How to best utilise self-directed, adult learning

If you need extra help with terminology you may like to refer to the Glossary of terms that is accessible within your Learning Management System (LMS) course access. This is located at: http://online.endeavour.edu.au. The Glossary of terms is located in the Study Skills section for which you can enrol yourself. Look for the link called “Prefix, Root, Suffix” to start creating your own glossary.

References to Units, chapters and sections of the set text in this document may apply to:


Topic references are given so that you can find the same information in Bryant B. & Knights K. 2007. Pharmacology for health professionals 2nd ed., Mosby, Sydney or the older edition, by using the Contents or Index.

See your textbook for how to login to http://evolve.elsevier.com/AU/Bryant/pharmacology

- An additional recommended (available from the library) resource that presents information in a simple concise manner is Aldred, E.M. 2009. Pharmacology: A handbook for complementary healthcare professionals, Elsevier, Edinburgh

Students may also need to refer to:

- Or
- Kumar, P. and Clark, M. 2013, Clinical medicine 8th ed, Saunders, Edinburgh

Texts on Anatomy and Physiology and Pathophysiology of similar depth would substitute.

How to best utilise tutorial resources, activities in the Reading Guide and online

The power of adult learning is that you will each find your own study pattern, and will use all of the available resources, and more from other online sources, to support this unique pattern. Some people leave certain activities until the exam study period. More effective learners though choose one activity that works in with their learning channels, and these students do this task each week, towards their allocated study time for Pharmacology. For example, if you’re an audio learner, you would read the relevant sections of the text out loud to yourself each week.

One particularly useful study pattern in Pharmacology is the compilation of a drug diary. At about Sessions 5 your Online Academic / Lecturer will introduce you to the drug diary approach, which is also summarised in this Reading Guide. This study approach is used as the basis of the second assignment. Students have found their Drug Diary to be a useful resource in clinic, when clients are taking western pharmaceutical therapy.
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Online break Week is included with the study week. Oncampus break Week differs Semester 1 and Semester due to a moving feast (Easter) but is usually Week 8.
SESSION 1: Introduction to Pharmacology

Session Aims:
This session will provide opportunities for students to:

- Address Learning Outcome(s) 1
- Become familiar with the Learning Outcomes and Assessment Tasks given in the Subject Outline, SO and to be inspired by the place of pharmaceutical therapy in the hierarchy of healing and evidence-related medicine

Session Topics

- Pharmacology
  - Pharmacotherapy
  - Drug Nomenclature
- Drug Therapies and Complementary Medicines (CM)
  - Over-the-counter, OTC, medications
- Legal and ethical considerations
  - Scheduling
- Introduction to Pharmacodynamics and Pharmacokinetics

Read the BIOP211 SO and pay particular attention to the Learning Outcomes, Set Texts and Assessment Tasks for Pharmacology. Make certain that you understand what is expected of you to complete this subject successfully. Once you have located and read the Subject Outline, SO, post any questions you may have to the Loop or ask your lecturer.

Textbook Location
Or

Research Pharmacotherapy: Clinical Use of Drugs by viewing
2. Also use the Pharmacology libguides to locate the TED talk by Dr Ben Goldacre (2012).

Summary

Introduction to Pharmacology
Pharmacology is the ‘study of drugs (legal and illegal, OTC and prescription medications, natural and synthetic chemicals, herbal preparations) including their actions and effects (both beneficial and potentially toxic) in living systems/tissues.

Pharmacology terminology
If you do find that you need extra help with the terminology, you can find a glossary at the following website http://www2.courses.vcu.edu/ptxed/phtx609/phtx441/glossary.htm

Start compiling your own glossary of terms; and add to it over each session using the Study Skills “prefix, root, suffix” software.

Drug Nomenclature
There are 3 types of drug names:
- Chemical
- Generic/non-proprietary
- Proprietary (brand or trade)

See Unit “Introduction to Pharmacology”, Read the section on Sources of Drugs up to the Section on
- Natural Products
  And the section on Drug Names and Classifications up to the section on
Other drug information sources: the Internet

**Therapeutic Classes**
Drugs are classified in therapeutic classes and sub-classes depending on their main indications and body system in which they act

- e.g. Alimentary System
  - hyperacidity, reflux and ulcers
  - antispasmodics
  - laxatives
  - antidiarrhoeals
  - digestive supplements and cholelitholytics
  - topical anorectal medications

**Over the Counter Medications (OTC)**
OTCs are bought by the public to treat minor illnesses and accounts for approximately 60% of all purchased medications. They are indicated for generally mild or self-limiting conditions and are considered safe and effective for self-treatment with a low incidence of severe adverse effects (or responses, ADR) and low potential for harm, if directions are followed correctly. You will later address lifespan issues that might impact on adverse drug events where correct dosing was not followed.

See Unit “Introduction to Pharmacology”, Chapter on “Over the Counter Drugs and Complementary Therapies” Sections on OTC Drugs, Benefits of OTC availability, Safety & Efficacy, Unscheduled drugs, Schedule 2 and 3 drugs, The Range of OTC drugs, Use of OTC drugs

**Complementary Medicines**
You will study these in more detail in your modalities. It is important to conceptualise that the principles of evidence-based medicine, safety, access, pharmacodynamics and pharmacokinetics apply to complementary medicines as well as western pharmaceuticals.

In the Unit “Introduction to Pharmacology”, Chapter on “Over the Counter Drugs and Complementary Therapies”, read the Sections from Complementary and Alternative Therapies up to Regulation of CAM

**Legal and Ethical Considerations**
In Australia, drugs are controlled by Commonwealth, State and Territory laws. The Therapeutic Goods Administration (TGA) is responsible for the registration of drugs for which therapeutic claims have been made on the basis of quality, efficacy and safety.

See Unit “Introduction to Pharmacology”, Chapter on “Legal and Ethical Foundations of Pharmacotherapy”

- Sections on Legal Aspects of Drug Use from International drug controls up to Sections on Medicines in pregnancy

**Schedules**
All medicines are inherently toxic and can cause harm and the degree of toxicity determines the schedule under which a drug is classified.

<table>
<thead>
<tr>
<th>S1</th>
<th>Unscheduled</th>
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<tbody>
<tr>
<td>S2</td>
<td>PHARMACY MEDICINE</td>
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<tr>
<td>S3</td>
<td>PHARMACIST ONLY MEDICINE</td>
</tr>
<tr>
<td>S4</td>
<td>PRESCRIPTION ONLY MEDICINE</td>
</tr>
<tr>
<td>S5</td>
<td>CAUTION readily available but require caution in handling, storage and use</td>
</tr>
<tr>
<td>S6</td>
<td>POISON, available but more hazardous/poisonous than S5</td>
</tr>
<tr>
<td>S7</td>
<td>DANGEROUS POISON, special precautions or individual regulations</td>
</tr>
<tr>
<td>S8</td>
<td>CONTROLLED DRUG, legitimate therapeutic uses but have addictive or abuse potential</td>
</tr>
<tr>
<td>S9</td>
<td>PROHIBITED SUBSTANCES, drugs of abuse, prohibited by law except for approved research purposes by the Governor</td>
</tr>
</tbody>
</table>
Pharmacotherapy
Pharmacotherapy is ‘The use of drugs in people for treating or preventing disease.’
Includes such factors as:
- drug characteristics and appropriateness of use in a given disease
- individual patient response
- compliance
- drug interactions
- concomitant disease states and therapies
- polypharmacy
- placebo response

Phases affecting drug activity
There are 3 key phases that affect drug activity
- Pharmaceutical phase
  - dissolution of the drug
- Pharmacodynamic phase
  - ‘what the drug does to the body’
- Pharmacokinetic phase
  - ‘what the body does to the drug’

Receptor agonists and antagonists
Agonists bind to and active receptors to produce the same response as the endogenous ligand. You studied many of these endogenous ligands in Anatomy and Physiology and you will review this material. Antagonists bind to and block access to the endogenous ligand diminishing the normal response.

Pharmacokinetics
‘The study of the kinetics of a drug during the process of absorption, distribution, metabolism and excretion.’

Pre / Post Session readings
The reading material to which the students are directed, can be used either as pre-reading or post-reading dependant on the students’ individual study requirements
- Bryant & Knights (2011; 2015)
  Research: Pharmacodynamics, Pharmacokinetics, Regulation of Drugs in Australia and NZ, Scheduling of pharmaceuticals, OTC and CM, Stages of Clinical Trials, SUSMP across States and Territories of Australia, Trans-Tasmanian Harmonisation

Add terms to your glossary

See Unit “Introduction to Pharmacology” Chapter on “Legal and Ethical Foundations of Pharmacotherapy”, Sections on Drug Development
- Sections on the Pharmaceutical industry up to Phase IV: Post-marketing Studies and Drug development in Australia

See Unit “Introduction to Pharmacology” Chapter on “Pharmacotherapy: Clinical Use of Drugs” Read from Section on Quality Use of Medicines
- Sections on Factors modifying responses to drugs, Pharmacokinetic factors, Pharmacodynamic factors and Individual and clinical factors

Read Unit 2 “Principles of Pharmacology” Chapter on “Molecular Aspects of Drug Action and Pharmacodynamics” Section on Drug Specificity, Selectivity and Affinity

See Unit 2 “Principles of Pharmacology” Chapter “Drug Absorption, Distribution, Metabolism and Excretion”
- Sections on “Drug Absorption, Distribution, Metabolism and Excretion” Chapter introduction and figures on inter-relationship between the above processes and the processes of disintegration and dissolution.
Revision Questions / Activities

Complete following:
1. Define pharmacokinetics and pharmacodynamics.
2. What schedule are prescription-only drugs?
3. What are the 3 key phases affecting drug activity and give a brief explanation of each?
4. How do pharmaceutical companies hasten and slow down the dissolution of a drug and what are the advantages speeding up the process?
5. Explain regulations governing over-the-counter medicines (OTC), prescription-only drugs and complementary medicines; and outline scheduling of these medicines.
6. Discuss the role of evidence-based medicine in the pre-clinical, clinical and post-marketing surveillance of OTC (over-the-counter) medicines, CM (complementary medicines) and pharmaceutical medicines.

Answer the following:
- From Bryant & Knights (2011; 2015)
  o Review Questions: “Drugs and Medicines” questions on generic and trade names, common pharmacological terms. “Pharmacotherapy: Clinical Use of Drugs” questions on compliance, polypharmacy and placebo. “Over-the-Counter Drugs and Complementary Therapies” questions on OTC, and prevalence and rationales for use of CM

- From subject website, Tutorial Activities re discussion of pharmacotherapy
  o Students revise Session 1 and practice use of MIMSONline and Medicines Complete (available through the Endeavour Library website LibGuides)
SESSION 2: Pharmacodynamics and Pharmacokinetics (Routes of Administration and Drug Absorption)

Session Aims:
This session will provide opportunities for students to:
- Address Learning Outcomes 1, 4
- Become familiar with the Learning Outcomes and Assessment Tasks for Pharmacodynamics and Pharmacokinetics and to be inspired by electronic resources covering Pharmacodynamics and Pharmacokinetics concepts

Session Topics
- Pharmacodynamics
- Pharmacokinetics
- Pharmacokinetics and Routes of Administration
  - Absorption

Tutorial topics:

Textbook Location

Chapter 5 “Molecular Aspects of Drug Action and Pharmacodynamics”
Chapter 6 “Drug Absorption, Distribution, Metabolism and Excretion”

Summary Pharmacodynamics and Pharmacokinetics (Routes of Administration & Absorption)

Pharmacodynamics
‘Study of the interaction between a drug and its molecular target and of the pharmacological response.’

Drugs do not confer any new functions; they modify existing physiological, biochemical or biophysical functions. With the exception of drugs that act on DNA, all Drugs act by binding to 4 main types of proteins (molecular target):
- carriers
- enzymes
- ion channels
- receptors
  - ligand-gated ion channels
  - G-protein-coupled receptors and 2nd messengers
  - kinase-linked receptors
  - nuclear receptors

📖 See Unit 2 “Principles of Pharmacology”
- Sections on Molecular Targets For Drug Action up to Receptor desensitization and turnover
Pharmacokinetics

'The study of the kinetics of a drug during the process of absorption, distribution, metabolism and excretion.'

- Absorption
  - Process by which unchanged drug proceeds from the site of administration into the blood.
  - 4 methods of absorption – absorption across biological membranes; membrane openings or pores; passive transport; active or carrier transport. Review this material on membrane structures [[in an Anatomy and Physiology textbook e.g. Tortora and Derrickson (2014)

Bioavailability is ‘the fraction of unchanged drug reaching the systemic circulation following administration by any route’ and will be less than 100% due to such factors as incomplete absorption, metabolism by the gut and liver biotransformation. This is affected by the extent of absorption and 1st pass metabolism.

See Unit 2 “Principles of Pharmacology”
- Sections on "Drug Absorption", “Key Pharmacokinetic Concept – Drug Bioavailability”, “Key Pharmacokinetic Concept – Hepatic First-Pass Effect”

Routes of administration

Route of drug administration can affect both the rate at which onset of action occurs and the extent of the response. The major categories are:

- parenteral –subcutaneous, intramuscular, intravenous, Intrathecal, epidermal
- inhalation
- topical
- oral

See Unit “Principles of Pharmacology”
- Section on “Routes of Drug Administration” up to Topical Route

- Summarize the actions of carriers, enzymes, ion channels and receptors.
- Summarize the routes of administration of drugs, advantages and disadvantages

The reading material to which the students are directed, can be used either as pre-reading or post-reading dependant on the students’ individual study requirements

Additional Reading (If you find other educationally-useful videos post them to the Loop)

- Add some of these terms to your growing glossary, and define the terms.
  - Interactive Clinical Pharmacology, 2009, Hitlab NZ, Christchurch Hospital and University of Otago Christchurch, New Zealand. See http://endeavour.llbguides.com and choose ‘Subject Guides: Pharmacology’
  - http://www2.courses.vcu.edu/ptxed/phtx609/phtx441/glossary.htm

- Here is a link to review the types of proteins targets that drug molecules use: Bioinformatics Research Group, 2011 Drug targets, Advanced Computing Research Laboratory, Institute of Computing Technology, Chinese Academy of Sciences
  - www.bioinfo.org.cn/flash_shows/flash_bioinfo/cgnmc07.swf (Just slide 7; not the other material on the human genome project)

And here is another, with some interactive animations:

University of Nottingham, 2008, Targets for drug action, RLO-CETL
- http://www.nottingham.ac.uk/nmp/sonet/rlos/bioproc/drug-targets/nctl79_drug_action.swf
Shows how a G-protein coupled receptor works. The example chosen is the adrenoreceptor for adrenaline (adrenaline = epinephrine, symbol A in the DNAtube, n.d., Action of epinephrine, DNAtube Scientific Videos Site and Convert Videos, http://www.dnatube.com/video/2952/action-of-epinephrine (Please note in your glossary that epinephrine is called adrenaline in Australia)

- Pharmacognosy video by Navindra Seeram, a natural products researcher from Rhode Island University
  Seeram, N. 2010, Navindra Seeram: Natural products researcher, University of Rhode Island http://www.youtube.com/watch?v=y1Vvm_Hw4ao&feature=related

- Shows good graphics for ion channels excitatory post-synaptic potentials, (EPSP)or inhibitory (IPSP) and how they are linked to conduction or inhibition of an action potential:

- Shows how a G-protein coupled receptors works:

- Drug Binding (simplified protein binding for drug action (also shows Na+/K+ excitability)):


- Video on Routes of Administration: the future. This shows crossing the skin barrier:
  herdasw, 2006, Drug delivery - The skin's the thing!, http://www.youtube.com/watch?v=-IL9ePKUGpY&feature=related &
  MicroNanophysics Research Laboratory Monash, 2006, Pulmonary drug delivery systems under development at MNRL, Monash, MNRL Monash University and Nanovic, http://www.youtube.com/watch?v=yU8jJ0HPhys&feature=related (no sound, graphics only, promotional)

Revision Questions / Activities
1. What are the four (4) main categories of the routes of administration and outline the advantages and disadvantages of each
2. Why is drug bioavailability less than 100% after oral administration and by which route(s) is it 100%?
3. Describe four (4) methods of absorption of drugs
4. Drug specificity is a theoretical ideal but drug selectivity is what is observed endogenously. Discuss the terms specificity and selectivity, using an example of an endogenous receptor system.
5. Explain these terms: (i) agonist, antagonist; (ii) affinity, potency,(iii) bioequivalent, bioavailability.

