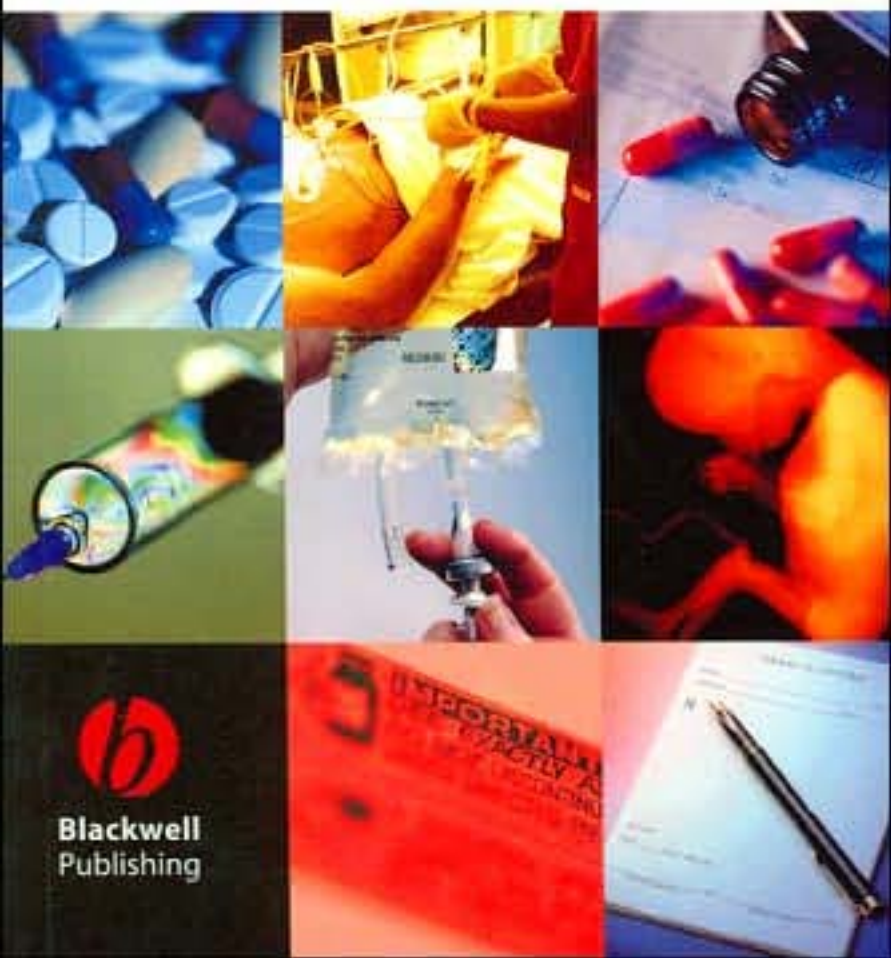
The hands-on guide to clinical pharmacology

SECOND EDITION

CHRISTOPHER TOFIELD
ALEXANDER MILSON
SUKHDEV CHATU



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Preface

The first edition of *Hands-on Guide to Clinical Pharmacology* was written whilst we were medical students at St Bartholomew's & The Royal London Hospital School of Medicine and Dentistry. At that time, we were in need of a practical yet concise set of notes to revise clinical pharmacology. What had initially been a collated set of revision notes was expanded upon, structured and turned into the first edition of this book. Some time has passed since then and, with research in pharmacology marching on, it became evident that an update was needed.

In this second edition, we have presented information on 127 drugs, which you are most likely to encounter on hospital wards or during your course of study. Sections containing both treatment regimens of common conditions and detailed information on the relevant drugs will help the reader obtain a better understanding of therapeutic management.

This book has a twofold purpose:

1 To provide a study aid for all students involved in the study of clinical pharmacology.

2 To serve as a user-friendly reference on the wards.

It has been designed as a learning tool and is not intended to provide an exhaustive account of clinical pharmacology. We have selected important interactions, adverse effects and contraindications as are relevant to students. Doses have purposely been omitted (with a few important exceptions) since these are not relevant to students and are best obtained from a local formulary. For a full list of interactions, adverse effects, contraindications and drug doses, the *British National Formulary* or other appropriate formulary should be consulted.

Whilst aiming to ensure accuracy of the text, we have at the same time attempted to maintain conciseness – a feature that is much valued by students. Those memories of impending exams with stacks of thick textbooks to read have not been forgotten!

We hope this book will help you come to grips with pharmacology in a clinical setting and, above all, take the stress out of pharmacology exams.

C. Tofield
A. Milson
S. Chatu

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Getting the first edition of *Hands-on Guide to Clinical Pharmacology* off the ground was a laborious undertaking, especially since at the time we were final year medical students at St Bartholomew's & the Royal London Hospital School of Medicine and Dentistry. We have particularly fond memories of our two pharmacology professors, who not only lent us a helping hand with the first edition of this book but also guided the medical students heroically through the weeks and days running up to pharmacology finals.

