DEDICATIONS

To my daughters Rosemary, Philippa and Alison, who continually inspire, encourage and amaze me; and to their children, as representatives of future generations to benefit from medical research and scholarship.

Bronwen J Bryant

To the Discipline of Pharmacology that has provided the foundation of my academic career and to those who enrich my life, my husband John and my family and friends.

Kathleen M 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

To my wife Angela and son Aidan with love (even though they’ll never read it).

Andrew Rowland
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Bronwen became fascinated with pharmacology while studying pharmacy at the University of Sydney. She completed an Honours year, then a Master of Science degree under the supervision of Associate Professor Diana Temple, with research in the areas of biochemical and cardiovascular pharmacology. After two years’ research at Riker Laboratories in Sydney, and work in both community and hospital pharmacies to gain registration and experience as a pharmacist, she moved to London and worked as a medical translator and editor.

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CONTENTS

About the Authors vi
Book at a Glance viii
Preface xv
Acknowledgements xvi
Notes to the User xviii
Figures xxiii
Clinical Interest Boxes xxvi
Drug Monographs xxvii
Drug Monographs A–Z xxviii

UNIT 1
INTRODUCTION TO PHARMACOLOGY 1
Chapter 1 Drugs and Medicines 1
Introduction 2
Drugs and Medicines 2
A Brief History of Pharmacology 4
Drug Discovery and Development 8
Drug Names and Classifications 26
Drug Information 32

Chapter 2 Legal, Clinical and Ethical Foundations of Pharmacotherapy 38
Legal Aspects of Pharmacotherapy 39
Clinical Aspects of Pharmacotherapy 51
Ethical Aspects of Pharmacotherapy 71

Chapter 3 Over-the-Counter Drugs and Complementary Therapies 79
Introduction 80
Over-the-Counter Drugs 80
Complementary and Alternative Therapies 87

UNIT 2
PRINCIPLES OF PHARMACOLOGY 103
Chapter 4 Molecular Drug Targets and Pharmacodynamics 103
Introduction 104
Drug Specificity, Selectivity and Affinity 104
Molecular Drug Targets 104
Pharmacodynamics 110

Chapter 5 Drug Absorption, Distribution, Metabolism and Excretion 117
Introduction 118
Drug Absorption 118
Distribution 127
Drug Metabolism 129
Excretion of Drugs and Drug Metabolites 132
Pharmacokinetics During Pregnancy and Early Life 133

Chapter 6 Pharmacogenetics and Individualised Drug Therapy 138
Introduction 139
Pharmacogenetics 139
Pharmacogenetics in Clinical Practice 142
Individualising Drug Dosing 146
Additional Applications of Genetics in Pharmacology 147

Chapter 7 Pharmacokinetics and Dosing Regimen 150
Introduction 151
Plasma Concentration–Time Profile of a Drug 151
Key Pharmacokinetic Concept: Clearance 152
Key Pharmacokinetic Concept: Volume of Distribution 155
Key Pharmacokinetic Concept: Half-Life 157
Saturable Metabolism 158
Dosage Measurements and Calculations 158

Chapter 8 Adverse Drug Reactions and Drug Interactions 163
Introduction 164
Definitions 164
Risk Factors for Developing an Adverse Drug Reaction 165
Drug Use in the Elderly 165
Incidence of Adverse Drug Reactions 167
Classification of Adverse Drug Reactions 167
Immune Modulating Drugs and Adverse Drug Reactions 169
Drug–Drug Interactions 170
Classification of Drug Interactions 171

UNIT 3
DRUGS AFFECTING THE PERIPHERAL NERVOUS SYSTEM 177
Chapter 9 Overview of the Autonomic and Somatic Nervous Systems: Drugs Affecting Cholinergic Transmission 177
Introduction: General Overview of the Autonomic and Somatic Nervous Systems 178
Neurochemical Transmission 183
Drugs Acting at Muscarinic Receptors 185
Acetylcholinesterase 189
Anticholinesterase Agents 190
Drugs Acting at Nicotinic Receptors 194
Somatic Nervous System 194
Neuromuscular Blocking Drugs 198
Reversal of Neuromuscular Blockade 200
xiv CONTENTS

Chapter 10 Overview of the Sympathetic Nervous System and Drugs Affecting Noradrenergic Transmission 203
Introduction 204
Drugs Acting at Adrenergic Receptors 208
Adrenoceptor Antagonists 215

UNIT 4
DRUGS AFFECTING THE CENTRAL NERVOUS SYSTEM 223
Chapter 11 Central Nervous System Overview and Anaesthetics 223
Introduction: The Central Nervous System 224
General Anaesthesia 236
Local Anaesthesia 250
Chapter 12 Analgesics 263
Introduction 264
Pain Management 266
Analgesic Drugs 273
Chapter 13 Antianxiety, Sedative and Hypnotic Drugs 294
Introduction: Sleep and Anxiety 295
Benzodiazepines 299
Other Anxiolytic and Sedative/Hypnotic Agents 304
Chapter 14 Antiepileptic Drugs 311
Introduction: Epilepsy 312
Antiepileptic Drug Therapy 316
Chapter 15 Psychotropic Agents 331
Introduction: Psychiatry and CNS Neurotransmitters 332
Clinical Aspects of Drug Therapy in Psychiatry 335
Antipsychotic Agents 339
Treatment of Affective Disorders 347
Chapter 16 Central Nervous System Stimulants 363
Introduction: History and Uses of Stimulants 364
Amphetamines 364
Methylxanthines 368
Chapter 17 Drugs for Neurodegenerative Disorders and Headache 374
Introduction 375
Drug Treatment of Movement Disorders 375
Dementias, Delirium and Stroke 386
Drug Treatment in Migraine and Other Headaches 390
Chapter 18 Drugs Affecting the Eye and Ear 397
Introduction 398
Drugs Affecting the Eye 398
Drugs Affecting the Ear 416
Chapter 19 Drug Dependence and Social Pharmacology 425
Introduction 426
Drug Abuse and Dependence 426

