ASAM REVIEW COURSE 2023

Pharmacology and Toxicology: Principles, Applications, and Limitations

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Financial Disclosure

Lewis S. Nelson, MD, MBA, FASAM

- No relevant disclosures

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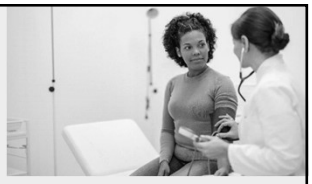
Learning Objectives



1. **Explain** the differences between and clinical relevance of tolerance, dependence, and hyperalgesia.
2. **Describe** the pharmacologic principles of pharmacokinetics and pharmacodynamics and how each impacts addiction risk and addiction treatment.
3. **Discuss** the interpretation pitfalls of screening and confirmatory urine drug tests in the management of patients with substance use.

3

Addiction Medicine IS Pharmacology

- Drugs have to get to the brain to elicit a response.
  - Blood brain barrier is an effective barricade
- The more rapidly the drugs reach the site of action the greater the reinforcement.
  - Dose and dose rate
  - Route of administration
  - Lipophilicity and other pharmacologic characteristics

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Pharmacokinetics and Pharmacodynamics

Absorption (Bioavailability)	Distribution	Elimination
Biotransformation	Dose Response (Clinical Effect)	Potency
Drug interaction	Tolerance	Dependence

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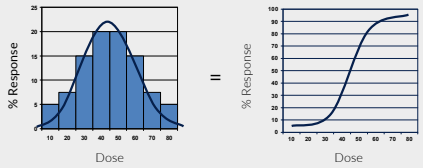
Dose-Response



Response = Anything (Blood pressure, Euphoria, Death)

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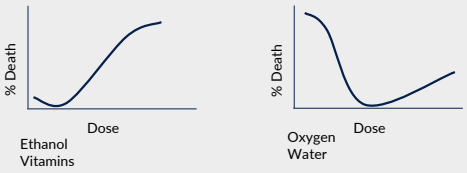
Dose-Response



Response = Death

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Potency

Rank order the potency at causing death:

Agent	LD50 (mg/kg)
Ethanol	5,000
Morphine	1
Nicotine	1
Botulinum	0.00001

Don't confuse potency with clinical effect

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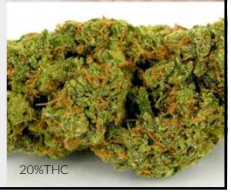
Which has more potent THC?

1980's weed

Trick question:
The THC is the same potency
The higher concentration weed is more "potent"

Don't confuse potency of a drug with its concentration

2020 weed



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Potency doesn't really matter

Agent	Potency (vs morphine)
Tramadol	0.2
Morphine	1
Oxycodone	1.3
Methadone	4
Heroin	4
Buprenorphine	30
Fentanyl	100
Carfentanil	10,000

Any of these drugs will kill you if you take enough

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What is There That is Not Poison?

"What is there that is not poison? All things are poison and nothing [is] without poison. Solely the dose determines that a thing is not a poison"

Paracelsus (1493-1541)
in *Third Defense*

"Dose Makes The Poison"

Philip Theophrastus Bombast von Hohenheim
aka PARACELSUS (1493-1541)

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Potency doesn't really matter

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Absorption

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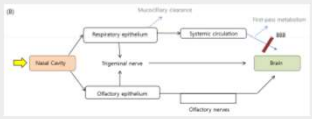
Routes of Administration

- Oral
  - Potentially extensive first-pass
- IV, IN, IM, SC, SL, buccal, inhalational, rectal
  - Bypass hepatic first-pass
- Intrathecal
  - Unique –bypass Blood Brain Barrier
- Transdermal
  - Bypass hepatic first-pass
  - Depot in skin/body fat can influence absorption
- Intranasal
  - May directly access CNS (nose-to-brain)



Hong, S. Pharmaceutics 2019;11:540

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Bioavailability

- The amount of unchanged drug reaching systemic circulation after administration is the bioavailability (F).
- F depends upon:
  - Route (IV is 100%)
  - Site specific membrane permeability
  - Drug transporter activity (p-glycoprotein)
  - First-pass metabolism (oral)