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Abbreviations

ABG	Arterial blood gas
ACE	Angiotensin-converting enzyme
ADH	Antidiuretic hormone
ADP	Adenosine diphosphate
AF	Atrial fibrillation
ALT	Alanine transaminase
AMP	Adenosine monophosphate
APTT	Activated partial thromboplastin time
5-ASA	5-aminosalicylic acid
AST	Aspartate transaminase
ATP	Adenosine triphosphate
AV	Atrioventricular
BCG	Bacillus Calmette–Guérin
BMI	Body mass index
BP	Blood pressure
BPH	Benign prostatic hyperplasia
CBT	Cognitive–behavioural therapy
CCU	Coronary care unit
cGMP	Cyclic guanosine monophosphate
CHD	Coronary heart disease
CMV	Cytomegalovirus
CNS	Central nervous system
COC	Combined oral contraceptive
COMT	Catechyl-O-methyl transferase
COPD	Chronic obstructive pulmonary disease
COX	Cyclo-oxygenase
CPR	Cardiopulmonary resuscitation
CSF	Cerebrospinal fluid
CT	Computerised tomography
CTG	Cardiotocography
CVA	Cerebrovascular accident
CXR	Chest X-ray
D.C.	direct current
DMARD	Disease-modifying antirheumatic drug
DNA	Deoxyribonucleic acid
DT	Diphtheria, tetanus
DTP	Diphtheria, tetanus, pertussis
EBV	Epstein–Barr virus
ECG	Electrocardiogram

ECT	Electroconvulsive therapy
FBC	Full blood count
FEV	Forced expiratory volume
FSH	Follicle-stimulating hormone
GA	General anaesthesia
GABA	Gamma-aminobutyric acid
GI	Gastrointestinal
GP	General Practitioner
GTN	Glyceryl trinitrate
HAART	Highly active antiretroviral therapy
Hb	Haemoglobin
HBsAg	Hepatitis B surface antigen
HDL	High-density lipoprotein
Hib	Haemophilus influenzae type b
HIV	Human immunodeficiency virus
HMG CoA	3-hydroxy 3-methylglutaryl co-enzyme A
HOCM	Hypertrophic obstructive cardiomyopathy
HRT	Hormone replacement therapy
5-HT	5-hydroxytryptamine
Ig	Immunoglobulin
IHD	Ischaemic heart disease
IM	Intramuscular
INR	International normalized ratio
ISA	Intrinsic sympathomimetic activity
ISDN	Isosorbide dinitrate
ISMN	Isosorbide mononitrate
ITU	Intensive therapy unit
IUCD	Intrauterine contraceptive device
IV	Intravenous
LABA	Long-acting beta 2 agonist
LDL	Low-density lipoprotein
LFT	Liver function test
LV	Left ventricular
LVF	Left ventricular failure
MAO	Monoamine oxidase
MAOI	Monoamine oxidase inhibitor
MI	Myocardial infarction
MMR	Measles, mumps, rubella
MRSA	Methicillin-resistant *Staphylococcus aureus*
NMDA	*N*-methyl-D-aspartate
NRTI	Nucleoside reverse transcriptase inhibitor
NSAID	Non-steroidal anti-inflammatory drug
PCA	Patient-controlled analgesia
PCI	Percutaneous coronary intervention
PDE_5	Phosphodiesterase type 5
PE	Pulmonary embolism

PEF	Peak expiratory flow
PID	Pelvic inflammatory disease
POP	Progestogen-only pill
PUVA	Psoralen with ultraviolet A
RNA	Ribonucleic acid
SA	Sinoatrial
SLE	Systemic lupus erythematosus
spp.	Species
SSRI	Selective serotonin reuptake inhibitor
SVT	Supraventricular tachycardia
TCA	Tricyclic antidepressant
TENS	Transcutaneous electrical nerve stimulation
TIBC	Total iron-binding capacity
TIVA	Total intravenous anaesthesia
tPA	tissue plasminogen activator
TSH	Thyroid-stimulating hormone
U&Es	Urea and electrolytes
UTI	Urinary tract infection
UVB	Ultraviolet B
VF	Ventricular fibrillation
VLDL	Very low–density lipoprotein
VRE	Vancomicin-resistant enterococci
VT	Ventricular tachycardia

CARDIOVASCULAR SYSTEM

Management guidelines (pp. 1–7)
Anaphylactic shock
Dysrhythmias
  Atrial fibrillation
    Paroxysmal
    Persistent
    Permanent
  Atrial flutter
  Supraventricular tachycardia
  Ventricular fibrillation
  Ventricular tachycardia
Heart failure
  Acute
  Chronic
Hyperlipidaemia
Hypertension
Ischaemic heart disease,
  Stable angina
  Unstable angina
  Myocardial infarction – ST elevation
  Post MI
Thromboembolism
  Deep vein thrombosis
  Pulmonary embolism

Drug classes (pp. 7–10)
ACE inhibitors
Beta blockers
Calcium channel blockers
Diuretics

Individual drugs (pp. 11–39)
Adenosine; Amiodarone; Amlodipine; Aspirin; Atenolol; Atropine; Bendrofluazide; Bezafibrate; Clopidogrel; Digoxin; Diltiazem; Dobutamine; Dopamine; Doxazosin; Epinephrine; Furosemide; Heparin; Losartan; Methyldopa; Nicorandil; Nitrates (GTN, ISDN, ISMN); Ramipril; Sildenafil; Simvastatin; Tenecteplase; Verapamil; Warfarin

ANAPHYLACTIC SHOCK

- Give 0.5 mg (0.5 ml of 1 : 1000) epinephrine IM (given IV if there is no central pulse or if severely unwell)
- Give high-flow oxygen through face mask
- Gain IV access
- Give 10 mg of an antihistamine IV (e.g. chlorpheniramine)
- Give 100–200 mg hydrocortisone IV

- Consider salbutamol nebuliser and IV aminophylline if bronchospasm present
- Administer IV fluids if required to maintain BP
- Repeat epinephrine IM every 5 min if no improvement, as guided by BP, pulse and respiratory function
- If still no improvement, consider intubation and mechanical ventilation
- **Follow-up**:
  - Suggest a medic alert bracelet naming culprit allergen
  - Identify allergen with skin prick testing at a later stage
  - Self-injected epinephrine may be necessary for the future

DYSRHYTHMIAS

Atrial fibrillation (AF)