UNIT 5
DRUGS AFFECTING THE HEART AND VASCULAR SYSTEM 463
Chapter 20 Drugs Affecting Cardiac Function 463
Introduction: The Heart 464
Drugs Affecting Cardiac Function 472
Dysrhythmias and Antiarrhythmic Drugs 478
Chapter 21 Drugs Affecting Vascular Smooth Muscle 488
Introduction: The Vascular System 489
Angina 490
Direct-Acting Vasodilator Drugs 491
Peripheral Vascular Disease 499
Indirect-Acting Vasodilator Drugs 499
Aldosterone-Receptor Antagonists 507
Chapter 22 Lipid-Lowering Drugs 511
Introduction: Dyslipidaemia 512
Management Strategies for Dyslipidaemia 515

UNIT 6
DRUGS AFFECTING THE URINARY SYSTEM 527
Chapter 23 Drugs Affecting the Kidney and Bladder 527
Introduction: The Kidneys 528
Diuretics 533
Drugs for Bladder Dysfunction 540

UNIT 7
DRUGS AFFECTING THE BLOOD 547
Chapter 24 Drugs Affecting Thrombosis and Haemostasis 547
Introduction 548
Anticoagulant Drugs 550
Antiplatelet Agents 555
Thrombolytic Drugs 559
Haemostatic and Antifibrinolytic Drugs 560
Chapter 25 Drugs Affecting the Haemopoietic System 565
Introduction 566
Haematinics 568
Haemopoietics 569
# UNIT 8
## DRUGS AFFECTING THE RESPIRATORY SYSTEM

<table>
<thead>
<tr>
<th>Chapter 26 Drugs Used in Respiratory Disorders</th>
<th>573</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction: The Respiratory System, Respiratory Disease and Its Treatment</td>
<td>574</td>
</tr>
<tr>
<td>Considerations for Drug Delivery to the Airways: Drugs by Inhalation</td>
<td>577</td>
</tr>
<tr>
<td>Medical Gases</td>
<td>579</td>
</tr>
<tr>
<td>Respiratory Stimulants and Depressants</td>
<td>582</td>
</tr>
<tr>
<td>Drugs Affecting Secretions and Mucociliary Transport</td>
<td>583</td>
</tr>
<tr>
<td>Drugs Affecting the Nose</td>
<td>584</td>
</tr>
<tr>
<td>Drug Treatment of Asthma</td>
<td>588</td>
</tr>
<tr>
<td>Drug Treatment of Chronic Obstructive Pulmonary Disease</td>
<td>601</td>
</tr>
<tr>
<td>Drugs Used in Respiratory Tract Infections</td>
<td>602</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chapter 31 Pharmacology of the Thyroid and the Parathyroid Glands</th>
<th>692</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>693</td>
</tr>
<tr>
<td>Pharmacotherapy of Thyroid Disorders</td>
<td>697</td>
</tr>
<tr>
<td>Pharmacotherapy of Parathyroid Disorders</td>
<td>703</td>
</tr>
<tr>
<td>Pharmacotherapy of Bone Disorders</td>
<td>707</td>
</tr>
</tbody>
</table>

# UNIT 9
## DRUGS AFFECTING THE GASTROINTESTINAL SYSTEM

<table>
<thead>
<tr>
<th>Chapter 27 Drugs Affecting the Upper and Lower Gastrointestinal Tract</th>
<th>611</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction: The Gastrointestinal System, Gastrointestinal Disease, and Drugs Affecting the Gastrointestinal System</td>
<td>612</td>
</tr>
<tr>
<td>The Lower Gastrointestinal Tract</td>
<td>631</td>
</tr>
</tbody>
</table>

# UNIT 10
## DRUGS AFFECTING THE ENDOCRINE SYSTEM

<table>
<thead>
<tr>
<th>Chapter 28 The Neuroendocrine System and Pituitary Gland</th>
<th>643</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>644</td>
</tr>
<tr>
<td>Hormones as Drugs</td>
<td>646</td>
</tr>
<tr>
<td>Neuroendocrine Controls: Hypothalamic Factors and Related Drugs</td>
<td>648</td>
</tr>
<tr>
<td>Anterior Pituitary Gland Hormones and Related Drugs</td>
<td>650</td>
</tr>
<tr>
<td>Posterior Pituitary Gland Hormones and Related Drugs</td>
<td>654</td>
</tr>
<tr>
<td>Chapter 29 Pharmacology of the Adrenal Cortex</td>
<td>658</td>
</tr>
<tr>
<td>Introduction</td>
<td>659</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>662</td>
</tr>
<tr>
<td>Glucocorticoids Used Clinically</td>
<td>664</td>
</tr>
<tr>
<td>Mineralocorticoids</td>
<td>669</td>
</tr>
<tr>
<td>Chapter 30 Pharmacology of the Endocrine Pancreas</td>
<td>672</td>
</tr>
<tr>
<td>Introduction</td>
<td>673</td>
</tr>
<tr>
<td>Pancreatic Hormones and Diabetes</td>
<td>673</td>
</tr>
<tr>
<td>Management of Type 2 Diabetes</td>
<td>683</td>
</tr>
</tbody>
</table>

# UNIT 11
## DRUGS AFFECTING THE REPRODUCTIVE SYSTEMS

<table>
<thead>
<tr>
<th>Chapter 32 Drugs Affecting the Female Reproductive System</th>
<th>715</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>716</td>
</tr>
<tr>
<td>Drugs Used in Gynaecological Disorders</td>
<td>719</td>
</tr>
<tr>
<td>Contraception</td>
<td>729</td>
</tr>
<tr>
<td>Drugs During Pregnancy, the Perinatal Period and Lactation</td>
<td>737</td>
</tr>
<tr>
<td>Menopause and Hormone Replacement Therapy</td>
<td>746</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chapter 33 Drugs Affecting the Male Reproductive System</th>
<th>752</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>753</td>
</tr>
<tr>
<td>Drugs Used in Male Reproductive Disorders</td>
<td>753</td>
</tr>
<tr>
<td>Contraception in Males</td>
<td>759</td>
</tr>
<tr>
<td>Drugs That Affect Sexual Functioning (Male and Female)</td>
<td>761</td>
</tr>
</tbody>
</table>