Answer the following:

From subject website,
Case Study (Elderly)
Activities on factors that can affect drug dosing regimes including
- Individual and lifespan aspects of drug therapy
- Drug use during pregnancy and lactation
- Pharmacokinetic aspects of drug use in children and the elderly

Activities supported by information sheets
SESSION 3: Pharmacokinetics and drug distribution, metabolism and excretion

Session Aims:
This session will provide opportunities for students to:
- Address Learning Outcomes 1, 4
- Become familiar with Learning Outcomes and Assessment Tasks for this Subject of Study and to become inspired by electronic resources covering Pharmacokinetics and Pharmacodynamics concepts

Session Topics

- Pharmacodynamics
- Pharmacokinetics
- Pharmacokinetics and Routes of Administration, absorption reviewed
  - Distribution
  - Metabolism
  - Excretion
  - Dosing Regimens
- Pharmacogenomics

Tutorial Topics and Study Strategies Discussion

Session 3 and 4 Study Strategies: subscribed database called Cochrane Database, available from the library website www.library.endeavour.edu.au

Textbook Location of Readings

Chapter 6 Drug Absorption, Distribution, Metabolism and Excretion

Summary Pharmacokinetics
Pharmacokinetics
‘The study of the kinetics of a drug during the process of absorption, distribution, metabolism and excretion.’
- Absorption
  - Process by which unchanged drug proceeds from the site of administration into the blood.
  - 4 methods of absorption – absorption across biological membranes; membrane openings or pores; passive transport; active or carrier transport
- Distribution
- Metabolism
- Elimination

See Unit “Principles of Pharmacology”
- Sections on “Drug Absorption, Distribution, Metabolism and Excretion” Chapter introduction and figures

Bioavailability is ‘the fraction of unchanged drug reaching the systemic circulation following administration by any route’ and will be less than 100% due to such factors as incomplete absorption, metabolism by the gut and liver biotransformation.
This is affected by the extent of absorption and 1\textsuperscript{st} pass metabolism.

See Unit “Principles of Pharmacology”
- Sections on “Drug Absorption”, “Key Pharmacokinetic Concept – Drug Bioavailability”, “Key Pharmacokinetic Concept – Hepatic First-Pass Effect”

**Routes of administration**

Route of drug administration can affect both the rate at which onset of action occurs and the extent of the response. The major categories are:
- parenteral – subcutaneous, intramuscular, intravenous, Intrathecal, epidermal
- inhalation
- topical
- oral

See Unit “Principles of Pharmacology”
- Section on “Routes of Drug Administration” up to Topical Route

**Distribution**

Once a drug has been absorbed into the systemic circulation, it is distributed to various target sites. Factors affecting distribution are:
- Plasma protein binding
- Tissue binding
- Blood brain barrier
- placental barrier
- Blood supply
- Capillary permeability
- Cardiovascular function

See Unit “Principles of Pharmacology”
- Sections on “Drug Distribution” up to Barriers to drug distribution

**Metabolism**

Most metabolism processes are carried out by enzymes and occurs in 2 phases which overlap. Some Pharmacology texts prefer to refer to them by their names only, as there is so much overlap.
- Phase I or preferably Functionalisation Reactions (oxidation / reduction and / or hydrolysis)
  - mostly due to cytochrome P450 (CYP) isoforms
  - sometimes the metabolites are more active than the pro-drug with longer half lives; sometimes the metabolites are toxic
- Phase II or preferably Conjugation Reactions (endogenous cofactor UDP-glucuronate, sulphate, acetyl CoA or glutathione)
  - involves the coupling of a drug /metabolite with an endogenous substrate to be excreted
- 1\textsuperscript{st} Pass Metabolism
  - refers to how much drug is left to enter systemic circulation after it has undergone liver biotransformation
  - higher 1\textsuperscript{st} pass metabolism → higher oral doses needed

See Unit “Principles of Pharmacology”
- Section on “Drug Metabolism”  up to Interindividual variability in drug metabolism including Hormonal factors

**Excretion**

Drugs continue to exert a pharmacological/toxic effect until it is eliminated.

**Route of excretion:**
- kidneys
- hepatic
- expired air
- sweat and saliva
- breast milk

See Unit “Principles of Pharmacology”
- Section on “Excretion of Drugs and Drug Metabolites” up to Key Points
Dosing Regimens
From a dosing point of view, the most important pharmacokinetic parameters are:
- therapeutic range
- steady state
- clearance (ability of an individual organ to or the whole body to eliminate a drug), needed to calculate maintenance dose rate = clearance X target steady-state plasma drug concentration
- volume of distribution, needed to calculate loading dose = volume of distribution X desired plasma concentration
- half life elimination (major indicator of the duration of action of a drug)
  - amount of time needed for the concentration of the drug in plasma to halve
  - the pharmacokinetic parameters used to calculate t½ are clearance and volume of distribution

Dosing issues: elderly, neonates and children, pregnancy, lactation.

Pharmacogenomics
Branch of pharmacology which deals with the influence of genetic variation on drug action and elimination.

Additional Reading

(If you find other educationally-useful videos add them to the Loop)

Add some of these terms to your growing glossary, and define the terms.
- Interactive Clinical Pharmacology, 2009, Interactive clinical pharmacology, Hitlab NZ, Christchurch Hospital and University of Otago Christchurch, New Zealand. See http://endeavour.libguides.com and choose ‘Subject Guides: Pharmacology’
- http://www2.courses.vcu.edu/ptxed/phtx609/phtx441/glossary.htm
- Chronic diseases such as cancer & individualized treatments using pharmacogenomics, 44 minutes: Ikediobi, O.N., 2009, Chronic disease management – cancer and pharmacogenomics, http://www.youtube.com/watch?v=KToH-lyxOqy&feature=related University of California San Francisco, School of Pharmacy, Osher Centre for Lifelong Learning and UCTV

Revision Questions / Activities
1. Define biotransformation. Briefly describe the enzyme systems involved in biotransformation of drugs and other exogenous substances.
2. Name the 2 phases in metabolism and outline what happen in each phase.
3. Differentiate between induction and inhibition with regards to enzyme pathways
4. If a drug has a high 1st pass metabolism, is a higher or lower dose required? Explain by discussing the physiological pathways that lead to a high first pass metabolism of a drug / herb.
5. How many half-lives does it take for a drug with a $\frac{1}{2}$ life of 5 hours and an initial concentration of 24 mg to reach less than 1 mg?

Answer the following:

  - Review questions from the Chapter “Molecular Aspects of Drug Action and Pharmacodynamics” See Session 2 for suggested questions to research and summarize.
  - Review questions from the Chapter “Drug Absorption, Distribution, Metabolism & Excretion” including questions on variability in absorption, drug transporters, bioequivalent and biosimilar

From subject website, Case Study (Elderly)

Activities on factors that can affect drug dosing regimes including

- Individual and lifespan aspects of drug therapy
- Drug use during pregnancy and lactation
- Pharmacokinetic aspects of drug use in children and the elderly

Activities supported by information sheets
SESSION 4: Principles and Mechanisms of Toxicology

Session Aims:
This session will provide opportunities for students to:
- Address Learning Outcome 6
- Become familiar with the Learning Outcomes and Assessment Tasks for this Subject of Study and to become inspired by electronic resources on Risk Characterisation involving western pharmaceuticals

Session Topics (assessed in the Assignment 1 Toxicology)
- Scope of Toxicology
- General Principles of Toxicology
- Mechanisms of Toxicology
- Dose-Response Curves including hormesis
- Absorption, distribution and excretion of toxins
- Biotransformation of xenobiotics
- Toxicokinetics

Tutorial Topics and Study Strategy Discussion

Tutorial Topics – (assessed in the Final Exam) Endogenous ligands, neuromodulators, Risk Characterisation by the TGA / Medsafe for New Drug Developments
- Vasodilation and NO, nitric oxide: Overview of the Haemopoietic System, Serotonin (Key Background Reading: Unit 7 Drugs Affecting the Blood, Chapter on “Drugs Affecting Thrombosis and Haemostasis” Section on Key Background);
- Unit 15 “Drugs Affecting Body Defences”, Read Sections Key Background, Resistance to Disease and Natural and Acquired Immunity to review Interleukin-1, IL-1, Interleukin-2, tumour necrosis factor-alpha, TNF-α, Prostaglandins and other mediators of inflammation and cytokines in immune responses.)
- Review of Noradrenaline (NA), adrenaline (A), dopamine (DA), serotonin (5-hydroxytryptamine, 5-HT) and acetylcholine (ACh), prostaglandins (PG) as endogenous ligands and the range of other neuromodulators and neurotransmitters

Textbook and Readings: Location
- Also, from Bryant & Knights (2011; 2015), Research: Drugs Affecting the Central Nervous System, Psychotomimetics, Drugs Affecting Fertility or Sexual Function, Vasodilation and NO, nitric oxide, Overview of the Haemopoietic System. Toxicology readings for Tutorial Activity 4 (available from subject website)

Toxicology – scope is wide and includes Pharmacology – summary:
Tutorial Topics - Risk Characterisation in Drug Development
Review Session 1 for the role of the Therapeutic Goods Administration, TGA, in Australia and Medsafe in New Zealand. International Clinical Trials and clinical trials in Australia and New Zealand especially Phase III trials and Phase IV Pharmacovigilance, are important processes in characterising the toxicological risk of pharmaceutical drugs, OTC, complementary medicines, CM.

Cannabinoids and Drug Development
From Session 1, Drug Development, the pharmacological use of cannabinoids (e.g. tetrahydrocannabinol, THC) could be to
- Enhance the potency of morphine which because of synergism will mean greatly reduced doses of the opioid narcotic. Further research into treating pain syndromes is being conducted. The role of opiates and opioids will be covered further in Sessions on Drugs Acting in the CNS.
- Cannabinoids have been used therapeutically for the purpose of increasing appetite (can be scheduled for purposes of research). As an adjunct in cancer therapy they may assist treating nausea (this concept is covered in Session 7 Drugs Used in Neoplastic Disease)
- decrease intraocular pressure (research into use in treating glaucoma)
Anandamide (arachidonyl ethanolamide) exerts endogenous cannabinoid activity; anti-anandamide drugs not approved and not released to the market in Australia for appetite control (major ADR of these drugs was depression). Anandamide is also called Bliss (Sanskrit word ananda = bliss; anandamide receptors also called bliss receptors).

Peptides and proteins as mediators and Drug Development
Some of the peptide hormones for which new drugs could be designed include:
- Neuroactive peptides such as the enkephalins and endorphins which are endogenous analgesics at opioid receptors. (Synergism with cannabinoids).
- Neuropeptide Y in the hypothalamus (when lowered, cuts down food intake. The co-transmitter neuropeptide Y enhances vasoconstrictive effects of noradrenaline.
- The enteric nervous system (works in conjunction with, but independent of, the CNS) releases several peptide neurotransmitters, serotonin (still in research stages) and nitric oxide.
- Cholecystokinin (CKK) a gastrointestinal peptide from the duodenum which stimulates the vagus nerve, sending signals to the hypothalamus to regulate body mass.
- Drugs that interfere with bradykinin production will block this pain mediator peripherally. None in clinical trials presently.

Nitric oxide and recent Drug Developments
NO, is a mediator of neurotransmission, neurodegeneration, vasodilation and immune responses. NO is the endogenous free radical thought to have influence as a mediator on endothelial cells and on the nervous system and implicated in mediation of eclampsia and the damage after a stroke. Nitric oxide is also known as Nitrogen monoxide, NO.
- Relaxes blood vessels
- Regulates amount of neurotransmitter released by nerve endings e.g. acetylcholine ACh
- Is involved in cellular immune response (explains some pathophysiology of Myocardial Infarction)
- New drugs such as Bosentan, used to treat primary pulmonary hypertension, block endothelin receptors which reduce amount of nitric oxide. Endothelin antagonists are being investigated for use in treatment-resistant hypertension and glaucoma.
- Sildenafil (Viagra® ) one mode of action in treating penis erectile dysfunction is to inhibit an enzyme [phosphodiesterase type 5 (PDE5)] thereby, prolonging the effect of vasodilatory nitrates , NO causes vasodilation
- Enteric NS (independent of CNS) releases NO; there is potential for fewer adverse effects if new drugs target this release (research needed?)

Serotonin (5-hydroxytryptamine) and recent Drug Developments
This is an exciting area of research, pre-clinical trials and some very pivotal Phase III and IV clinical trials. Some drugs affecting appetite have had approval removed by the TGA because of Phase IV data. Tutorial discussion of serotonin’s role as an endogenous ligand is important to understanding some of the drugs that will be discussed in sessions on Drugs Acting in the CNS, particularly anti-depressants.
See Unit “Introduction to Pharmacology”

- Section on “Drug Discovery and Development” up to and including Ethical aspects of clinical trials

### Scope, General Principles and Mechanisms Toxicology e.g. - Adverse Drug Reactions (ADR)


Mechanisms relevant to the study of Pharmacology will be explored: adverse drug reactions; antidotes e.g. to overdose and heavy metal poisoning. Alcohol Toxicology & Toxicokinetics for Session 11 and 12, Drugs affecting the CNS.

