Psych 181: Lecture 3

Overview of Pharmaceutical Industry

Drug nomenclature and classification

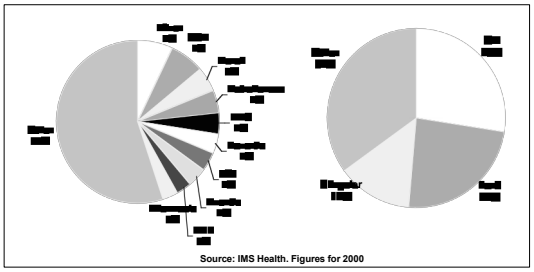
Pharmacokinetics

Pharmacodynamics

Professor Anagnostaras

Market Share & Competition

Pharmaceutical **Automobile**



Source: IMS Health. Figures for 2000

Demographics

- **Highly prevalent neuro-psychochological disorders:**
  - **Insomnia (60 million)**
  - **Migraine (40 million)**
  - **Depression (20 million)**
  - **Anxiety Disorders (19 million)**
  - **Alzheimer's (4 million)**
  - **Schizophrenia (3 million)**
  - **Stroke (3 million)**
  - **Head Injury (2.5 million)**
  - **Parkinson's disease (1.5 million)**
  - **Pain (#1 Patients' complaint)**

Pricing

Determine margins, research capacity, and internationalization.

U.S. is the only country globally with a“free pricing policy” -- new drugs cost about $2-3 per pill or "whatever the market will bear”

This results in higher R&D success and higher profits.

US VS. CANADA DRUG PRICES (VERMONT VS MONTREAL) XXX

Azmacort	**Methotrexate, 2.5 mg., 28**	**Prozac, 20 mg., 45**
$50.70 US	$47.84 US	$105.64 US
$18.85 CA	$21.00 CA	$43.00 CA
$31.85	$26.84	$62.64
63%	56%	59%
Celebrex, 100 mg/cap, 60	**Pravachol, 20 mg., 30**	**Welbutrin, 1 2x daily SR150 mg, 60**
$77.15 US	$64.38 US	$81.98 US
$33.75 CA	$47.50 CA	$45.00 CA
$43.40	$16.88	$36.98
56%	26%	45%
Flonase Nasal	**Prilosec, 20 mg, 90**	**Zocor, 80 mg, 30**
$46.00 US	$360.50 US	$101.82 US
$23.00 CA	$170.36 CA	$60.00 CA
$23.00	$190.14	$41.82
50%	53%	41%
Lipitor, 20 mg., 90	**Propulsid, 20 mg, 200**	**Zoloft, 50 mg., 30**
$229.93 US	$289.20 US	$62.00 US
$164.00 CA	$200.00 CA	$31.00 CA
$65.93	$89.20	$31.00
29%	31%	50%

http://bernie.house.gov/prescriptions/drugsheet.asp

Outline of Drug Development

Discern unmet medical need

Biology

Discover mechanism of action of disease

Identify target protein

Screen known compounds against target

Chemistry

Chemically develop promising leads

Find 1-2 potential drugs

Pharmacology

Toxicity, pharmacology

Clinical Trials

Approaches to drug discovery

- Successful candidate drug in rats (or mice)
- Test in monkeys for toxicity and efficacy
- Market evaluation
  - jobs from entire unit can be lost in a day
  - big problem for scientist retention
- Clinical trials
- Approval
  - every aspect of drug is regulated
  - e.g., specific manufacturing process can take years to approve (Regulatory affairs dept).

Pharmacology: overview

Nomenclature & Classification
Pharmacokinetics
Pharmacodynamics

Principles of Pharmacology

Pharmacology

- **"The branch of medicine that deals with the uses, effects, and modes of actions of drugs".**

(The New Shorter Oxford English Dictionary)

Principles of Pharmacology

Drug Nomenclature

What is a drug?
(Pharmakon (G.), poisons and medicines)

Substance that is used, "primarily to bring about a change in some existing process or state, be it psychological, physiological or biochemical"

Sources of psychoactive agents

1. Naturally occurring

Examples:

Ephedrine, which is extracted from plant indigenous to China, ma huang (Ephedra equisetina).

