PHARMACODYNAMICS: Dosage & Drug Effects (p.1)

"**pharmacokinetics**" – what the body does to the drug
"**pharmacodynamics**" – what the drug does to the body

1. Dose-response curve (DRC)

For a single dose, describes the effect of a single dose of drug over time

More commonly, describes the effect of multiple doses of increasing drug amounts

describes a drug's effect over a range of doses from a low dose to a high dose, from "no effect" to "maximum effect"

relationship between the amount of drug & magnitude of the effect the drug produces at that amount/dose

X-axis: dose of drug, often represented in mg of drug/Kg of body wt.

Y-axis: magnitude of the effect (response) from low to high

Can do a DRC for an **individual *S* or for group data**

Can do a DRC **for each dependent variable** (DV) or effect that the drug produces: e.g. aspirin, DVs: subjective pain levels, stomach irritation, platelet suppression, body temperature, etc.

Note: **a given drug usually produces many effects**…

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2. **Additional Aspects of the DRC**

"**threshold response**" – dosage at which go from "no response" to "some response", a point where the **first measurable effect** is observed

"**slope**" of DRC – does is rise rapidly or slowly over increasing doses?

Clinical implications for a **slowly increasing gradual slope**

For a **steeply rising slope**

Implies a ***narrower*** "**therapeutic range**", between the threshold point and the maximal (& possibly toxic) point on the dosage axis

"**maximum**" point on DRC (for desired effects)

the DRC will show a dosage beyond which no further increases in dose will produce no further increases in effect, this is the point of **maximum effectiveness** or "**efficacy**"

S cannot show any greater response to the drug, may indicate that all the RSs for that drug are saturated/occupied by drug molecules

When this is group data, this is the point where 100% of the *Ss* all show response X (e.g. are now all headache free, show a reduction of depressive symptoms by at least 80%, etc.)

If the dose *is* increased further, you observe no further improvement or change in behavior

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2.**Additional Aspects of DRC** (cont.)

"**potency**" will be the comparison of two or more drugs in their **relative efficacy at what dose levels**

Looking at the maximum effect that 2+ drugs will produce (measured by the same DV) at what dosage for each drug

Or can compare what dosage is needed for each drug to produce behavioral effect X

Duration of response

Can also see on a DRC for a single *S*

Typically do not see this in group data DRCs, where are graphing what the maximal behavior response seen as different doses, irrespective of how long the effect lasts

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3. **"Main" Effects vs. "Side" Effects**

any drug will produce one than one effect in the body, and often will produce many changes in behavior….why?

only **one** (or a very few) of these effects (behavioral changes) is considered the **main or desirable effect**

the many other effects are considered to be **other or side effects**

SEs can range from inconsequential to a nuisance to dangerous

these effects may be of little significance, have little consequence

these effects may be of moderate significance, have a moderately strong effects on the *S*

If effects are moderate/severe and are adverse, will contribute to noncompliance/nonadherence behavior

if one or more effects is strong and is **desirable**, then the drug may be **used for more than one purpose** (e.g. aspirin, e.g. antidepressants)

"off-label" use

SEs (and SE severity) usually increase as **dose levels increase**

So, using lower dose levels are desirable

But may need to increase dose levels to get enough of main effect, So now **drug potency** becomes an issue

If SEs continue to be a problem, sometimes must add a 2nd drug to counter the SEs…this 2nd drug will have SEs…leads to pharmacologically "chasing one's tail"

"iatrogenic" effects

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4. **"Effective" vs. "Lethal" Doses**

effective dose (**ED**), lethal dose (**LD**)

The ED is a dose that produced a given effect in a specific percentage of the Ss (e.g. 10% or 80%), so is usually based on group data

ED 10 or ED 80

Note: each drug has an ED DRC for each and every single effect

That is, all main effects and all side effects

But practically, we are interested in a limited number of such curves

ED for the major beneficial main effect

"ED" for the major adverse side effects

"ED" for the lethal side effects (or LD)

ED l for main effect = threshold effect

ED 99 for main effect = maximum effective dose

ED 50 for main effect = a standard reference point, the **median** effective dose where 50% of the Ss has responded well (defined, e.g., as a 80% reduction in depressive Sxs) to the drug

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4.Effective & Lethal Doses (cont.)