	Route		
	Oral	Sublingual	Buccal
Buprenorphine	10%	30%	50%
	Oral	Sublingual	Intranasal
Naloxone	1%	20%	50%
	Oral		
Morphine	33%		
Oxycodone	75%		

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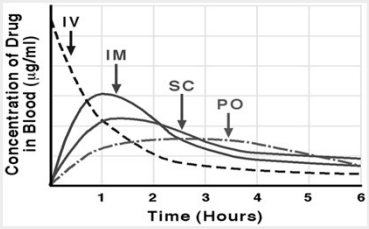
Area Under the Curve (AUC)



Wolff K, et al. The SAGE Handbook of Drug & Alcohol Studies

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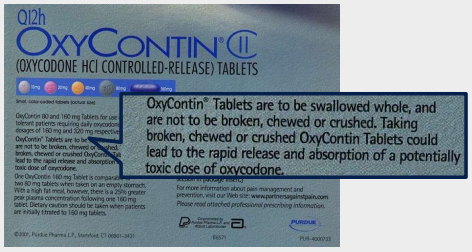

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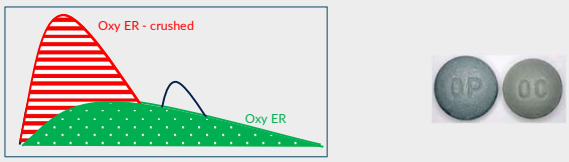

How to Abuse **OP OxyContin**, How to Get High **OP OxyContin** - Bluelight
www.bluelight.org/.../526671-How-to-Abuse-**OP-OxyContin**-How-to-Get-High-**OP-OxyContin**
How to Abuse **OP OxyContin**, How to Get High **OP OxyContin** So far the only legit way to abuse/get high off of the new **OP OxyContin** is what I ...

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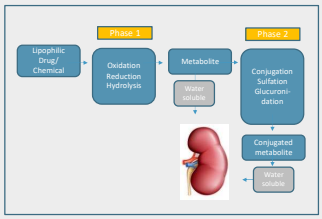
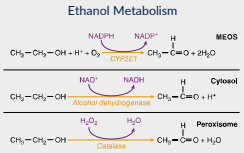
Biotransformation





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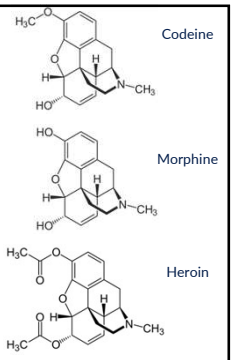
Activation through Biotransformation

- Codeine is demethylated in the liver to morphine
  - Occurs via CYP2D6
  - Codeine is a "pro-drug" (drug undergoes hepatic biotransformation or 'metabolism' to its active component
  - Lisdexamfetamine (Vyvanse™) is another example of a pro-drug

Fun pharm fact: *heroin does not bind to the mu receptor. Metabolism occurs in the CSF.*



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Biotransformation

TABLE 11–1 Characteristics of Different Cytochrome P450 Enzymes

CYP Enzyme	1A2	2B6	2C9	2C19	2D6	2E1	3A4
Percent of liver CYPs	4%–16%	2%–5%	5%–29%	1%–4%	1%–4%	6%–17%	15%–37%
Contribution to enterocyte CYPs	None	None	Minor	Minor	Minor	Minor	70%
Organs other than liver with enzyme	Lung	Kidney	Small intestine, nasal mucosa, heart	Small intestine, nasal mucosa, heart	Small intestine, kidney, lung, heart	Lung, small intestine, kidney	Much in small intestine; some in kidney, nasal mucosa, lung, stomach
Percent of metabolism of typically used pharmaceuticals	9%	7%	13%	7%	20%	3%	30 %
Polymorphisms*	No	Yes	Yes	Yes	Yes	No	No
Allelic Frequency							
Decreased Activity							
African American		38%–62%	0%–3%	10%–17%	14%–30%		
Asian	—	14%–25%	2%–8%	25%–39%	47%–94%	—	—
Caucasian		23%–39%	16%–23%	6%–16%	31%–45%		
Increased Activity							
African American		0%–25%		15%–27%			
Asian	—	5%–15%	—	0%–2%	1%	—	—
Caucasian		6%		21%–25%	1%–9%		
Ethiopian					30%		

*Polymorphism is a genetic change that exists in at least 1% of the human population. Intergenerational allelic variations exist even in those listed as "No" for polymorphism.

