LESSON:1

Fundamentals of Pharmacology

L1 LEARNING OUTCOMES:

-Differences between pharmacology, therapeutics, pharmacy and toxicology
-Define the term “drug” and explain how drugs are categorised and named, giving examples
-Summarise the key mechanisms by which drugs might produce their effects
-Explain what is meant by the pharmacokinetic and pharmacodynamic properties in drugs
-Recognise the importance of absorption, distribution, metabolism, and excretion (ADME) of drugs in determining their therapeutic effectiveness

PHARMACOLOGY:

-The science of drugs; their mechanisms of action
-How their effects can be measured
-Their discovery, design, and development
-Their actions on the organism and the actions of the organism on them.

THERAPEUTICS :

The medicinal use of drugs to treat or relieve the symptoms of disease.

PHARMACY:

How drugs are formulated and dispensed for use as medicines.

TOXICOLOGY:

The branch of pharmacology that focuses on the harmful effects of chemicals, including drugs.

WHAT IS A DRUG?

A chemical substance of known structure other than a nutrient or an essential dietary ingredient, which, when administered to living organism, produces a biological effect.

NAMING DRUGS

Drugs that are used therapeutically typically have at least three names.
chemical name
common name
proprietary name

e.g.
(RS)-2-(4-(2-methylpropyl)phenyl)propanoic acid
Ibuprofen
Nurofen

Drugs are usually grouped according to therapeutic use,
e.g. analgesics, antihypertensives, antibiotics
Or sometimes by mechanism of actions,
e.g. cyclooxygenase inhibitor, beta-blocker
For example,
Ibuprofen —> cyclooxygenase inhibitor —> acs as an analgesic

HOW DRUGS PRODUCE THEIR EFFECTS:

-Drugs are exogenous molecules that mimic or block the actions of endogenous molecules.
Exogenous: growing or originating from outside an organism.
Endogenous: growing or originating from within an organism.
"A drug will not work unless it is bound."Paul Ehrlich (1854-1915)
-The vast majority of drugs bind to molecular target proteins
-These target proteins include:
Receptors for neurotransmitters or hormones
Enzymes
Ion channels
Carrier or transporter molecules

COMPLEMENTARITY

The small drug molecules that bind to large target proteins are called ligands.
How well a drug "fits" into its binding site is governed by the size and flexibility of the drug (steric factors)
How well the drug binds to its target protein is determined by the nature of the chemical bonds that form between the drug molecule and its binding site.
Most drugs (ligands) bind reversibly to the target protein through hydrophobic interactions and hydrogen bonds plus weaker Van der Waals interaction.
Some bind irreversibly through covalent interactions.
Ultimately this leads to the formation of a ligand-protein complex which alters the activity of the protein in some way.

SPECIFICITY AND SELECTIVITY

For a drug to be useful therapeutically it must be very selective in its action.
e.g. an antihypertensive drug that lowers blood pressure, but at the same time causes severe gastrointestinal problems, is not going to be useful in treating patients with high blood pressure.
One way of achieving this selectivity is to design drugs that bind with a high degree of

specificity to their target protein. Ideally they will bind ONLY to their target protein and no others.
In reality, no drug binds with complete specificity, though some get close, and this is one reason why no drug is free from unwanted side effects.

PHARMACODYNAMICS AND PHARMACOKINETICS

Pharmacodynamics: what the drug does to the body
i.e. the consequences of the drugs's actions at a molecular level on the physiology of an organism.

Pharmacokinetics: what the body does to the drug
i.e. how the drug is "handled" by the organism.
e.g. how it gets to its site of action, how it is metabolised or how it is distributed to the different organs.
When drugs are being developed for therapeutic use, a true understanding of the drugs effectiveness only comes when pharmacodynamics and pharmacokinetics are considered together, so-called PK/PD studies.

ADME: ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION

These are the critical elements of pharmacokinetics.
Each can be influenced by the properties of the drug
e.g. absorption of a drug from the gut will be influenced by whether the drug is stable in the acid environment of the stomach; and the characteristics of the person taking the drug.
a patient suffering from liver damage will not metabolise a drug as well as a patient with a healthy liver.