LD 1 is the dose where one observes 1% of the Ss dying (the "threshold" dose for lethal effects)
note: lethal doses are ***estimated*** for humans based on animal data and adjusted by body weight to humans (mg/Kg body weight)… implications…

LD 99 is dose where one observes 99% of the Ss dying (the maximum "efficacy" for the drug)
LD 50 is the median lethal dose level where 50% of Ss are expected to die

Note: ideally one would like a drug that had a very low ED50 and a very high LD50

the "**therapeutic index**" = is a measure of drug safety, a ratio between two doses: **LD50/ED50**
e.g. for drug X, 90mg/9mg = TI of l0
the larger the TI, the safer the drug
values of 20+ are considered good, 100+ is very good
values < 10 are considered very risky

the "**toxicity index**" = a measure of how close the lowest lethal dose is to the highest effective dose: **LD1/ED99**
ratio of one means is the same dose, want a number that is _____?

The "**protective index**" = a measure of how close the effective dose is to the dose where you see non-lethal side effects: **ED50 for SEs/ED50**
ratio of one means is the same dose, want a number that is _____?

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5. **Time Course of Drug**

T1 = administer drug
T2 = onset of action at RSs
T3 = onset of behavioral changes
T4 = behavioral changes return to baseline
Tmax = time to maximum effect

T2 & T3 are fastest for IV injected drugs & for inhaled drugs

"duration" of drug effect can also be considered to be that period of time that the drug is "therapeutic", often is equal of one ½ life

slow absorption --- increased T2, increased latency to T3 as well
increased dosage --- shorter latency period (decreased T2 & T3), and increased duration of effect (T4)
several factors affect these T values: metabolism, redistribution, elimination, drug tolerance

the time course of a drug needs to be tailored to meet clinical needs:
e.g.cute care, often want a rapid onset and rapid offset
e.g. in SOI, want rapid onset and medium offset times
e.g. in SMI, want medium offset time if drug taken *h.s.*, want short onset and short offset times if taken *p.r.n*.
e.g. want long duration of effect if treating a chronic condition

time-release capsules (special enteric coatings)
in-dwelling pumps (surgically implanted)

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6. **Variability of Effects**

variability is actually another characteristic of the DRC, along with slope, efficacy, potency, etc.

a given drug at a given dose level will have **different effects on each *S*** (between *S* variance) and **different effects on a given *S* at different times** (within *S* variance)

sources of between S variance: age, sex, race, co-medical conditions, past drug use, etc.

sources of within S variance: time of day, menstrual cycle, co-medical conditions, other drugs taken, etc.

the DRC, based on **group data**, average over these sources of variance

several patterns of unusual reaction to drug (that contribute to variance):

"**over-reactions**", including hypersensitivity/supersensitivity/hyper-reactivity

"**under-reactions**", or insensitivity

"**idiosyncratic responses**"

"**paradoxical responses**"

"**discontinuation/withdrawal responses**"

usually get a "rebound" response that are "opposite" the drug's response, esp. of D/C'd abruptly

e.g. opiates --- SE of constipation, when D/C --- diarrhea

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7. General Issues re. **Multiple Drug Doses**

Usually want to **maintain a steady state** of drug level in body over a **long period of time** (e.g. months) for psychiatric drugs

Thus, drugs should be **given at uniform intervals roughly equal to the drug's ½ life**

e.g. if drug X as a half life of 8 hours, then give drug t.i.d./q.8h.

Want to keep the drug at therapeutic levels/**within** the **therapeutic window/ range** for the drug; do not want the drug level in the body to drop below this range, and certainly do not want the drug level to drop to zero before the next dose of the drug is given

Do not want the drug level to be too high either when the next dose is given either…why?

Want the drug to reach a "**steady state**" in the body

The second "**Rule of Five**": **If drug is taken at intervals equal of the half-life of the drug, it takes about 5 (**to 6**) doses of the drug to reach steady state levels in the body**

If it is desirable to very quickly build up the amount of a drug in the body, then one can sometimes give a "**loading dose**" (larger than normal dose), which is then followed by lower/maintenance doses at half-life intervals