Cocaine, from the leaves of the coca plant

Opium, extracted from the unripe seed pods of the opium poppy

Sources of psychoactive agents

2. Semisynthetics

Examples:
Heroin (from morphine)
LSD (from fungi that grow on grain)

Sources of psychoactive agents

3. Synthetics

Examples:

Methadone (synthetic opiate)

Amphetamine (powerful stimulant)

Sources of psychoactive agents

- **Opium**
- **Morphine**
- **Heroin**
- **Methadone**

Naming Pharmaceuticals

- **Chemical name**
- **Manufacturer's laboratory designation**
- **Chemical group name**
- **Generic or nonproprietary name**
- **Proprietary (brand) name**
- **General-use name**
- **Street names**

Drug classification

- By Origin
- By Action Relative to a Prototype
- Therapeutic Use
- Mechanism of Action
- Chemical Structure

Drug classification

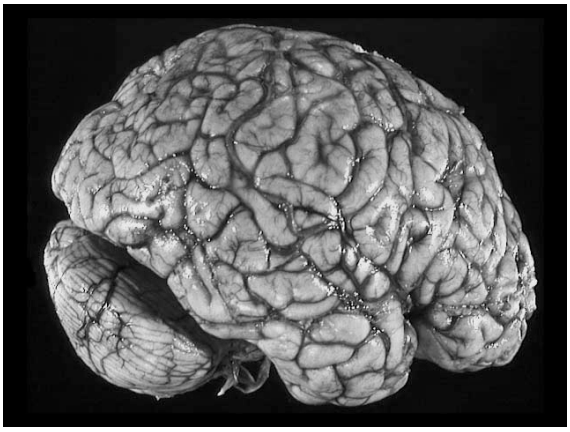
Behavioral effects

- CNS depressants
  - Sedative hypnotics
  - Anxiolytics
- Stimulants
- Narcotic analgesics
- Hallucinogens (psychedelics)
- Others

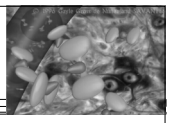
Drug classification

Legal Classification (Drug Schedules)

- Schedule I (heroin, psilocybin, LSD, THC, mescaline)
- Schedule II (morphine, cocaine, amphetamines)
- Schedule III (ASA w/codeine, anabolic steroids)
- Schedule IV (diazepam, phenothiazines)
- Schedule V (cough syrup with codeine)
- Unscheduled Drugs (aspirin, tylenol, Prozac)
- Some states have Schedule VI (inhalants)



Pharmacokinetics



Area of pharmacology dealing with, "the absorption, distribution, biotransformation and excretion of drugs"

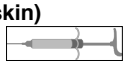
Pharmacokinetics

Factors

- Route of administration
- Absorption and distribution
- Inactivation
- Elimination

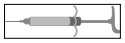
Routes of administration

- Oral (p.o., per os, via the mouth)
- Parenteral injection (through the skin)
  - ✓ Subcutaneous (s.c., s.q., subq)
  - ✓ Intramuscular (i.m.)
  - ✓ Intravenous (i.v.)
  - ✓ Intraperitoneal (i.p., same as i.c.)
- Pulmonary absorption (inhalation)
- Topical application



Common administration abbreviations (mostly latin)

b.i.d.	Twice a day
t.i.d.	Three times a day
q.i.d.	Four times a day
p.r.n.	as needed
q_	every (e.g., q3h, qd, q3d)
u.d.	as directed
r.t.c.	round the clock
m.g.	milligram, mcg = microgram
n.p.o.	nothing by mouth
h.s.	At bedtime
p.c.	after a meal

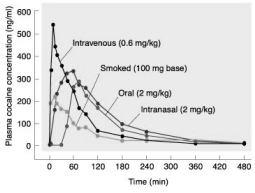


Routes of administration

► Concentration of Cocaine in Blood Plasma

Drug half-life varies as a function of route of administration

Half-life = time for plasma drug conc. to fall to half of peak level



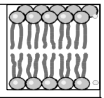
Source: Adapted from Feldman, Meyer, and Quenzer, 1997; after Jones, 1990.