The World Health Organization modified definition for adverse drug reactions (ADR) is used in the context of this course. An ADR is a harmful or unpleasant reaction that results from an intervention related to the use of a medicinal product. This reaction allows prediction of hazards and risks for future administration/registration. The ADR then warrants specific treatment, alteration of the dosage regimen or withdrawal of the product.

Some important examples in Pharmacology from history:

- remedies and poisons; Mayan and Chinese cultures, documented avoidance of medicinal substances which were too poisonous
- literature reports historical use of medications such as digitalis and reports of its adverse reactions, though this was not the term that the literature, from four hundred years ago, used to describe unwanted responses
- The teratogenic effect of thalidomide, usually causes absence of long bones of limbs in the foetus (ADR, teratogenic at any dose).
- Female offspring of women who received stilbestrol during pregnancy have an increased risk of vaginal cancer (ADR, teratogenic at any dose).
- The toxic metabolite of paracetamol, N-acetyl-p-benzoquinone imine, may cause liver failure by depleting reduced glutathione. Mechanism of toxicity: metabolism, a pharmacokinetic mechanism). Overdose is treated with acetylcysteine which restores glutathione levels in the liver. Overdose is an adverse drug event and not an ADR. Chronic use of paracetamol leads to liver toxicity, ADR type C.
- Methyldopa elicits antibodies to the surface of red blood cells and thereby cause haemolytic anaemia. Hypersensitivities (types I, II, III, IV) are adverse drug reactions of type B (bizarre), high morbidity. Quinine (anti-malarial) causes thrombocytopenia by the same mechanism (type II hypersensitivity).
- Nephrotoxicity resulting from inhibition of prostaglandin synthesis probably results from excessive administration of ibuprofen (non-steroidal anti-inflammatory drug) which used in treating rheumatoid arthritis long term. This is ADR type C (continuous, from long term use). NSAIDs also reduce renal flow and promote retention of salts and water (indirect interaction, via an ADR, with antihypertensive, inhibiting their action). Hypertension from use of NSAIDs is an ADR type A (augmented) – commonest category
- An important mechanism from Toxicology: Exposure to mercury (heavy metal) during pregnancy primarily causes abnormal development of the foetal brain

### Adverse Drug Events

In contrast, adverse drug events include: drug overdose, withdrawal symptoms, drug abuse or error in administration. The drug overdose may be deliberate or may be as a result of failure of equipment such as infusion pumps. Checks involving the five Rs (the right drug, to the right patient, via the right route, in the right dose, and with right frequency) overcome errors in administration of drugs.
Adverse Drug Effects
Anaphylaxis (Type 1 Hypersensitivity) and other types of hypersensitivity, occur via a different biochemical and physiological mechanism to the way the drug operates. Thus the term ‘reaction’ is inappropriate as this is an effect of the drug but not a reaction to its normal operation. However, the terms ADE and ADR tend to be used interchangeably in the literature.

See Unit “Principles of Pharmacology”
- Sections on “Adverse Drug Reactions and Drug Interactions” Chapter Introduction and Definitions, “Classification of Adverse Drug Reactions”

Drug-Drug Interactions
Reference texts such as MIMS Annual (Index to Drug Interactions Table), Avery’s Drug Interactions (Appendix B: Guide to Clinically Important Drug Interactions) and Australian Medicines Handbook (Appendix A) publish known and reported risks of drug interactions. Online resources can be purchased which give access to drug interactions information e.g. MIMS Online. While at Endeavour, access to online resources is available through Libguides.

- Drug Interactions which are Pharmacodynamics effects
  - Addition of Action
  - Synergism of action.
  - Inhibition of action (direct effect on the two exogenous chemicals’ modes of action).

- Pharmacokinetics effects
  - Absorption effects
  - Distribution effects
  - Metabolism effects.
  - Excretion effects.

- Physicochemical interactions are physical and chemical effects which may also have effects on the Pharmacodynamics and / or pharmacokinetics of the two interacting drugs:
  - e.g. Competition for binding proteins and active transport
  - pH interactions

Dosing times and dosing instructions may need to be adjusted when a patient has concomitant disorders and is taking many pharmaceutical and complementary and alternative medicines, to avoid drug interactions. This is an issue in dosing regimens in the elderly and other at risk groups.

See Unit “Principles of Pharmacology”
- Sections on “Drug-Drug Interactions” and “Metabolic Drug Interactions Involving Nutrients and Herbal Medicines” and “Strategies for Limiting Adverse Drug Reactions and Drug Interactions” up to Key points

Risk Assessment
The Therapeutic Goods Administration, TGA, now takes a risk assessment approach to ADR and interactions. Once hazards are known and reported future events and responses are managed in terms of the risk. Problems with herbal toxicities are reported in the medical literature. Pharmaceuticals and Complementary Medicines, CM therapies, are reported to the Therapeutic Goods Administration, TGA, (http://www.tga.gov.au/safety/problem.htm) by both health professionals and consumers.

Hazards are identified by: structure / activity relationships, in vitro, in silico and short term tests, animal bioassay and epidemiology. Risks are identified by: exposure/nonexposure, prospective / retrospective time sequence methods, comparative data, prevalence studies, epidemiological data and molecular epidemiology markers (human genome project advances). As well as putting together the picture of toxicity, with heavy metals and other environmental and industrial poisons, it is important to put together the picture of exposure. You will research these exposure principles and risk characterisation processes in your assignment.
Dose-Response Curves
Pharmacokinetics of drug interactions

- Agonist alone (Review)
- Agonist and enhancer
- Agonist and inhibitor
  - Competitive inhibitor
  - Non-competitive inhibitor

Predicting dosage from Effective Concentration 50% EC50%, (50% of maximal effective dose) ED50, effective dose 50%, lethal dose 50% LD50 and toxic dose 50% TD50 – population studies, 50% of test animals.

Dose-Response curves are used to calculate and report median measures of toxicity; LD50 important in Material Safety Data Sheets, MSDS (TD50 have some applications) and in animal studies. Toxicity and exposure, as well as managing the risks, are better monitored in some populations (animal studies, humans) using Lowest observed adverse effect level (LOAEL) and No observed adverse effect level (threshold measures of toxicity).

- LOAEL is lowest tested dose of a substance which has been shown to have harmful effects on humans or animals. It can apply to a particular study, species (e.g. rat, dog), or all studies on a particular substance.
- NOAEL is the highest significant response point on the dose response curve (NOAEL does not mean “risk free” but assists to assess risk).
- LD50 is median lethal dose, often reported in Material Safety Data Sheets (MSDS) for educating and communicating about hazards and risks.

Hormesis: students will research this type of dose-response curve in their assignments, if they choose radiations (U-shaped response curve), ethanol (J-shaped response curve) as a solvent and other potential xenobiotics in plants or other living systems. Hormesis has many applications to the area of Toxicology e.g. nutritional medicine and natural therapies including Herbal Medicine studies applied to the area of Toxicology.

- See Unit “Introduction to Pharmacology”
- Section on Animal rights in “Legal and Ethical Foundations of Pharmacotherapy”
- See Unit “Principles of Pharmacology”
- Sections on “Pharmacodynamics”, up to Key Points

Absorption, Distribution and Excretion of Toxins

Progress often comes with a cost. Progress in science, technology and in many other areas of industrial activity involves use of metals, biological and industrial poisons. Metals are used in cars, electronics, paint, pigment, deodorants, beauty products, drugs. The extensive use of metals leads to widespread potential exposure which results in an accumulation of metals in selective organs and tissues of the body with a potential for chronic toxicity. Acute toxicity usually occurs after ingesting or inhaling metal fumes or gaseous metal compounds. Deodorants and make-up creams also contain metals which could be the cause of biological accumulation of metals in the organs. These toxic chemicals make their way into the environment. Research into the effects of metals and minerals on our health suggests that the toxic effects of metals cause physiological alterations, reproductive toxicity and behavioural alteration. Heavy metal testing is done on hair, nails as well as urine. In these tests metals and minerals are monitored in Biological Monitoring Programs.

Tools involved in examining the nature, properties, identification, effects and treatment of poisons including the study of adverse drug reactions: small scale trial and large scale RCCT, activity / structure studies of drugs and poisons, in vivo bioassays, in silico, animal studies, epidemiology.
Biotransformation of Xenobiotics
Xenobiotics are foreign compounds usually of organic origin. Drugs used in Pharmacotherapy are therefore Xenobiotics.

Biotransformation is the process of metabolising xenobiotics to active or inactive metabolites. Thus, pharmacokinetics involves the study of biotransformation (metabolizing) of drugs. Foods can be biotransformed (tyramine effect, monoamine oxidase) or can inhibit Cytochrome P450 family of enzymes (grapefruit juice). Foods can affect how drugs work. Alcohol can affect how some drugs work (induces an isof orm of cytochrome P450).

Biotransformation of exogenous organic compounds is important in Toxicology. Chemicals which enter the body are then biotransformed into toxic substances or metabolized to increase their excretion from the body.

Toxicokinetics
Pharmacotherapy assumes that a particular concentration of a drug will have the desired therapeutic effect and that adverse effects will be negligible. Pharmacokinetics measures that drug concentration. Toxicokinetics measure safety margin at usual drug concentrations.

From a dosing point of view, the most important pharmacokinetic parameters and toxicokinetic parameters are:

- **Therapeutic range** – drugs, range of concentrations at which a drug or other therapeutic agent is effective with minimal toxicity
- **Clearance (Cl)** - drugs (maintenance dose), xenobiotic (non-drug) clear from all compartments
- **Volume of distribution (Vd)** – drugs (loading dose), xenobiotic (non-drug), often ≥2 compartments
- **Half-life elimination (t½)** - drugs (dosing interval), xenobiotics (non-drug) sufficient 1/2 to clear toxin

Measure of safety margin (theoretical therapeutic index = ratio dose required to produce a toxic effect / dose required to produce desired therapeutic response, TI = TD90/ED50 (where ED related to EC effective concentration of drug related to maximal effective concentration, whereas ED30 relevant to population studies))

Measure of exposure, margin of safety = LD1/ED99. If the xenobiotic is a non-drug, then estimated exposed dose of human population is subtracted from NOAEL, used to measure a margin of safety.

Other uses of dose-response curves, animal population studies or human epidemiology studies: hormesis. Alcohol is an example of a toxin that shows hormesis (u-shaped dose-response curve, therapeutic value at low exposure in adult populations and toxic at chronic high dose exposure).

Tutorial – Review of Endogenous Ligands, Neuromodulators and the roles of NA and ACh
Proposed neurotransmitters or neuromodulators, for further study and drug development, include purines, NO, vasoactive intestinal peptide, dopamine and serotonin. Nitric oxide, NO(g), has neurotransmitter-like functions in the CNS and regulates the amount of neurotransmitter released by nerve endings e.g. acetylcholine ACh (see above). Other new areas for potential drug development could include purines as Adenosine is a neuromodulator. Adenosine triphosphate is a co-transmitter with neurotransmitters. Adenosine diphosphate stimulates platelet aggregation; chemicals related to prostaglandins, have a similar role (see below).

See Unit 4 “Drugs Affecting the Central Nervous System” “Central Nervous System Overview …..”

- Sections on Criteria for central neurotransmitter status and Section headed Other CNS neurotransmitters.

Prostaglandins (PG)
Prostaglandins could be neuromodulators (released by neighbouring neurones to a sensory neurone, thus make the perception stronger e.g. pain perception).

- **5-HT** (serotonin)

See above re Drug Development. 5-HT modulates neurones where NA is the neurotransmitter.

Immune response mediators
Review interleukins 1 and 2 (IL-1, IL-2), TNF-α, bradykinin (and many others – area for potential drug development)
See Unit "Drugs Affecting Body Defences”, “Anti-inflammatory and Immunomodulating Drugs"

Section on TNF-α antagonists and Cytokine modulators

Additional Reading

If you find other educationally-useful videos add them to the Loop / forums

- [www.medsafe.govt.nz](http://www.medsafe.govt.nz) Pharmacovigilance & monitoring

Revision Questions / Activities – Lecture Topics

1. Give examples of ADR from types A to F, using drugs / herbs. Define ADR and ADE
2. Give examples of type 1 (anaphylactic, IgE), type II (cytotoxic), type III (immune complex) and type IV (delayed) hypersensitivity reactions (ADR type B Bizarre.) involving drugs or herbs.
3. Explain the term therapeutic index using digoxin and lithium as your examples.
4. Explain LOAEL, NOAEL, TD50 and LD50 from dose response curves and epidemiological studies. Discuss margins of safety using threshold data.
5. Give examples of additive and synergistic drug interactions (related pharmacodynamics e.g. anticoagulant/anti-platelet, monoamine oxidase inhibitors and food / drugs)
6. Give examples of inhibitory drug interactions (reduced effectiveness): (indirect pharmacodynamics e.g. drugs that have ADR hypokalaemia which makes digoxin more toxic; drugs that cause hypertension as an ADR inhibit antihypertensives.
7. Give examples of drug / herb interactions that have a pharmacokinetic mechanism (due to absorption, distribution, metabolism or excretion effect).
8. RCCT, Pharmacovigilance and pharmaco-surveillance data (TGA) are important for risk assessment. Small scale clinical trials are important for hazard identification. Research and explain each of these terms: small scale trial, RCCT, pharmacovigilance and surveillance, [http://www.tga.gov.au/safety/australian-pharmacovigilance-sponsors.htm](http://www.tga.gov.au/safety/australian-pharmacovigilance-sponsors.htm), hazard, risk.

Revision Questions / Activities for Tutorial Topics (assessed in the final exam)

1. Summarize the effects mediated by: 5-HT, purines, NO (g), mediators, that make them current or future targets for finding drugs that are agonists / antagonists, especially any aspects that modify actions of noradrenaline, NA, and Acetylcholine, the two most common neurotransmitters. Briefly summarize the concept of new drug developments using physiological examples from the following endogenous ligands or neuromodulators: cannabinoids, bio-active peptides, prostaglandins.
2. Since Pharmacology is within the scope of Toxicology, the terms absorption, distribution, biotransformation (metabolism when discussing drugs), elimination, volume of distribution, clearance, t ½ are used in both areas of studies. Explain each term. These concepts will be developed further in your Toxicology research assignment.
3. Since Pharmacology is within the scope of Toxicology, there are other important overlapping concepts. Lifespan groups at particular risk in Toxicology are the same groups identified in Pharmacology. Discuss greater risk of exposure to accidental overdose in young children (e.g. paracetamol). Discuss risk of exposure to heavy metals in pregnancy or young children. These general concepts will be developed further in your Toxicology research assignment.
From subject website, Assignment for Research on Toxicology
Review from BIOH111 & BIOH122 and research activities
- Local hormones – inflammation and immune reactions
- Cholinergic transmission and Noradrenergic transmission
  Introduction to serotonin and dopamine as neurotransmitters

Answer these questions:
- From Bryant Knights, Review Questions: Adverse Drug Reactions and Drug Interactions
- From subject website, Assignment Research topics, Toxicology
  Tutorial questions to complete in regard to the following topics
  - Risk Assessment (Klaasen & Watkins, 2010)
  - Adverse drug reactions (ADR) and drug interactions.
SESSION 5: Drugs Affecting Microbes

Session Aims:
This session will provide opportunities for students to:

- Address Learning Outcomes 2, 3, 4 & 5
- Use the Reading Guide approach of compiling a drug diary; covering Learning Outcomes and Assessment Tasks for this Subject of Study.