- Look for and treat any underlying cause
- **Paroxysmal AF**
  - Self-terminating, usually lasts less than 48 h
  - If recurrent, consider warfarin and antiarrhythmic drugs (e.g. sotalol, amiodarone)
- **Persistent AF**
  - Lasts more than 48 h and can be converted to sinus rhythm either chemically (amiodarone, sotalol or flecainide) or with synchronised D.C. shock
  - In cases of synchronised D.C. shock, administer warfarin for 1 month, then give D.C. shock under general anaesthetic to revert to sinus rhythm (only if no structural heart lesions are present) and continue warfarin for 1 month thereafter. If haemodynamically unstable, D.C. cardiovert without warfarin.
- **Permanent AF**
  - Digoxin for rate control and warfarin for anticoagulation (give aspirin if warfarin is contraindicated or inappropriate)
  - If digoxin fails, add or use a calcium channel blocker, beta blocker or amiodarone
  - Consider pacemaker if all else fails

Atrial flutter

- Look for and treat any underlying cause
- Treat as for acute AF
- In chronic atrial flutter maintain on warfarin and antiarrhythmic medication (e.g. sotalol, amiodarone)

Supraventricular tachycardia (SVT)

- Perform vagal manoeuvres (e.g. carotid sinus massage, immersion of the face in cold water)
- If this fails, give IV adenosine or IV verapamil
- If the patient is haemodynamically compromised, give synchronised D.C. shock under sedation or under short-acting GA (e.g. propofol)

• Other antiarrhythmics that can be tried are beta blockers, verapamil and amiodarone
• In chronic paroxysmal SVT consider regular antiarrhythmics (e.g. amiodarone, disopyramide) or electrical ablation of abnormal foci

Ventricular fibrillation (VF, pulseless VT)

• Protocols for the management of VF and pulseless VT are subject to constant updates. Consult current European Resuscitation Council or other appropriate guidelines.

Ventricular tachycardia with a pulse (VT)

• Look for and treat underlying causes and correct electrolyte imbalances
• Give IV lidocaine
• If this fails, give IV amiodarone or other antiarrhythmics or perform overdrive pacing
• Proceed to synchronised D.C. shock if patient is symptomatic, in cases of circulatory collapse or if there is no response to antiarrhythmic drugs
• Once recovered, consider implantable defibrillator or electrical ablation of abnormal foci

HEART FAILURE – ACUTE

• Sit the patient up
• Give 100% oxygen through face mask (24% in COPD)
• Give IV furosemide and GTN spray or tablet
• Give IV diamorphine with IV antiemetic (e.g. metoclopramide)
• If no improvement, consider IV GTN infusion (only if systolic BP > 100 mmHg)
• In cardiogenic shock (signified by falling BP) consider positive inotropes (dopamine, dobutamine) and intra-aortic balloon pump

HEART FAILURE – CHRONIC

• Treat any underlying cause (e.g. hypertension, valvular heart disease, IHD)
• Reduce salt intake and alter modifiable risk factors (e.g. smoking, obesity)
• If still symptomatic, give a loop diuretic (e.g. furosemide, bumetanide); a thiazide diuretic can be added (e.g. bendrofluazide or metalozone)
• If still symptomatic, add an ACE inhibitor (e.g. ramipril)
• If still no improvement, consider digoxin
• Vasodilators (e.g. hydralazine), oral nitrates (e.g. ISMN) and beta blockers (metoprolol, bisoprolol, carvedilol) can also be used

• Spironolactone (a potassium-sparing diuretic) has been shown to be of benefit in chronic heart failure
• Start warfarin to prevent thromboembolic events if AF is present or if there is significant cardiomegaly
• Consider cardiac transplant or biventricular pacing as a last resort (if patient meets criteria)
• Offer influenza vaccine

HYPERLIPIDAEMIA

• Advise weight reduction and decrease alcohol consumption if applicable
• Advise low-fat diet, substitute chicken and turkey for red meat and encourage fish, vegetables and fibre
• Treat any underlying causes of hyperlipidaemia: hypothyroidism, diabetes mellitus, chronic alcohol intake, drugs (e.g. thiazide diuretics, beta blockers)
• **Hypercholesterolaemia**: treat with an HMG CoA reductase inhibitor (e.g. simvastatin) if cholesterol levels > 5.5 mmol/L; treat regardless of lipid levels if IHD present
• Bile acid resins (e.g. cholestyramine), nicotinic acid, ezetimibe and fibrates can also be used to decrease cholesterol levels
• In **hypertriglyceridaemia**, fibrates (e.g. bezafibrate) are 1st line therapy but nicotinic acid can also be used
• In **mixed hyperlipidaemia** (high cholesterol and high triglycerides), statins or a combination of fibrates and statins can be used

HYPERTENSION

• Alter modifiable risk factors (e.g. smoking, obesity, alcohol, salt intake)
• Rule out secondary causes of hypertension (e.g. renal artery stenosis, Cushing's disease, coarctation of the aorta)
• Indications for treatment vary but generally treat if:
  • Systolic BP sustained > 160 mmHg or
  • Diastolic BP sustained > 100 mmHg
• Treat if diastolic BP 90–99 mmHg or systolic BP 140–159 mmHg in the presence of end-organ damage or if other risk factors (e.g. IHD, diabetes) present
• If BP 135–139/85–89 mmHg, reassess annually
• If BP $< 135/85$ mmHg, reassess 5-yearly

The following classes of antihypertensives are used in various combinations (tailored to the individual):
1 Thiazide diuretics (e.g. bendrofluazide)
2 Beta blockers (e.g. atenolol)
3 ACE inhibitors (e.g. captopril)
4 Calcium channel blockers (e.g. nifedipine)
5 Angiotensin II receptor antagonists (e.g. losartan)
6 Alpha blockers (e.g. doxazosin)
7 Centrally acting agents (e.g. methyldopa, moxonidine)

