

## PHARMACODYNAMICS: Tolerance & Dependence (p.1)

**1.tolerance** is defined either as getting less and less response to the drug at the usual dosage, or as having to administer more and more of the drug to get the same effect

i.e. the **DRC is shifted to the right** (ED50 increases)

note: **LD50 may be unchanged**...implications

note: **negative SEs may not show tolerance**, even when main effect does

there are several **types** (causes) of tolerance:

### metabolic/dispositional tolerance

due to changes (increases) in liver enzymes (**liver enzyme induction**)

which leads to more rapid/complete biotransformation of drug

usually takes weeks to develop

is often the basis of “**cross tolerance**” between two drugs (see below)

can gradually **shorten the 1/2 life** of a drug

### neuronal/cellular/physiological/pharmacodynamic tolerance

most likely due to changes (“down regulation” usually) in the # of RSs

on neurons or related changes (e.g. less NT released, decrease in sensitivity of RSs, etc.)

usually takes days or weeks to develop

### behavioral tolerance

learned behavioral adjustments that compensate for drug effects, which

then looks like the drug is having less of an effect

usually takes weeks to develop

### conditioned tolerance

a special case of behavioral tolerance

a set of learned/conditioned behavioral/physiological adjustments

that the S makes that **compensate for the drug's effects**

**is triggered by conditioned stimuli (cues) that are associated with the administration of that drug**

## PHARMACODYNAMICS: Tolerance & Dependence (p.2)

### behavioral tolerance (cont.)

#### conditioned tolerance (cont.)

cues could include drug paraphenalia, time of day, location, other persons, smells, a particular emotion, etc.

cues associated with the act of taking the drug can be quite varied

note: **these conditioned responses are *not* observed if *S* takes the drug under novel conditions** (e.g. in a new location, with new people, different time of day, etc.)

thus, *S*'s body does not make compensatory responses (that normally would "balance out" at least some of the drug's effects --- which **can then lead to a drug O.D. effect**

### cross-tolerance

when *S* takes drug A repeatedly, *S* will now show tolerance to newly introduced drug B

usually thought to be caused by liver enzyme induction (from A),

but there may be other mechanisms as well

e.g. ETOH and barbiturates

e.g. all opiates

e.g. all BZDs

### reverse tolerance/sensitization

as *S* repeatedly takes drug, the effects become more and more, or in order to get the same effect must keep on **lowering** dose levels

i.e. DRC shifts to the *left* (unusual)

mechanisms not always fully understood...could be **liver enzyme inhibition** in some cases

### acute tolerance/tachyphylaxis

a **very rapid development of tolerance**

sometimes within a few minutes or hours

develops **often between the first and second administrations** of drug  
unknown mechanisms...maybe all the RSs occupied by the 1<sup>st</sup> dose?

## PHARMACODYNAMICS: Tolerance & Dependence (p.3)

Note: **tolerance effects often develop at different rates for each different drug effect...**

**Ideal** – is to see rapid tolerance developing to negative SEs and no tolerance developing to main effect

note: with **cocaine**, tolerance develops rapidly to the euphoriant effects of the drug, so S tends to take more and more drug but, tolerance develops only very slowly to the toxic cardiovascular effects of the drug --- cardiac arrest

### 2. Physical Dependence

describes the body's set of various & multiple physiological responses that are observed after repeated drug doses  
often are "compensatory" responses  
develop presumably to try to keep body physiology in "balance", in some sort of normal/homeostatic range  
will continue as long as S continues to take drug X

### 3. Withdrawal Symptoms

occur when S has developed physical dependence on drug X and when drug X is *abruptly* D/C'd  
*abrupt* D/Cing of drug X allows one to observe these mostly "compensatory" responses that have presumably been going on all the while S was taking drug X but were unobserved directly  
if get withdrawal Sxs with abrupt D/C, can infer prior physical dependence has developed  
are usually unpleasant to S, but usually not "horrible"  
usually last for days/few weeks  
are **not** seen if drug X is D/C'd gradually, tapered off slowly  
note: case of a **long 1/2 life drug vs. a short 1/2 life drug**  
should **not** be confused with the "cravings" for drug X that can occur

## **PHARMACODYNAMICS: Tolerance & Dependence** (p.4)

### 4. **Psychological Dependence or “Craving Behavior”**

older term, now phased out, is “psychological” dependence  
which seemed to imply that these behaviors had no physical basis...

Not true!

**These intense cravings for drug X are the basis for addiction**

**And are both neurological/physiological and conditioned to cues**

Cannot be changed easily by “relearning” or “will power”, and sadly  
certainly not by punishment/incarceration...

Craving behavior is **not the same thing as withdrawal Sxs**