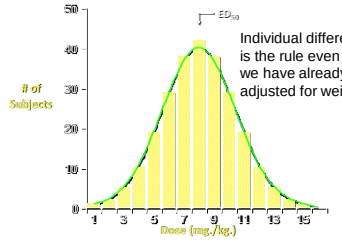
•Dose

- 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)

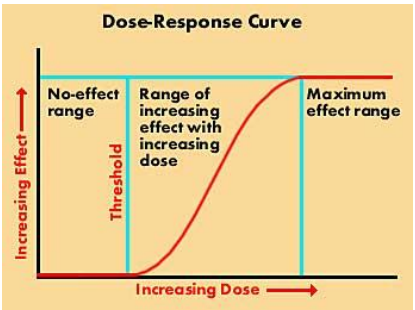
What Dose Will Produce the Desired Effect in Different People?



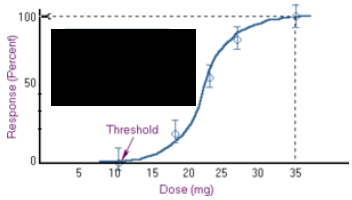
Individual differences is the rule even when we have already adjusted for weight

•The Dose-Response Curve (DRC)

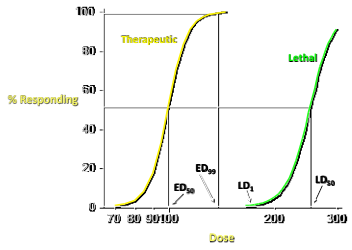
- Graphic representation relating the amount of drug administered to the response produced
- Response may be represented as intensity of response OR as % of group responding at each dose
- **Curve is for a particular drug effect only**
- Different effects of a drug may show different dose-response relationships.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



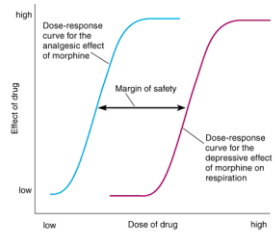
% Who Get Desired Response at Each Dose



Therapeutic vs. Toxic Effects

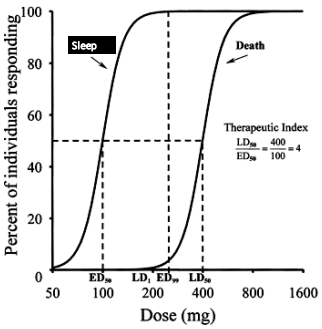


► Dose-Response Curves for the Analgesic and Depressant Effects of Morphine



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

HALF-LIVES AND EQUIVALENT POTENCIES OF BENZODIAZEPINE ANXIOLYTICS

Benzodiazepine	Half-life (hrs) [active metabolite]	Approximate equivalent oral dosages (mg)
Alprazolam (Xanax)	6-12	0.5
Clonazepam (Klonepin)	18-50	0.5
Lorazepam (Ativan)	10-20	1
Diazepam (Valium)	20-100 [26-200]	10
Chlordiazepoxide (Librium)	5-30	25
Clorazepate (Tranxene)	[36-200]	15
Oxazepam (Serax)	4-15	20

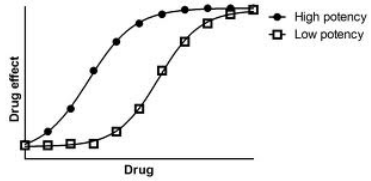
Does this mean alprazolam is better??

●Sample Contents of Some Coated Tablets:

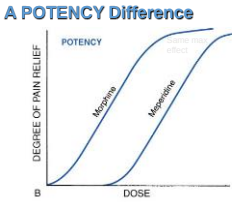
- 5 mg active drug
- 30 mg sugars
- 6 mg cornstarch
- 9 mg miscellaneous
- 10 mg coating

- 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.

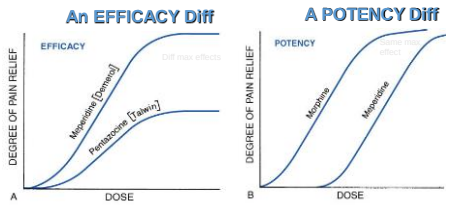
Potency Differences



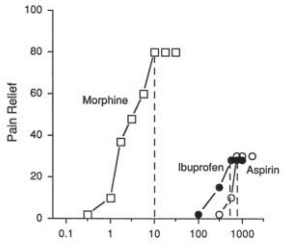
Dose-Response Curves Showing Difference in Potency



Dose-Response Curves Showing Difference in Efficacy & Potency



●Comparing Curves



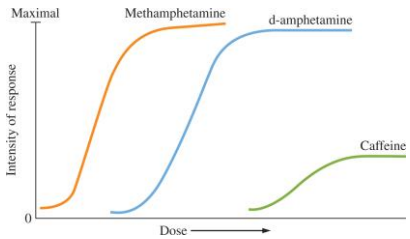


Figure 3.13
Claire D. Advokat, Joseph E. Comaty, Robert M. Julien: Julien's Primer of Drug Action, Thirteenth Edition
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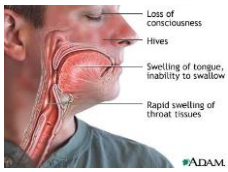
●Side-Effects of Drugs

- 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.voutube.com/watch?v=TTcL7u05aUU

•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

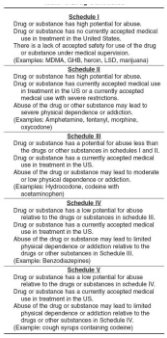
- Drug Abuse Warning Network (DAWN)
- Nearly 1 in 7 ER visits is related to drugs
- Nearly 1/3 of drug-related visits are due to illicit drugs only
- 28% were related to medications only
- 26% were related to "alcohol in combination" with some other drug(s)
- (DAWN .pdf file)

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



Schedule I
Drug or substance has high potential for abuse.
Drug or substance has no currently accepted medical use in treatment in the United States.
There is a lack of accepted safety for use of the drug or substance under medical supervision.
(Examples: MDMA, GHB, heroin, LSD, marijuana)

Schedule II
Drug or substance has high potential for abuse.
Drug or substance has currently accepted medical use in treatment in the US or a currently accepted medical use with severe restrictions.
Abuse of the drug or other substance may lead to severe physical dependence or addiction.
(Examples: Amphetamine, fentanyl, morphine, oxycodone)

Schedule III
Drug or substance has a potential for abuse less than the drugs or other substances in schedules I and II.
Drug or substance has a currently accepted medical use in treatment in the US.
Abuse of the drug or substance may lead to moderate or low physical dependence or addiction.
(Examples: Hydrocodone, codeine with acetaminophen)

Schedule IV
Drug or substance has a low potential for abuse relative to the drugs or substances in schedule III.
Drug or substance has a currently accepted medical use in treatment in the US.
Abuse of the drug or substance may lead to limited physical dependence or addiction relative to the drugs or other substances in Schedule III.
(Example: Benzodiazepines)

Schedule V
Drug or substance has a low potential for abuse relative to the drugs or substances in schedule IV.
Drug or substance has a currently accepted medical use in treatment in the US.
Abuse of the drug or substance may lead to limited physical dependence or addition relative to the drugs or other substances in Schedule IV.
(Example: cough syrups containing codeine)

- DEA's Schedule of Controlled Substances

●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.