ISCHAEMIC HEART DISEASE

Stable angina

- Alter modifiable risk factors (smoking, hypertension, hyperlipidaemia, diabetes mellitus, obesity, diet, lack of exercise)
- 1st line therapy: sublingual GTN spray/tablet or skin patch for acute attacks
- Regular aspirin (if allergic or unable to tolerate aspirin, give clopidogrel)
- Maintenance therapy: beta blocker (e.g. atenolol)
- If still symptomatic, add a calcium channel blocker or a long-acting oral nitrate (isosorbide mononitrate or isosorbide dinitrate)
- If still symptomatic, give maintenance triple therapy (beta blocker, calcium channel blocker and a long-acting nitrate) + GTN for acute attacks
- *Note*: Do not give beta blockers with verapamil due to serious interactions
- Nicorandil, a potassium channel activator with vasodilator properties, is being increasingly used in the management of angina
- Last resort is coronary angioplasty or coronary bypass surgery

Unstable angina/non–ST elevation MI/non–Q wave MI

- Grouped together as acute coronary syndromes, since management is identical until blood results (cardiac enzymes) are known. These conditions are initially controlled medically and then investigated with a view to surgery or angioplasty.
- Give 100% oxygen through face mask (24% in COPD)
- Start regular oral aspirin (antiplatelet effect)
- Give oral clopidogrel (antiplatelet activity)
- Give subcutaneous low–molecular weight heparin or IV heparin (to prevent infarction in acute attack)
- Give IV nitrates (e.g. GTN), an oral beta blocker and an oral calcium channel blocker (e.g. amlodipine)
- If still symptomatic, start glycoprotein IIb/IIIa receptor antagonist (e.g. tirofiban – antiplatelet activity); usually started if intervention is anticipated, these drugs reduce events during and after PCI
- If still symptomatic, consider emergency coronary angioplasty or coronary bypass surgery

Myocardial infarction (ST elevation)

- Sit the patient up (to ease breathing and reduce venous return to the heart)
- Give 100% oxygen through face mask (24% in COPD)
- Attach cardiac monitor and perform 12-lead ECG
- Take blood for FBC, U&Es, cardiac enzymes, lipids and random glucose

- If patient is diabetic, commence on insulin sliding scale for 24 h, then subcutaneous insulin for 3 months post MI (if not already on insulin)
- For pain relief give IV diamorphine with IV antiemetic (e.g. metoclopramide)
- Limit infarct size:
  - Give aspirin (chewed or dissolved in water); if allergic to aspirin give clopidogrel
  - Give thrombolytic therapy if not contraindicated, preferably within 12 h following MI (streptokinase or tenecteplase)
- Give IV beta blocker if not contraindicated and if haemodynamically stable (aim to maintain heart rate of 55–65 beats per minute)
- Admit to coronary care unit
- Maintain serum potassium of 4–5 mmol/L to prevent cardiac dysrhythmias

Post myocardial infarction

- Heparin infusion or low–molecular weight heparin (enoxaparin or dalteparin) may be given to maintain vessel patency (usually for 5 days)
- If pain persists, IV nitrates (e.g. GTN) and diamorphine can be given
- If ST elevation persists, consider repeat thrombolysis or emergency angiogram with PCI or bypass surgery
- Look for and treat any complications:
  - Tachydysrhythmias – antiarrhythmic drugs, D.C. shock or overdrive pacing
  - Bradydysrhythmias – IV atropine, pacing
  - LVF with pulmonary oedema – IV furosemide followed by long-term ACE inhibitor
  - Cardiogenic shock – IV dopamine and IV dobutamine
  - Ventricular septal rupture/rupture of papillary muscle – urgent surgery
- Prevention of reinfarction:
  - Alter modifiable risk factors (smoking, obesity, hyperlipidaemia, hypertension, diabetes mellitus)
  - Daily aspirin for life, and a beta blocker (e.g. atenolol) for a minimum of 2–3 years
  - Long-term ACE inhibitor (e.g. ramipril) regardless of LV function
  - Add a statin (e.g. simvastatin)
- Advise no driving for 1 month and no work for 2 months
- Usually stay in CCU for 5 days
- ECG stress test on day 5:
  - If satisfactory, follow up in clinic 4–6 weeks later
  - If positive, or if ischaemic chest pain post MI, consider coronary angiogram and appropriate intervention with surgery or PCI as in- or outpatient

THROMBOEMBOLISM

Deep vein thrombosis

- Give IV or low–molecular weight subcutaneous heparin with oral warfarin
- Discontinue heparin when INR reaches therapeutic range
- Consider thrombolytic therapy (e.g. streptokinase) in cases of large thrombi
- Continue warfarin for a minimum of 3–6 months
- Look for and treat underlying cause
- Consider thrombophilia screen if no risk factors for DVT are present

Pulmonary embolism

- Perform investigations to help confirm diagnosis (d-dimer, ABGs, ECG, CXR, V/Q scan, CT pulmonary angiogram)
- Attach cardiac monitor
- Give 100% oxygen through face mask (24% in COPD)
- Give an NSAID for pleuritic pain
- For continuing pain, consider IV diamorphine + IV antiemetic (e.g. metoclopramide)
- Give an IV heparin loading dose followed by heparin infusion or low–molecular weight heparin
- Start oral warfarin at the same time as heparin and continue warfarin for 6 months (discontinue heparin when INR reaches therapeutic range)
- Consider thrombolytic therapy (e.g. streptokinase) if patient is haemodynamically unstable
- Look for and treat any underlying cause

Drug classes

ACE INHIBITORS

- Many types of ACE inhibitors exist, all of which have similar properties. They include captopril, lisinopril, enalapril, cilazapril, perindopril, quinapril and ramipril.