Session Topics
- Principles of antibiotic therapy
- Penicillin, cephalosporins, quinolones, macrolide antibiotics
- Sulphonamide-trimethoprim combination
- Antifungals
- Antivirals
- Anti-retrovirals in the treatment of HIV

Textbook Location of readings

Research Overview of Antimicrobial Chemotherapy and Antibiotic Resistance, Antibacterial Drugs, Antifungal and Antiviral Drugs

Summary

Principles of antibiotic therapy:
4 main mechanisms of action;

- Penicillin, cephalosporins, quinolones, macrolide antibiotics; mechanisms of action, main features. Beta-lactamase inhibitors to overcome resistance in penicillins, cephalosporins and Carbapenems. Other aspects of resistance specific to these agents.
- Sulphonamide-trimethoprim combination: aspects of resistance specific to these agents; main features including mechanism of action (synergism)
- Antifungals e.g. Caspofungin, griseofulvin, Amphotericin B, flucytosine, azole antifungals: types of mycoses treated; mechanisms of action, adverse reactions & other main features. Emerging antifungal resistance. Metronidazole used for anaerobic bacterial, protozoal and fungal infections: mechanism of action, indications, main features.
- Antivirals: DNA Polymerase Inhibitors (e.g.acyclovir) mechanism of action, indications and other main features. Antivirals used against Influenza A & B (amantadine and oseltamivir neuraminidase inhibitor): mechanisms of action, main features.
- Anti-retrovirals in the treatment of HIV: nucleoside reverse transcriptase inhibitors (NRTI) e.g. zidovudine; non-nucleoside reverse transcriptase inhibitors (NNRTIs) e.g. efavirenz; Protease Inhibitors (PI) e.g. saquinavir. Enfuvirtide, tenofovir, mechanism of action irreversible blocking of receptor glycoprotein 41, gp41. The need for HAART and other combination therapies to avoid antiretroviral drug resistance.

Issues include resistance, superinfection, guidelines for use of antibiotics, role of host defence mechanisms, dosage & duration of therapy.

Additional readings

Fink, 2012, Pharmacology; Antibiotics, Principles & the Penicillins by Professor Fink, accessed at https://www.youtube.com/watch?v=EDYfZ-DcNnw&list=PLekhi82QS2PahYNzzQow72dLyaLAXi2dDJ&index=24

Eric’s medical lectures, 2013, Mechanisms and classification of antibiotics (antibiotics lecture 3), accessed at https://www.youtube.com/watch?v=NGwP471sehI
**Revision Questions / Activities**

1. Discuss the four main mechanisms of antimicrobials and state which mechanism occurs with the use of:
   a) β-lactams e.g. penicillins, cephalosporins;
   b) sulphonamethoxazole-trimethoprim;
   c) quinolones;
   d) macrolides;
   e) tetracyclines;
   f) metronidazole across all of its spectrum of activity;
   g) flucytosine antifungal;
   h) amphotericin antifungal;
   i) caspofungin. State if the effect is microbicidal or microbiostatic.

2. Discuss one major ADR, other than hypersensitivity (type B) or gastrointestinal symptoms for:
   a) tetracycline;
   b) sulphonamethoxazole-trimethoprim;
   c) erythromycin (a macrolide);
   d) penicillins;
   e) cefalosporins;
   f) ciprofloxacin (quinolone).

3. Research *Candida albicans* and how unfortunately some resistant strains of this fungus are emerging in the community and hospitals. Use your knowledge of how resistance emerged among bacteria and mutable viruses like HIV-1 and Influenza A virus, to write a brief statement on what practices might have encouraged emergence of these resistant strains of a fungus.

4. Discuss unique targets in viruses that do not have a human equivalent and so should not therefore produce excessive adverse effects on human DNA synthesis, RNA synthesis and other cellular functions.

5. Discuss the isoform CYP3A4 and list some antivirals that increase this cytochrome P450 isoform activity.

6. Discuss dosing regimens (HAART) for effective treatment of HIV and how this should ensure emergence of much fewer drug-resistance strains of HIV-1.

**Tutorial Activities** (Assessable in the Final Exam, and can be included in your Drug Mini-Monograph Assignment if negotiated with your Online Academic/Lecturer. You CANNOT cover microbial toxins and anti-microbials for both your Toxicology Assignment AND drug Mini-monograph)

Discuss these pharmaceutical medications. 10 marks for (i) examples and mode of action (must state if microbiostatic or microbicidal for bacterial and fungal infections (ii) indications (iii) mechanism of action (iv) efficacy and limitations or cautions / contra-indications (v) adverse effects. Mark your own answer using the Pharmacology text or online resources. Alternatively, peer review each other’s answers, allocating 10 marks per drug class or sub-class or drug or 10 marks for the statement on how all members of society play a part in prevention of microbial resistance to antimicrobial drugs including antibiotics.

- Penicillins and cephalosporins
- metronidazole
- Anti-fungals used systemically
- Anti-retrovirals
- Thus make a general statement about ways that prescribers and all other health care practitioners and the general public can work together to prevent emergence of resistant strains of microbes. Use examples from session 5 (anti-viral drugs, anti-bacterial and anti-Candida drugs (antibiotics). For antibacterials used in triple therapy for treating PUD, peptic ulcer disease - See Session 8)

- From Bryant & Knights (2011; 2015)
  Review questions: Overview of Antimicrobial Chemotherapy and Antibiotic Resistance, Antimicrobial Drugs, Antifungal and Antiviral Drugs

*From Endeavour LMS subject website, review questions*
Session 6 Drugs Affecting Body Defences

Session Aims:
This session will provide opportunities for students to:
- Address Learning Outcomes 2, 3, 5
- Use the Reading Guide / Drug Diary approach of studying Pharmacology; covering Learning Outcomes and Assessment Tasks for this Subject of Study.

Session Topics
- Anti-inflammatory and immunosuppressant drugs
  - Non-steroidal anti-inflammatory drugs, NSAIDs
  - Paracetamol
- Corticosteroids
- Drugs for the treatment of Rheumatoid and Osteoarthritis
  - Disease-modifying anti-rheumatic drugs, DMARDs
  - NSAIDs
- Drug for the treatment of Gout
  - acute attack
  - prophylaxis

Textbook, Location of Readings

Research Drugs Affecting Body Defences, Anti-inflammatory and Immunomodulating Drugs, Overview of Mediators of Inflammation, Allergy and the Immune Response

Summary
Body resistance to disease
When a chemical, foreign body or micro-organism invades the body, the body will try to eliminate it by eliciting an inflammatory response
 See Unit “Drugs Affecting Body Defences”
  ➢ Section on “Resistance to Disease” “Non-specific resistance – inflammation”

Drug treatment of inflammatory joint diseases
Diseases that can be treated include osteoarthritis (OA), rheumatoid arthritis (RA), gout, psoriatic arthritis, reactive arthritis, septic arthritis, mechanical injury.
- Using a pathophysiology text, summarize the cause and pathogenesis for these diseases.

Goals of therapy:
- reduce pain
- reduce stiffness
- increase mobility
- minimise disability
- prevent/minimise progression of deformity
- improve quality of life
Drug treatment includes the use of drugs that suppress the immune system, inhibit inflammatory cell migration, enzyme release and prostaglandin synthesis.

Non Steroidal Anti-Inflammatory Drugs (NSAIDs)
One of the most commonly administered group of drugs worldwide.
Can be used for mild to moderate pain, fever, inflammation, prevent platelet aggregation, RA, OA and various acute and chronic musculoskeletal and soft tissue inflammations
 See Unit “Drugs Affecting Body Defences”
  ➢ Section on “Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)”
Mechanism of Action, M of A, of the NSAIDs (non-steroidal anti-inflammatory drugs): inhibit the biosynthesis of prostaglandins and reduce the inflammatory response by inhibiting the COX pathways
- Study the figure showing the inflammatory pathways (COX-1 & COX-2)

Chemical Classes of NSAIDs include:
- **Salicylates**
  - Aspirin
- **Coxibs**
  - Celecoxib
- **Propionic acid derivatives**
  - Ibuprofen
- **Indoleacetic acids**
  - Indomethacin
- **Fenemates**
  - Mefenamic acid
- **Oxicams**
  - Piroxicam

Pharmacokinetics
Oral absorption is very good, metabolised by the liver and excreted by the kidneys

Adverse Effects
Include gastritis, ulceration and haemorrhage, may precipitate asthma attacks

Contraindications/Cautions
NSAIDs are contraindicated for the following:
- Asthma
- Active ulcer disease
Caution is required in people with:
- compromised cardiac function and/or hypertension
- the elderly, debilitated patient

Drug Interaction
NSAIDs interact with the following drugs:
- Antihypertensives
- Diuretics
- Lithium
- Probenecid (anti-gout therapy, see below)
- Warfarin
- See appendix 3 (Bryant & Knights 2011; 2015) or Veitch et al (2014) Herbal medicines monographs on herbs

Aspirin and Paracetamol
Both aspirin and paracetamol have analgesic properties however they differ in that paracetamol does not have any anti-inflammatory activity.

☞ Summarize the pharmacodynamics, pharmacokinetics, adverse effects, drug interactions and warnings and contraindications of both of these drugs in your Drug Diary
☞ See Unit “Drugs Affecting the Central Nervous System”
  - Sections on Aspirin and other salicylates. Paracetamol up to NSAIDs and polypharmacy

Corticosteroids
Corticosteroids (CS), often abbreviated to GCS, glucocorticosteroids when used to alter metabolic actions of white blood cells, WBC) are frequently used in the management of RA however as with NSAIDs, these drugs do not appear to alter the progression of the disease
- Session on Drugs Affecting the Endocrine System will review the pharmacodynamics, pharmacokinetics, adverse effects, drug interactions and warnings and contraindications of glucocorticoids.
Summarize the indications, examples, adverse effects, drug interactions and warnings and contraindications of corticosteroids. Ensure that this information is in your Drug Diary.

See Unit “Principles of Pharmacology”
- Sections on “Immune-modulating Drugs and Adverse Drug Reactions”

See Unit “Drugs Affecting the Endocrine System”
- In the section called “Hormones and Drugs Affecting Bone”, Read the section on Corticosteroids only
- In the section called “Pharmacology of the Adrenal Cortex”, Read “Glucocorticoids”

**Disease Modifying Anti-rheumatic Drugs (DMARDs)**

Term used to describe a group of therapeutic agents which have the potential to reduce or prevent joint damage and preserve joint integrity. The therapeutic goal is to intervene in the disease before joints are damaged however they have a slow onset of action with a delay of 1-6 months before evidence of clinical response.

Drugs classified as DMARDs:
- hydroxychloroquine
- sulfasalazine
- methotrexate, MTX
- gold compounds
- D-penicillamine

Summarize the pharmacodynamics, pharmacokinetics, adverse effects, drug interactions and warnings and contraindications of these drugs in your Drug Diary (e.g. under DMARDs though most of them have other indications as well)

In Unit “Drugs Affecting Body Defences”
- Section on “Disease-Modifying Antirheumatic drugs (DMARDs) up to hydroxychloroquine
- TNF-α antagonists (tumour necrosis factor) and Cytokine modulators, review aspects covered in Session 4 on Drug Development

**Drug treatment in Gout**

The treatment goals are to:
- abort an attack
- prevent recurrent acute gout attacks
- prevent uric acid stone formation in the kidneys
- reduce or prevent disease complications

Management will involve strategies for both acute attacks and chronic prevention/minimising risk of further attacks. Drug therapies include:
- NSAIDs
- Colchicine
- Glucocorticoids
- Uricosuric agents
- Allopurinol (also used to treat hyperuricaemia See Session on Anti-neoplastic Drugs)

Review the pharmacodynamics, pharmacokinetics, adverse effects, drug interactions and warnings and contraindications of the drugs that are already in your summary. Add colchicine, uricosurics and allopurinol to your summary (Drug Diary).

In Unit “Drugs Affecting Body Defences”, “Anti-Inflammatory and Immunomodulating Drugs”

Read section on Drugs Used for the Treatment of Gout up to and including Probenicid

**Additional Resources**

If you find other educationally-useful videos, add them to the Loop / forum

Handout of Rheumatoid Arthritis and Gout (downloaded along with the Session 6 tutorial)
Revision Questions / Activities

1. Describe the mechanism of action of NSAIDs (non-s_________ anti-__________ drugs)
2. What is the benefit of selective COX II inhibitors? (C____-o_________ ase II Inhibitors)
3. Name 6 different classes of NSAIDs.
4. Outline the major adverse effect of NSAIDs and explain the rationale behind why this happens.
5. List 3 contraindications & warnings involved with the use of NSAIDs
6. Compare and contrast aspirin and paracetamol (include M of A, indications, adverse effects, contraindications).
7. Outline how aspirin exerts its anticoagulant/antiplatelet effect.
8. What are the 2 properties that corticosteroids exhibit?
9. Corticosteroids have many adverse effects. Name 5.
10. Outline the advantages that DMARDs have over other drugs used in the treatment of RA.
    D____-m_________ anti-__________ drugs. R_________ A______-tls.
11. What drugs are used in an acute attack of gout?
12. What drugs are used to prevent subsequent attacks of gout?

Answer the following:

- From Bryant & Knights (2011; 2015)
  - Review questions: Drugs Affecting Body Defences: Anti-inflammatory & Immunomodulating Drugs. Especially questions reviewing the inflammatory response, complement, allergic (hypersensitivity) reactions, hyperuricaemia, probenicid

- From subject website, review quiz, Students discuss their “Drug Diaries” in class or in on-line forums, and compile a Class/ Cohort Flow Chart / Table of Drug Treatments in RA and gout

The following can be included in your Drug Mini-monograph assignment or could be on the final exam:
Discuss these medications that work on Immune Responses or similar. 10 marks for
(i) examples (ii) indications (iii) mechanism of action (iv) efficacy and limitations or cautions / contra-indications (v) adverse effects. Mark your own answers using the Pharmacology text or online resources. Alternatively, peer review each other’s answers, allocating 10 marks per drug class:

- Non-selective COX inhibitors
- Selective COX inhibitors
- DMARDs (disease-modifying anti-rheumatic drugs)
- Corticosteroids to treat musculoskeletal diseases e.g. RA (rheumatoid arthritis)
- Anti-gout drugs, both prophylactics and those needed to treat the acute attacks
SESSION 7: Drugs affecting the Reproductive System
Drugs in Neoplastic Disease

Session Aims:
This session will provide opportunities for students to:
• Address Learning Outcomes 2, 3, 4, & 5
• Use the Reading Guide approach of compiling a drug diary; covering Learning Outcomes and Assessment Tasks for this Subject of Study.

