Pharmacology of Addictive Disorders

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Disclosure
Thomas Kosten, MD

No conflicts of interest or disclosures for this presentation

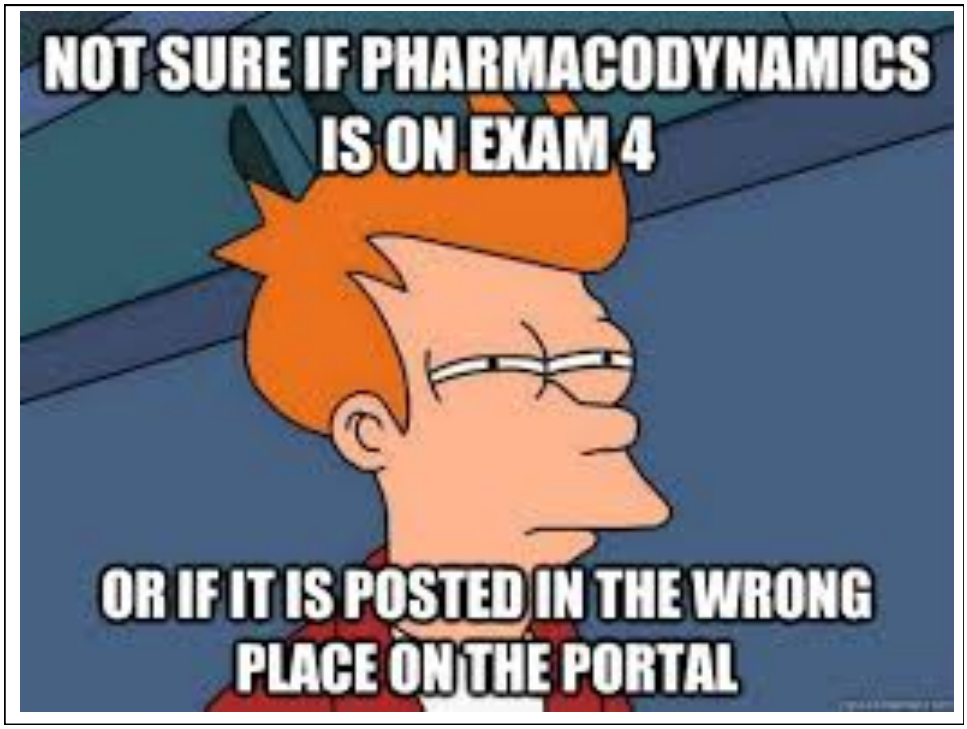
Learning Objectives

The learner should be competent in:

1. Drug Metabolism and Principles of Drug Interactions (Pharmaco-kinetics & -dynamics)
2. Impact of Route of Drug Administration
3. Genetic/sex-based variation of metabolism
4. Reinforcement
5. Tolerance and withdrawal
6. Cross-Tolerance
7. Physical Dependence
8. Conditioning
9. Sensitization
10. General overview of pharmacotherapy for drugs

References

Kosten TR (Pharmacology editor), Ries, Fiellin, Miller, Saitz (General Editors). *Principles of Addiction Medicine, 5th edition.* Lippincott Williams & Wilkins, 2014. Washington, DC: American Society of Addiction Medicine.


NOT SURE IF PHARMACODYNAMICS IS ON EXAM 4
OR IF IT IS POSTED IN THE WRONG PLACE ON THE PORTAL


I'M INTO
PHARMACO
KINETICS

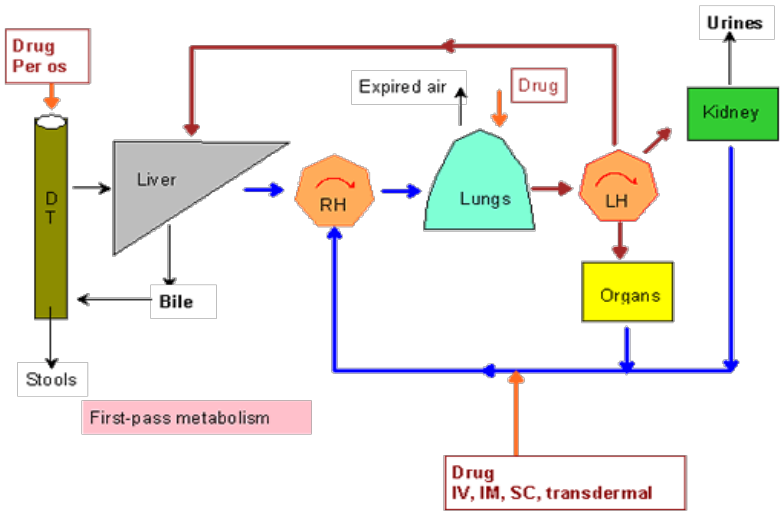
Question #1

TRUE OF FALSE?

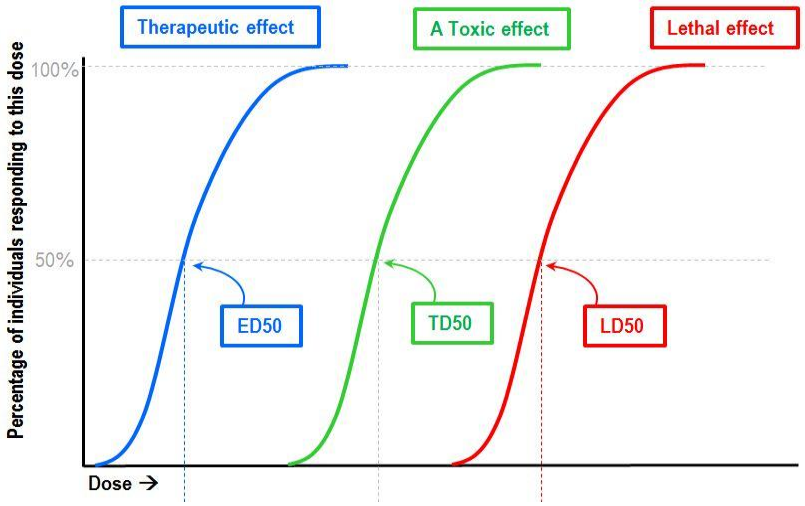
The inactivation of a drug when orally but not when parenterally administered is usually called first pass metabolism.