ABSORPTION

How much and how quickly the drug enters the system
Influenced by the chemical properties of the drug
its molecular size
its lipid solubility, in turn influenced by its ionisation
its chemical stability
Rate of absorption depends upon the route by which the drug is administered

ROUTES OF ADMINISTRATION :

- oral (po): swallowed (tablet, capsule, liquid)
- rectal: suppository containing drug
- nasal: applied to nasal membranes (drops, fine powder, spray)
- sublingual: held beneath the tongue (usually tablets or capsules)
- topical: applied directly to affected area (creams, patches; eye-drops)

- inhalational: inhaled (gas, fine powder, vapour, smoke)
- intra-arterial (ia): injected into an artery - very rare in human medicine (liquid)
- intracerebroventricular (icv): injected into the cerebral ventricles (liquid)
- intradermal: injected under the skin layer (liquid or suspension)
- intramuscular (im): injected into the muscle mass(liquid or suspension)
- intrathecal (it): injected into the membranes that enclose the spinal cord
- intravaginal: pessary containing drug
- intravenous (iv): 'bolus' or 'infusion' injected into a vein (liquid)
- subcutaneous (sc): injected just beneath skin (liquid or suspension)
- transdermal: by diffusion through the skin from an adherent patch

DISTRIBUTION:

where does the drug go after it has been absorbed?
Usually drugs are distributed around the body by circulating in blood plasma and diffusing through the tissues dissolved in the extracellular fluid (ECF)
The ability of a drug to dissolve in plasma or ECF is determined by its water (aqueous) solubility.
When studying drug action we usually measure its concentration in blood plasma, the assumption being that the concentration in plasma will be related to the concentration of the drug at its site of action (in the brain, for example).
Of course, things are never that simple.

INTERFERING FACTORS

-Does the patient have adequate circulation?
-Does the drug bind to proteins in blood plasma, in particular albumin.
-drugs bound to albumin are “trapped” in plasma
-Does the drug “partition” into body fat stores; drugs dissolved in body fat are not active.
-Can the drug gain access to the organ it acts on?
-most notable here is the brain which s protected by the “blood brain barrier (BBB)”. Many drugs struggle to cross the BBB.
To “quantify” the impact of these factors we measure a parameter called the Volume of Distribution (Vd) which is the volume the drug would occupy IF the total amount administered was dissolved in solution at the same concentration as that found in blood plasma.

METABOLISM AND EXCRETION
These two factors determine how long the effects of a drug last.

METABOLISM

Drugs are usually metabolised (broken down) in the liver to metabolites which are in turn excreted by the kidneys.
But things to consider include;

-does the patient have a healthy liver?
-how effective are the liver enzymes?
e.g. genetic differences between patients
-are the metabolites active ?
e.g. codeine is metabolised to morphine
-are the metabolites toxic?
e.g. paracetamol toxicity is due to a harmful metabolite, not paracetamol itself.

EXCRETION

Whilst most drugs (or at least their metabolites) are excreted in the urine, other routes of excretion include the faeces, sweat, bile, breath and breast milk.

HALF-LIFE (t½)

metabolism and excretion determines a drug's half life
Half-life: the time it takes for the plasma concentration (A) to fall by half.

CLEARANCE

Related to a drug's half life,
Clearance: the volume of blood plasma cleared of the drug in unit time
e.g. ml of plasma per minute or litres of plasma per hour

L2 LEARNING OUTCOMES:

-Identify key moments in the history of the pharmaceutical industry
-List the main sources of drugs, giving example from each source
-Describe the key stages in the drug discovery process
-Explain what is meant by the term "structure-activity relationship" and why it is important in drug development.

KEY DATES IN PHARMACOLOGY AS A SCIENCE

4000 BC: Poppy extracts used by Babylonians
1550 BC: Egyptian Ebers papyrus lists 400 remedies
460 BC: Hippocrates born
1493-1541: Paracelsus "All remedies are poisons"
1530: Paracelsus dissolved opium in alcohol to produce "laudanum"
1803: Setürner isolates morphine from opium
1856: Claude Bernard shows that curare blocks neuromuscular transmission
1905: The concept of drug receptors developed by John Langley.
1906: The concept of drug receptors developed by Paul Ehrlich.
Mid 1900s: AJ Clark, Heinz Schild, John Gaddum consolidate our ideas of drug-receptor interactions.