Session Topics
• Contraceptives and their effects
• Hormone Replacement therapy
• SERMS in treating post-menopausal symptoms
• Bisphosphonates and SERMs in the treatment of Osteoporosis
• Cancer and chemotherapeutic drugs
• Adverse effects of chemotherapy and adjuncts/support (see bisphosphonates, SERMS and others)

Textbook, Location of Readings and Textbook questions

Research: Male & Female Reproductive Systems, Drugs Affecting the Female Reproductive System, Overview of Neoplasia & Cancer Chemotherapy, Antineoplastic Agents, Adjunctive treatments: Treatment of adverse drug reactions, Treatment of problems due to bony metastases, Complementary medicine[s] CM modalities
• From Bryant & Knights (2011; 2015)
  o Review questions: Drugs Affecting the Female Reproductive System; Antineoplastic Agents.
    ❖ Questions that assist you to review the hypothalamic and pituitary hormones, negative feedback, three endogenous oestrogens and endogenous progesterone and synthetic products. Add these synthetic products and their formulations to your drug diary.
    📖 for Antineoplastic agents, questions that assist you to review cell cycling and its regulation, growth of cancers and the hallmark characteristics of cancer cells, terminology used in Oncology (study of cancer), adverse effects common to cytotoxic agents
    📖 for “Drugs Affecting Fertility or Sexual Function” only attempt questions on advantages/disadvantages of drug contraceptive methods, combination oral contraceptives (combined oral contraceptives, COC), pharmacokinetic data for progestogens.
    📖 For case studies, see Case Study below Mrs P from your textbook website plus questions in the Review on your Endeavour LMS

Summary
• Contraceptives and their effects: Combination, Minipill, Emergency Contraception.
• Hormone Replacement therapy (perimenopausal and postmenopausal). Post-menopausal: Women’s Health Initiative (WHI) & Heart Estrogen/Progestin Replacement Study (HERS) findings: osteoporosis, cardiovascular risks, endometrial cancer, breast cancer.
• SERMS in treating post-menopausal symptoms: e.g. raloxifene, mechanism of action and main features are important.
• Bisphosphonates and SERMs in the treatment of Osteoporosis: alendronate, mechanism of action and main features. Bisphosphonates: Paget’s disease, prevention and treatment of postmenopausal osteoporosis, preventing and treating corticosteroid-induced osteoporosis, palliative care when body
metastasis occurs. See below, Adjunctive Treatment: Adverse drug reaction to chemotherapeutic agents and other cancer treatments

- Cancer and chemotherapeutic drugs: cytotoxic drugs (e.g. cyclophosphamide, antibiotics, platinum compounds, vinca alkaloids, methotrexate) mechanisms of action, main features. Hormones: immunosuppressive agents i.e. glucocorticoids and anti-oestrogens
- Adverse effects of chemotherapy. Supportive Therapy needed could include:
  - anti-nausea & vomiting agents (See Corticosteroids, covered in several sessions including Sessions 5 and 10; corticosteroids also produce a euphoria, considered an ADR previously but an indication for their use in cancer chemotherapy and in palliative care),
  - platelets for myelosuppression, or immunostimulatory preparations to counteract myelosuppression
  - immunomodulatory agents (corticosteroids once again for lymphoid and myeloid tumours, aldesleukin & others from Session 4 immune mediators),
  - bisphosphonates (See this Session, Session 7; indicated when cancer has metastasised to bone);
  - analgesics from Sessions 6 and 12, Opioids are used in palliative care (See Session on Drugs Affecting the CNS).
  - Metoclopramide (mode of action prokinetic, see Session 8 Drugs Affecting the Gastro-intestinal tract).
  - Hyperuricaemia is treated with allopurinol (see Session 6) – tumour lysis by the chemotherapeutic agent causes excessive production of uric acid from adenine and guanine metabolism (purines from DNA and RNA); hence a xanthine oxidase inhibitor is needed or a treatment with a synthetic enzyme
  - CM (complementary medicine) modalities. See Clinical Interest Box 42-6: Complementary and alternative therapies in cancer.

Additional Reading and Animations

If you find other educationally-useful videos, add them to the Loop / Forums


Revision Questions / Activities

1. What do the terms Mini Pill and combination OCP mean in oral contraception? The pharmacotherapeutic aspects will be discussed in tutorial activities.
2. Pharmaco-therapeutic use of a combined oestrogen-progestogen in HRT will be discussed in the tutorial activities. Since the WHI study (on healthy postmenopausal women) and Heart Estrogen/Progestin Replacement Study (HERS) (postmenopausal women with coronary disease) discuss short term versus long term use of HRT and the risk of stroke, breast cancer, venous thromboembolism.
3. In tutorial activities the pharmaco-therapeutic use of selective estrogen receptor modulators (SERMs) such as raloxifene in protecting against osteoporosis and cardiovascular disease will be discussed. What is their effect on risk of breast and uterine cancers with the use of SERMs?
4. In the tutorial activities the pharmaco-therapeutic aspects of anti-neoplastic agents, the cytotoxic agents (alkylating agents, antimetabolites and mitotic inhibitors) will be discussed. Give an example of each cytotoxic agent. Antibiotic antitumour drugs work by many mechanisms but are generally cell-cycle non-specific. Give some examples of antineoplastic antibiotics.
5. Research examples of complementary medicine, CM, used in cancer to treat bone marrow suppression, hypercalcaemia, hyperuricaemia and bone resorption associated with cancer treatment. The western medicine pharmaceuticals will be discussed in the tutorial activities.
The following can be included in your Drug Mini-monograph assignment or could be on the final exam:

Discuss these pharmaceutical medications. 10 marks for (i) examples (ii) indications (iii) mechanism of action (iv) efficacy and limitations or cautions / contra-indications (v) adverse effects. Mark your own answers using the Pharmacology text or online resources. Alternatively, peer review each other’s answers, allocating 10 marks per drug class:

- Oral contraceptive pill formulations
- Selective oestrogen receptor modulators (SERMs)
- Hormone replacement therapy with oestrogen-component or combined HRT
- Antineoplastics
- Adjuncts used with chemotherapeutic agents

- From Bryant & Knights (2011; 2015)
  o Review questions: Drugs Affecting the Female Reproductive System; Antineoplastic Agents.

From subject website, review quiz and Case study:

Mrs P is a 55 year old and has started taking tamoxifene to reduce the risk of recurrence of her oestrogen-receptor-positive breast cancer. She is experiencing hot flushes and would like to try a herbal medicine to relieve these symptoms. Check soya, red clover (contain isoflavones) and black cohosh on Herbal section of Medicines Complete™ (see LibGuides link on the Endeavour Library site). Alternatively, see http://evolve.elsevier.com/AU/Bryant/pharmacology Complementary and Alternative Medicine content with crossword puzzles and choose <Case Studies>

Black cohosh to date has not been reported to interact with tamoxifene and black cohosh in in vitro and animal studies (Veitch, Smith, Barnes, Anderson and Phillipson, 2014) has been shown to have

- anti-inflammatory properties
- oestrogenic activity
- bone density reduction activity
- all of the above

Isoflavones, which are found in red clover and soya, may

- reverse tamoxifene’s antioestrogenic effect on breast tissue, perhaps by a pharmacodynamics interaction
- promote tamoxifene’s anti-oestrogenic effect on breast tissue, perhaps by a pharmacodynamics interaction
- reduce bone density
- a. and b.

What further advice would you give to Mrs P.?

- Continue with the oestrogen antagonist, Tamoxifene, but that the hot flushes could be an adverse effect of the Tamoxifene
- Avoid isoflavone-containing herbal remedies due to possible interactions with Tamoxifene, though the data is conflicting
- Advise Mrs P to report any herbal remedies that she takes to yourself and the general practitioner, as Tamoxifene is metabolized to an active drug and metabolism could be enhanced or inhibited
- All of the above
References

SESSION 8: Drugs Affecting the Blood Lipid-lowering Drugs

Drugs Affecting the Gastrointestinal System

Session Aims:
This session will provide opportunities for students to:
- Address Learning Outcomes 2, 3, 4 & 5
- Use the Reading Guide’s Drug Diary approach to study, this covers Learning Outcomes and Assessment Tasks for this Subject of Study.

Drugs affecting the Blood
- Warfarin
- Antiplatelet drugs

Lipid lowering drugs
- The mode of action and other characteristics of drugs used to lower lipids in the body
- The use of nicotinic acid in hyperlipidaemia

Drugs affecting the Gastrointestinal System
- Proton pump inhibitors
- H₂ antagonists
- Cytoprotective agents and antacids
- Antispasmodics
- Antiemetics

Textbook Location of Sections to Read
- Bryant B. & Knights K. 2015 Pharmacology for health professionals 4th ed, Mosby, Sydney

Research:
- Drugs Affecting Haemostasis, Thrombosis & Haemopoietic System;
- Overview the GIT and Drugs Affecting the Gastrointestinal Tract (indicated for GORD and PUD, nausea and vomiting, particularly).
- Read Drugs Affecting the Lower GIT, & their use in Irritable Bowel Disease (IBD) and Irritable Bowel Syndrome (IBS), diarrhoea / constipation. Lipid Lowering Drugs
- Unit 5 Drugs Affecting the Heart and Vascular System: Chapter on “Lipid-lowering Drugs”

Summary

Drugs affecting the Blood:
Warfarin is anticoagulant and aspirin is antiplatelet aggregation. Both cause excessive bleeding as the main adverse effect. It is therefore important to know alternatives and their adverse effects.
- Warfarin, mode of action: depletion of clotting factor VII then X, IX and prothrombin; vitamin K analogue; vitamin K antidote in overdose. Adverse effects; exaggerated bleeding. Warnings/Precautions/Contraindications: tend to relate to bleeding disorders. Indications: anticoagulant. Monitor with International Normalized Ratio (INR). Compare with low molecular weight heparins (LMWH) for limitations and indications, Use in Pregnancy. Also compare with thrombolytic agents that break up existing clots: anticoagulants warfarin and heparin are prophylactic only against clot formation and have no action on existing clots. Warfarin has many drug interactions.
- Antiplatelet drugs: aspirin, clopidogrel, ticlopyamide, abciximab: know the mechanism of action of aspirin and how other anti-platelet drugs differ. With aspirin also know main features and adverse effects.

Lipid lowering drugs
Know the mode of action and other characteristics of drugs used to lower lipids in the body. An integral part of therapy, principle non-drug measures are Dietary modification; Weight reduction in the obese; Reduction
in excessive alcohol consumption; Cessation of smoking; Exercise; Reducing stress. Hydroxymethylglutaryl CoA reductase Inhibitors, HMG-CoA reductase inhibitors (statins) the mainstay therapy: mode of action is their action against the important key enzyme in cholesterol synthesis, HMG CoA reductase. Drug therapies: Fibrates; Bile acid sequestrants (resins): know main features such as indications and limitations and modes of action. As the name suggests, bile-acid-binding resins bind the bile acids which are cholesteryl ester salts that emulsify fats. Hence this interferes with entero-hepatic recycling of cholesterol (review the role of gut normal flora in this process, physiological aspects and biochemistry of bile salt formation).

Nicotinic acid is used in hyperlipidaemia. Formulations in Australia do not contribute towards client compliance.

**Drugs affecting the Gastrointestinal System**

- Proton pump inhibitors e.g. omeprazole in PUD and GORD. Hydrogen ions H+ are protons. The target of the drugs is the protein in parietal cells which pumps the H+ions.
- H2 antagonists e.g. Ranitidine (e.g. Zantac®), Cimetidine (e.g. Tagamet®) in PUD & GORD. The target is the H2 receptor for histamine on the parietal cells.
- Cytoprotective agents (sucralfate and misoprostol) and antacids in GORD, dyspepsia, PUD. Know the different Mechanisms of action.
- Drug interactions for PPI (proton pump inhibitors) and Anti-H2 agents are important examples of pharmacokinetic processes affecting absorption of many drugs.
- Antispasmodsics (antimuscarinics) e.g. Hyoscine, atropine in travel sickness. This will be covered in detail in Books on Drugs Affecting the Peripheral nervous system PNS and drugs affecting the Central Nervous System, CNS.
- Know use of loperamide in diarrhoea and irritable bowel syndrome or irritable bowel disease (Crohn’s disease, Ulcerative Colitis) when diarrhoea predominates. Traveller’s diarrhea, food poisoning (intoxication), gastro-enteritis viruses are some other causes of diarrhoea.
- Antiemetics e.g. metoclopramide. Metoclopramide is pro-kinetic in its Mechanism of action, but also review the Chemo-receptor Trigger Zone, CTZ, where it may also have actions. For indications of anti-emetics review adverse effects of the anti-neoplastics and drugs used as adjuncts to treat these ADR.

**Revision Questions / Activities**

1. Why must warfarin therapy be monitored by laboratory blood coagulation tests, despite the burden this often places on the client? How would a natural health practitioner explain the importance of this monitoring to the client? See previous session’s tutorial activities on pharmacology of warfarin.
2. Protamine and vitamin K counteract excessive coagulation (that is they are antidotes). Discuss the term antidote using warfarin as your example.
3. Summarize non-pharmacological management of hyperlipidaemia and lipid lowering drugs. The pharmaceutical therapies will be covered in detail in the tutorial activities.
4. (a) Review the factors that regulate secretion of gastric juice: neural (parasympathetic), hormonal (gastrin, histamine). The mechanism of action of the major antacids, proton pump inhibitors and H2 antagonists will be covered in the tutorial activities below.
   (b) Describe gastro-oesophageal reflux (GORD) and its treatment. Describe peptic ulcer disease and its treatment. The two cytoprotective agents and a few of the major antacids and how they work in treating peptic ulcer disease will be covered in the tutorial activities below.
   (c) Why do health professionals including natural health practitioners need to be aware of the chemistry and actions of antacids?
   (d) Discuss Helicobacter pylori and the treatment of peptic ulcer disease, PUD.
5. Discuss metoclopramide (Pramine ™ Maxolon ™) as an anti-emetic that acts on D2 receptors in the stomach and chemoreceptive trigger zone. To which drug class does it belong? Discuss its use in cancer chemotherapy-induced vomiting. (Also see Session on adjuncts to treat ADR of anti-neoplastic agents)

**Tutorial activities / Forum posts.** These could be included in your Drug Mini-monographs assignment or could be on the final exam:

For the following drugs/ drug classes list the (i) indications, (ii) mechanism of action, (iii) contra-indications or warnings and (iv) adverse drug reactions (ADR). For Warfarin (v) use the Libguides eBook by Veitch, Smith, Barnes, Anderson, and Phillipson, (2014) to find other coumarins. For the other drug classes (v) give at least two examples. Use peer review to mark your responses out of 10 marks
• Lipid lowering drugs hydroxymethylglutarylCoA reductase inhibitors
• Lipid lowering drugs fibrates and bile acid binding resins
• Warfarin and its antidote (antagonist in overdose) – Review session 4 on antidotes
• Cytoprotective agents,
• Antacids,
• Proton pump inhibitors, PPI, and
• Anti-H2 antihistamines.

