• 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 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>
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<tr>
<td>20</td>
<td>5</td>
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<tr>
<td>30</td>
<td>7</td>
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<tr>
<td>40</td>
<td>9</td>
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<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

• The Dose-Response Curve (DRC)

- 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.
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

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.
Potency Differences

Dose-Response Curves Showing Difference in Potency

Dose-Response Curves Showing Difference in Efficacy & Potency

- **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”.
  - Every drug has some side-effects that are quite common & others that occur more rarely.
  - Side effects may be mild, disturbing or even dangerous.
  - Potentially serious side-effects are often called “adverse reactions”. Each year over 100,000 die from adverse reactions to properly prescribed drugs.
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

http://www.youtube.com/watch?v=TTcL7u5s7aUU

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.

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.
  - 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

Physical or Physiological Dependence:

- 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.

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

- 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

- 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-Related ER Visits

- 33% medications only
- 25% illicit drugs only
- 11% alcohol and meds
- 11% alcohol and illicit
- 8% illicit and meds
- 7% alcohol only (*recorded only for underage, not adults)
- 5% alcohol, meds and illicit

Many Ways of Classifying Drugs

- By their availability/commercial status
  - Prescription vs nonprescription or OTC drugs; generic vs brand name; licit vs illicit drugs
- By their potential for abuse
  - Schedules of Controlled Substances
- By their typical effects/uses/actions
  - Depressants; stimulants
  - Anticonvulsants; antidepressants
  - SSRIs; MAOIs
- Others: by their origin; by chemical structure

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.