TRUE

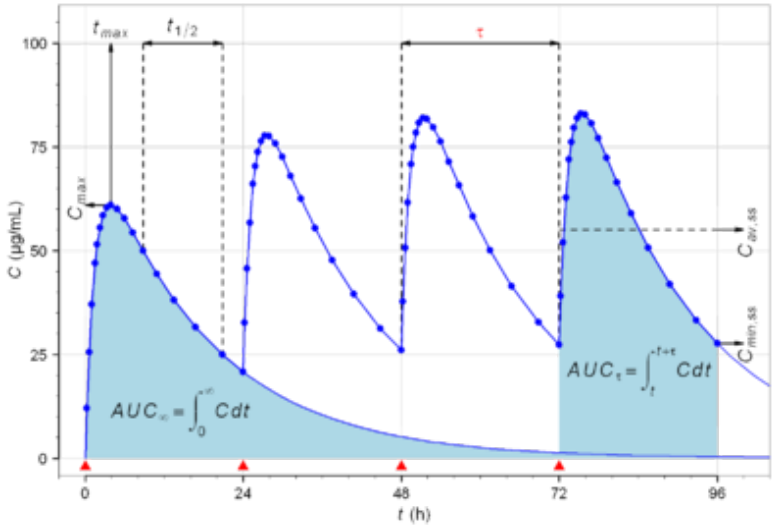
Pharmacokinetics: Where do drugs go in the body



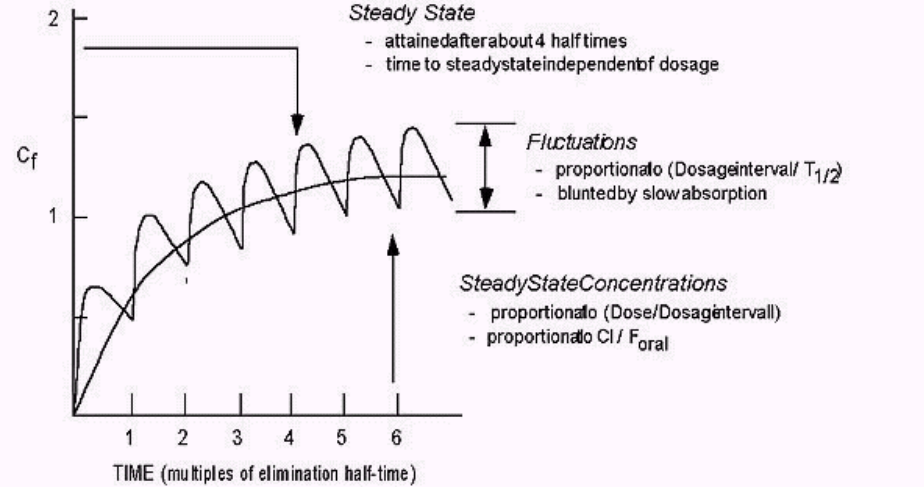
Pharmacokinetics: Therapeutic vs Toxic dose response curves



Pharmacokinetics: Half-life and Dosing interval



Pharmacokinetics: Steady State



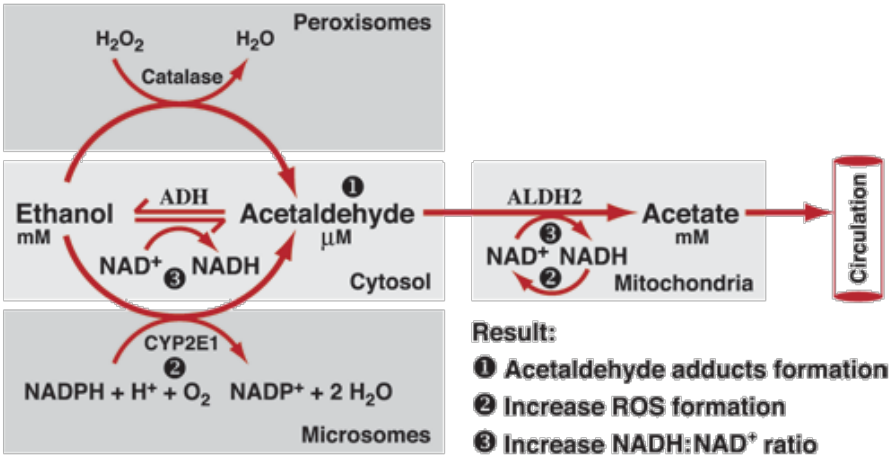
Question #2

TRUE OF FALSE?