Additional Resources

If you find other educationally-useful videos, add them to the Loop / Forums


From subject website, review diseases Peptic Ulcer Disease, PUD, GORD, in Handout on PUD & GORD, Practice using Drug Monographs and Herbal Medicines Monographs from Medicines Complete (LibGuides link on Endeavour Library Website). Then reflect on the case study and answer the Quiz on Mr U below:

Mr U, a 45 year old man, is currently not on anti-hypertensive therapy. Mr U is about to start triple therapy with antibiotics and a proton pump inhibitor. This is to eradicate Helicobacter pylori following a positive 13C urea breath test and endoscopy, which revealed two duodenal ulcers. He asks you as his complementary health practitioner if he can use ginger to relieve pain in his gut area. What would you recommend for Mr U? Check on Martindale (Brayfield, 2014) or Herbal section of Medicines Complete ™ (Veitch et al, 2014) (see LibGuides link on the Endeavour Library site). Alternatively, see http://evolve.elsevier.com/AU/Bryant/pharmacology Complementary and Alternative Medicine content with crossword puzzles and choose <Case Studies>

As Mr U’s complementary health practitioner, you warn him that ginger improves gastro-intestinal motility but that ginger also

a) lowers blood pressure and so would aggravate Mr U’s hypertension
b) stimulates gastric acid secretion which would aggravate Mr U’s duodenal pain
c) stimulates the growth of normal flora organisms in the bowel
d) inhibits metabolizing enzymes for his antibiotic

As his complementary health practitioner, you recommend that Mr U try probiotics to

a) decrease the adverse effects of antibiotic therapy
b) counteract the antibiotic induced diarrhoea  
c) stimulate the growth of normal flora organisms in the bowel  
d) all of the above  

What mucoprotective herbs could be recommended for Mr U?  

a) ginger and acetyl salicylic acid (ASA) from willow bark  
b) marshmallow and liquorice  
c) peppermint oil  
d) there are no mucoprotective herbal remedies  

Of the herbal remedies given in the previous question, ginger, ASA (a salicylate) from willow bark, marshmallow, liquorice, which one is also anti-inflammatory and antibacterial, making it a valuable herbal medicine for peptic ulcer disease?  

a) Ginger  
b) Acetylsalicylic acid, ASA, from willow bark  
c) Marshmallow  
d) Liquorice  

What further advice or management strategies would you suggest for Mr U?  

a) Check his blood pressure and if needed, encourage him to see a general practitioner regarding anti-hypertensive medication  
b) Check for herb-drug interactions once the anti-hypertensive medication is known to you  
c) Get Mr U to inform his general practitioner about herbal medicines that he is currently taking  
d) All of the above  

References  

SESSION 9: Drugs affecting the Endocrine System

Session Aims:
This session will provide opportunities for students to:
- Address Learning Outcomes 2,3,4 & 5
- Use the Reading Guide’s Drug Diary approach to study, this covers Learning Outcomes and Assessment Tasks for this Subject of Study.

Session Topics
- Thyroxine and thioamides (also known as thioureas) in the treatment of thyroid dysfunction
- Insulin, biguanides and sulfonylureas for the treatment of Diabetes Mellitus
- Corticosteroids and their pharmacological effects

Textbook Location, other readings and text questions

Research: The Endocrine Pancreas and Management of Diabetes Mellitus

Research: Drugs Affecting the Endocrine System, Overview of the Hypothalamus-Pituitary Axis, Pituitary and Endocrine System, The Thyroid Gland and Antithyroid Drugs, The Adrenal Cortex (General Aspects of the Adrenal Glands and Glucocorticoids), Review also the Unit “Drugs Affecting the Endocrine System” in the section called “Hormones and Drugs Affecting Bone”, Read the section on Corticosteroids only. In the section called “Pharmacology of the Adrenal Cortex”, Read “Glucocorticoids”

In “The Thyroid Gland and Antithyroid Drugs” concentrate on questions on synthesis of T3 and T4, thyroid hormones when used clinically as drugs, thionamide derivatives and iodine, hypo- and hyper-thyroid disorders

In “Pharmacology of the Adrenal Cortex” concentrate on questions on immunosuppressant and anti-inflammatory actions of glucocorticoids but do not the review of the three types of steroid hormones.

In “The Endocrine Pancreas and Management of Diabetes Mellitus” concentrate on questions on the role of insulin in regulating blood glucose levels, human insulin, formulations and regimens for administration of insulin, choosing between sulfonyl urea agents in treating type 2 DM, MolA of oral hypoglycaemics.

For case study questions see:
- From Endeavour LMS subject website, review quiz and Case Study (Drugs in Sport and Adolescence).

Summary – Drugs used in hypothyroidism and hyperthyroidism, DM types 1 and 2, Corticosteroids
- Thyroxine hormonal replacement therapy, thyroxine HRT is needed in both hyperthyroidism & hypothyroidism. Unique to hyperthyroid disorders: Need for antithyroid treatments before hormone replacement therapy. Anti-thyroid treatments to render the person euthyroid are varied but concentrate on pharmaceutical preparations in your Drug Diary, such as propylthiouracil and carbimazole (thioamides also called thioureas) in the treatment of thyroid dysfunction. Then discuss how the euthyroid status is maintained using thyroxine HRT. Need for monitoring especially cardiac monitoring and TSH levels. Liothyronine (T3) for emergency
- Insulin, biguanides and sulfonylureas for the treatment of Diabetes Mellitus. Formulations and onsets of action, insulin. Obesity and choice of oral hypoglycaemias: metformin can be used in people who are obese; glibenclamide should not be used in the client who is obese as there will be a weight gain. Know general features of insulins and oral hypoglycaemias and how lifestyle management is integral to drug treatment.
- Corticosteroids and their pharmacological effects: review immunosuppressant and anti-inflammatory modes of action; many adverse effects including metabolic, CNS. Dosage especially in chronic use (use in asthma will be reviewed again in Session 13 Drugs Affecting Respiratory Diseases).

Additional Resources

If you find other educationally-useful videos, add them to the Loop / forums

Revision Questions / Activities

1. Review the roles of TSH and ACTH in the hypothalamus-pituitary-target organ axis.
2. Name the two main thyroid hormones, state their physiological actions. Their role as drugs in hormone replacement therapy, hypothyroidism and hyperthyroidism will be discussed in the tutorial activities.
3. Discuss hyperthyroidism and the goals of treatment: Briefly discuss pharmacotherapy to achieve the euthyroid state with use of antithyroid drugs (thioureas and radioactive $^{131}$I), TSH levels in euthyroid state, then use of hormone replacement therapy T4. Some of these will be discussed in detail in the tutorial activities.
4. Review the action of glucocorticoids on the target (receptor in cytoplasm, DNA/mRNA) and effect on COX-2 synthesis, collagenase synthesis, synthesis of anti-inflammatory mediators. In the tutorial activities the pharmacotherapy role in anti-inflammation, immunosuppression, action on histamine, prostaglandins and leukotriene production will be discussed as well as explaining the ADR eg paper-thin skin (effect on collagenase synthesis).
5. Summarize the ADR of glucocorticoids (especially type C, chronic use) under these headings: cushingoid effects on metabolism; suppression of hypothalamus-pituitary-adrenal axis; effects of their mineralocorticoid actions; musculoskeletal abnormalities.
6. Discuss the need to avoid use of glucocorticoids in children, local administration to avoid ADR, alternate day dosage regimens and avoiding > 4 weeks use, avoiding abrupt withdrawal and titrating doses.
7. Why is insulin life-saving in the treatment of type 1, some people with type 2 and type 3 (gestational) diabetes? The use of short-acting, intermediate and long acting insulin formulations and other pharmaco-therapeutic aspects will be covered in the tutorial activities.
8. Discuss the reasons for choice of metformin (a biguanide) versus a sulphonylurea (e.g. glibenclamide) in DM type 2. The pharmaco-therapeutic aspects of these two oral hypoglycaemic sub-classes will be discussed in the tutorial activities.

Tutorial Activities These could be included in the Drug Mini-monographs assignment or could be on the final exam:

Discuss these medications acting on Endocrine functions. 10 marks for (i) examples (ii) indications (iii) mechanism of action (iv) efficacy and limitations or cautions / contra-indications (iv) adverse effects. Mark your own answer using the Pharmacology text or online resources. Alternatively, peer review each other’s answers, allocating 10 marks per drug class

- Glucocorticoids
- Sulphonyl ureas and biguanides (oral hypoglycaemics)
- All formulations of insulin
- Thyroxine and liothyronine (drugs used in hypothyroidism and other indications)
- Thioamides (also known as Thioureas) e.g. carbimazole, propylthiouracil (drugs used in hyperthyroidism)
SESSION 10: **Drugs affecting the Peripheral Nervous System**

**Session Aims:**
This session will provide opportunities for students to:
- Address Learning Outcomes 2, 3, 4 & 5
- Use the Reading Guide approach of compiling Drug Diaries; this covers Learning Outcomes and Assessment Tasks for this Subject of Study.

**Session Topics**
- Neurotransmitters and their antagonists in the Peripheral Nervous System (PNS)
  - neurotransmitters involved in both the Sympathetic NS (SNS) and Parasympathetic (PSNS), their receptors and involvement in physiological responses
- Anti-muscarinic drugs and their effects
- Adrenergic and anti-adrenergic drugs and their effects
- Somatic Nervous System and the Neuromuscular junction
- Acetylcholinesterase activity

**Textbook, Location of Readings**

Research: Drugs Affecting the Peripheral Nervous System, Overview of the ANS, Cholinergic Transmission, Noradrenergic Transmission, Overview of the Somatic NS & Drugs Affecting Neuromuscular Transmission

**Summary**
In this lesson we look at drugs that affect the Peripheral Nervous System (PNS). The Nervous system is divided into the central nervous system (CNS) and the peripheral nervous system (PNS). The peripheral nervous system is further subdivided into the autonomic nervous system (ANS) which is made up of the sympathetic nervous system (SNS) and the parasympathetic nervous system (PSNS) and the somatic nervous system

**Overview of the Autonomic Nervous System**
- Bryant & Knights (2011; 2015):
  - See Unit "Drugs Affecting the Peripheral Nervous System", Chapter on "Overview of the ANS...."
  - Section on Key Background, The autonomic nervous system up to Anatomical differences between the subdivisions of the ANS

**Drugs affecting cholinergic transmission**
These drugs involve the PSNS and affect acetylcholine (ACh) and can elicit either a cholinergic or anticholinergic response

Cholinergic drugs (muscarinic receptor agonists/parasympathomimetic) mimic the action of ACh on the PSNS

Anticholinergic drugs (muscarinic receptor antagonists, antimuscarinic, anticholinergic, parasympatholytic) antagonist or block the action of acetylcholine at the muscarinic receptor sites.

**Atropine & Hyoscine**
Muscarinic antagonists

**Bethanechol**
Muscarinic receptor agonist
Add Bethanechol to your summary (Drug Diary): the pharmacodynamics (Mode of Action, M of A), indications, ADR

See Unit “Drugs Affecting the Peripheral Nervous System”, Chapter “Overview of the ANS and Drugs Affecting Cholinergic Transmission”
- Section on Acetylcholine and Cholinergic Transmission up to and including Key Points

Drugs affecting noradrenergic transmission
These drugs involve the SNS and affect the sympathetic/adrenergic nervous system through the action of adrenaline, noradrenaline and dopamine

Classes of adrenergic drugs:
- Direct acting sympathomimetic (agonists)
- Indirect-acting sympathomimetic
- Adrenoreceptor antagonists/sympatholytic (blockers)

Adrenaline (A)
Is used in the emergency treatment of acute anaphylactic shock and severe allergic reaction, as an adjunct to local anaesthetics, as a haemostatic agent to control superficial bleeding, in ocular surgery to prevent bleeding and to treat cardiac arrest

Add in your Drug Diary the pharmacodynamics, pharmacokinetics, adverse effects, drug interactions and warnings and contraindications of adrenaline when used as a drug

Noradrenaline (NA)
Used to restore blood pressure in acute hypotensive states.