# UNIT 12
## DRUGS USED IN NEOPLASTIC DISEASES

<table>
<thead>
<tr>
<th>Chapter 34 Overview of the Treatment of Cancer</th>
<th>769</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>770</td>
</tr>
<tr>
<td>Treatment of cancer</td>
<td>771</td>
</tr>
<tr>
<td>Clinical Aspects of Treating Cancer</td>
<td>776</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chapter 35 Antineoplastic Drugs</th>
<th>784</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytotoxic Antineoplastic Drugs</td>
<td>785</td>
</tr>
<tr>
<td>Hormonal Antineoplastic Drugs</td>
<td>795</td>
</tr>
<tr>
<td>Non-Cytotoxic Antineoplastic Drugs</td>
<td>798</td>
</tr>
<tr>
<td>Immunomodulatory Drugs</td>
<td>803</td>
</tr>
<tr>
<td>Adjunct Therapies</td>
<td>806</td>
</tr>
<tr>
<td>Palliative Care</td>
<td>808</td>
</tr>
</tbody>
</table>

# UNIT 13
## DRUGS AFFECTING MICROORGANISMS

<table>
<thead>
<tr>
<th>Chapter 36 Overview of Antimicrobial Chemotherapy and Antibiotic Resistance</th>
<th>813</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>814</td>
</tr>
<tr>
<td>Antimicrobial Therapy</td>
<td>815</td>
</tr>
<tr>
<td>Antibiotic Resistance</td>
<td>817</td>
</tr>
<tr>
<td>Combating Antimicrobial Drug Resistance</td>
<td>819</td>
</tr>
</tbody>
</table>
Chapter 37 Antibacterial Drugs 824
Introduction 825
Inhibitors of Bacterial Cell Wall Synthesis 825
Inhibitors of Bacterial Protein Synthesis 832
Inhibitors of DNA Synthesis 837
Miscellaneous Antibiotics 838
Urinary Tract Antimicrobials 838

Chapter 38 Antifungal and Antiviral Drugs 842
Treatment of Fungal Infections 843
Treatment of Viral Infection 846
Treatment of Herpesviruses 847
Treatment of Influenza and Viral Respiratory Infection 849
Treatment of Hepatitis B 850
Treatment of Hepatitis C 850
Treatment of Human Immunodeficiency Virus 853

Chapter 39 Antiprotazoal, Antimycobacterial and Anthelmintic Drugs 862
Protozoal Infections 863
Mycobacterial Infections 868
Helminth Infections 874

UNIT 14 DRUGS AFFECTING BODY DEFENCES 879

Chapter 40 Antiinflammatory and Immunomodulating Drugs 879
Introduction 880
Non-Steroidal Antiinflammatory Drugs 882
Disease-Modifying Antirheumatic Drugs 886
Immunosuppressant Drugs 891
Immunostimulant Drugs 896
Histamine and Histamine-Receptor Antagonists (Antihistamines) 896
Drugs Used for the Treatment of Gout 899

Chapter 41 Drugs Affecting the Skin 905
Introduction 906
Application of Drugs to the Skin 907

UNIT 15 SPECIAL TOPICS 933

Chapter 42 Drugs in Sport 933
Introduction: History of Drugs in Sport 934
Use and Abuse of Drugs in Sport 934
Drugs and Methods Banned in Sports 939
Substances Permitted in Sports 944
Drug Testing 945
Ethical Aspects of Drugs in Sport 947

Chapter 43 Pharmacotherapy of Obesity 951
Introduction 952
Health Risks Associated With Obesity 952
Pathophysiology of Obesity 953
Management of Obesity 956
The Future 958

APPENDICES
Appendix 1 Abbreviations 971
Appendix 2 Glossary 975
Appendix 3 Common Abbreviations and Symbols Used in Prescriptions 990
Appendix 4 Dose Calculation Examples 992
Figure and Picture Credits 999
Index 1001
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 fifth 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 Australian, New Zealand Māori and Pacific Islander 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 fifth edition.

As much of pharmacology is predicated on an understanding of physiology and biochemistry, the fifth 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 organizations. Many of the figures have been redrawn and new figures included to enhance understanding and interest. This edition also features:

◆ new Key Points boxes that provide a snapshot of important and relevant 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
◆ 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 and updated Clinical Interest Boxes, including descriptions of items of special interest specific to New Zealand and of typical pharmacological treatment of common diseases and conditions
◆ annotated references as a guide to the quality, readability or informative nature of new reviews on drugs and the management of major diseases, and guidelines for clinical choice and use of drugs
◆ enhanced information on the use of complementary and alternative medicine (CAM) modalities, and on interactions between drugs and CAM 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 emphasising always 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 fifth 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.

2018
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Colleagues and Editors
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**Chapter Focus**

Dyslipidaemia, or increased plasma concentrations of cholesterol and triglycerides, is clinically associated with atherosclerosis. Atherosclerosis is characterised by cholesterol deposits in the lining of arteries, which eventually produce degenerative changes and obstruct blood flow. Atherosclerosis can result in angina, heart failure, myocardial infarction, cerebral artery disease and renal artery insufficiency. It is also a factor in hypertension. The treatment guidelines for the management of dyslipidaemia include dietary and lifestyle modifications and drug treatment.