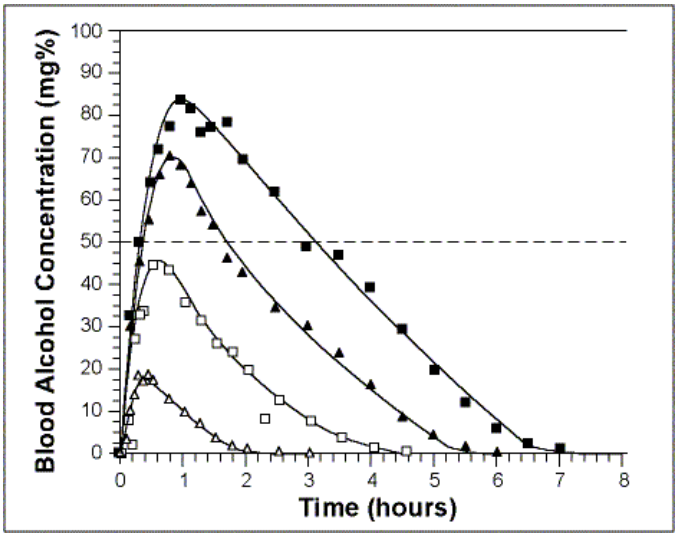
Blocking metabolism of alcohol by aldehyde dehydrogenase leads to the disulfiram reaction.

FALSE

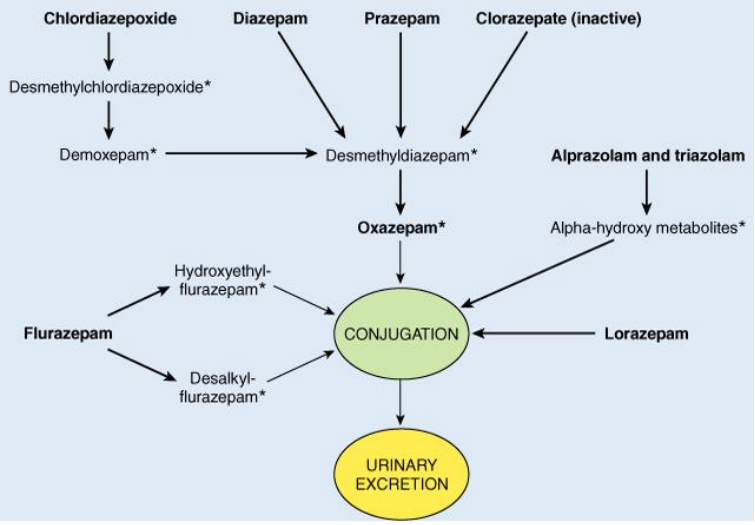
Metabolism of Alcohol: Disulfiram



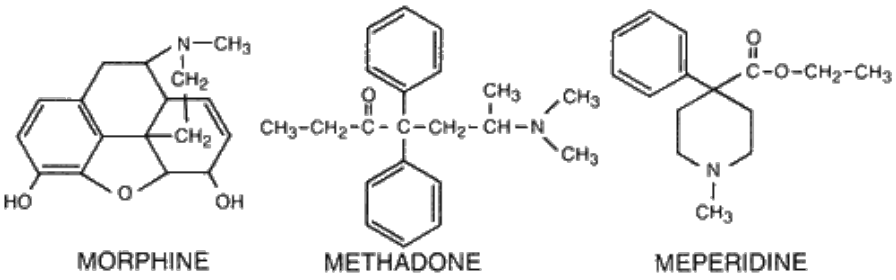
Linear Alcohol Metabolism



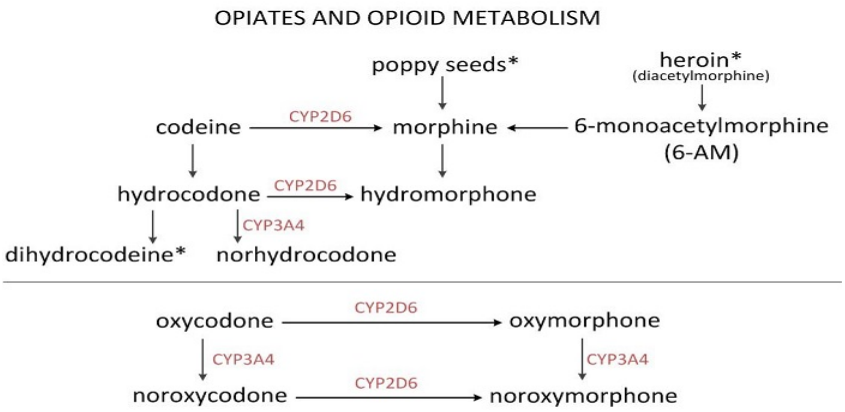
Benzodiazepine Metabolism



Types of Opiates



Morphine Metabolism



Shown in red are the major cytochrome P450 enzymes involved in phase I metabolism; patterns of drug metabolites may reflect the metabolic phenotype of the patient. Actual proportions of individual metabolites will vary.

Pharmacogenetic testing is available for CYP2D6.

Phase II reactions (eg, glucuronide conjugation) are not shown but are prominent for most compounds.

*Not specifically detected by the *Opiates – Confirmation/Quantification, Urine,* assay

Clinical aspects of Opiate Pharmacokinetics

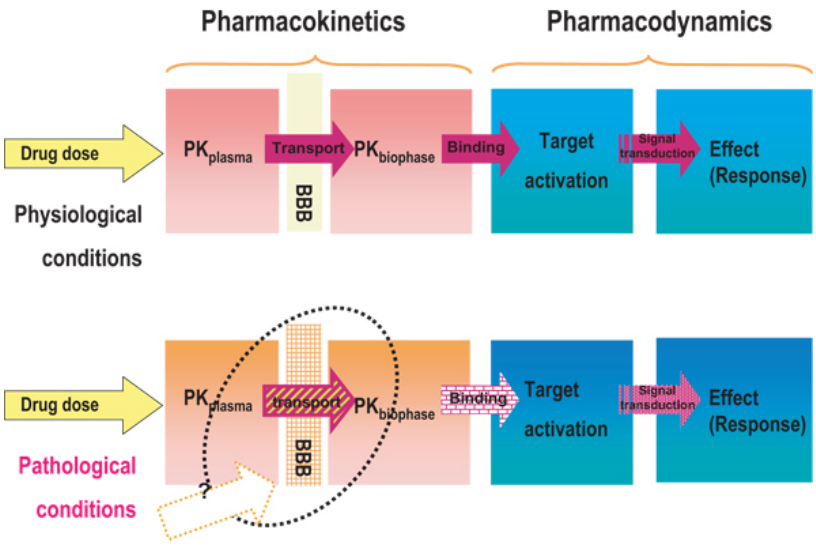
Table 3 – Opioids: Aspects of pharmacokinetics and dosing via