Add in your Drug Diary the pharmacodynamics, pharmacokinetics, adverse effects, drug interactions and warnings and contraindications of noradrenaline when used as a drug

Isoprenaline
Synthetic catecholamine used as a cardiac stimulant and in the treatment of septic shock, hypovolaemic states, congestive heart failure (CHF) and cardiogenic shock

Add isoprenaline to your summary (Drug Diary): pharmacodynamics, indications, ADR

Dopamine
Immediate precursor to NA and A and is used in the treatment of circulatory shock, haemodynamic imbalances caused by MI, open heart surgery and Congestive Heart Failure, CHF

Add dopamine to your summary (Drug Diary): the pharmacodynamics, pharmacokinetics, adverse effects, drug interactions and warnings and contraindications of this drug

α-Selective antagonists (Prazosin)
Used for the treatment of hypertension and symptomatic relief of urinary obstruction in Benign Prostatic Hyperplasia, BPH

Add the α-Selective antagonist prazosin to your summary (Drug Diary): pharmacodynamics, pharmacokinetics, adverse effects, drug interactions and warnings and contraindications of this drug

β-Blockers
Used in the treatment of hypertension, angina pectoris, myocardial infarct (MI) and glaucoma

Add in your Drug Diary the pharmacodynamics, pharmacokinetics, adverse effects, drug interactions and warnings and contraindications of β-blockers (…..-olol) drugs

See Unit “Drugs Affecting the Peripheral Nervous System” Chapter on “Overview of the Sympathetic Nervous System and Drugs Affecting Noradrenergic Transmission”

Somatic Nervous System
Division of the Peripheral NS that co-ordinates external respiration, posture and consciously controlled functions, including movement. Drugs may be used to block neuromuscular transmission as an adjunct to anaesthesia leading to muscle relaxation.
There are 2 types of neuromuscular blocking drugs. These are:

- non-depolarising (competitive)
- depolarising (nicotinic agonists)

Summarize in your Drug Diary the mechanism of action of both of these types of neuromuscular blocking drugs

Anticholinesterase Agents
These are used to reverse the effects of the neuromuscular blocking drugs after anaesthesia

See Unit "Drugs Affecting the Peripheral Nervous System", Chapter on “Overview of the Somatic NS and Drugs Affecting Neuromuscular Transmission”

Additional Resources

- Shows how a G-protein coupled receptor works. The example chosen is the adrenoreceptor for adrenaline (adrenaline = epinephrine, symbol A in the BIOP211_SN01toSN04_PharmacologyPharmacokinetics_Notes.pdf)
  (please note in your Glossary that epinephrine is called adrenaline in Australia)

- Shows good graphics for ion channels excitatory post-synaptic potentials, (EPSP)or inhibitory (IPSP) and how they are linked to conduction or inhibition of an action potential:

- Shows how a G-protein coupled receptors works:

- Drug Binding (simplified protein binding for drug action (also shows Na⁺/K⁺ excitability)):

Revision Questions / Activities
1. Which key neurotransmitter is involved in the Parasympathetic nervous system (PSNS) and which 2 types of receptors does it activate?
2. Name 1 cholinergic drug and outline its Mechanism of Action, M o A.
3. List 5 anticholinergic adverse effects
4. What are the 3 classes of adrenergic drugs?
5. Describe the cardiac effects of adrenaline.
6. What conditions is adrenaline contraindicated in?
7. How does noradrenaline differ from adrenaline in its actions? What is it therapeutically used for?
8. Compare and contrast alpha and beta blockers.
9. What receptors does ACh act upon?
10. Outline the 2 types of neuromuscular blocking drugs (Mechanism of Action, M o A).
11. What is the antidote for anticholinesterase agents?

Answer the following
- From Bryant & Knights (2011; 2015)
Review questions: Overview ANS, Drugs acting at muscarinic receptors, Drugs affecting noradrenergic transmission, Overview Somatic NS & Drugs Affecting Neuromuscular Transmission

From subject website Case Studies Drugs used in the Peripheral NS

Tutorial Activities These could be included in the Drug Mini-monographs assignment or could be on the final exam:
Discuss these medications acting in the Peripheral Nervous System, PNS. 10 marks for (i) examples (for adrenaline hormone, give other catecholamines that are neurotransmitters but also used as drugs) (ii) indications (iii) mechanism of action (iv) efficacy and limitations or cautions / contra-indications (v) adverse effects. Mark your own answer using the Pharmacology text or online resources. Alternatively, peer review each other’s answers, allocating 10 marks per drug class

- Adrenergic hormones as drugs, adrenaline (called epinephrine in the USA)
- Synthetic adrenergic agents e.g. isoprenaline
- Indirect acting sympathomimetic agents
- Alpha-selective antagonists
- Beta blockers
- Neuromuscular blocking drugs
- Anticholinesterase drugs (also known as AChE-ase Inhibitors)
SESSION 11: Drugs affecting the Central Nervous System (I)

Session Aims:
This session will provide opportunities for students to:
- Address Learning Outcomes 2, 3, 4, & 5
- Use the Drug Diary approach of studying pharmacology, as detailed below in the Reading Guide; covers Learning Outcomes and Assessment Tasks for this Subject of Study.

Session Topics
- Benzodiazepines
- Monoamine oxidase inhibitors (MAOI), selective serotonin reuptake inhibitors (SSRIs), tri-cyclic antidepressants (TCA) and the treatment of depression
- Lithium and the treatment of bipolar disorder and mania
- Anti-epileptic drugs
- Antipsychotics in the treatment of schizophrenia
- Levodopa (L-Dopa) - carbidopa in the relief of Parkinson’s symptoms
- Central nervous system (CNS) depressants e.g. alcohol

Textbook Location of Readings

Research: Antianxiety, Sedative & Hypnotic Drugs; Anti-epileptic Drugs; Psychotropic Agents; Drug treatment of Parkinson’s disease, Drugs used in Migraine & other Headaches; CNS Depressants (Alcohol)

Summary
- See Unit “Drugs Affecting the Central Nervous System”, Chapter on “Anti-anxiety, Sedative and Hypnotic Drugs”
  - Section on Key Background: Sleep and Anxiety.
- Summarize the pathophysiology and signs and symptoms of anxiety and insomnia

Benzodiazepines
These drugs are the most commonly prescribed drugs for the treatment of both anxiety and insomnia.
- See Unit “Drugs Affecting the Central Nervous System”, Chapter on “Anti-anxiety, Sedative and Hypnotic Drugs”
  - Section on Benzodiazepines.

Summarize in your Drug Diary the pharmacodynamics, pharmacokinetics, adverse effects, drug interactions and warnings and contraindications of benzodiazepines

Treatment of Affective Disorders
There is no single factor identified as to the cause of affective disorders. These include depression, mania and bipolar disorder. A possible theory is that of the monoamine theory where an imbalance in the centrally acting catecholamine neurotransmitters are believed to be the cause.

- See Unit “Drugs Affecting the Central Nervous System”, Chapter on “Psychotropic Agents”
  - Section Treatment of Affective Disorders, up to Key Points

Depression
Depression can be divided into 3 main classes:
- major depressive disorder
- bipolar affective disorder
- dysthymia

Summarize the pathophysiology, aetiology and signs and symptoms of depression
Drugs used for depression
There are 4 main groups of antidepressants:
- Tricyclic antidepressants (TCA)
- Selective Serotonin Reuptake Inhibitors (SSRIs) and Selective Noradrenaline reuptake Inhibitors (SNRI) and Noradrenaline Serotonin Reuptake Inhibitors (NSRI)
- Monoamine Oxidase Inhibitors (MAOI) and reversible inhibitors of monoamine oxidase

Summarize in your Drug Diary the pharmacodynamics, pharmacokinetics, adverse effects, drug interactions and warnings and contraindications of TCAs, SSRIs, SNRI, MAOI and RIMA

Bipolar Disorder
Characterised by cyclic episodes of elation (mania) or depression and is associated with various behavioural features such as psychotic symptoms

Summarize the pathophysiology, aetiology and signs and symptoms of bipolar disorder
Summarize in your Drug Diary the pharmacodynamics, pharmacokinetics, adverse effects, drug interactions and warnings and contraindications of Lithium

Epilepsy
Describes a group of neurological disorders characterised by recurrent sporadic episodes of convulsive seizures.

See Unit “Drugs Affecting the Central Nervous System”, Chapter on “Anti-epileptic Drugs”

Summarize the pathophysiology, aetiology and signs and symptoms of epilepsy

There are 3 main groups of anti-epileptic drugs. AEDs could
- enhance GABA-mediated inhibition of neural activity
- inhibit sodium channel function, thus blocking repetitive depolarisation of neurons
- miscellaneous

Summarize in your Drug Diary the main indications, pharmacodynamics (M of A) and ADR of Barbiturates, Phenytoin, Topiramate, Sodium valproate and Gabapentin

Schizophrenia
Manifested by disordered mood, thought, perception and volition leading to delusion, withdrawal and loss of insight.

See Unit “Drugs Affecting the Central Nervous System”, Chapter on “Psychotropic agents”
- Section on Antipsychotic Agents up to Conventional (typical) antipsychotics

Summarize the pathophysiology, aetiology and signs and symptoms of schizophrenia

The typical and atypical antipsychotic drugs are used to treat this disorder
Summarize in your Drug Diary the pharmacodynamics (M of A), pharmacokinetics, adverse effects, drug interactions and warnings and contraindications of typical and atypical antipsychotic drugs

Parkinson’s Disease
Progressively debilitating disorder of the basal ganglia, characterised by tremor at rest, bradykinesia, forward flexion of the trunk, muscle rigidity, loss of postural reflexes and weakness.

See Unit “Drugs Affecting the Central Nervous System”, Chapter on “Drugs for Neurodegenerative Disorders……”
- Section on Parkinson’s Disease up to Monographs on Levodopa-Carbipoda

Summarize the pathophysiology, aetiology and signs and symptoms of Parkinson’s Disease
Summarize in your Drug Diary the pharmacodynamics, pharmacokinetics, adverse effects, drug interactions and warnings and contraindications of Levodopa (L-Dopa)-Carbidopa

CNS depressants
Alcohol is a CNS depressant with multiple effects across body systems

See Unit “Drugs Affecting the Central Nervous System”, Chapter on “Drug Dependence and Social Pharmacology”
- Section on Pharmacological effects of ethanol, up to Problems from alcohol abuse
From a pathophysiology text eg Kumar & Clark (eds) (2013), Research Alcohol in Chapter 5 "Nutrition" thiamine deficiency and section on Alcohol and Chapter 22 "Neurological Disease" look for the section on Toxic neuropathies (Jarman, 2013)

Summarize the toxic effects and toxicokinetics of alcohol

Additional Resources

If you find other educationally-useful videos, add them to the Loop / forums

- From a pathophysiology text eg Kumar & Clark (eds) (2013), Research Alcohol in Chapter 5 "Nutrition" thiamine deficiency and section on Alcohol and Chapter 22 "Neurological Disease" look for the section on Toxic neuropathies (Jarman, 2013)

Revision Questions / Activities

1. Which neurotransmitter do benzodiazepines act upon?
2. Benzodiazepines have different half-lives. How is this used therapeutically and give examples of the indications for this?
3. Outline the adverse effects of Benzodiazepines, BZD
4. Compare and contrast TCAs, SSRIs and MAOI (Include Mechanism of Action, adverse effects and indications and give an example of each). TCA = T_-C_____ antidepressants, SSRI = S_________ S________ R________ Inhibitors, MAOI = M_-A_____ O__________ase Inhibitors
5. What is the drug of choice in the treatment of bipolar affective disorder?
6. Outline some of the adverse effects of Lithium and explain why these happen?
7. Give the three therapeutic classes of anti-epileptic drugs and give examples of AEDs (Anti-E______ Drugs) from each class.
8. What advantage do the atypical have over the typicals in the treatment of Schizophrenia?
9. What is the Mechanism of Action of carbipoda and how does it improve the efficacy of Levodopa (L-Dopa) ?

Answer the following:

- From Bryant & Knights (2011; 2015)
  - Review questions: Antianxiety, Sedative & Hypnotic Drugs; Anti-epileptic Drugs; Psychotropic Agents; Drug treatment of Parkinson's disease, Drugs used in Migraine & other Headaches; CNS Depressants (Alcohol)

From Endeavour LMS subject website, Case Study on Schizophrenia

Tutorial Activities These could be included in the Drug Mini-monographs assignment or could be on the final exam:

Discuss these pharmaceutical medications. 10 marks for (i) examples (for lithium and Levodopa (L-Dopa) discuss therapeutic index or pharmacokinetics) (ii) indications (iii) mechanism of action (iv) efficacy and limitations or cautions / contra-indications (v) adverse effects. Mark your own answer using the Pharmacology text or online resources. Alternatively, peer review each other's answers, allocating 10 marks per drug class

- Sedatives and anxiolytics
- Monoamine oxidase inhibitors (MAOI), selective serotonin reuptake inhibitors (SSRIs), tri-cyclic antidepressants (TCA) and the treatment of depression
- Lithium and the treatment of bipolar disorder and mania
- Anti-epileptic drugs
- Antipsychotics in the treatment of schizophrenia
- Levodopa (L-Dopa) -carbidopa in the relief of Parkinson's symptoms
SESSION 12 Drugs affecting the Central Nervous System (II)

Session Aims:
This session will provide opportunities for students to:
- Address Learning Outcomes 2, 3, 4 & 5
- Use the Reading Guide approach to compiling a Drug Diary; this covers the Learning Outcomes and Assessment Tasks for this Subject of Study.

Session Topics
- Endogenous substances involved in pain
- Opioid analgesics
- Opioid antagonists
- Non-opioid analgesics

Textbook, Location of Readings

Research: overview of the CNS, Analgesics

Summary

The Central Nervous System (CNS)
The CNS is composed of the brain and spinal cord and essentially controls all functions of the body.
- Read Bryant & Knights (2011; 2015)
  - Overview of the Central Nervous System up to Action potentials and ion channels

CNS and drug therapies
Drugs affecting the CNS are very important in pharmacology and most drugs used to treat disorders of the CNS do so via modification of neurotransmission

Pain
Pain is a symptom experienced by nearly everyone and each person’s experience is individual and subjective. It is a protective mechanism to warn the body to do something differently. Inflammation of tissues generally leads to pain and drugs with both analgesic and anti-inflammatory properties are useful

Opioid Analgesics
There are high concentrations of opioid receptors throughout the body that are involved in pain transmission and perception and the natural opioids (endorphins and enkephalins) act by enhancing inhibitory effects at these receptors.
Examples of these drugs are:
- Morphine
- Codeine
- Buprenorphine
- Summarize the pharmacodynamics, pharmacokinetics, adverse effects, drug interactions and warnings and contraindications of opioid analgesic drugs

Opioid Antagonists
Naloxone and naltrexone are competitive opioid antagonists that displace opioid analgesics from opioid receptors thus reversing their effects.

Non opioid analgesics
Examples are paracetamol and NSAIDs
- Review the pharmacodynamics, pharmacokinetics, adverse effects, drug interactions and warnings and contraindications of paracetamol and NSAIDs
- See Unit “Drugs Affecting the Central Nervous System”, Chapter on Analgesics
Pre / Post Session readings

The reading material that the students are directed to can be used either as pre-reading or post-reading dependant on the student’s individual study requirements

- From Bryant & Knights (2011; 2015):
  Research: Drugs Affecting the Central Nervous System, Analgesics

Additional Reading

- If you find other educationally-useful videos, add them to the Loop / forums

Revision Questions / Activities

1. Name 5 neurotransmitters involved in the CNS.
2. Describe factors that both raise and lower the pain threshold.
3. Name 2 opioid analgesics and outline the MoA (Mechanism of Action), indications, adverse effects and warnings and contraindications of each of these.
4. Describe the effect that opioid analgesics have on the pupils of the eyes.
5. Name one of the most common adverse effects of opioid analgesics and outline how this can be used beneficially (review Session 8 Drugs affecting the Gastro-intestinal Tract)
6. What benefit does paracetamol have over NSAIDs(N_\_S_________ A__________ I_________ Drugs) in the treatment of pain?