**Key Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>apo</td>
<td>apolipoprotein</td>
</tr>
<tr>
<td>CAD</td>
<td>coronary artery disease</td>
</tr>
<tr>
<td>HDL</td>
<td>high-density lipoproteins</td>
</tr>
<tr>
<td>HMG-CoA</td>
<td>3-hydroxy-3-methylglutaryl coenzyme A</td>
</tr>
<tr>
<td>IDL</td>
<td>intermediate-density lipoproteins</td>
</tr>
<tr>
<td>LDL</td>
<td>low-density lipoproteins</td>
</tr>
<tr>
<td>LPL</td>
<td>lipoprotein lipase</td>
</tr>
<tr>
<td>PCSK</td>
<td>proprotein convertase subtilisin/kexin type 9</td>
</tr>
<tr>
<td>PPAR</td>
<td>peroxisome proliferator activated receptor</td>
</tr>
<tr>
<td>VLDL</td>
<td>very-low-density lipoproteins</td>
</tr>
</tbody>
</table>

**Key Terms**
apolipoproteins
atherosclerosis
chylomicrons
dyslipidaemia
high-density lipoproteins
HMG-CoA reductase
lipoprotein lipase
lipoproteins
low-density lipoproteins
proprotein convertase subtilisin/kexin type 9
very-low-density lipoproteins

**Key Drug Groups**

- Bile acid-binding resins: **colestyramine** (cholestyramine), **colestipol**
- Fibrates: **fenofibrate**, **gemfibrozil**
- HMG-CoA reductase inhibitors (commonly known as statins): **atorvastatin** (DM 22.1), **fluvastatin**, **pravastatin**, **rosuvastatin**, **simvastatin**
- PCSK9 inhibitors: **alirocumab**, **evolocumab** (DM 22.2)
- Additional drugs: **ezetimibe**, **nicotinic acid**
INTRODUCTION: DYSLIPIDAEMIA

DYSLIPIDAEMIA is a metabolic disorder characterised by increased concentrations of lipids and lipoproteins. Lipid-lowering drugs are used along with dietary modifications and exercise to treat dyslipidaemia. Clinical and experimental studies have provided evidence of an important relationship between high levels of circulating triglycerides and cholesterol and atherosclerosis. Atherosclerosis, a disorder that involves large- and medium-sized arteries, is characterised by cholesterol deposits in the arterial wall, which eventually produce degenerative changes and obstruct blood flow.

Atherosclerosis is a causative factor in coronary artery disease (CAD), which can result in angina, heart failure and myocardial infarction (MI); cerebral arterial disease that results in senility or cerebrovascular accidents; peripheral arterial occlusive disease, which can cause gangrene and loss of limb; and renal arterial insufficiency. It is also a factor in hypertension.

Lipids do not circulate freely in the bloodstream. Instead, they are transported as complexes called lipoproteins, which are assembled from a mixture of lipids and proteins. They are generally spherical in shape and comprise an interior core, consisting of cholesteryl esters and triglycerides, which are covered by a layer of phospholipids, free cholesterol and apolipoproteins (apo), which are located near the surface. Hyperlipoproteinaemias are always associated with an increased concentration of one or more lipoproteins.

APOLIPOPROTEINS

Apolipoproteins have a variety of functions: they serve as ligands for cell receptors, activate enzymes involved in lipoprotein metabolism and provide structure for the lipoprotein. If apolipoprotein metabolism is impaired, an increased risk of atherosclerosis exists; thus, plasma concentrations of apolipoproteins are important in evaluating lipid disorders. The apolipoproteins include apoA-I, apoA-II, apoA-IV, apoA-V, apoB-100, apoB-48, apoC-I, apoC-II, apoC-III, apoE and apo(a). The latter is associated with Lp(a), a lipoprotein (structurally related to plasminogen) that promotes thrombosis. Apolipoprotein A-I is thought to confer the beneficial effect of high-density lipoproteins (HDL); HDL particles that have both A-I and A-II appear not to be as atheroprotective. In contrast, a deficiency of the C-II apolipoprotein in very-low-density lipoprotein (VLDL) particles results in impaired triglyceride metabolism and hypertriglyceridaemia.

CLASSIFICATION OF LIPOPROTEINS

Chylomicrons are the largest plasma lipoproteins and transport dietary cholesterol and triglycerides absorbed from the gastrointestinal tract (GIT) to the liver. This is known as the exogenous pathway, whereas the lipoproteins transporting cholesterol between the liver and peripheral cells are part of the endogenous pathway. Chylomicrons consist mainly of triglycerides (85–95%) and are produced in the small intestine during absorption of a fatty meal. They are cleared from the bloodstream by lipoprotein lipase (LPL) after 12–14 hours. The chylomicron that remains following the removal of the triglyceride content is cleared rapidly by the liver and is not converted into low-density lipoprotein (LDLs). The three primary lipoproteins found in the blood of fasting individuals are VLDLs, LDLs and HDLs. The intermediate-density lipoproteins (IDLs) have short half-lives (from minutes to a few hours) and their concentrations in plasma tend to be very low.

Very-low-density lipoproteins

VLDLs, which carry lipid from the liver to the peripheral cells, contain a large amount of triglyceride (50–65%) and 20–30% cholesterol, and are formed in the liver from endogenously synthesised triglycerides, cholesterol and phospholipid. These lipoproteins contain 15–20% of the total blood cholesterol and most of the triglyceride found in the body. The apolipoproteins apoB-100, apoE and apoC-I-III are synthesised in the liver and, once incorporated, result in the final assembly of VLDL. After VLDL particles are secreted from the liver into the circulation, their triglyceride content is released as a result of the action of the enzyme LPL, which is located in the endothelium of adipose, muscle and cardiac tissue capillaries. As the triglycerides are hydrolysed by LPL, the resulting free fatty acids are taken up by adjacent tissues. Drugs that enhance the action of LPL (e.g. the fibrates) will lower plasma triglyceride concentrations.