Drug	Dosing route	Pharmacokinetic aspects
Morphine	Oral (including the slow-release form), intravenous, intramuscular, intrathecal	Half-life 3-4 hours Converted to active metabolite (morphine-6-glicuronide)
Heroin	Intravenous, intramuscular, smoked, oral	Half-life < 1 hour Partly metabolized to morphine
Methadone	Oral, intravenous, intramuscular	Half-life > 24 hours No active metabolite
Pethidine	Oral, intramuscular	Half-life 2-4 hours Active metabolite (norpethidine)
Buprenorphine	Sublingual, intrathecal, subcutaneous, intravenous, intramuscular	Half-life de 12 hours Slow onset of action Inactivated by the oral via due to first-pass effect
Fentanyl	Intravenous, epidural, transdermal patch	Half-life de 1-2 hours
Codeine	Oral	Acts as pro-drug Metabolized to morphine and other active opioids

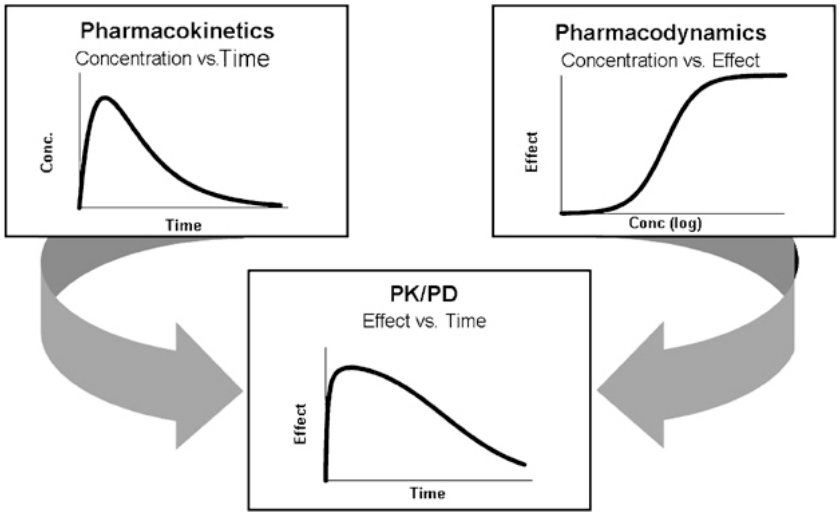
Key enzymes & metabolites

- Alcohol: acetaldehyde (acetaldehyde dehydrogenase - disulfiram)
- Nicotine: cotinine (CYP2A6)
- Opiates: Nor-meperidine & seizure activity.
  - Fentanyl, oxycodone & SSRI: Serotonin syndrome
- Cocaine: cholinesterase, cocaethylene
- Marijuana: tetrahydrocannabinol (THC)
- Hallucinogens: most enter the brain rapidly, with minimal metabolism and are renally excreted

Pharmaco-kinetics vs. -dynamics



Pharmaco-kinetics vs. -dynamics



Pharmacodynamics
Opiate Analgesia (50% maximum)

Medication	Brain concentration
• Fentanyl	• 5 ng/g
• Morphine	• 20 ng/g
• Meperidine	• 2000 ng/g

Pharmacodynamic differences due to Pharmacokinetic differences

MALE ALCOHOL IMPAIRMENT CHART

APPROXIMATE BLOOD ALCOHOL PERCENTAGE

DRINKS	BODY WEIGHT IN POUNDS										
	140	160	180	200	220	240	260	280	300	320	
1	.04	.04	.03	.02	.02	.02	.02	.01	.01	.01	IMPAIRMENT BEGINS
2	.09	.07	.06	.05	.04	.04	.03	.03	.02	.02	DRIVING SKILLS AFFECTED
3	.13	.11	.09	.08	.07	.06	.05	.04	.04	.03	POSSIBLE CRIMINAL PENALTIES
4	.18	.15	.12	.10	.09	.08	.07	.06	.05	.04	
5	.22	.18	.15	.13	.11	.10	.08	.07	.06	.05	
6	.26	.22	.18	.16	.13	.12	.10	.09	.07	.06	
7	.30	.26	.21	.18	.16	.14	.12	.10	.09	.08	LEGALLY INTOXICATED
8	.35	.29	.24	.21	.18	.16	.13	.12	.10	.09	CRIMINAL PENALTIES
9	.40	.33	.27	.24	.20	.17	.15	.13	.11	.10	
10	.43	.36	.31	.26	.22	.19	.17	.14	.12	.11	

Your body can get rid of one drink per hour.
Each 1.5 oz. of 80 proof liquor, 12 oz. of beer or 5 oz. of table wine = 1 drink.

Question #3

TRUE OR FALSE?

