• Definition of a Drug:
  • Any chemical substance, natural or man-made (usually excluding nutrients, water, or oxygen), that - by its chemical nature - alters biological structure or functioning when administered and absorbed.
  • Pharmacology is the discipline that studies drug effects on living systems.

• Psychoactive Drug:
  • Any drug that affects feelings, perceptions, thought processes, and/or behavior.
  • All psychoactive drugs exert their effects by altering the functioning of the nervous system.
  • The study of how drugs affect behavior and psychological processes is “psychopharmacology”.

• How about when we see a physiological or behavioral effect even though what the person took contained no active chemicals?

• Placebo & Placebo Effects
  • Placebo - typically an inert (chemically inactive) substance administered like a drug
  • Placebo effect - any psychological or physiological effect or portion of an effect that is due to expectation/belief rather than chemical action
  • * Some part of effects seen after taking a real drug may also be due to expectation.

Placebo Effect
  • [http://www.youtube.com/watch?v=yfRVcaAnp18](http://www.youtube.com/watch?v=yfRVcaAnp18)

Double Blind Study of Treatment for Depression
  • 38% of placebo group (top row) and 52% of drug group (bottom) improved, but they showed different changes in brain activity.
  • Imaging of quantitative EEG
• Because of expectation effects, the best drug research is done using double blind procedures (“drug” is identified by code number only so neither the participants nor the data collector knows who is getting the placebo or who is getting the drug until after the study)

Our First Drug Issue

• The case of Kathleen O'Leary and her husband and their refused prescription

Our First Drug Issue

• http://pharmacy.about.com/od/Management/a/Pharmacists-Conscience-Rights-When-Is-It-Ok-To-Refusal-To-Fill-A-Prescription.htm

Following a Drug Through the Body

1. Administration – Get drug into person.
2. Absorption - Drug gets into bloodstream
3. Distribution - Blood carries drug to tissues
4. Drug Action - Drug interacts with cells
5. Termination of Effect, Metabolism and/or Elimination

What does “kinetic or kinetics” refer to?
1,2,3,5 = Pharmacokinetics
4= Pharmacodynamics

Oral Route

• Easy, convenient, accepted
• Gradual onset (5-30 min) with 75% absorbed within 2-3 hrs but may not be complete for 6-8 hrs; provides a longer lasting effect .
• Reversible for a while
• But: Not all drugs well absorbed, not all can withstand stomach acids; some upset stomach, some require large pills/capsules
• Absorption variable depending on drug, genetics, stomach contents; dosing not precise; some drug may be lost to “first-pass metabolism”
First-Pass Metabolism

Some of drug absorbed from GI tract is immediately metabolized as it goes through liver or through G-I wall.

Some Absorption-Related Food/Drug Interactions

- Grapefruit juice increases absorption of antihistamines, codeine, tranquilizers, cardiovascular & AIDS drugs
- Pop, fruit or veggie juice or vitamins with iron can decrease absorption of erythromycin
- Dairy foods or other calcium rich items decrease absorption of tetracycline
- But food in stomach may improve absorption of other drugs (e.g. Inderal (propanolol))
- Excess dietary salt may decrease lithium levels; low salt levels may increase lithium levels

Something New: “Prodrugs”

- May orally administer a “prodrug” (something that will be turned into an active drug in your stomach but won’t be active otherwise)
- Example: Vyvanse for ADHD
- Lysine attached to d-amphetamine makes it inactive until the lysine is removed in stomach. The d-amphetamine won’t be active if snorted or ground up and injected.

A Narcotic “Lollipop”

Inhalation

- Inhalation of gases/vapors and/or particles
- Rapid absorption & fastest route to brain (5-8 seconds)
- Fairly easy
- But: Many drugs cannot be inhaled
- Dose can be difficult to control
- There is no drug depot or reserve Inhalation via smoking presents special risks.