DEVELOPMENT OF THE PHARMACEUTICAL INDUSTRY

~Biomedical sciences, notably pharmacology
~Chemistry, notably synthetic organic chemistry
~Therapeutics and a better understanding of disease mechanisms
The modern pharmaceutical industry emerged at the intersection between these three critical areas

KEY DATES IN THE DEVELOPMENT OF THE PHARMACEUTICAL INDUSTRY

1900: Paul Ehrlich shows syphilis can be treated with arsenical compounds.
1932: "Prontosil" the first sulphonamide antibacterial developed by the Bayer company. Led to era of drug development led by chemists
1960s, 70s and 80s: The era of "rational drug design" e.g. beta blockers, ACE inhibitors. Led by pharmacologists such as Sir James Black.
1990s: The drug discovery process revolutionised by techniques such as high throughput screening and combinatorial chemistry.
2000 to date: Increasing development of "biologicals" e.g. human insulin or anti cancer antibodies.
2002: Human genome mapped
20006: Northwick Park Phase 1 clinical trial went wrong

THE DRUG DISCOVERY PROCESS

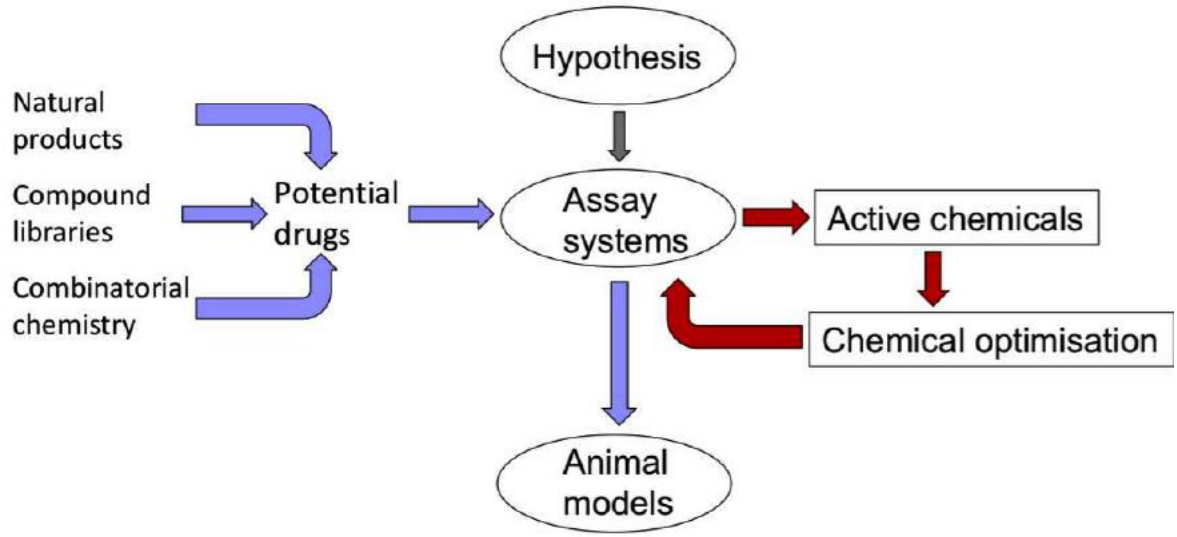
Basic research in universities for example
Leads to a better understanding of physiology and disease mechanisms
—>
Identification of potential drug targets
Looking for molecular targets (usually proteins) that play a crucial role in the disease
—>
Hypothesis generated
A drug that acts on that target to change its activity will be effective in treating disease

OTHER CONSIDERATIONS DURING THE DRUG DEVELOPMENT PROCESS

-Safety issues
will the drug harm patients or the environment?
-Ethical issues
is development of such a drug civilised behaviour? e.g. cognitive enhancers
- Intellectual property
is the drug covered by a patent?
is the basic hypothesis someone else's intellectual property?
- Cost

does it make good business sense to develop a drug to treat a particular condition?