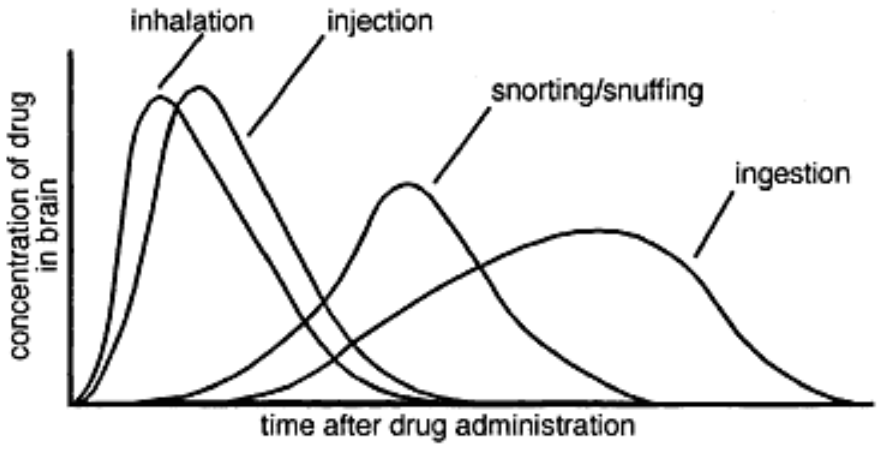
The levels of cocaine in both blood and brain peak about 10 times faster when smoked than when used intranasally.

TRUE

Pharmacokinetics: Cocaine route of administration

Route	Peak	Duration
• IV or smoked	30-90 sec	20 min
• Nasal	30 min	2 hrs
• Gastrointestinal	60-90 min	>3 hrs

Pharmacokinetics: Routes of administration

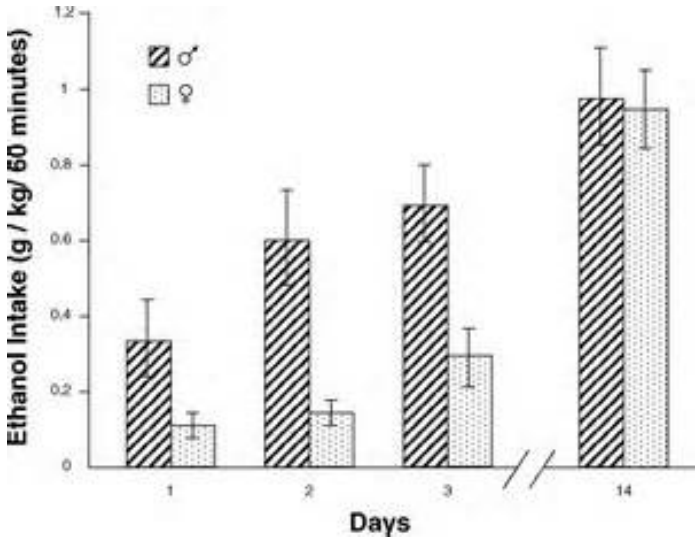


Gender Differences

- Alcohol blood levels about 25% higher in women with same alcohol intake
- Alcoholic hypo-glycemia more common in women
- Nicotine metabolized faster in women & even faster during pregnancy (estrogen & CYP2A6)
- Methadone metabolized faster in women & even faster during pregnancy (estrogen & CYP2A6)