Indications

- Hypertension
- Heart failure
- Post MI
- Diabetic nephropathy

Note

- ACE inhibitors are generally well tolerated and have been shown to reduce mortality and morbidity in patients with heart failure (they are thought to prevent enlargement of the left

ventricle). Dry cough is a typical adverse effect and occurs in about 20% of patients taking ACE inhibitors.
• Angiotensin II receptor antagonists, such as losartan, have similar effects but their usefulness in heart failure has not yet been established.

BETA BLOCKERS

• There are two types of beta receptors: beta 1 and beta 2
• Beta 1 receptors are found in the heart
• Most other beta receptors are beta 2 receptors and are found in the peripheral vasculature, kidneys, skeletal muscle and airways

Types of Beta blockers

1 Selective (blocking beta 1 receptors): atenolol, bisoprolol and metoprolol
2 Non-selective (blocking both beta 1 and beta 2 receptors): nadolol, propranolol and timolol
• *Note*: Selective beta 1 blockers may also block beta 2 receptors to some extent, especially in high doses
• Beta blockers can also be either water-soluble, which are excreted renally unchanged (atenolol, celiprolol, nadolol, sotalol), or lipid-soluble, which are metabolised by the liver prior to excretion (metoprolol, propranolol)
• Some act as partial agonists (i.e. have ISA properties), such as celiprolol, oxprenolol and pindolol. They can simultaneously block and stimulate beta receptors. This results in less bradycardia and less peripheral vasoconstriction than with other beta blockers.
• Labetolol and carvedilol block both alpha and beta receptors

Indications

• Hypertension
• IHD
• Cardiac dysrhythmias
• Secondary prophylaxis in MI
• Heart failure

Non-selective beta blockers can further be used in:
• Thyrotoxicosis (for symptom control)
• Prophylaxis of migraine
• Glaucoma
• Anxiety (for prevention of palpitations, tremor and tachycardia)
• Essential tremor
• Secondary prophylaxis of oesophageal varices

Effects

Beta blockers can cause the following effects:
• Beta 1 receptor blockade – decreased force of myocardial contraction and decreased heart rate

• Beta 2 receptor blockade in the kidneys – decreased renin release and hence lowered BP
• Beta 2 receptor blockade in skeletal muscle – tiredness
• Beta 2 receptor blockade in the airways – bronchospasm
• Beta 2 receptor blockade in blood vessels– peripheral vasoconstriction (i.e. cold extremities)
• Lipid-soluble beta blockers cross the blood–brain barrier and can cause sleep disturbance and nightmares (this also applies to water-soluble beta blockers, but to a lesser extent)

CALCIUM CHANNEL BLOCKERS

Types of calcium channel blockers
1 Dihydropyridines: amlodipine, felodipine, nicardipine, nifedipine, nimodipine, nisoldipine, isradipine
2 Phenylalkalamines: verapamil
3 Benzothiazepines: diltiazem

Indications

• Hypertension
• Angina
• Supraventricular dysrhythmias (verapamil or diltiazem)

Mechanism of action

• All calcium channel blockers act on L-type calcium channels at different sites:
  • Myocardium
  • The conducting system of the heart
  • Vascular smooth muscle

Dihydropyridines

• Dihydropyridines act mainly on peripheral and coronary vasculature and are therefore used to treat angina (usually combined with a beta blocker)
• Dihydropyridines can be used alone in the treatment of hypertension or can be safely combined with a beta blocker
• Dihydropyridines have very few cardiac effects

Verapamil and diltiazem

• Verapamil and diltiazem act both on the heart and on peripheral blood vessels. They decrease heart rate, force of contraction and have antiarrhythmic properties. They also cause peripheral vasodilatation and dilatation of coronary arteries.
• Verapamil and diltiazem must be used with extreme caution if given with beta blockers, due to hazardous interactions such as asystole and AV node block

DIURETICS

Types of diuretics

1 Thiazides: bendrofluazide, benzthiazide, chlorthalidone, clopamide, cyclopenthiazide, hydrochlorothiazide, hydroflumethiazide, indapamide, metalozone, xipamide
2 Loop diuretics: furosemide, bumetanide, torasemide
3 Potassium-sparing: spironolactone, amiloride, triamterene
4 Carbonic anhydrase inhibitors: acetazolamide, dorzolamide
5 Osmotic: mannitol

Indications

- Hypertension (thiazides)
- Chronic heart failure (loop diuretics, thiazides or in combination)
- Oedema (loop diuretics, thiazides or in combination)
- Glaucoma (acetazolamide, dorzolamide or mannitol)
- Raised intracranial pressure (mannitol)

Note

- Loop diuretics are the most effective diuretics, followed by thiazides.
- Potassium-sparing diuretics are weak and not normally used on their own. They are usually given with loop diuretics or thiazides to prevent hypokalaemia.
- Potassium-sparing diuretics should not normally be used with ACE inhibitors as dangerous hyperkalaemia may result.
- Loop and thiazide diuretics act synergistically and are effective in the treatment of resistant oedema.

Adenosine

Class: Antiarrhythmic agent

Indications

- Paroxysmal supraventricular dysrhythmias
- To differentiate between SVT with aberrant conduction and VT

Mechanism of action

- Adenosine acts on the SA and AV nodes by binding to adenosine receptors in the conducting tissue of the heart and by activating potassium channels. This slows conduction in the heart and causes a decrease in the heart rate.