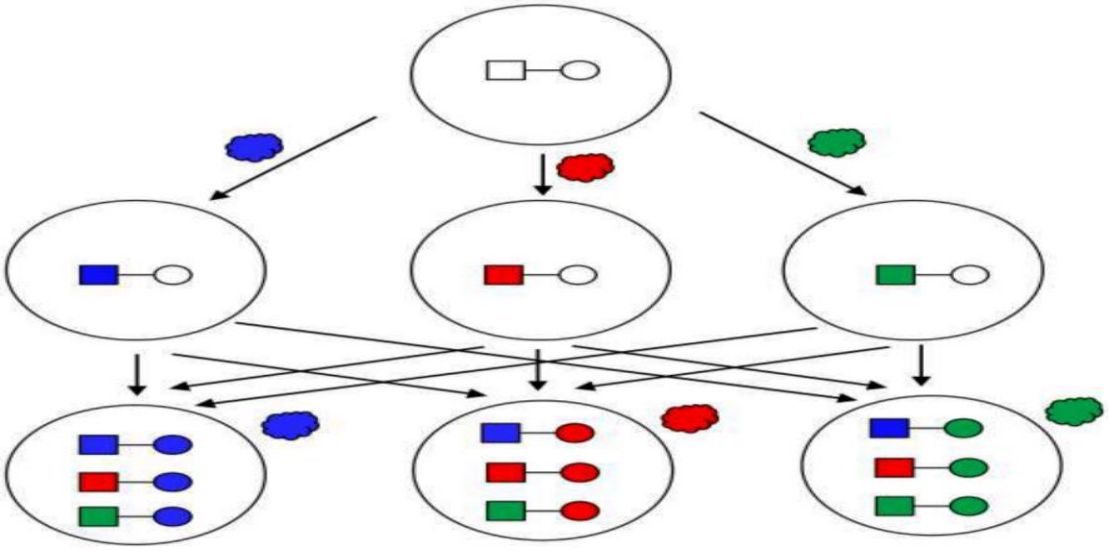
DRUG DISCOVERY



WHERE DO DRUGS COME FROM?
Many are natural products or “derivatives” of natural products (so called semi-synthetic drugs)

COMBINATORIAL CHEMISTRY

Imagine a molecular skeleton with 2 attachment points (square and circle)
We react the first attachment point with 3 different substituents (red, blue, green)
The products of the first reaction are then mixed, and the second attachment point reacted with the same 3 substituents
Now imagine if you had a skeleton with 3 attachment points and 8 different substituents



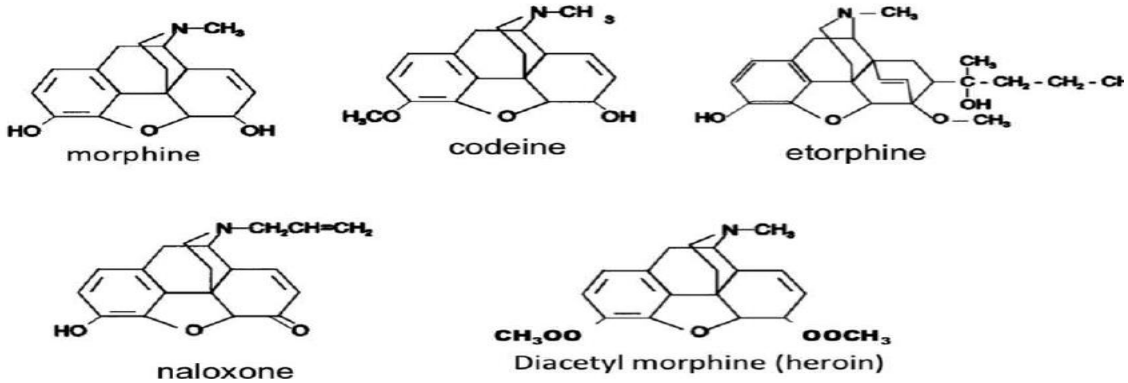
2 attachment points with 3 substituents yields 3 x 3 = 9 different compounds
3 attachment points with 8 substituents yields 8 x 8 x 8 = 512 different compounds