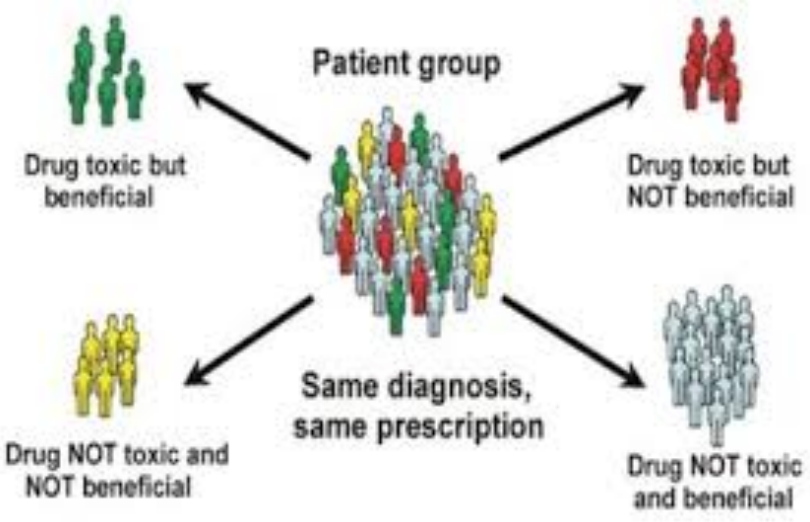
Gender Differences: ETOH Intoxication

Initial tolerance differences disappear

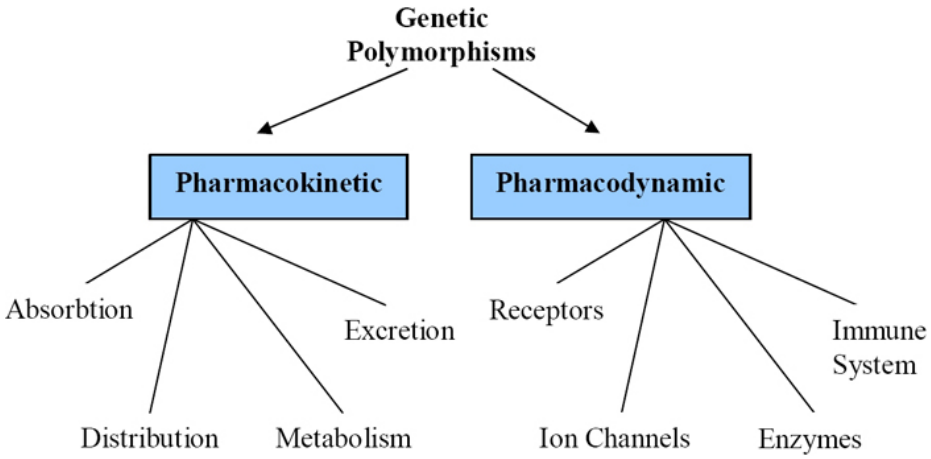


Genetic variation leads to complicated connections among Drugs

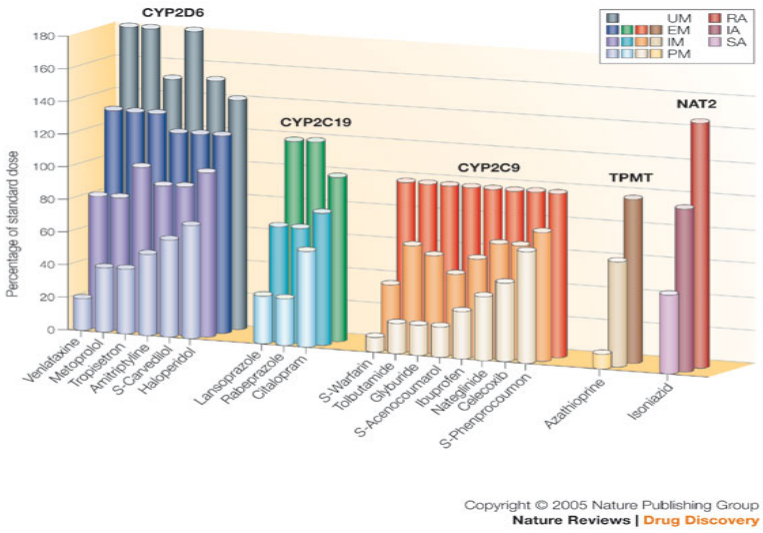
Pharmacogenetics: Why?



Genetic Effects on Drugs: Pharmaco-kinetic vs. -dynamic



Pharmacogenetics: Liver metabolism CYP enzymes and drug levels



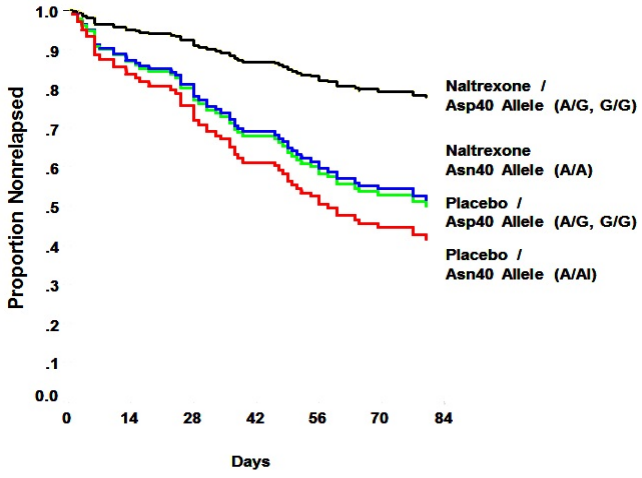
Opiate Metabolism and Pharmacogenetics

SUBSTRATES OF CYTOCHROME P450 AND GLUCURONIDATION ENZYMES

	Cytochrome P450 (CYP)								UDP—Glucuronosyltransferase (UGT)				
	1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A4/5	1A1	1A3	1A8/9	2B7	2B15
acetaminophen													
buprenorphine													
codeine						A							
fentanyl													
hydrocodone						A							
hydromorphone													
ibuprofen													
meperidine					A								
methadone													
morphine													
naproxen													
oxycodone						A							
oxymorphone													
propoxyphene													
tapentadol													
tramadol						A							

A — activation — major pathway — minor pathway

Pharmacogenetics: Alcohol treatment response: Naltrexone and Relapse Rate

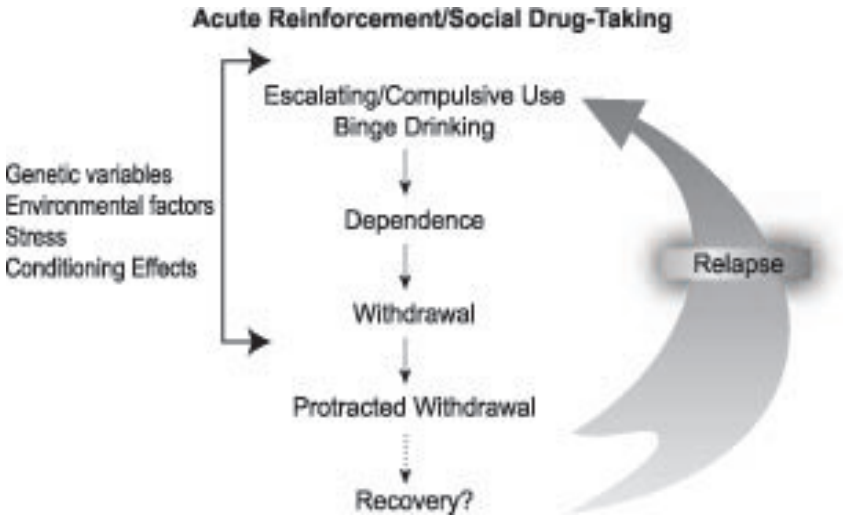


Oslin DW, et al. *Neuropsychopharmacology*. 2003;28(8):1546-1552.