Injection

- Subcutaneous (SC) or “skin-popping”
  - Slowest injection route; can irritate skin
  - Often used for insulin injections
- Intramuscular (IM)
  - Intermediate speed depending on muscle selected (arm faster than butt) & vehicle (oil or micro-encapsulated injections in butt, e.g. “depot” injections of antipsychotics, or long-acting naltrexone for recovering addicts, absorbed over weeks)
  - Easier to do than intravenous
• IV Injection or Infusion
  - Intravenous (IV)
  - Fast (~ 15 seconds to brain)
  - Bypasses absorption obstacles
  - Most difficult & risky route
  - All injection routes give good control of dose

Implanted medication port for IV access

Injection Problems
  - Intravenous route most dangerous because of risk of possible life-threatening reactions or allergic responses
  - Risk of clots or emboli due to particles, air bubbles
  - Must use sterile procedures or risk infection.
  - Site of injections deteriorates with repeated injections.
  - Not reversible

Miscellaneous
  - Sublingual (under tongue); buccal (held in cheek, like Nicorette gum) – absorbed through mucous membranes
  - Intranasal (sprays or snorting)
  - Topical; Transdermal
  - Rectal (suppository or enema)
  - Implantable

Sublingual
  - Nitroglycerin for fast relief of angina pain
  - Suboxone for recovering narcotic addicts (buprenorphine + naloxone)

Intranasal
  - Decongestant Spray
  - Imitrex Nasal Spray for Migraines

Nicotine Replacements
  - Nicotine Nasal Spray
  - Nicotine Transdermal Patch
• Other Transdermals

- Nitroglycerin for angina
- Contraceptive patch
- Scopolamine motion sickness patch
- Fentanyl for pain
- EMSAM for depression

New Developments

- Patches consisting of tiny (pain-free) microneedles to replace things like insulin injections
- Low frequency ultrasound waves or elec. current can also increase absorption

New 3 Day Insulin Patch

New long-acting patches for migraine, antipsychotics and Parkinson’s disease meds are being tested for commercial release

Drug Implants

- New Implanon implanted contraceptive (single progestin rod)
- Implanted pump to relieve chronic pain
- Other implants under development: e.g. antipsychotic implant

Routes Vary in:

- Form of drug
- Dose necessary & absorption
- Time course (start & length of effect)
- Intensity of drug effects: inhalation & intravenous most intense
- Risks & benefits

Route-Related Differences in Drug Time Course
**Following a Drug Through the Body**

1. Administration – Get drug into person.
2. Absorption - Drug gets into bloodstream
3. Distribution - Blood carries drug to tissues
4. Drug Action - Drug interacts with cells
5. Termination of Effect, Metabolism and/or Elimination
   - Study of 1,2,3, & 5 = pharmacokinetics
   - Study of action = pharmacodynamics

**Distribution**

- Bloodstream distributes drug widely (not just to the problem area)
- Drugs vary in how fast they leave blood (depends on concentration, fat-solubility of drug & whether it binds to proteins in blood)
- Presence of other drugs can alter this speed – this is one source of drug-drug interactions

**Limitations to Distribution:**

- the “blood-brain barrier” excludes or slows entry of many drugs into brain. (Psychoactive drugs are the fat-soluble ones that do make it into brain.)
- the “placental barrier” excludes some large molecule chemicals but does NOT exclude psychoactive drugs.

**Why Do Drug Effects End?**

- Drug may be “biotransformed” or metabolized by liver, then excreted by kidney.
- Drug may be excreted by kidney unchanged.
- Some drugs may leave in feces or other bodily fluids (milk, sweat, breath)
- Some molecules may be broken down at site of action (e.g. receptor sites in CNS) or before they are even absorbed
- Drug effect may end because the drug moves away from the site of action (e.g. from brain to body fat)

**Meet the Families**
Cytochrome P450 (CYP) Enzymes

- Families of enzymes found in liver & GI tract
- Metabolize or break down lots of chemicals
- Different subfamilies handle different drugs
- Anything that affects these enzymes will affect drug metabolism
  - “Grapefruit juice effect” – blocks CYPs in GI tract
  - Some drugs increase these enzymes (e.g. Tegretol); others decrease or divert the action of these enzymes (e.g. Prozac)
  - Reason behind lots of drug interactions

Don’t Take With Grapefruit

- Anti-anxiety  Buspirone ; benzodiazepines
- Antidepressant  Sertraline (Zoloft)
- Antihistamine  Fexofenadine (Allegra)
- Anti-seizure  Carbamazepine (Carbatrol, Tegretol)
- Calcium channel blocker  Nifedipine (Procardia),
- Statins  Simvastatin (Zocor), lovastatin (Mevacor), atorvastatin (Lipitor)
  - (this is just a partial list – check your meds)

Rate of Metabolism

- Your genetic makeup influences how quickly you metabolize different drugs. DNA tests can now determine if you are a normal, slow or fast metabolizer of certain drug categories.