Low-density lipoproteins

When triglyceride hydrolysis is almost complete, the remnant VLDL (termed IDL) is released from the capillary endothelium and re-enters the circulation. Approximately 40–50% of the IDL is cleared from plasma by the liver via LDL receptors, which recognise the apoB-100 and apoE components of the remnants. The remainder of the IDL is converted to the cholesterol-rich lipoprotein LDL, which contains 60–70% of total blood cholesterol; its relationship with the development of atherosclerosis has resulted in its label of ‘bad’ cholesterol. LDL particles have a half-life of 1–2 days, which accounts for their high concentration in plasma in comparison to VLDL and IDL. The quantity and density of systemic LDL particles correlate with the risk of atherosclerosis, and elevated LDL levels indicate that an individual has a greater risk of developing atherosclerosis. LDL (~75%) is cleared from plasma mainly via hepatic LDL receptors, and defects in the LDL receptor gene are associated with high plasma concentrations of LDL and familial hypercholesterolaemia.
High-density lipoproteins

The function of HDL is to carry about 25% of plasma cholesterol from the periphery back to the liver, where it is processed into bile acids. As the cholesterol HDL carries is ultimately for excretion, it is known as ‘good’ cholesterol. HDLs are the smallest and most dense lipoproteins and can be separated based on density into HDL2 (larger and more cholesterol-rich) and HDL3 particles (smaller, less cholesterol-rich). Their function is to transfer cholesterol from peripheral cells to the liver, either directly or by exchanging cholesteryl esters for triglycerides from LDL and VLDL. This exchange is mediated by cholesteryl ester transfer protein and accounts for approximately 66% of the removal of cholesterol from HDL. The LDL particles are then cleared from plasma by LDL receptors principally in the liver, and the level of hepatic LDL receptors generally controls the level of circulating LDL in humans. High levels of HDL are considered beneficial and decrease the risk of coronary heart disease (CHD). This transport mechanism prevents the accumulation of cholesterol in the arterial walls, thereby providing protection against the development of atherosclerosis.

SYNTHESIS AND DEGRADATION OF LDL RECEPTORS

Plasma lipoproteins are usually in a state of dynamic equilibrium. When the liver and tissues outside the liver need cholesterol, they increase the synthesis of LDL receptors on their respective cell surfaces (Fig 22.1). These receptors are necessary for the binding of LDL, thus enabling the release of free fatty acids. When the cellular need for cholesterol is met, the synthesis of LDL receptors decreases, and this controls the plasma level of LDL. The enzyme that ‘up’ or ‘down’ regulates the LDL receptor in response to the cell cholesterol concentration is PCSK9 (proprotein convertase subtilisin/kexin type 9), which belongs to a family of proprotein convertases that help maintain homeostasis of cell surface receptors such as the LDL receptor. Simply, when PCSK9 attaches to an LDL receptor it is internalised, making the receptor susceptible to lysosomal degradation and thus decreasing the number of LDL receptors. If PCSK9 is not bound to the LDL receptor when it is internalised, it is not degraded in the lysosome and instead is recycled to the cell surface where it continues to clear LDL. (See Fig 22.3, later, on PCSK9 inhibitors.) Modulation of the number of hepatic LDL receptors is an integral part of the therapeutic approach to the management of hypercholesterolaemia. Figure 22.1 illustrates cholesterol transport in tissues and indicates the sites of action of the lipid-lowering drugs discussed in the following sections.

HYPERLIPOPROTEINAEMIAS

Dyslipidaemias can be classed as primary or secondary. The primary, or genetically determined, hyperlipoproteinaemia forms are classified into six phenotypes, depending on the lipoprotein particle elevated (Table 22.1). Phenotypes IIa and IIb carry the highest risk of atherosclerosis, while phenotypes II and IV have a moderately elevated risk. Factors such as diabetes mellitus, obesity, hypothyroidism, nephrotic syndrome, excess alcohol consumption and drug treatment (e.g. corticosteroids, thiazide diuretics) constitute the secondary causes of dyslipidaemia. In these cases, investigation of underlying disease pathology or current drug treatment is necessary before instituting lipid-lowering drug therapy.

<table>
<thead>
<tr>
<th>PHENOTYPE</th>
<th>DISORDER</th>
<th>LIPOPROTEIN ELEVATED</th>
<th>LIPIDS ELEVATED</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Familial lipoprotein lipase deficiency</td>
<td>Chylomicrons</td>
<td>Triglycerides</td>
</tr>
<tr>
<td>IIa</td>
<td>Familial hypercholesterolaemia</td>
<td>LDL</td>
<td>Cholesterol</td>
</tr>
<tr>
<td>IIb</td>
<td>Familial combined hyperlipidaemia</td>
<td>LDL + VLDL</td>
<td>Cholesterol triglycerides</td>
</tr>
<tr>
<td>III</td>
<td>Familial dysbetalipoproteinaemia</td>
<td>Chylomicron remnants + IDL</td>
<td>Triglycerides + cholesterol</td>
</tr>
<tr>
<td>IV</td>
<td>Familial hypertriglyceridaemia</td>
<td>VLDL</td>
<td>Triglycerides</td>
</tr>
<tr>
<td>V</td>
<td>Severe hypertriglyceridaemia</td>
<td>Chylomicron remnants + VLDL</td>
<td>Triglycerides&gt;cholesterol</td>
</tr>
</tbody>
</table>

KEY POINTS: Dyslipidaemia

- Dyslipidaemia is a metabolic disorder characterised by increased concentrations of plasma cholesterol and triglycerides and can be classified as primary or secondary.
- High circulating levels of cholesterol and triglycerides have been associated with atherosclerosis, a disorder in which lipids are deposited in the linings of medium- and large-sized
arteries, eventually producing degenerative changes and obstructing blood flow.

- Atherosclerosis is a causative factor in CAD, which in turn can result in angina, heart failure, MI, cerebral artery disease, peripheral artery occlusive disease and renal arterial insufficiency.

- The primary lipoproteins found in the blood of fasting individuals are VLDL, LDL (‘bad’) and HDL (‘good’).

- In non-pathological conditions, lipoproteins, cholesterol and LDL receptors are usually in a state of dynamic equilibrium.

**FIGURE 22.1**
Schematic diagram of cholesterol transport in the tissues, with sites of action of the main drugs affecting lipoprotein metabolism.