Adverse effects

- *Common*: chest pain, bronchospasm, flushing, light-headedness, nausea (all transient, usually lasting a few seconds)
- *Rare*: severe bradycardia, transient asystole, hypotension

Contraindications

- Asthma
- 2nd or 3rd degree heart block (unless pacemaker in situ)
- Sick sinus syndrome

Interactions

- *Dipyridamole*: this enhances adenosine effects
- *Theophylline*: this inhibits the action of adenosine by blocking adenosine receptors

Route of administration

- IV

Note

- Prior to administration of adenosine the patient should be warned about the transient adverse effects such as chest pain, as they may cause great distress.
- Adenosine has a very short duration of action (about 8 seconds), therefore adverse effects are mostly short-lived.

Amiodarone

Class: Antiarrhythmic agent

Indications

- Supraventricular dysrhythmias
- Ventricular dysrhythmias (including VF and pulseless VT in cardiac arrest)

Mechanism of action

- Amiodarone prolongs the refractory period in all parts of the conducting system of the heart. This decreases the speed of impulses moving through the heart.
- Amiodarone also has some beta-blocking and some weak calcium channel–blocking properties.

Adverse effects

- *Common*: reversible corneal deposits (in long-term use), photosensitive rash
- *Rare*: hypo- or hyperthyroidism, pulmonary fibrosis, hepatitis, neurological symptoms (e.g. tremor, ataxia), peripheral neuropathy, grey skin colour, metallic taste in the mouth, myopathy

Contraindications

- Cardiac conduction defects (e.g. sick sinus syndrome)
- Thyroid disease
- Pregnancy
- Breastfeeding
- Iodine allergy (as amiodarone contains iodine)

Interactions

- *Beta blockers*: concomitant use of amiodarone and beta blockers increases the risk of AV block, bradycardia and myocardial depression
- *Digoxin*: amiodarone increases the plasma concentration of digoxin
- *Diltiazem*, *verapamil*: concomitant use of amiodarone with diltiazem or verapamil increases the risk of AV block, bradycardia and myocardial depression
- *Phenytoin*: amiodarone inhibits the metabolism of phenytoin
- *Warfarin*: amiodarone enhances the effect of warfarin by inhibiting its metabolism

Route of administration

- Oral, IV

Note

- Thyroid function and LFTs should be monitored every 6 months whilst on treatment with amiodarone.
- Pulmonary function tests should be performed prior to and during treatment with amiodarone in order to detect any developing pulmonary fibrosis.
- Patients should be advised to use sunblock to prevent photosensitivity rash.
- Amiodarone has a half-life of about 36 days and therefore interactions can occur long after the drug has been stopped.

Amlodipine

Class: Calcium channel blocker

Indications

- Hypertension
- Prophylaxis and treatment of angina

Mechanism of action

- Amlodipine inhibits the influx of calcium into vascular smooth muscle (and, to a lesser extent, into myocardium) by binding to the L-type calcium channels, especially in arterioles. This results in relaxation of vascular smooth muscle with a subsequent decrease in peripheral resistance and BP.
- Amlodipine dilates coronary arteries, which contributes to its antianginal effect.

Adverse effects

- *Common*: headache, flushing, ankle swelling, dizziness
- *Rare*: urinary frequency, GI disturbances, mood changes, palpitations, impotence

Contraindications

- Pregnancy and breastfeeding
- Cardiogenic shock
- Advanced aortic stenosis
- Unstable angina

Interactions

- *Antihypertensives*: amlodipine increases the hypotensive effect

Route of administration

- Oral

Note

- Amlodipine can be safely used in asthmatics, for whom beta blockers are contraindicated.
- For best effect in severe angina, amlodipine should be combined with a beta blocker.

Related drugs

- Other dihydropyridine calcium channel blockers: felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine, nisoldipine

Aspirin

Class: Non-steroidal anti-inflammatory drug (NSAID)

Indications

- Prophylaxis of MI, ischaemic stroke, transient ischaemic attacks
- Mild to moderate pain and inflammation
- Pyrexia

Mechanism of action

- Aspirin irreversibly inhibits the enzymes COX-1 and COX-2. This leads to the inhibition of prostaglandin synthesis and hence to:
  1 a decrease in vascular permeability and vasodilatation (anti-inflammatory effect);
  2 a decrease in sensitisation of pain afferents (analgesic effect); and
  3 a decrease in the effect of prostaglandins on the hypothalamus (antipyretic effect).
- Platelets contain a high concentration of cyclo-oxygenase 1 (COX-1), which is necessary for thromboxane A_2 production. Aspirin inhibits this process and hence inhibits thrombus formation (antiplatelet effect).

Adverse effects

- *Common*: GI irritation (gastritis, gastric ulcer, bleeding), bleeding tendency
- *Rare*: bronchospasm, rash, thrombocytopenia, renal failure

Contraindications

- Children under 16 (as aspirin may cause Reye's syndrome) except when specifically indicated (e.g. juvenile arthritis)
- Previous or active peptic ulcer
- Gout (aspirin inhibits uric acid excretion)
- Bleeding disorders (e.g. haemophilia)
- Breastfeeding
- History of hypersensitivity

Interactions

- *SSRIs*: concomitant use of aspirin and SSRIs increases the risk of bleeding
- *Warfarin*: concomitant use of aspirin and warfarin increases the risk of bleeding

Route of administration

- Oral, rectal

Note

- The risk of gastric irritation can be reduced by taking aspirin after food or by using the enteric-coated form.
- In high doses aspirin can lead to salicylate intoxication (dizziness, tinnitus, deafness).
- Aspirin is associated with Reye's syndrome in children under 16 years of age (a condition characterised by encephalitis and liver failure). Paracetamol is thus the preferred option in this age group.