Answer the following:

- From Bryant & Knights (2011; 2015)
  - Review questions: Analgesics

From Endeavour LMS subject website, and Case Study, Session 11 and Paracetamol (also reviews Session 6 non-opioid analgesics)

- Migraines and the various acute and prophylactic treatments – Case Study

Tutorial Activities These could be included in the Drug Mini-monographs assignment or could be on the final exam:

Discuss these pharmaceutical medications. 10 marks for (i) examples (for paracetamol, give other non-opioid analgesics that may not necessarily have CNS actions but have similar indications) (ii) indications (iii) mechanism of action (iv) efficacy and limitations or cautions / contra-indications (v) adverse effects. Mark your own answer using the Pharmacology text or online resources. Alternatively, peer review each other’s answers, allocating 10 marks per drug class

- Opiates and opioids
- Opioid antagonists
- Paracetamol
- Anti-migraine preparations, including prophylactics and those used for acute attacks
SESSION 13: Drugs Affecting the Cardiovascular System, Drugs Affecting the Respiratory System

Session Aims:
This session will provide opportunities for students to:
- Address Learning Outcomes 2, 3, 4 & 5
- Use the Reading Guide approach to compiling a Drug Diary. To use higher processes (cohesion, application and synthesis) on concepts in the Drug Diary and to critique achievement of Learning Outcomes towards the Final examination Assessment Task in BIOP211 Pharmacology.

Session Topics
Drugs affecting the Cardiovascular System –
- Briefly describe blood pressure and its causes
- Anti-hypertensives and their mode of action
- Give a brief overview of angina
- Anti anginal drugs and their mode of action
- The mode of action and important features of drugs used to manage heart disease

Drugs affecting the Respiratory System
- Drugs in the treatment of asthma
  - β2 agonists, methylxanthine (theophylline), anti-muscarinics, anti-allergy and anti-inflammatories
- Actions and adverse effects of anti-tussives, expectorants, mucolytics and decongestants
- Anti-histamines

Textbook Location of Readings

Research: Overview the Respiratory System and Drugs Used in Respiratory Disorders; “Key Background”, “Drug Delivery by the Inhalation Route”, Respiratory Depressants, , “Drugs Affecting Secretions & Mucociliary Transport”, “Drug Treatment of Asthma”, H-1-receptor antagonists (anti-histamines)

Research: Overview of Heart & Vascular System, Drugs Affecting Cardiac Function Cardiac glycosides Digoxin, Drugs Affecting Vascular Smooth Muscle, including “Key Background”, “Angina”, “Direct-Acting Vasodilator Drugs”, Management of hypertension

Summary
Drugs affecting the Cardiovascular System –
- Briefly describe blood pressure and its causes: Cardiac output: the volume of blood ejected by the left ventricle per unit of time; Peripheral resistance: resistance of the blood vessels to the flow of blood
- Blood Pressure = Cardiac Output x Total Peripheral Resistance; Defined as elevated systolic blood pressure, diastolic blood pressure (Australian Institute for Health and Welfare, 2011, Chapter 4, p.21)
  Part of this report can be accessed at http://www.heartfoundation.org.au. Non-pharmacological measures must be followed for aims of pharmacological treatment of hypertension to be achievable: Weight and alcohol reduction; Limiting dietary sodium intake; Programme of regular physical activity.
- Anti-hypertensives and their mode of action: Diuretics; β-blockers; ACE-inhibitors; Angiotensin II receptor antagonists; Calcium channel blockers; Alpha-blockers; Hydralazine; Centrally-acting drugs. Know important features such as Mode of Action (MoA), of these anti-hypertensives as well.
- Give a brief overview of angina: Ischaemic heart disease has many clinical manifestations, including stable angina, unstable angina, Prinzmetal’s angina, silent myocardial ischaemia, acute coronary insufficiency and myocardial infarction. Of these, angina is the most frequently encountered symptom.
• Anti anginal drugs and their mode of action, MofA: prophylactic management of stable angina with β-blockers; Calcium channel blockers; Nitrates; Potassium channel openers. Know important features of these anti-anginals as well.
• The mode of action, MofA, and important features of drugs used to manage heart disease: Modifiable risk factors include: Hypertension; Hyperlipidaemia (See Session 8 Lipid-lowering drugs for a review of this modifiable risk); Diabetes Mellitus; Cigarette smoking; Obesity. Diuretics MofA covered under hypertension); Vasodilators: ACE-inhibitors (MofA covered under hypertension); Peripheral vasodilators (MofA covered under angina); Inotropic vasodilators; β-Blockers (very few indicated for Congestive Cardiac Failure CCF but one e.g. Carvedilol); Positive inotropic agents e.g. Digoxin (cardiac glycoside); Dopamine antagonists; Anti-arrhythmic agents — see metoprolol, sotalol in the tutorial handout for ADR and Use with Caution as well as indications of these beta-blockers).

Drugs Affecting the Respiratory System – corticosteroids
Corticosteroids and their pharmacological effects: immunosuppressant and anti-inflammatory modes of action; many adverse effects including metabolic, CNS. Dosage especially in asthma and other chronic use is to use the lowest dose possible while balancing adverse effects. Dosage in children is problematic because of effects on growth and bone density (review adverse effects of steroids).

Drugs affecting the Respiratory System – anti-asthmatics.
Asthma is caused by bronchoconstriction with inflammation and bronchial hyper-responsiveness. Histamine is released from Mast Cell during the inflammatory stage.

Drugs in the treatment of asthma
β2 agonists, methylxanthines, anti-muscarinics, anti-allergy and anti-inflammatories
○ Relievers: SABA, Short-acting β2 agonists (SABA) Salbutamol (e.g. Ventolin®), terbutaline (e.g. Bricanyl®), Short-acting methylxanthine is Theophylline, Anticholinergics e.g. Ipratropium (e.g. Atrovent®)(used more frequently in COPD than asthma)
○ Symptom controllers: LABA (Salmeterol, eformoterol, salbutamol long acting formulations), provide prolonged bronchodilation for up to 12 hours in adult and childhood asthma.
○ Preventers: Inhaled corticosteroids (ICS) e.g. Beclomethasone (Qvar®), budesonide (Pulmicort®); Chromones (often used in children) e.g. Sodium cromoglycate (Cromese®) which stabilizes mast cells. nedocromil (Tilade®) (Anti-inflammatory), Leukotriene receptor antagonists (LTRA) e.g.Zafirlukast

Know dosage regimens and strategies to avoid adverse effects with glucocorticoids: local administration to avoid systemic ADR, alternate day dosage regimens and avoiding > 4 weeks use, avoiding abrupt withdrawal and titrating doses.

Drugs affecting the Respiratory System – anti-tussives, expectorants, mucolytics, cough mixtures
Actions and adverse effects: of anti-tussives (not for productive coughs); expectorants (change amount or characteristics of mucus); mucolytics (e.g. acetylcysteine, also an antidote in paracetamol overdose); and decongestants (and other active ingredients in cough mixtures). Adverse effects expectorants and mucolytics mild at doses used.

Adverse effects cough suppressants (opioids): Nausea, vomiting, drowsiness, sedation, constipation, dependence, withdrawal (common with other opioids).

Many over the counter preparations (OTC) available as cough mixtures and treatments for symptoms of Lower Respiratory Tract Infections LRTI, Upper Respiratory Tract Infection URTI symptoms rhinitis, sinusitis etc; Patients tend to self-manage / ask pharmacist but there is little documented evidence of true efficacy or benefit. There are few adverse effects at the doses used. Cough mixtures and cold/flu preparations are usually multi-ingredient preparations including one or more of the following: Antitussives; antipyretic/ analgesics; expectorants; antihistamine; Mucolytics; vitamin C; menthol; camphor; cetlypyridium CI; decongestants; antimuscarinics.

Anti-tussives (cough suppressants) are usually narcotics (opioids) and derivatives of Codeine Examples: pholcodeine / dihydrocodeine). Dextromethorphan (a morphine derivative). Usually reserved for dry hacking non-productive coughs. Interrupt the cough reflex by direct depression of the medullary cough centre. Reduce the severity and frequency of cough at doses used, rather than suppress it, as there is a need to be able to clear excess mucus from the lungs.
Drugs affecting the Respiratory System – antihistamines

- Diphenhydramine (Benadryl®), Dextchlorpheniramine (Demazin®), Polaramine®, Loratidine (Claratyne®), Promethazine (Phenergan®). Indications – respiratory disorders e.g. rhinitis (allergic/histamine component).

- Mechanism of action - block histamine-induced vasodilation, decreasing capillary permeability, erythema and oedema at H1 receptors. Reduce excessive mucus by a secondary antimuscarinic action;

- Know adverse effects & explain reason behind the CNS induced drowsiness (discuss receptor specificity). Adverse effects of Antihistamines: Sedation, unco-ordination, lack of concentration, lassitude, blurred vision, constipation, urinary retention.

- Warnings & Precautions: The older H1 – antihistamines (promethazine, diphenhydramine) have powerful sedative effects. Additive effect with other CNS depressants including alcohol.

Additional Reading

- If you find other educationally-useful videos, add them to the Forums / Loop


Revision Questions / Activities

1. Review the advantages and disadvantages of administering drugs by the inhalation route.

2. Research Therapeutic Drug Monitoring and discuss, digoxin, how it can itself cause arrhythmias, its therapeutic index, how toxicity is treated.

3. Name three types of angina pectoris and describe the treatment using vasodilators (organic nitrates, calcium channel blockers, potassium channel activators)

4. Why is it important to control hypertension? and describe the treatment of hypertension using diuretics, vasodilators, drugs that act on the renin-angiotensin-aldosterone system and centrally acting agents. These drugs will be covered below in tutorial activities.

5. Why do most people on an ACE Inhibitor develop a cough?

6. Summarize the non-pharmacological management of hypertension and explain why combination drug therapies are often required. The anti-hypertensive drug therapies will be covered in the tutorial

7. Discuss the need to avoid use of glucocorticoids in children, local administration to avoid ADR, alternate day dosage regimens and avoiding > 4 weeks use, avoiding abrupt withdrawal and titrating doses.

8. Discuss the mucolytic acetylcysteine. What are its adverse effects? Name another indication other than as a mucolytic (Review Session 4 on antidotes).

9. Review the autacoid mediators: leukotrienes, histamine, prostaglandins; cyclic AMP, cAMP, and the neurotransmitter, acetylcholine and the hormone adrenaline in the pathophysiology of asthma. The mechanisms of action of the major anti-asthma drugs will be covered below in the tutorial activities.
Tutorial Activities – These drugs may be negotiated for inclusion in your Drug Mini-Monographs assignment if you have completed Pathology and Clinical Sciences 1 (BIOC211) as a pre-requisite. They are on the final exam.

For the following drugs/ drug classes list the (i) indications, (ii) mechanism of action, (iii) contra-indications or warnings and (iv) adverse drug reactions (ADR) (v) give at least two examples. For theophylline, the xanthine derivative, give at least two food / herb interactions that clients should avoid. Use peer review to mark your responses out of 10 marks

- Loop diuretics
- Thiazide and thiazide-like (indapamide) diuretics
- Potassium-sparing diuretics
- Theophylline (xanthine derivative), mast cell stabilizers, beta2-agonists, cromones (also briefly mention use of glucocorticoids) (anti-asthma drugs)
- Glucocorticoids (Respiratory system indications – see above anti-asthma drugs)
- Anti-arrhythmic drugs (many but concentrate on calcium channel blockers – below – and beta-adrenergic blockers given in the tutorial handout)
- Calcium channel blocking drugs (all indications)
- Angiotensin Converting Enzyme inhibitors ACE I, and Anti-angiotensin II Receptor agents (Anti-All)

Answer the following:

From Bryant & Knights (2011; 2015)

- Review questions: Cardiac Glycosides, Drugs Affecting Smooth Muscle. Also in the Unit Drugs Affecting the Heart and Vascular System, Chapter on “Drugs Affecting Vascular Smooth Muscle” complete questions on glyceryl trinitrate, calcium-channel blocking drugs, renin-angiotensin-aldosterone system, ACE inhibitor cough, aldosterone-receptor antagonists, combination anti-hypertensives. For case studies, see case study Mrs F below and Endeavour LMS quiz

- Drugs Used in Respiratory Disorders (Asthma and questions on anti-tussives, expectorants, mucolytics and decongestants, antihistamines). Please ensure that corticosteroids (glucocorticosteroids) have been entered into your Drug Diary as indicated in asthma and other LRT diseases.

- From Endeavour LMS subject website, review quiz including a Case Study on Drugs Affecting the cardiovascular system

- Another Case Study on CCF: Mrs F, a 64 year-old patient with heart failure is on regular medications including digoxin and an anti-hypertensive medication. She speaks to her complementary health practitioner about a newspaper article that promotes hawthorn as a treatment for a weak heart. Mrs F tells you that she wants to try hawthorn. How would you counsel her as her complementary health practitioner?

Check on Martindale (Brayfield, 2014) or Veitch, Smith Barnes, Anderson and Phillipson (2014) which are some eBooks from Medicines Complete ™ (see LibGuides link on the Endeavour Library site) or alternatively, see http://evolve.elsevier.com/AU/Bryant/pharmacology Complementary and Alternative Medicine content with crossword puzzles and choose <Case Studies>

In making a recommendation to Mrs F, you research digoxin. You find that the mode of action of digoxin is

- A positive inotropic effect (greater force of contraction)
- A positive chronotropic effect (greater heart rate)
- A positive effect on conduction (faster conduction through the atrio-ventricular, AV, node)
- All of the above.

You also summarize hawthorn’s effects for Mrs F. In your summary, you discuss how hawthorn

- improves coronary blood flow
- stabilises heart rhythm
- has a positive inotropic effect (greater force of contraction)
- all of the above
You explain to Mrs F that there is a serious consequence of taking digoxin and hawthorn together. That consequence is an interaction based on:

a. increased metabolism of digoxin due to inhibition of liver and gastro-intestinal tract enzymes.
b. a pharmaco-chemical interaction where there is a pH interaction.
c. pharmacokinetics where both drugs compete for albumin binding sites and so there is less active drug.
d. pharmacodynamics where there is an additive or synergistic effect on the force of contraction of the heart.

If hawthorn interacts with her blood pressure lowering medication the interaction could be to:

a. metabolise the anti-hypertensive faster making Mrs F’s blood pressure drop excessively
b. pharmacodynamically add to give a greater rise in her blood pressure
c. potentiate the blood pressure lowering effects making orthostatic hypotension more likely
d. neutralize its pH

In managing Mrs F’s heart failure what other advice is necessary? If Mrs F does take the hawthorn she needs to:

a. keep in contact with you and her general practitioner (gp) regularly
b. inform her pharmacist about herbal remedies she is taking
c. tell you and her gp about any episodes of dizziness
d. all of the above

Furthermore, what monitoring would be required in Mrs F’s case, if she was to choose to take hawthorn, as well as her two currently prescribed medications?

a. Blood glucose levels
b. Serum urea and creatinine
c. Blood pressure
d. All of the above

References