- The rate of metabolism of most drugs varies with the concentration of drug in the body:
  - more metabolized/hr when concentration is high
  - less metabolized/hr as the concentration drops

Playing for Change

- [http://www.youtube.com/watch?v=Us-TVg40ExM](http://www.youtube.com/watch?v=Us-TVg40ExM)
- [http://www.youtube.com/watch?v=4xjPODksI08](http://www.youtube.com/watch?v=4xjPODksI08)
- [http://www.youtube.com/watch?v=fgWFxFg7-GU](http://www.youtube.com/watch?v=fgWFxFg7-GU)

The “Half-Life” of a Drug:

- The time it takes for half the available drug to be eliminated from the body, as measured by a 50% drop in blood levels.
- With each successive half-life another 50% of the remaining drug in the blood will be eliminated
- Knowing half-life is important for understanding time course of drug and how often to administer it.
- A drug’s effects may be longer and more intense if liver and/or kidney are not functioning up to par.

If you are a drinker, imagine that you go out drinking (on an empty stomach). How much or how many of the standard drinks above would you have to drink to JUST START FEELING the ALCOHOL?

Example: Caffeine

- Drank 8 oz. Starbucks coffee containing 250 mg caffeine at 7 PM
- Caffeine half-life “on average”: 3.5-5 hrs (I'm using 5 hr in this example)
- Midnite – 125 mg left in your body
  - 5 AM  62.5 mg left in body
  - 10 AM  31.25 mg left in body
  - 3 PM  15.6 mg left in body
  - 8 PM  7.8 mg
  - 1 AM  3.9 mg  (98% has been eliminated in after 6 half-lifes – almost drug-free

Sample Average Half-Lives

- Aspirin .5-1.5 hrs
- Morphine 1.5-2.5 hrs
- Tetracycline 2.5-5.5 hrs
- Haldol 6-18 hrs
- Lithium 18-30 hrs
- Valium ~30 hrs in young,
  - several days in elderly

An Exception to the Rule

- Alcohol is metabolized at a steady rate, regardless of the concentration of the drug in the body. On AVERAGE the liver metabolizes slightly less than 1 STANDARD drink per hour, whether you have 1 drink in your body or 20.

Dose and Its Relationship to Drug Effects

Think about your prescription & OTC medications. How is the dose usually expressed?

Dose

- Most drugs have doses expressed in milligrams (mg.) (thousandths of a gram)
  - e.g. 200 mg tablet of ibuprofen
- Exceptions: LSD (50-150 micrograms (millionths)); fentanyl – a fraction of a milligram (.05 mg-.10mg)

What’s the Right Dose for Me?

- A rule to remember:
- **Wide individual variability in drug response**
- We differ in absorption, distribution, drug action, and/or elimination.

  - For example, our question of how much beer or wine you have to drink before you just start to feel the alcohol?
What Dose Will Produce the Desired Effect in Different People?

<table>
<thead>
<tr>
<th>Dose (mg./kg.)</th>
<th># of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>30</td>
<td>7</td>
</tr>
<tr>
<td>40</td>
<td>9</td>
</tr>
<tr>
<td>50</td>
<td>11</td>
</tr>
<tr>
<td>60</td>
<td>13</td>
</tr>
<tr>
<td>70</td>
<td>15</td>
</tr>
</tbody>
</table>

Individual differences is the rule even when we have already adjusted for weight.