Routes of administration

Effects of route of administration on rate of absorption are due to many factors:

- Surface area available for absorption
- Blood circulation at the site of administration
- Amount of drug destroyed immediately
- Extent of binding to inert substances

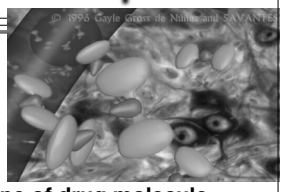
Drug distribution



Drug Transport Across Membranes

- Most important factor in achieving active dose at site of action (e.g., brain)
- Drug must pass through many cell membranes
  - (Cells in gut, blood vessels, glial cells, neurons)

Mechanism of transport

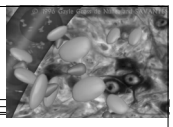


Passive diffusion

Limits:

- size and shape of drug molecule
- lipid solubility of drug
- degree drug is ionized (charged)

Lipid solubility

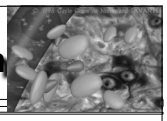


Ionization is the major factor:

When drugs are ionized (charged) they become much less lipid soluble, and drugs tend to become ionized when dissolved in solution

More ionized > less lipid soluble > less absorption > less effect

Degree of ionization



Major factors:

- **Is the drug a weak acid or weak base**
  (most drugs are weak acids or bases)
- **Is the solvent an acid or a base**
  (drugs that are weak acids ionize more in basic [alkaline] environments, and drugs that are weak bases ionize more in acidic environments)

Ion trapping - aspirin

Aspirin is a weak acid with a pKa of 3.5

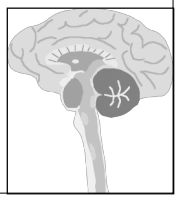
- **in stomach (pH 2-3), most aspirin not ionized**
- **in intestine (pH 5-6), more ionized**
  aspirin better absorbed from stomach
- **in blood (pH 7.4), most ionized**
  once aspirin moves from stomach to blood is trapped in blood (not move easily from blood back to stomach)

Absorption - Other factors

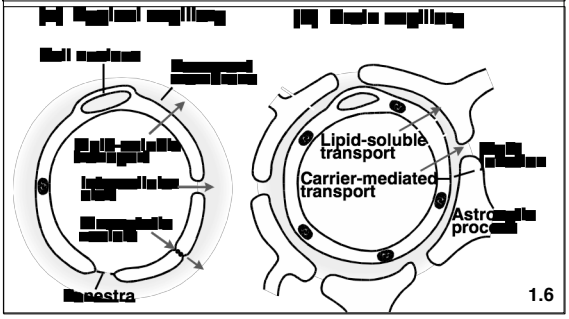
- Drug must be able to survive low pH
- Even if ionized and not very lipid soluble, digestive track has enormous surface area so may still get significant absorption
- Other special barriers

Blood-Brain Barrier

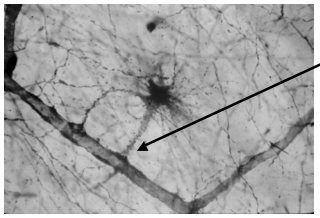
Limits the ability of drugs to reach the brain, even when they can reach other tissues



Blood-Brain Barrier



Astroglia: help comprise blood-brain barrier



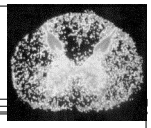
astroglia sends processes which cover blood vessel

Pharmacokinetics

Drug Inactivation and Elimination

- Inactivation usually by metabolism (biotransformation) to inactive forms (liver major site)
- Elimination (metabolites or unchanged drug; kidney major site)
  - but also lungs, sweat, saliva, feces or milk

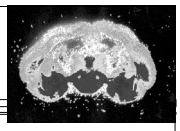
Pharmacodynamics



"The study of the biochemical effects of drugs and their mechanism of action"

Objective is identification of the primary actions of a drug

Receptors

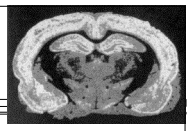


The initial site of action of biologically active agents, including drugs

(The molecule a drug interacts with to initiate its biological effects)