Atenolol

Class: Beta blocker

Indications

- Hypertension
- Angina
- Supraventricular dysrhythmias
- Secondary prophylaxis of MI

Mechanism of action

- Atenolol reduces heart rate and force of myocardial contraction by acting on beta 1 receptors in the heart. This results in decreased workload of the heart; hence its use in angina.
- Renin production by the kidney is also reduced by atenolol, which contributes to its antihypertensive effect.
- Atenolol decreases the effects of sympathetic activity on the heart with a resulting decrease in conduction and in action potential initiation; hence its use as an antiarrythmic.

Adverse effects

- *Common*: lethargy (usually ceases after long-term use), bradycardia and AV block, hypotension, cold peripheries
- *Rare*: bronchospasm, worsened or precipitated heart failure, nightmares, impotence

Contraindications

- Asthma
- Uncontrolled heart failure (including cardiogenic shock)
- Cardiac conduction defects (e.g. 2nd and 3rd degree heart block)
- Bradycardia
- COPD
- Metabolic acidosis
- Hypotension

Interactions

- *Diltiazem*: concomitant use of diltiazem and atenolol increases the risk of bradycardia and AV block
- *Verapamil*: the risk of heart failure, severe hypotension and asystole is increased if atenolol is given with verapamil

Route of administration

- Oral, IV

Note

- Atenolol is selective for beta 1 receptors, but at high doses it can also block beta 2 receptors, thus causing bronchospasm.
- Abrupt withdrawal of atenolol may worsen angina.
- Beta blockers may mask the symptoms of hypoglycaemia caused by oral hypoglycaemics or insulin.

Related drugs

- Bisoprolol, carvedilol, celiprolol, esmolol, labetolol, metoprolol, nadolol, oxprenolol, pindolol, propranolol, sotalol, timolol

Atropine

Class: Muscarinic antagonist

Indications

- Cardiac arrest
- Bradycardia
- Organophosphorus poisoning
- For paralysis of the ciliary muscle (allowing measurement of the refractive error in children)
- Anterior uveitis
- Irritable bowel syndrome

Mechanism of action

- Atropine decreases the activity of the parasympathetic nervous system by blocking the action of acetylcholine on muscarinic receptors. This leads to pupillary dilatation, bronchodilatation, increase in heart rate and decreased secretions from sweat, salivary and bronchial glands.
- Atropine also reduces gut motility and bronchial secretions.

Adverse effects

- *Common*: antimuscarinic effects (e.g. dry mouth, blurred vision, constipation, dilated pupils)
- *Rare*: confusion (especially in the elderly), palpitations, irritation of the eye (when given as eye drops), acute urinary retention

Contraindications

- Prostatic hypertrophy
- Closed-angle glaucoma
- Paralytic ileus
- Myasthenia gravis
- Pyloric stenosis

Interactions

- *TCAs*, *MAOIs and antihistamines*: increased risk of antimuscarinic side-effects

Route of administration

- Oral (rarely used for irritable bowel syndrome), IV (bradycardia, cardiac arrest), IM (organophosphorus poisoning), eye drops

Note

- Atropine can be used to reverse the adverse effects of neostigmine (e.g. excessive bradycardia). In this case it is given IV.
- When used in anterior uveitis, aim of treatment is to prevent complications.
- Occasionally atropine is given with anaesthetics such as propofol, halothane and suxamethonium to prevent bradycardia and hypotension during general anaesthesia.
- Atropine is also used to decrease salivary and bronchial secretions that are increased during intubation prior to surgery.

Related drugs

- Hyoscine hydrobromide

Bendrofluazide

Class: Thiazide diuretic

Indications

- Hypertension
- Heart failure
- Oedema secondary to liver disease, nephrotic syndrome, low protein diet or heart failure
- Prophylaxis of calcium-containing renal stones

Mechanism of action

- Bendrofluazide acts on the proximal part of the distal tubule in the nephron where it inhibits Na^+ and Cl^- reabsorption. This leads to increased excretion of Na^+, Cl^- and water, which stimulates potassium excretion further down in the distal tubule. All these events lead to hypokalaemia, hyponatraemia and a decrease in intravascular volume.
- Reduced intravascular volume causes an initial decrease in cardiac output (hence initial antihypertensive effect), but a reduction in peripheral resistance is responsible for lowering BP in the long term.

Adverse effects

- *Common*: hypokalaemia, dehydration, postural hypotension
- *Rare*: impotence, hyperuricaemia, hyperglycaemia, hyperlipidaemia, hypercalcaemia, thrombocytopenia, hyponatraemia, photosensitivity, pancreatitis

Contraindications

- Hypokalaemia, hyponatraemia, hypercalcaemia
- Severe hepatic and renal impairment
- Gout
- Addison's disease

Interactions

- *Digoxin*: hypokalaemia caused by bendrofluazide potentiates the effects of digoxin
- *Lithium*: bendrofluazide increases the plasma concentration of lithium

Route of administration

- Oral

Note

- Low doses of bendrofluazide cause minimal biochemical disturbance and are fully effective at lowering BP. Higher doses do not decrease BP any further, but make biochemical adverse effects more likely.
- Prolonged use at high doses may lead to hypokalaemia, which may cause cardiac dysrhythmias (hence potassium levels must be monitored). If high doses are prescribed, it is recommended to combine bendrofluazide with either potassium supplements, a potassium-sparing diuretic (e.g. amiloride) or an ACE inhibitor.

Related drugs

- Chlorthalidone, cyclopenthiazide, hydrochlorothiazide, indapamide, metalozone, xipamide

Bezafibrate

Class: Fibrate

Indications

- Hyperlipidaemia

Mechanism of action

- Bezafibrate reduces triglyceride levels by stimulating the enzyme lipoprotein lipase, which converts triglycerides into fatty acids and glycerol.
- Bezafibrate also reduces cholesterol levels (to a lesser extent than triglycerides) by reducing cholesterol production in the liver. It decreases circulating LDL levels and also increases the levels of beneficial HDL.