- So what dose should the manufacturer sell and recommend on the package?
- Most often choose the average dose or ED50 – a dose which will be effective for 50% of the people (even though some actually needed less and some need more)

### The Dose-Response Curve

- Graphic representation relating the amount of drug administered to the response produced
- Response may be represented as intensity of response OR as % of group responding at each dose
- Curve is for a particular drug effect only
- Different effects of a drug may show different dose-response relationships.
- All drugs have multiple effects.

### Dose-Response Curve

- No-effect range
- Range of increasing effect with increasing dose
- Maximum effect range
- Increasing Dose

### % Who Get Desired Response at Each Dose

Dose-effect curves for perceived sexual arousal and a physiological measure of sexual arousal at different low to moderate dosages of alcohol.
**A Biphasic Dose-Effect Curve**

For some drug effects, the D-R curve has a different shape. This figure illustrates a biphasic dose-effect curve, which shows how the response changes with different doses of the drug.

**Therapeutic vs. Toxic Effects**

![Graph showing therapeutic and toxic effects](image)

**Measures of a Drug’s Safety**

- **Therapeutic Index or Ratio** compares the average LD to the average ED.
- **LD50/ED50** (based on animal research): - THC: Ti=1000, Valium: Ti=100 - Morphine: Ti=70, Alcohol: Ti=10 - Digoxin: Ti=2, Lithium: Ti=1.8
- More conservative “Safety Margin” compares LD1/ED99 (basically asking whether there is any overlap of the ED and LD dose-response curves).

**Potency vs Effectiveness**

- **Potency** – related to the dose of drug required to produce a particular effect.
- **Efficacy or Effectiveness** – related to the maximum possible effect obtainable from a particular drug.
Potency Differences

Both drugs can produce the effect but need higher dose of lower potency drug.

Does this mean alprazolam is better??

Sample Contents of Some Coated Tablets:

- 5 mg active drug
- 30 mg sugars
- 6 mg cornstarch
- 9 mg miscellaneous
- 10 mg coating

With many of today’s drugs potency is not an important feature – drugs are already so potent that they have to add filler to make the pill large enough to handle.

Dose-Response Curves Showing Difference in Efficacy & Potency

An EFFICACY Diff

A POTENCY Diff

Comparing Curves

Side-Effects of Drugs

- Say it with me: All drugs produce multiple effects!
- “Side-effects” are the effects not sought by the user.
- One person’s desired effect may be another person’s “side effect”.
- Side effects may be mild, disturbing or even dangerous.
- Potentially serious side-effects are often called “adverse reactions”.
- Every drug has some side-effects that are quite common & others that occur more rarely.
Some Adverse Reactions:
Hypersensitivity
- An allergic response to a drug, usually (but not always) after the person has become sensitized to it. May cause rash, swelling, fever, or, in the worst cases, anaphylactic shock. Anaphylaxis is a life-threatening medical emergency.

Signs of anaphylaxis:
- tingling lips and mouth
- flushing of face, body
- itchy eyes, nose, face
- hives
- eyes and face swelling
- wheezing
- Symptoms rapidly progress to:
  - weakness, dizziness
  - throat swelling closed
  - low blood pressure
  - cardiac arrhythmia
  - loss of consciousness
  - possible death

Some Adverse Reactions:
Idiosyncratic Response
- Rare, unpredictable, highly individual response to a drug. The user may be at the extremes of the dose-response curve or may exhibit unusual physiological or behavioral responses to the drug.

Some U.S. Statistics
- 106,000 known deaths/yr due to adverse reactions to properly used drugs
- 3-4% of hospitalizations lead to adverse reactions
- 7,000 additional known deaths due to medication errors
- Don’t know the # of non-fatal problems.

Added Risks With Street Drugs
- Actual drug composition unknown
- Dose variable and unknown
- Possibly harmful diluents/contaminants
- Street drugs may also involve particularly risky routes of administration.