C = cholesterol; CETP = cholesteryl ester transport protein; HDL = high-density lipoprotein; HMG-CoA reductase = 3-hydroxy-3-methylglutaryl-CoA reductase; LDL = low-density lipoprotein; MVA = mevalonate; NPC1L1 = a cholesterol transporter in the brush border of enterocytes; VLDL = very-low-density lipoprotein.

Source: Adapted from Rang et al (2012), Figure 23.1; used with permission.
Atorvastatin is a second-generation synthetic drug that resembles the natural substrate HMG-CoA; hence, it is a reversible inhibitor of HMG-CoA reductase. Unlike simvastatin, atorvastatin is administered as the active hydroxy acid form.

**Indications**
Atorvastatin is indicated for the treatment of hypercholesterolaemia and mixed hyperlipidaemia.

**Pharmacokinetics**
Atorvastatin is well absorbed and maximum plasma concentrations occur within 1–2 hours. Bioavailability is low (~12%), which may be accounted for by high hepatic first-pass metabolism and presystemic (gut wall) metabolism. Two active metabolites have been detected in plasma, 2-hydroxy-atorvastatin and 4-hydroxy-atorvastatin, both of which are in equilibrium with their respective inactive lactone forms. CYP3A4 is the main enzyme responsible for formation of the two active metabolites, which are then glucuronidated by UGT1A1 and UGT1A3. The biliary route is the main route of elimination of atorvastatin and its metabolites with <2% excreted as unchanged drug in urine; hence, changes in renal function have no significant effect on the pharmacokinetics of atorvastatin. The half-life of atorvastatin is ~20 hours, which may be increased in individuals with hepatic disease.

**Drug interactions**
See Drug Interactions 22.1.

**Adverse reactions**
Common adverse reactions include:
- GIT discomfort, headaches, insomnia and dizziness
- an elevation of hepatic transaminase levels within the first few weeks of treatment (dose-related, start at lower end of the dosage range).
- development of myopathy, which can progress to rhabdomyolysis and renal failure. The latter is more likely when the statins are combined with inhibitors of CYP3A4, but an increased incidence has also been observed in combination with the fibrate class of lipid-lowering drugs and nicotinic acid.

**Dosage and administration**
The initial dose is 10 mg, increasing to a maximum of 80 mg daily. Effectiveness of the dose is determined by monitoring plasma lipids. Atorvastatin is also available in combination with amlodipine for patients stabilised on at least 5 mg of amlodipine daily and in combination with ezetimibe to increase reduction in LDL-C.

**Warnings and contraindications**
Use of atorvastatin is contraindicated in the following instances:
- where there is a condition of preexisting liver disease
- in women of childbearing age unless adequate contraceptive cover is assured (Pregnancy Safety Category D)
- in people with severe intercurrent illness (infection, trauma).

Triglycerides. The widespread use of these drugs worldwide is attributable to their proven efficacy in randomised clinical trials in reducing CAD, angina, strokes and the need for angioplasty and coronary artery bypass grafts.

In addition to beneficial effects on lipid profiles, the statins have a number of other ‘antiatherosclerotic’ or pleiotropic effects (Corsini et al, 1999). Clearly, these actions may contribute to the overall beneficial effects observed with statin therapy. These include:
- beneficial effects on endothelial function
- reduced vascular inflammatory response
- reduced platelet aggregability
- modification of thrombus formation
- stabilisation of atherosclerotic plaques
- decreased smooth muscle cell migration and proliferation
- increased fibrinolytic activity
- decrease in C-reactive protein, a marker of inflammation and coronary heart disease risk (Chan et al, 2004).

**Pharmacokinetics**
At the pharmacokinetic level the statins currently available have some important differences, which are summarised in Table 22.3. Atorvastatin, fluvastatin, pravastatin and rosuvastatin are administered as the active β-hydroxy acid form, whereas simvastatin is administered as an inactive lactone (a prodrug) that requires metabolic activation by the liver to the active hydroxy acid form. Although rosuvastatin is the most hydrophilic statin and simvastatin is more lipophilic, all statins are absorbed rapidly following oral administration, reaching peak concentrations within 5 hours. Food variably affects absorption: there is no apparent effect on the absorption of simvastatin and rosuvastatin, while bioavailability of fluvastatin, pravastatin and atorvastatin is decreased. However, the overall lipid-lowering efficacy of statins is not affected by whether the statin is taken with an evening meal or at bedtime.

All of the statins have low systemic bioavailability, indicating extensive first-pass metabolism. With the exception of pravastatin, which is metabolised by cytosolic sulfotransferases (SULT), all statins are substrates for cytochrome P450 (CYP). Fluvastatin exhibits saturable first-pass metabolism and is metabolised by CYP2C9 and, to a lesser extent, by CYP3A4; atorvastatin and simvastatin are metabolised by CYP3A4; while rosuvastatin is metabolised to a minimal extent by CYP2C9 and CYP2C19.

Interaction with various drug transporters is complex. Atorvastatin is both a substrate and an inhibitor of the efflux transporter P-glycoprotein and a substrate and an...
inhibitor of the sinusoidal uptake organic anion transporter OATP1B1. Pravastatin is a substrate of OATP1B1, OATP2B1 and OATP1B3 (all expressed on the basolateral membrane on human hepatocytes), which contributes to the efficient hepatic uptake of pravastatin. Hepatic uptake by the various transporters enhances the pharmacological effect of the statins by delivering the drugs directly to the liver as the target organ. Together, hepatic uptake and extensive first-pass metabolism minimise the ‘escape’ of the drug into the systemic circulation, hence limiting the adverse effects in muscle tissue.

The predominant route of excretion of the statins is via the faeces, with renal excretion accounting for <2% with atorvastatin, 6% with fluvastatin, 20% with pravastatin and 30% with rosuvastatin. An initial response is seen within 1–2 weeks and the maximum therapeutic response occurs within 4–6 weeks of chronic drug administration. Bile acid-binding resins can impede absorption, so statins should be administered either 1 hour before or 4 hours after administration of the resin.