Adverse effects

- *Common*: nausea, abdominal discomfort, headache
- *Rare*: myositis syndrome (muscle pain, stiffness, weakness), impotence, rash, pruritus, gallstones

Contraindications

- Hepatic impairment
- Pregnancy and breastfeeding
- Nephrotic syndrome
- Gallbladder disease
- Primary biliary cirrhosis

Interactions

- *HMG CoA reductase inhibitors*: concomitant use of bezafibrate and HMG CoA reductase inhibitors increases the risk of myositis syndrome
- *Warfarin*: bezafibrate potentiates the anticoagulant effect of warfarin by displacing it from plasma protein binding sites

Route of administration

- Oral

Note

- Drug treatment of hyperlipidaemia is recommended when patients fail to respond to dietary measures.
- It has been shown that fibrates are less effective than statins in the prevention of cardiovascular events (e.g. MI).

Related drugs

- Ciprofibrate, fenofibrate, gemfibrozil

Clopidogrel

Class: Antiplatelet drug

Indications

- Prevention of vascular events after ischaemic stroke, after MI and in peripheral vascular disease
- Acute coronary syndromes

Mechanism of action

- Clopidogrel irreversibly modifies ADP receptors on platelets and thus prevents ADP from binding to them. This prevents activation of glycoprotein GpIIB/IIIa complex and therefore prevents platelet aggregation.
- Platelets exposed to clopidogrel are affected for the rest of their lifespan, which is 8–10 days.

Adverse effects

- *Rare*: bleeding (GI tract, intracranial), abdominal pain, diarrhoea, peptic ulcers, neutropenia, thrombotic thrombocytopenic purpura, hepatic impairment

Contraindications

- Active bleeding
- Breastfeeding

Interactions

- *Anticoagulants/other antiplatelet drugs*: these increase the risk of bleeding
- *NSAIDs*: these increase the risk of bleeding

Route of administration

- Oral

Note

- Clopidogrel is used when aspirin is contraindicated or not tolerated.
- Clopidogrel can be added to aspirin in the treatment of acute coronary syndromes for a more effective antiplatelet effect.

Related drugs

- Other antiplatelet drugs: abciximab, aspirin, dipyridamole, eptifibatide, tirofiban

Digoxin

Class: Cardiac glycoside

Indications

- Supraventricular dysrhythmias
- Heart failure

Mechanism of action

- The primary action of digoxin on the heart is to inhibit the Na^+/K^+ ATP pump. This increases intracellular Na^+ concentration, which in turn inhibits the Na^+/Ca^{2+} exchanger and hence the amount of calcium pumped out of the cell. These events lead to increased intracellular calcium in myocardial cells, which increases the force of myocardial contraction.
- Digoxin slows the heart rate by increasing vagal activity. It also slows conduction through the AV node (hence its use in dysrhythmias).

Adverse effects

- *Common*: nausea, vomiting, anorexia, diarrhoea, digoxin toxicity in overdose (e.g. cardiac dysrhythmias)
- *Rare*: gynaecomastia in chronic use, confusion, hallucinations, yellow vision

Contraindications

- 2nd degree heart block
- Hypertrophic obstructive cardiomyopathy
- Wolff–Parkinson–White syndrome

Interactions

- *Amiodarone*, *propafenone*, *quinidine*: these antiarrhythmic drugs increase the risk of digoxin toxicity
- *Diltiazem*, *nicardipine*, *verapamil*: these increase the risk of digoxin toxicity

Route of administration

- Oral, IV (for emergency loading dose)

Note

- In heart failure, digoxin does not reduce mortality but improves symptoms and reduces the frequency of hospital admissions at the expense of possible digoxin toxicity.
- Digoxin has a narrow therapeutic window and therefore requires therapeutic drug monitoring.
- The risk of digoxin toxicity is greater in hypokalaemia. Patients receiving digoxin and potassium-losing diuretics may therefore require potassium supplements or a potassium-sparing diuretic.
- Hypomagnesaemia, hypercalcaemia and hypothyroidism also increase the risk of digoxin toxicity.

Related drugs

- Digitoxin

Diltiazem

Class: Calcium channel blocker

Indications

- Prophylaxis and treatment of angina
- Hypertension

Mechanism of action

- Diltiazem inhibits the influx of calcium into vascular smooth muscle and myocardium by binding to the L-type calcium channels. This results in:
  1 relaxation of vascular smooth muscle with subsequent decrease in peripheral resistance and BP;
  2 decreased myocardial contractility; and
  3 slowed conduction at the AV node and prolonged refractory period (hence its use as an antiarrhythmic).
- Reduction in afterload, myocardial contractility and heart rate lead to reduced oxygen consumption, thereby relieving angina.

Adverse effects

- *Common*: headache, nausea, dizziness, hypotension, bradycardia, ankle swelling
- *Rare*: lethargy, rash, AV block

Contraindications

- Severe bradycardia
- 2nd and 3rd degree heart block
- Sick sinus syndrome
- Heart failure
- Pregnancy and breastfeeding

Interactions

- *Antiarrhythmics*: diltiazem may potentiate the myocardial depression caused by other antiarrhythmic drugs
- *Beta blockers*: these increase the risk of AV block and bradycardia if given with diltiazem
- *Digoxin*: diltiazem increases the plasma concentration of digoxin
- *Theophylline*: diltiazem enhances the effects of theophylline

Route of administration

- Oral

Note

- Diltiazem can be used in patients with coronary artery spasm (Prinzmetal's angina).
- Diltiazem has the fewest adverse effects of all calcium channel blockers.
- It has a short half-life due to extensive first-pass metabolism.

Related drugs

- Verapamil