Reinforcement: NOT

Reinforcement vs. Punishment: Varies in the eyes of the beholder

Reinforcement



Reinforcement: Light vs Dark sides

"Light Side" of Addiction: Positive Reinforcement

	Baseline alcohol self-administration	"Binge"-like alcohol self-administration	Progressive ratio/second-order reinforcement schedules	Alcohol priming–induced reinstatement	Alcohol-conditioned cue-induced reinstatement
Dopamine antagonist	↓	↓			↓
Opioid antagonist	↓	↓	↓	↓	↓

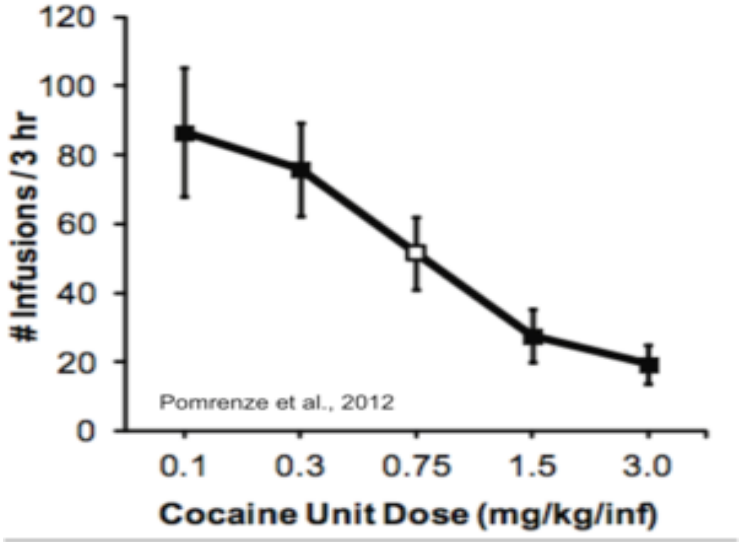
"Dark Side" of Addiction: Negative Reinforcement

	Baseline alcohol self-administration or place preference	Withdrawal-induced anxiety-like or aversive responses	Dependence-induced increases in self-administration	Stress-induced reinstatement
Corticotropin-releasing factor antagonist	—	↓	↓	↓
Neuropeptide Y	—	↓	↓	

Tolerance and Withdrawal

1. Tolerance
   a. increased amounts needed to achieve the desired effect OR
   b. diminished effect w/ continued use of same amount
2. Withdrawal
   a. characteristic withdrawal syndrome OR
   b. substance is taken to avoid withdrawal
   c. physiological withdrawal signs not required for dependence

Acute Tolerance to Cocaine



Question #4

TRUE OR FALSE?

Alcohol and chlordiazepoxide are cross-tolerant, while nicotine and cotinine are not cross-tolerant.

TRUE

Cross-tolerance

- **Cross-tolerance** occurs when someone who is tolerant to the effects of a certain drug also develops a tolerance to another drug.
- The drugs typically have similar functions or effects – e.g. same cell receptor.
- Cross-tolerance: anti-anxiety & illicit drugs
  - Benzodiazepines, Barbiturates, alcohols
  - Morphine, codeine, methadone
  - Amphetamine, cocaine
  - Alcohol and Cannabis or nicotine?

Switching opiates & Cross-tolerance

Opiate type	Oral	Injected
• Morphine	60 mg	10 mg
• Codeine	200 mg	130 mg
• Hydromorphone	7.5 mg	1.5 mg
• Fentanyl	NA	0.1 mg

Withdrawal and Cross-tolerance

- Withdrawal follows from physical dependence and consists of abstinence symptoms that occur when the drug is discontinued
- These symptoms are drug specific ranging from potentially fatal in alcoholic delirium tremens to "bad case of flu" in opiates to few physical symptoms in stimulants
- Cross-tolerance is important for treatment where Drug A will stop withdrawal symptoms caused by Drug B

Physical Dependence
Alcohol withdrawal & screening scales

- Withdrawal rating scale
  - Clinical Institute Withdrawal Assessment (CIWA)
- Dependence
  - # of DSM-V criteria: 2=dependence, severity to 7
- Screening
  - Not for severity of withdrawal or dependence
  - Breath alcohol
  - Urine alcohol, glucuronide
  - Blood carbohydrate deficient transferrin

Physical Dependence
Opiate withdrawal & screening

- Withdrawal rating scale
  - Clinical Observed Withdrawal Scale (COWS)
  - Himmelsback rating scale
- Dependence
  - # of DSM-V criteria: 2=dependence, severity to 7
  - Naloxone challenge (IV, IM, not oral)
- Screening
  - Not for severity of withdrawal or dependence
  - Urine opiate metabolites: five classes to test

Physical Dependence
Nicotine withdrawal & screening

- No rating scale for nicotine withdrawal
- Nicotine dependence
  - Fagerstrom scale: Most commonly used measure
  - # of DSM-V criteria: 2=dependence, severity up to 7
- Nicotine screening
  - Quantity & frequency of cigarettes or nicotine per day
  - Urine, blood, saliva cotinine levels
  - Breath carbon monoxide

Physical Dependence
Marijuana withdrawal & screening

- Withdrawal rating scale (use opiate scale)
  - Clinician Observed Withdrawal Scale (COWS)
  - Slow onset, appears mild, mostly irritability, insomnia
- Dependence
  - # of DSM-V criteria: 2=dependence, severity to 7
  - Rimonaband (off market in USA), not naloxone
- Screening
  - Quantity & frequency of joints per day
  - Urine cannabinoids (THC) – can last weeks after stopping
  - "Spice" can be wide variety of substances