HIGH THROUGHPUT SCREENING

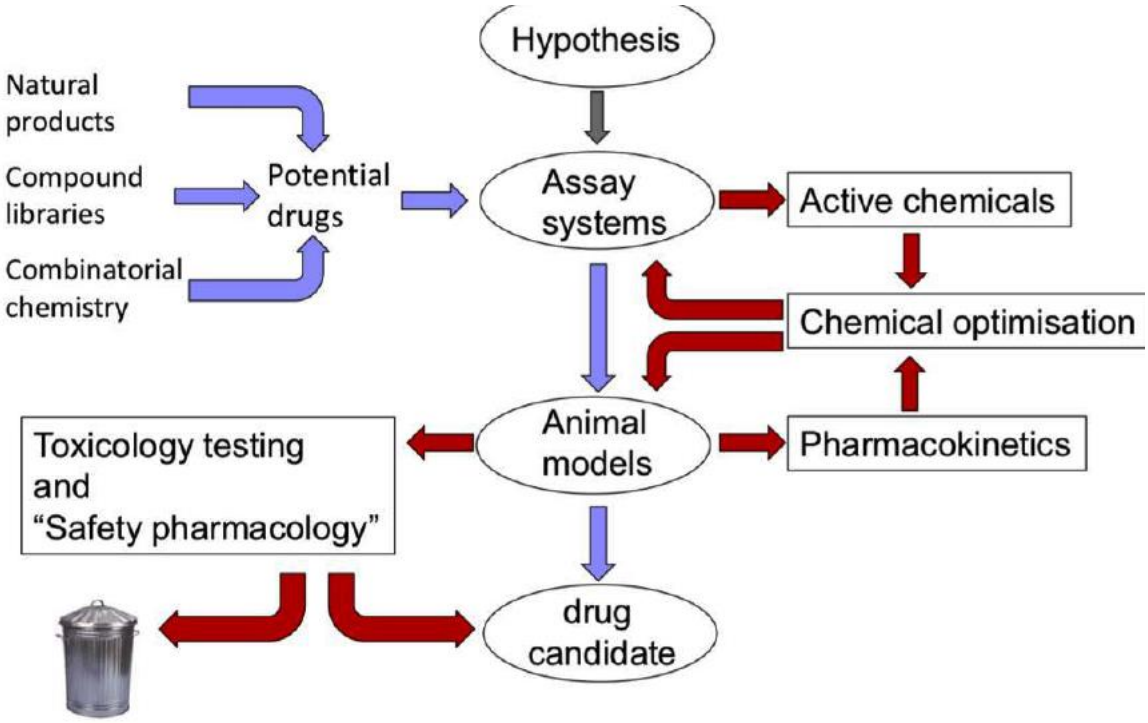
Once we have chemical compound libraries, the problem then becomes how we identify which of the compounds in the library have the required biological activity.
This involves using ever more complex "assay" techniques that are able to filter out the potential drugs.
The early assays must be able to "screen" lots of compounds and identify potential activity very quickly, hence the term high throughput screening.
Such screens are usually highly automated, performed by robots.
Imagine a scenario where we are looking to develop a drug that will competitively inhibit an enzyme to prevent blood clotting and so reduce the risk of stroke in elderly patients

Purpose	Throughput	"Quality" of output	Example
Do any of our library compounds bind to the enzyme?	High ; Up to 50,000 per day	Low; doesn't usually tell you much beyond "it binds"	Robotic e.g. on purified enzyme produced by bacteria
Do any of the compounds competitively inhibit the enzyme? Are they selective?	Medium Up to 100 per day	High; details on a drugs affinity and whether it acts on the enzyme in the way you want; and with a degree of specificity	Effects on enzyme activity in blood along with a panel of other enzymes with similarity to that you are interested in.
Do any of our compounds prevent blood clotting (proof of concept)	Low Up to 10 per day	Hopefully high if your hypothesis is correct!	A functional assay that measures clotting time

STRUCTURE ACTIVITY RELATIONSHIPS (SARs)
Can be used to optimise the properties of promising drug candidates