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Biotransformation

Genetically based alterations in gene product function.

Despite rare polymorphism, 3A4 is a major cause of drug interactions

Methadone

- Primarily responsible for metabolism
- Some HIV meds induce 3A4
- Variability (despite minimal polymorphism) complicates induction

TABLE 11–1 Characteristics of Different Cytochrome P450 Enzymes[28,33,723]

	2B6	2C9	2C19	2D6	2E1	3A4
Percent of human liver	2%–5%	5%–29%	1%–4%	1%–4%	6%–17%	15%–37%
Percent of metabolism of typically used pharmaceuticals	None	Minor	Minor	Minor	Minor	70%
Location	Kidney	Small intestine, nasal mucosa, heart	Small intestine, nasal mucosa, heart	Small intestine, kidney, lung, heart	Lung, small intestine, kidney	Much in small intestine; some in kidney, nasal mucosa, lung, stomach
Percent of metabolism of typically used pharmaceuticals	9%	7%	13%	7%	20%	3%	30 %
Polymorphisms[a]	No	Yes			No	No
Allelic Frequency						
Decreased Activity						
African American	—	38%–62%			—	—
Asian		14%–25%				
Caucasian		23%–39%				
Increased Activity						
African American	—	0%–25%			—	—
Asian		5%–15%				
Caucasian		6%				
Ethiopian						

[a] Polymorphism is a genetic change that exists in at least 1% of the human population. Interpersonal allelic variations exist even in those listed as "No" for polymorphism.

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Distribution

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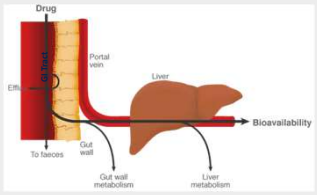
First Pass Hepatic Metabolism

Bypass first pass



www.doctoralerts.com

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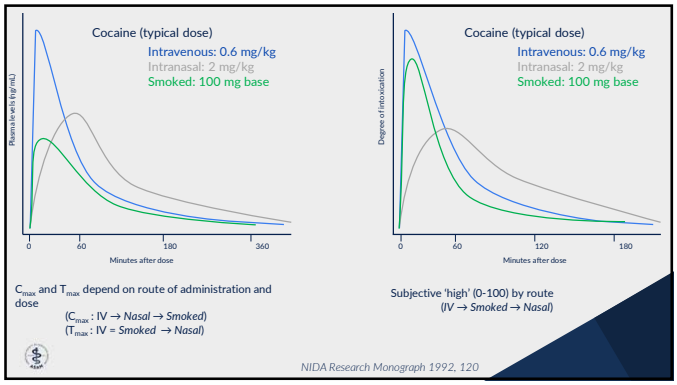
Cocaine (typical dose)
Intravenous: 0.6 mg/kg
Intranasal: 2 mg/kg
Smoked: 100 mg base
Plasma levels (ng/mL)
Minutes after dose
Cocaine (typical dose)
Intravenous: 0.6 mg/kg
Intranasal: 2 mg/kg
Smoked: 100 mg base
Degree of intoxication
Minutes after dose
Cmax and Tmax depend on route of administration and dose
(Cmax : IV → Nasal → Smoked)
(Tmax : IV = Smoked → Nasal)
Subjective 'high' (0-100) by route
(IV → Smoked → Nasal)
NIDA Research Monograph 1992, 120