- To have an effect a drug must reach its receptor
  - Its ability to get to the receptor is the realm of pharmacokinetics
  - What it does when it gets there is the realm of pharmacodynamics

Receptors



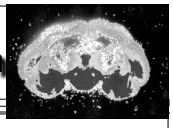
D + R = DR > pharmacological effect

Drug receptor interactions may involve many different types of chemical bonds, but usually weak non-covalent interactions that are reversible

(For example, ionic or electrostatic interactions)

Drug associates and then rapidly dissociates

Law of Mass Action

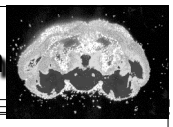


D + R = DR* > effect

The active complex (DR*) leads to a cellular response that is in proportion to the fraction of receptors occupied

- Drugs do not produce new or unique cellular responses but only modify the rate of ongoing cellular events

Law of Mass Action

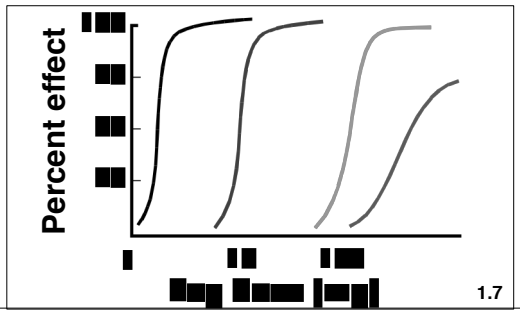


according to **D + R = DR* > effect**

- **The magnitude of a drug effect should be proportional to the number of receptors occupied by the drug, and**
- **A drug should have a maximal effect when all receptors are occupied**

This relationship is described by the dose-effect curve

Dose-effect curves



The dose-effect curve

For an AGONIST

A drug that binds to receptor and has a pharmacological effect

Major characteristics are :

- **Potency**

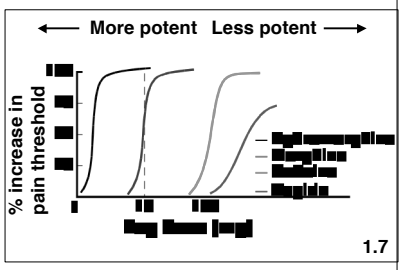
  Location (left-right) on a dose-effect curve

- **Maximum effect**

  Dose where increases in dose produce no further increase in effect

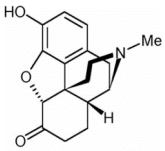
Potency

- Accessibility
- Affinity (K_d, dissociation constant)
- Efficacy (intrinsic activity)

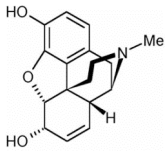


Potency

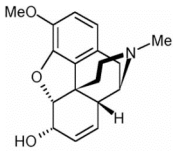
hydromorphone



morphine

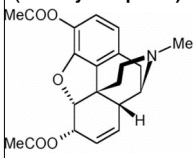


codeine

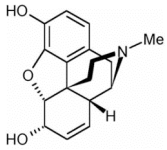


Potency

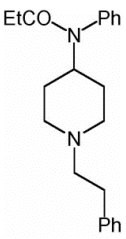
Heroin (diacetylmorphine)



morphine

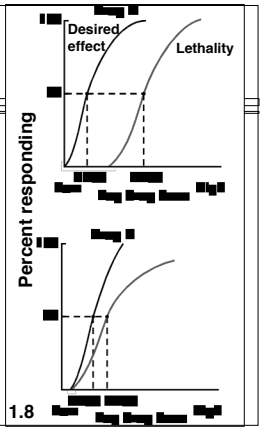


fentanyl



Potency

- ED_{50} - Dose that produces an effect in 50% of a population
- LD_{50} - Dose that kills 50% (TD = toxic dose)
- TI - Therapeutic Index (LD_{50} /ED_{50})
- Safety Margin = $LD_{50} - ED_{50}$

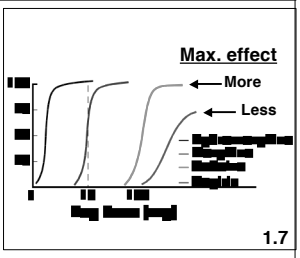


1.8

Maximum Effect

Drugs vary in their ability to produce an effect

- They may act by different mechanisms (at different receptors)
- They may have more or less efficacy at the same receptor



1.7

Side effects and specificity

All drugs have multiple effects

- All drugs are "dirty"
- Degree depends on dose, specificity etc.

