Pharmacokinetics vs. Pharmacodynamics:

Pharmacodynamics is what drugs do to your body – what receptors the drugs bind to, whether they are agonists or antagonists.

Pharmacokinetics is what your body does to drugs:

Absorption
Distribution – spreading throughout your various tissues
Metabolism – breaking down drugs
Excretion

Absorption:

**Bioavailability:** What percentage of the drug makes it into the blood

Playing with bioavailability: Drugs which are much better absorbed by injection than orally will be requested as pills and then injected by addicts. Examples:
- Hydromorphone (Dilaudid): 5 times stronger IV
- Oxymorphone (Opana): 10 times stronger IV
- Methylphenidate (Ritalin): 2-3 times stronger IV or snorted

**Speed of onset:** How fast a drug gets absorbed, and thus how fast it kicks in. Faster onset means more euphoria. We will see why later.

Different routes of administration:

*Benefits of each?*
*Hazards of each?*
*Examples of each?*

Oral

Intranasal (snorted)

Inhalation (smoking, inhalers)

Rectal (suppositories, enemas, gels and liquids)

Transdermal (patches)
Parenteral (into bloodstream):

- Intravenous
- Intramuscular
- Subcutaneous
- Intrarterial

Spinal:

- Epidural – right outside the spinal cord
- Intrathecal – into the cerebrospinal fluid inside the spinal cord

Absorption >

Dopamine and reward:

See slides

Dopamine released in a special place (the nucleus accumbens) signals good outcomes

- Sex
- Food

Dopamine signals unexpected rewards

Dopamine reinforces the behavior that led to the good outcome

This is learning

Behaviors which cause dopamine release will be repeated

Dopamine motivates behavior

- Provides energy
- Focuses attention on the goal
Absorption > Dopamine and Reward >
Addiction:

**Seeing** the drug causes more DA release than **taking** the drug
  Thus seeing the drug will **motivate** the behaviors needed to acquire and take the drug, it will boost focus

Addictive drugs cause more DA release than **natural rewards**, and thus:
- Natural rewards do not please addicts
- Natural rewards cannot motivate addicts
- Punishments cannot deter addicts

The addictive drug is **much more salient** than any other motivators

Liking vs. Wanting:

- Different pathways

  Addicts **don’t like** (**enjoy**) **drugs**, not as much as they used to

  Addicts **do want** **drugs**

  Addicts **don’t want or like anything else**

Faster onset means **more euphoric** and **more addictive**

Why?

- Fast spike mimics natural reward

  Closer temporal correlation leads to **more learning**, especially unconscious association of the drug-taking behavior with the reward

Examples:

**Methadone** – it is a full opioid agonist, every bit as potent as heroin or morphine, but it is less additive because it kicks in slowly. Also, it lasts a long time, which prevents
withdrawal, and leads to less frequent drug taking. Taking drugs more often means **more opportunities for learning**.

Crack vs. powder cocaine

IV vs. snorted heroin

Smoked vs. snorted meth

See slides…

Absorption > Dopamine and Reward >

**ADHD:**

ADHD is treated with stimulants that boost dopamine (and norepinephrine), why does this work?

Dopamine normally facilitates goal-directed behavior by:
• Increasing motivation
• Focusing attention on the goal
• Providing energy to work towards the goal
• Speeding learning and reinforcing memory

**Why does DA speed learning and increase motivation?**

**Why aren’t ADHD drugs addictive?**

**Distribution:**

Multicompartment redistribution: The drug level in the brain **spikes** up very high and very fast, but the drug levels **quickly fall** as the drug **redistributes** into other tissues and thus gets **diluted**

**Why does this happen?**
• Blood gets the drug first
• Then brain
Then viscera
Then muscles
Then finally fat

What is required to make a drug with a funky spike and then redistribution?
Fast absorption (IV or maybe smoked)
Fast crossing of blood-brain-barrier

Examples:

Metabolism:

This is how your body chemically modifies drugs.
Metabolism occurs mostly in the liver, or else it is widely distributed.
Metabolism produces metabolites
Some metabolites are active drugs

Prodrugs: Chemicals that are inactive, but are metabolized into active drugs

Examples:

GBL and 1,4-BD – The latter was found in children’s toys

Hepatic portal circulation: All chemicals in the stomach and small intestines must go through the liver before reaching the regular bloodstream
It often cuts down on bioavailability
This is called first-pass metabolism

Why did this evolve?

Ways to bypass:

Intranasal (snorting)
Inhalation
Injection
Intrarectal (only 50% bypasses portal circulation)
Intravaginal
Why are intranasal, intrarectal, and intravaginal administration hazardous?

Excretion:

In feces

*How did it get there?*

In urine (kidneys)

Amphetamine excretion depends on urine pH.

*How can we modify urine pH?*

*What chemistry technique is this reminiscent of?*\(^1\)

Playing with ADME:

See slides

*What phase of ADME is being modified in each of these examples?*

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1 Extraction – when you have two solvents and you let the solute *distribute* between the two according to the *partition coefficient*, the ratio indicating how much of the solute can “fit” in each of the two liquids.