Physical Dependence Sedatives/Benzodiazepines

- Withdrawal rating scale (use alcohol scale)
  - Clinical Interview Withdrawal Assessment (CIWA)
- Dependence
  - # of DSM-V criteria: 2=dependence, severity to 7
  - Flumazenil (risk of seizures)
- Screening
  - Not for severity of withdrawal or dependence
  - Urine benzodiazepines – many metabolites
  - Barbiturates & GHB - uncommon

Physical Dependence Stimulant withdrawal & screening

- Withdrawal rating scale
  - No standardized scale, see DSM-V criteria
  - Few physiological symptoms, mostly irritability, insomnia
- Dependence
  - # of DSM-V criteria: 2=dependence, severity up to 7
- Screening
  - Quantity & frequency of "dimes" or $ per day
  - Urine benzoylecognine or amphetamine metabolites

Physical Dependence Hallucinogens

- Withdrawal rating scale
  - None, typically rapid tolerance & no withdrawal
- Dependence
  - # of DSM-V criteria: 2=dependence, severity to 7
- Screening
  - Quantity & frequency of pills taken
  - Urine metabolites – LSD, PCP, ketamine, mescaline, many others, hard to detect due to very low levels

Conditioning

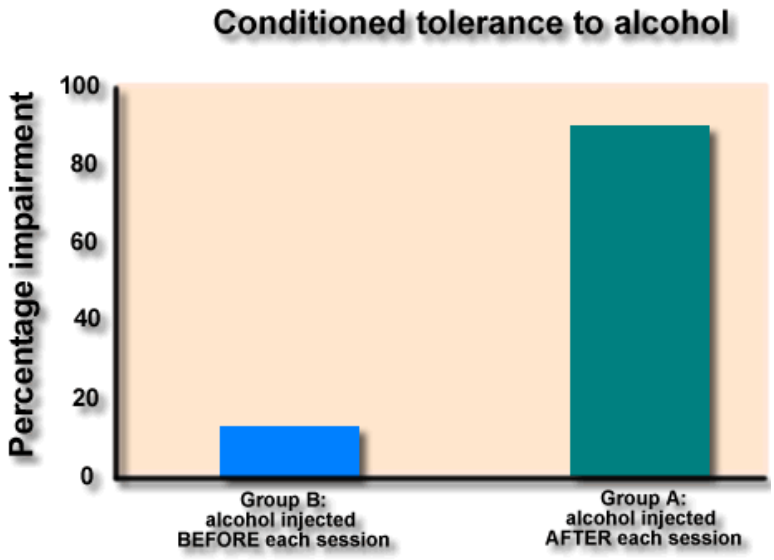
INITIAL EXPOSURE TO DRUG

Neutral stimuli	*unconditioned stimulus (US)*	*unconditioned response (UR)*
environmental stimuli associated with drug administration	→ drug effects on brain →	compensatory reactions to drug

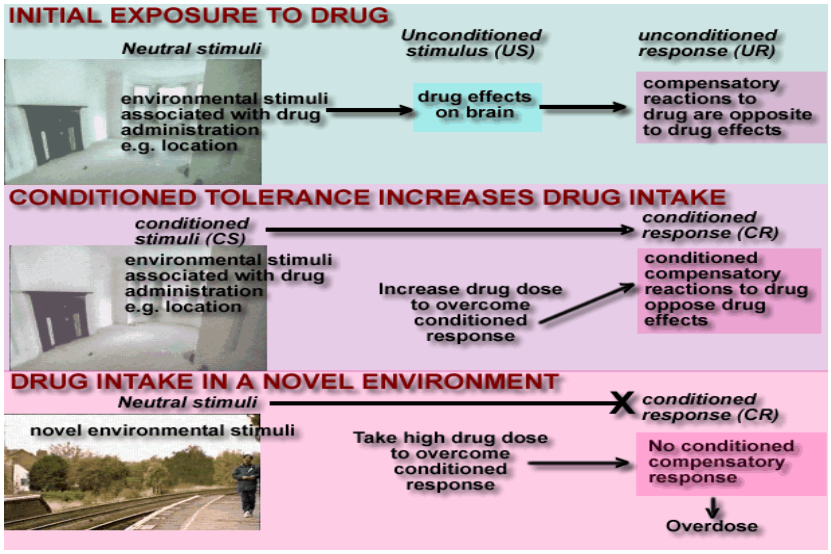
SUBSEQUENT REACTIONS

conditioned stimulus (CS)	*conditioned response (CR)*
environmental stimuli associated with drug administration →	compensatory reactions to drug

Conditioning and Tolerance



Conditioning and Tolerance



Sensitization

- Increased locomotion in rodents after repeated high doses of abused drugs
  - e.g. cocaine, nicotine, opiates, alcohol
- Human equivalents?
  - Seizures, withdrawal, panic, hyperalgesia
- Cross-sensitization between drugs and other conditions like stress
- Conditioned drug-like effect to environment
- Sensitized brain mechanisms may control motivation for drug seeking in addictions

General overview of pharmacotherapy for drugs

- FDA approved medications vs. "off label" use
- Alcohol: disulfiram, naltrexone, acamprosate
- Opiates: methadone, buprenorphine, naltrexone including depot formulation
- Nicotine: replacement, bupropion, varenicline
- "Off label"
  - Detoxification vs. Relapse prevention
  - Duration of exposure to agent

Good luck with your STUDY

I could not cover everything,
But remember the BOOK does!

Kosten TR (Pharmacology editor), Ries, Fiellin, Miller, Saitz (General Editors). *Principles of Addiction Medicine, 5th edition.* Lippincott Williams & Wilkins, 2014. Washington, DC: American Society of Addiction Medicine.

A toast to your exam study!