DRUG DISCOVERY AND DEVELOPMENT



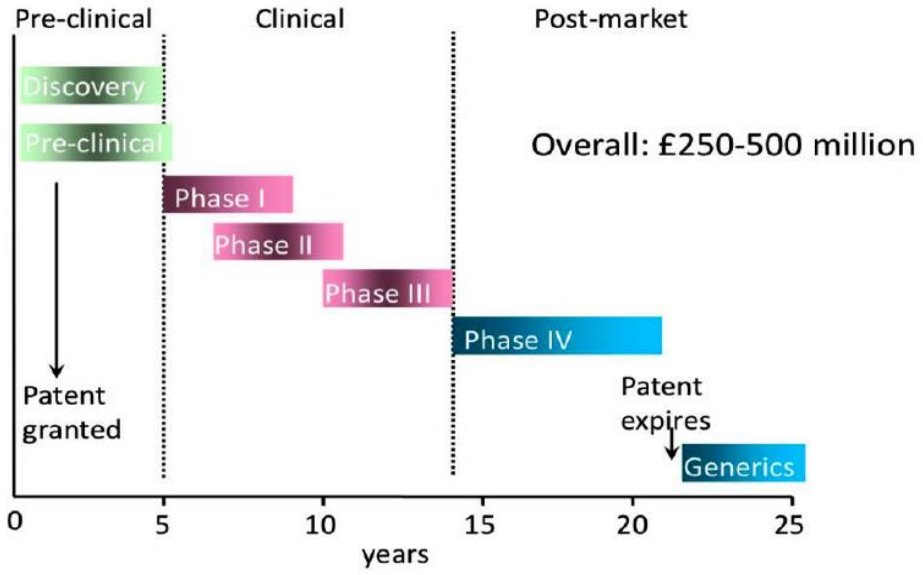
CLINICAL TRIALS

Up until now we have only considered "pre-clinical" development; out drug candidate has not yet been in humans.

The pre-clinical stage typically takes 5-10 years, and results in one or two drug candidates being taken forward into human clinical trials.

Importantly, the patent for a new dug is granted early in the pre-clinical sage and lasts for 20 years, after which time anyone can copy the drug, without the associated development costs (so-called "generic" drugs)

Pharmaceutical companies are under pressure therefore to get their drug to market as soon as possible to recoup the development costs (including those for drugs that failed) before the patent expires.



PHASE I
Exploratory; first in man
Chronic toxicity of drugs will have been assessed in ≥ 2 mammalian species (1 non rodent)
Last 6 months to a year and the purpose is to check for;
SAFETY (potentially dangerous side effects)
TOLERABILITY (unpleasant symptoms e.g. headache, nausea)
Involve a small number (40-60) of healthy volunteers exposed to escalating doses in specialised facilities
Placebo controlled, randomised, double-blind
May involve selected subject groups (male, female, elderly, ethnicity)

PHASE II
Efficacy, proof of concept and safety
Primary purpose is to determine how clinically effective the drug is in patients, and to confirm safety and tolerability
Phase IIa
Exploratory
50-200 patients; approximately 1 year
Dose and treatment regimen based on Phase 1 results
Usually placebo-controlled, randomised, double-blind
Phase IIb
Confirmatory
200-500 patients; approximately 2 years
Safety and efficacy compared to placebo or current treatment in randomised double-blind design

PHASE III
Full scale evaluation of how effective and safe the treatment is compared to current

standard treatment (or placebo)
-Drug is tested in typically 2000-10,000 patients, often in multi-centres, and including different groups (age etc)
-Lasts several years (especially in chronic disease scenario)
-Provides data to support registration; once completed can apply for registration for use in specified condition

DRUG REGULATORY BODIES
-Medicines and Healthcare Regulatory Agency (MHRA; UK)
-European Medicines Agency (EMA; European Union)
-Food and Drug Administration (FDA; USA)
-China Food and Drug Administration (CFDA)
-Central Drugs Standard Control Organization (CDSCO; India)
-Pharmaceutical and Medical Devices Agency (PMDA; Japan)

PHASE IV CLINICAL TRIALS (ongoing)
Conducted once drug is licensed and on the market;
Pharmacovigilance
Post-market surveillance
"Yellow Card" system in UK
Designed to monitor consequences of increasing exposure
Rare or very rare long-term adverse effects
Unpredictable drug interaction
Also yield information on the drug's efficacy in sub-groups of the population (elderly, young)