Signs of Drug Distress
- slowed respiration (16-20 inhalations/min is normal)
- cyanosis
- fast (>140), slow (<50), or irregular pulse
- high temperature
- loss of consciousness
- extreme behavioral change (agitated, aggressive, suicidal)
Other Drug “Toxicity” Data

- Drug Abuse Warning Network (DAWN)
- Nearly 1 in 7 ER visits is related to drugs
- Nearly 1/3 of drug-related visits are due to illicit drugs only
- 28% were related to medications only
- 26% were related to “alcohol in combination” with some other drug(s)
- (DAWN .pdf file)

Drug Names

- Chemical or structural name – describes molecule
- Generic name – official, nonproprietary
- Brand or trade name – owned by a company
- Street names

Examples:

- sodium 5-ethyl-5-(1-methyl butyl)barbiturate
- sodium pentobarbital
- Nembutal
- bluebirds

Generic vs Brand Name Drugs

- Are generics equivalent?
  - By law, the active ingredient(s) must be chemically and biologically equivalent
  - Will generic availability decrease drug development research? Are generic substitutions fair to brand-name companies? States vary in their laws about substitution.

Americans average ~12.6 prescriptions
~69% of prescriptions dispensed in US are for generics
Takes 10-15 years to bring a new prescription drug to market

You’ve taken this dose of this drug before, but this time you don’t experience the same degree of effect. Why?
Tolerance

- Tolerance: progressively decreasing drug effects due to regular, repeated administration.
- Some tolerance may begin to develop within a single episode of use (acute tolerance), but tolerance from regular use (protracted tolerance) is even more significant.
- To experience the original degree of drug response the individual must increase their dose.

But:

- All effects of a drug may not show equal degrees of tolerance.
- And, under certain conditions, we might experience reverse tolerance or sensitization – an increased (sometimes dangerous) response after repeated use.

Mechanisms by Which Tolerance Occurs:

- Metabolic tolerance (increased liver metabolism of drug)
- Pharmacodynamic, cellular adaptive or “tissue tolerance” (cells at drug’s site of action adapt to the drug)
- Behavioral or conditioned tolerance (learning/conditioning leads to decreased drug effects)

Example of Conditioned Tolerance

- Group A & Group B rats receive same dose of drug for 10 days.
- Group A always gets drug in the same setting while Group B gets the drug in a new and different setting each day.
- After 10 days Group A shows more tolerance/less drug response.
- The setting cues trigger learned counterreactions that decrease the effects of the drug

Physical or Physiological Dependence:

- Rats with tolerance were more likely to survive the usual LD100
  - Only 32% died if tested in the setting where they usually received injections
  - 64% died if tested in a situation not previously associated with drug administration

- Body physiologically adapts to, and (to a certain extent) compensates for the regular presence of the drug.
- Adaptation/compensatory processes result in tolerance & produce withdrawal symptoms when drug levels drop.
- Most withdrawal symptoms are the opposite of the drug effect.
Cross-Tolerance & Cross-Dependence

- Tolerance to a drug often extends to other (usually chemically related) drugs.
- When physical dependence occurs, other chemically-related drugs can “satisfy” that dependency & prevent withdrawal.

You’ve taken this dose of this drug before, but this time you don’t experience the same degree of effect. Why?

May Be Due to Drug Interactions

- Drug Interactions: Having more than 1 drug in your body can change the experienced effects
- The presence of another drug may alter absorption, distribution, metabolism, elimination, and/or receptor interactions.

Some interaction examples:

- Additive (1+1=2) - Effects of 2 analgesics in Excedrin add together
- Synergistic (1+1=3) - Taking alcohol + another depressant can lead to more than the sum of their effects (synergism)
- Potentiating (0+1=2) - Tagamet, Zantac, birth control pills, or erythromycin can potentiate sedative effects of benzodiazepines like Xanax
- Antagonistic - Smoking can decrease the effectiveness of a wide range of medications
- Altered Side Effects - Taking alcohol and aspirin increases stomach upset

http://www.drugs.com/drug_interactions.php

Many Ways of Classifying Drugs

- By their availability/commercial status
  - Prescription vs nonprescription/OTC drugs; Licit vs illicit drugs
- By their potential for abuse
  - Schedules of Controlled Substances (I-V)
- By their typical effects/uses/actions
  - Depressants; stimulants
  - Anticonvulsants; antidepressants
  - SSRIs; MAOIs
- Others: by their origin; by chemical structure