Drug interactions

Potential drug interactions with the statins should always be considered, especially as these drugs are often one of multiple medications taken by people with CV disease. Interactions occur with drugs that can either inhibit or induce CYP enzymes and with other drugs that may be substrates for transporters. Fluvastatin and rosuvastatin are metabolised by CYP2C9 and pravastatin by SULT and hence they are less subject to interactions than the other statins (see DI 22.1).

Adverse drug reactions

Although these drugs are well tolerated, adverse drug reactions (ADRs) include:

- stomach cramps or pain, constipation or diarrhoea, nausea
- headache, sleep disturbances (e.g. insomnia, nightmares)
- myalgia and, rarely, myopathy, rhabdomyolysis, muscle pain or weakness. Severe tiredness or flu-like symptoms should be reported to the treating health professional.

Warnings and contraindications

These drugs are used cautiously and at the lowest dose in persons with hepatic or renal impairment because the risk of myopathy and rhabdomyolysis is related to the dose of statin administered and the plasma drug concentration. Hence, reduction in the metabolism of statins (e.g. impaired hepatic function) or the excretion of statins and their active metabolites (e.g. impaired renal function) will increase the likelihood of these adverse effects.

They are avoided in people with hypersensitivity to any HMG-CoA reductase inhibitor, organ transplant recipients receiving immunosuppressant drugs, and people with any disease state or condition that may predispose them to renal failure. They are also avoided in women planning pregnancy or with inadequate contraception.

Statins and adverse muscular effects

In general, the statins are well tolerated. However, one adverse drug reaction relates to muscle toxicity (Table 22.4). This ranges from myalgia (common) through to myopathy, myositis and rhabdomyolysis (rare). Currently, there is no consensus on the exact definition of statin-induced myopathy and the underlying mechanisms are poorly understood (Joy & Hegele, 2009). Predisposing factors include older age, female, excessive alcohol intake and concomitant administration of fibrates, ciclosporin (cyclosporin), protease inhibitors, macrolide antibiotics or amiodarone. Statin treatment should be ceased if persistent unexplained muscle pain occurs and the creatine kinase level is elevated. In the absence of any identified cause of the myopathy (e.g. hypothyroidism, neuromuscular diseases), statin therapy may be recommenced after a month if the creatine kinase level is within the normal range.

<table>
<thead>
<tr>
<th>DRUG INTERACTIONS 22.1 Atorvastatin and simvastatin</th>
<th>POSSIBLE EFFECTS AND MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DRUG</strong></td>
<td><strong>POSSIBLE EFFECTS AND MANAGEMENT</strong></td>
</tr>
<tr>
<td>Clarithromycin, diltiazem, HIV protease inhibitors, antifungal drugs (itraconazole and fluconazole)</td>
<td>Increased plasma concentration of atorvastatin and simvastatin. Increased risk of myopathy or rhabdomyolysis. Stop statin for duration of treatment or use an alternative (e.g. pravastatin). Some combinations contraindicated by manufacturer.</td>
</tr>
<tr>
<td>Grapefruit juice</td>
<td>Should be avoided if taking atorvastatin or simvastatin because grapefruit juice inhibits presystemic metabolism of both of these drugs by CYP3A4. Inhibition of presystemic metabolism leads to increased bioavailability and hence an increased plasma drug concentration and the likelihood of adverse effects – in particular, myalgia and myopathy.</td>
</tr>
<tr>
<td>St John’s wort</td>
<td>Induction of CYP3A4 activity may decrease plasma concentration of both atorvastatin and simvastatin, decreasing clinical effect. Avoid combination with St John’s wort.</td>
</tr>
</tbody>
</table>

*This is not an exhaustive list and multiple interactions with other drugs have been reported. Consult relevant drug information sources before administering atorvastatin or simvastatin.
triglycerides. It is primarily used as an adjunct to diet for the treatment of hypercholesterolaemia and homozygous phytosterolaemia.

Ezetimibe is conjugated in the intestine, forming an active glucuronide, which accounts for approximately 90% of the drug in plasma after 30 minutes. Ezetimibe and ezetimibe glucuronide are then transported to the liver and subsequently secreted in bile back into the intestine (enterohepatic recycling). The half-life of both is approximately 22 hours, and about 80% of the administered dose is excreted in faeces and about 11% in urine. As ezetimibe is not metabolised to any major extent in the liver, significant interactions with the majority of drugs used to treat dyslipidaemia are not a major issue. However, coadministration with colestyremlamine reduces bioavailability, and hence these drugs should be administered several hours apart.

Ezetimibe is administered once daily as a 10 mg dose. Commonly, ezetimibe causes headache and diarrhoea and, as with the statins, muscle disorders (e.g. myalgia, muscle cramps, weakness and pain) have been reported. Combinations of ezetimibe (10 mg) and simvastatin (10–80 mg) or atorvastatin (10–80 mg) or rosuvastatin (5–40 mg) increases the lipid-lowering effect of the statin by up to 20% and is a valuable combination for individuals who are unable to tolerate a higher dose of a statin.

Fish oils

In general, the consumption of omega-3 fatty acids by humans has decreased as a result of marked changes in dietary habits. One of the active components of fish oil is docosahexaenoic acid (DHA), which is present in oily fish such as mackerel, salmon and tuna. Consumption of a fish-rich diet is thought to account for the lower incidence of coronary heart disease in the Japanese and in Greenland Inuit. Omega-3 fatty acids are thought to exert their beneficial effects through reducing VLDL formation and accelerating VLDL metabolism to LDL particles. This ultimately reduces triglyceride levels, but also potentially increases LDL-C levels. Similar to the fibrates, omega-3 fatty acids have a high affinity for PPARs and may upregulate the metabolism of fatty acids in the liver. Current evidence indicates that, when used at the recommended dosage (4 g/day) in individuals with very high triglycerides, omega-3 fatty acids reduce triglycerides by ~45% and VLDL-C by ~50%. In Australia, Omacor® capsules contain 385 mg EPA and 320 mg DHA; one capsule daily (with food) is recommended after an MI or four capsules daily (with food) for the treatment of hypertriglyceridaemia.