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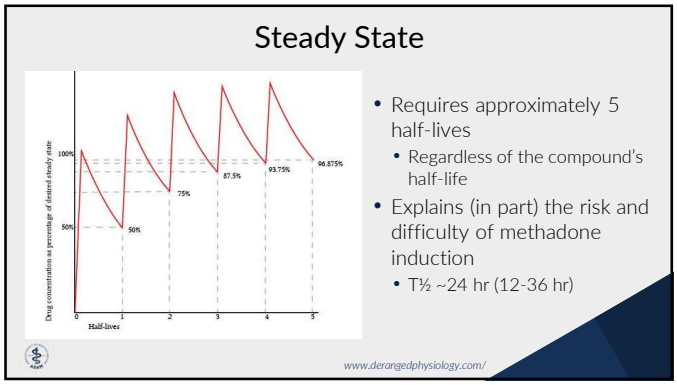
Steady State
Drug concentration as percentage of desired steady state
Half-lives
96.875%
93.75%
87.5%
75%
50%
• Requires approximately 5 half-lives
• Regardless of the compound's half-life
• Explains (in part) the risk and difficulty of methadone induction
• T½ ~24 hr (12-36 hr)
www.derangedphysiology.com/

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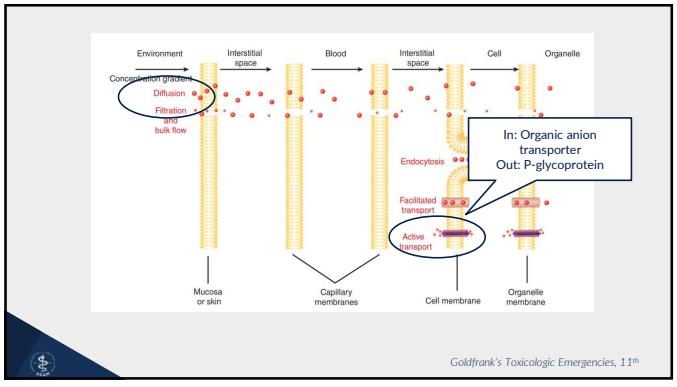
Environment
Interstitial space
Blood
Interstitial space
Cell
Organelle
Concentration gradient
Diffusion
Filtration and bulk flow
Endocytosis
Facilitated transport
Active transport
In: Organic anion transporter
Out: P-glycoprotein
Mucosa or skin
Capillary membranes
Cell membrane
Organelle membrane
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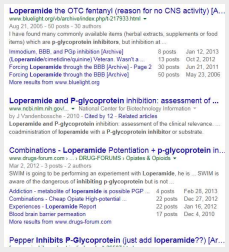
P-Glycoprotein



"Street pharmacologists" understand these principles

Loperamide and p-glycoprotein inhibitors

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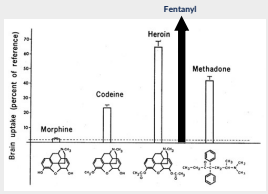
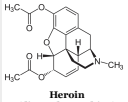
Lipophilicity

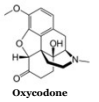
Lipophilicity = Reward = Abuse liability

Drug	LogP
Buprenorphine	4.98
Fentanyl	4.05
Methadone	3.93
Naloxone	2.09
Hydromorphone	1.6
Heroin	1.58
Morphine	0.89




Morphine


Heroin (diacetyl morphine)


Oxycodone

Oldendorf WH. Science. 1972

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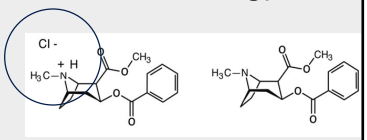
Addiction Medicine IS Pharmacology




Cocaine hydrochloride (salt)


Cocaine base (alkaloidal)

Changes in the pharmacologic properties of a substance and how it is used can lead to dramatically different levels of reward and reinforcement

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Elimination

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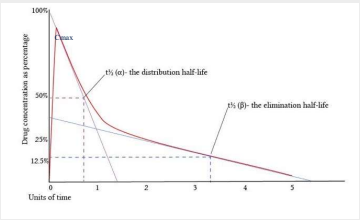
T1/2 (Half-life) is The Time For Cmax to Fall by Half