Side effects are unwanted or undesirable effects (although are "real" effects)

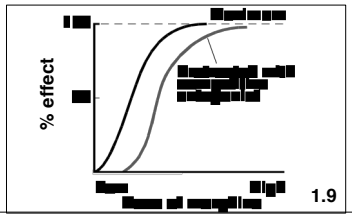
Agonists vs Antagonists

- **Agonist**
  - **A drug that binds to receptor and has a cellular (pharmacological) effect**
- **Antagonist**
  - **A drug that binds to a receptor but produces no direct cellular effect**

Antagonists produce their effects by blocking the action of an agonist, or an endogenous ligand (e.g., a transmitter), at that receptor

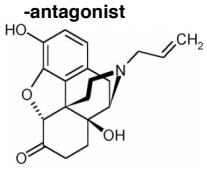
Competitive antagonists

- **Binds to same receptor as agonist**
- **Shift dose-effect for agonist to right**
- **Effect can be overcome by sufficient dose**

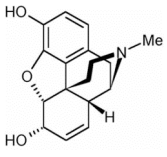


Competitive antagonists

naloxone (Narcan)
-antagonist

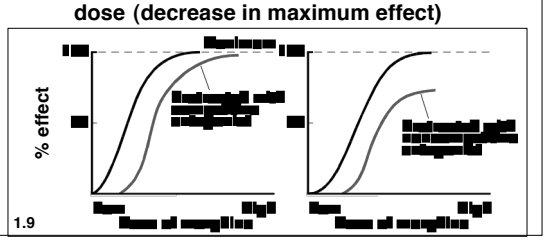


morphine



Noncompetitive antagonists

- Shift dose-effect for agonist to right
- Effect can not be overcome by sufficient dose (decrease in maximum effect)

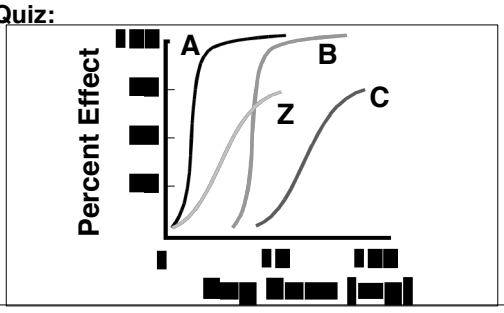


Noncompetitive antagonists

- Agonist can only act on the population of receptors not effected by the antagonist
  (May be reversible or irreversible)
- Irreversible may form long-lasting bond with receptor
- Reversible acts to prevent agonist-receptor coupling (e.g., on different site than agonist, through different mechanism)

Dose-effect curves

Quiz:



Tolerance and sensitization

The effects of a drug may change with repeated administration

Tolerance

- Decreased response with repeated administration, or
- A higher dose is required to produce the original effect (shift to right)

Cross-tolerance

Tolerance and sensitization

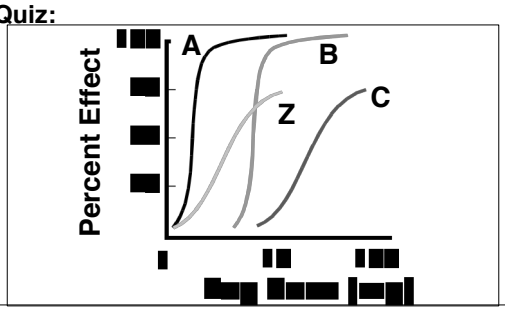
Sensitization

- Increased response with repeated administration, or
- A lower dose is required to produce the original effect (shift to left)

- Cross sensitization

Dose-effect curves

Quiz:



Tolerance and sensitization

May involve multiple mechanisms

- **Pharmacokinetic (dispositional) changes**
- **Pharmacodynamic changes (cellular adaptations)**
- **Behavioral (learning) factors**