINKING SCENARIO

Barbara, a 52-year-old female, recently experienced discomfort in her chest, arm, neck and jaw that lasted a couple of minutes. After an exercise tolerance test Barbara was diagnosed with stable angina. To relieve angina pain actively as it happens, her GP prescribed 400 microg glyceryl trinitrate spray to be administered sublingually. To prevent future episodes of angina Barbara was also prescribed aspirin 100 mg orally daily and atenolol 25 mg orally daily.

1. Discuss how we know the medicines that Barbara has been prescribed are safe and effective.
2. Discuss what the Poisons Standard (the SUSMP) is. Discuss the different levels of controls in access, supply/provision, labelling, storage, records and advertising for each of Barbara's prescribed drugs.

Barbara elects to have an electronic prescription, and her prescriber sends her a QR code via a text message to her phone. Barbara then forwards this QR code to her local pharmacy to be dispensed. The pharmacy has Barbara's Medicare and Commonwealth concession card details on file.

3. Outline what makes a legal prescription. Outline what makes a valid Pharmaceutical Benefits Scheme prescription.
4. Consistent with the National Health (Pharmaceutical Benefits) Amendment (Active Ingredient Prescribing) Regulations Barbara's GP used active ingredient prescribing. Discuss what active ingredient prescribing is and its benefits.
5. Discuss some of the benefits of electronic prescribing over paper-based prescribing.

Clinical aspects of pharmacotherapy

Introduction

To optimise use of drugs in a rational, clinically effective and cost-effective way, health professionals need to understand: the evidence on which clinical decisions are based; necessary decision-making processes before drugs are chosen, prescribed or advised; how prescriptions are written and dispensed; the types of formulations in which drugs are administered; and the factors that affect how people respond to drugs – in fact, basically the whole of clinical pharmacology!

Quality use of medicines

The foundation and chief purpose of pharmacotherapy is **Quality Use of Medicines** (QUM), described in Australia's *National Medicines Policy* (see 'Online resources') as the judicious, appropriate, safe and effective use of medicines. Specifically, QUM means:

- selecting management options wisely
- if a medicine is needed, selecting that medicine wisely – this means taking into consideration the person, the clinical condition, the benefits and harms of the medicine (based on the best evidence), the dosage and length of treatment, other medical conditions, other medicines the person may be taking, monitoring considerations and cost (to the individual, community and the healthcare system)
- using medicines safely and effectively – monitoring outcomes, minimising misuse, under- and overuse.

Some professional groups have incorporated a QUM policy within their own charter; for example, the Podiatry Board of Australia's Prescribing Information concludes with the necessity to have access to various reference texts and databases, plus 'access to Quality Use of Medicines principles' (see 'Online resources').

Evidence-based health care

Health professionals should practise **evidence-based medicine** (EBM)[1] – 'the conscientious, explicit and judicious use of current best evidence in making decisions about the medical care of individual patients' (Sackett et al. 1995).

1 Although the terms 'medicine' and 'medical' are sometimes used to imply health care provided by doctors, in the wider sense the term is defined as 'the branch of science devoted to the prevention of disease and the restoration of the sick to health' (The American Heritage Medical Dictionary 2007), so EBM is practised by a wide range of health professionals.