- Distribution t½
  - Redistribution t½
- Terminal elimination t½
  - Context sensitive t½
  - Apparent t½

Drug	Half life (distrib)	Half life (redistrib)	Half life (term)	LogP
Fentanyl	2 min	12 min	480 min	4.05
Methadone	120 min	---	1440 min	3.93

Note: all half-lives have ranges, not shown

www.derangedphysiology.com/

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Receptor Pharmacology

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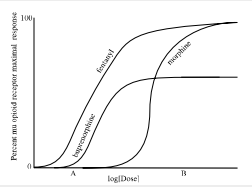
Efficacy

Ligand	% Efficacy
Full agonist	E = 100
Partial agonist	0 < E < 100
Antagonist	E = 0
Inverse agonist	E < 0



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Affinity

Ligand	Ki (Affinity) (nmol)
Hydrocodone	41.58
Oxycodone	25.87
Heroin	9.6
Methadone	3.38
Fentanyl	1.35
Morphine	1.14
Naloxone	1.1
Hydromorphone	0.6
Buprenorphine	0.21

Volpe DA. Uniform assessment and ranking of opioid Mu receptor binding constants for selected opioid drugs. Reg Toxicol Pharmacol 2011

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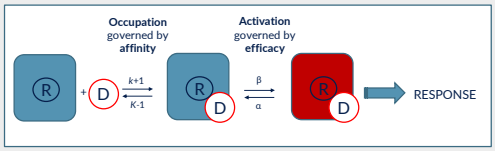
Receptor kinetics
On-off



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Pharmacodynamics

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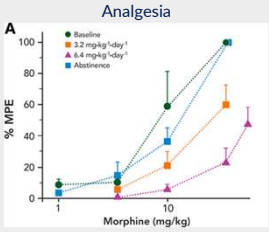
Tolerance

- Tolerance is the reduction in response to a drug after its repeated administration
- Tolerance shifts the dose-response curve to the right
  - Higher doses than initial doses to achieve the same effect

Analgesia



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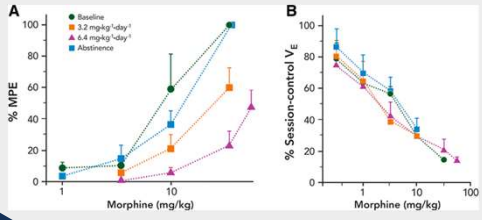
Differential Tolerance

Analgesia

Respiratory depression



Hayhurst. Anesthesiology 2016;124:483-8

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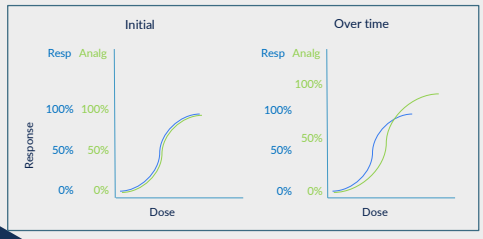
The Paradox of Differential Tolerance



Tolerance to analgesia is rapid
Tolerance to respiratory depression is slow

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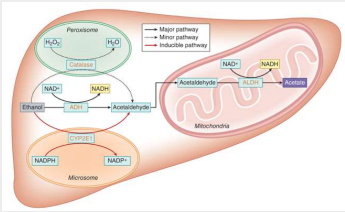
Pharmacokinetic Tolerance

- A consequence of increased metabolism after a drug is repeatedly administered
- Results in less drug being available at the receptor for drug activity.
- Ethanol
  - Although ADH is not inducible, CYP2E1 is
  - Accounts for more rapid elimination of alcohol in heavy, chronic users



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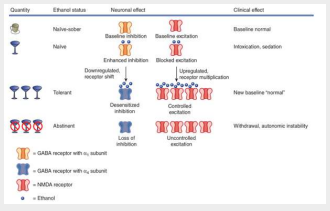
Pharmacodynamic Tolerance