Although fish oil supplements appear to be relatively safe, high doses may increase bleeding time. In 2012, the US Food and Drug Administration advised that Lovaza® used chronically at doses of 4 g/day may, in persons with preexisting atrial fibrillation/flutter, cause a recurrence of symptomatic atrial fibrillation/flutter. The patient information leaflet/warnings and precautions information were updated accordingly to reflect these new data. Fish oil may be added to a lipid-lowering drug regimen, but a daily dose needs to be calculated according to the EPA and DHA content of the individual fish oil supplements (see CIB 22.2). Current guidelines from the Heart Foundation suggest eating a healthy diet rich in fruit and vegetables and consuming ~500 mg per day of combined DHA and EPA through a combination of two or three serves (150 g serve) of oily fish per week or fish oil capsules or liquid food and drink enriched with marine omega-3 polyunsaturated fatty acids (see ‘Online resources’).

**CLINICAL INTEREST BOX 22.2 Are fish oils and omega-3 fatty acids beneficial in CV disease?**

Humans are unable to synthesise linoleic acid and alpha linolenic acid, and hence must obtain these fatty acids from dietary sources. The latter gives rise to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). A rich dietary source is fish oil, and it has long been recognised that races that consume large quantities of fish (e.g. Greenland Inuit) appear to be afforded protection against atherosclerosis. Multiple studies published prior to 2000 that included participants with or without CV disease reported that omega-3 fatty acids or supplements with omega-3 fatty acids were beneficial in reducing CV mortality. These data informed the guidelines of many learned societies (e.g. the American Heart Association, the Australian Heart Foundation), which recommended the inclusion of omega-3 fatty acids in the diet of at-risk individuals and those with documented CAD. Over the past 10 years, studies have questioned the value of supplementing with omega-3 fatty acids because no clear benefit in terms of reducing CV events has been demonstrated. Many questions remain unanswered; the optimal dose of omega-3 fatty acids, the role of combined use with a statin, and their role in preventing the development of heart failure. These answers will be forthcoming from further clinical studies.


**KEY POINTS: Lipid-lowering drugs**

- In the absence of a satisfactory reduction of high plasma lipid levels through exercise, diet and lifestyle modification, lipid-lowering drugs are used to treat dyslipidaemia.
- In Australia, the PBS criteria for subsidy of lipid-modifying drugs reflect treatment according to the risk of future CV events. Persons eligible for subsidy at any cholesterol concentration include those with
symptomatic coronary or cerebrovascular or peripheral vascular disease; or at high risk (e.g. diabetes mellitus or with a family history of symptomatic coronary heart disease); or who are Aboriginal or Torres Strait Islanders with diabetes mellitus.

- Effectiveness of lipid-lowering drugs varies depending on the specific type of dyslipidaemia.
- The main classes of lipid-lowering drugs are the HMG-CoA reductase inhibitors (‘statins’), PCSK9 inhibitors, bile acid-binding resins and fibrates.
- Statins (HMG-CoA reductase inhibitors) significantly reduce the risk of coronary heart disease, stroke and death in individuals undergoing treatment for >5 years.
- The new PCSK9 inhibitors substantially reduce LDL-C, and long-term trials are ongoing to determine their safety, efficacy and impact on CV disease outcomes.
- Colestyramine and colestipol are non-absorbable anion-exchange resins, also called bile acid sequestrants.
- The HMG-CoA reductase inhibitors and bile acid-binding resins are subject to numerous drug interactions.
- Gemfibrozil and fenofibrate are more effective in reducing VLDL that is rich in triglycerides than in lowering LDL that is high in cholesterol.
- Ezetimibe is a novel lipid-lowering drug that inhibits intestinal absorption of both cholesterol and phytosterols. It is effective in inhibiting both intestinal absorption of dietary cholesterol and reabsorption of cholesterol excreted in bile.
- Additional agents used to treat dyslipidaemia include nicotinic acid and fish oils.

<table>
<thead>
<tr>
<th>THERAPEUTIC GROUP</th>
<th>PHARMACOLOGICAL GROUP</th>
<th>KEY EXAMPLES</th>
<th>KEY PAGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid-lowering drugs</td>
<td>Statins (HMG-CoA reductase inhibitors)</td>
<td>atorvastatin</td>
<td>516</td>
</tr>
<tr>
<td></td>
<td></td>
<td>fluvastatin</td>
<td>515</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pravastatin</td>
<td>515</td>
</tr>
<tr>
<td></td>
<td></td>
<td>rosuvastatin</td>
<td>515</td>
</tr>
<tr>
<td></td>
<td></td>
<td>simvastatin</td>
<td>515</td>
</tr>
<tr>
<td>PCSK9 inhibitors</td>
<td>alirocumab</td>
<td>519</td>
<td></td>
</tr>
<tr>
<td>Bile acid-binding resins</td>
<td>colestyramine</td>
<td>519</td>
<td></td>
</tr>
<tr>
<td></td>
<td>colestipol</td>
<td>519</td>
<td></td>
</tr>
<tr>
<td>Fibrates</td>
<td>fenofibrate</td>
<td>520</td>
<td></td>
</tr>
<tr>
<td>Other drugs for dyslipidaemia</td>
<td>ezetimibe</td>
<td>522</td>
<td></td>
</tr>
<tr>
<td></td>
<td>fish oils</td>
<td>523</td>
<td></td>
</tr>
<tr>
<td></td>
<td>nicotinic acid</td>
<td>522</td>
<td></td>
</tr>
</tbody>
</table>

**Review exercises**

1. You are discussing dietary fat with your mother, who asks you to explain what happens to the cholesterol she eats (exogenous pathway) and what happens to the cholesterol her body makes (endogenous pathway). Make a list of the points you will discuss. Also include an explanation of familial dyslipidaemias and why your mother’s diet may be important.

2. Mrs R has been prescribed atorvastatin. As the prescribing healthcare professional, explain to Mrs R how atorvastatin works, and describe the beneficial effects you expect to see in her plasma.