- Down-regulation of receptors (higher drug concentration needed)
  - Desensitization of GABA (ethanol)
    - Receptor conformation
  - Desensitization of MOR (opioid)
    - Signal transduction
    - Decreased density (internalization)
- Up-regulation of receptors
  - Increased number of NMDA



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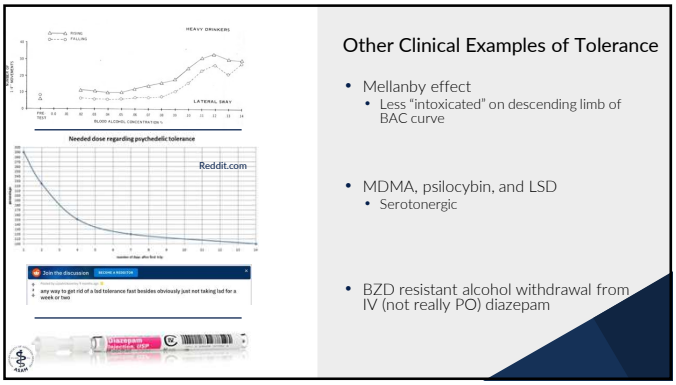

Other Clinical Examples of Tolerance

- Mellanby effect
  - Less "intoxicated" on descending limb of BAC curve
- MDMA, psilocybin, and LSD
  - Serotonergic
- BZD resistant alcohol withdrawal from IV (not really PO) diazepam

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Conditioned Tolerance

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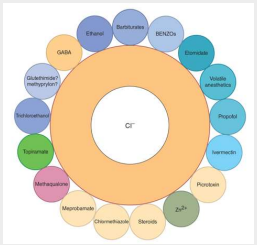
Cross-Tolerance

- Tolerance to the repeated use of a specific drug in a given category is generalized to other drugs with the same structural or mechanistic category.



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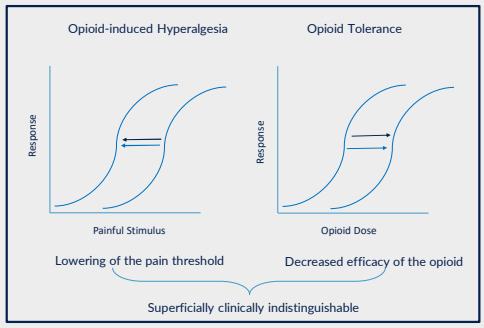

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Physical Dependence

- A state that develops as a result of adaptation and the resetting of homeostatic mechanisms
- Withdrawal syndrome can occur in physically dependent person when the drug is abruptly stopped or dose reduced
  - Typically improves on restarting the drug
  - Can be a "point of no-return"
- Can occur with both addictive and non-addictive use of drugs
  - Caffeine, nicotine
- And with therapeutic use
  - Clonidine

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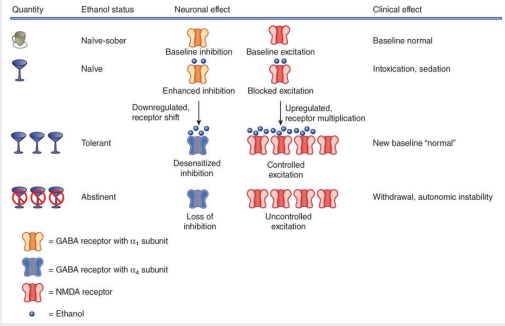

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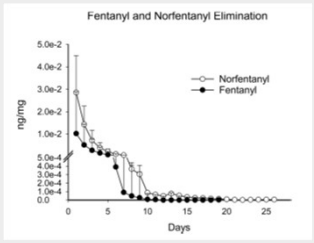
Physical Dependence ~ Withdrawal Severity

- Depth of dependence related to extent and duration of exposure
  - Receptor adaptation

Protracted renal clearance of fentanyl in persons with opioid use disorder

Andrew S. Huhn[a,b,c,*], J. Gregory Hobelmann[a,d], George A. Oyler[a], Eric C. Strain[a]



Huhn AS, et al. Drug Alcohol Depend 2020;108:147

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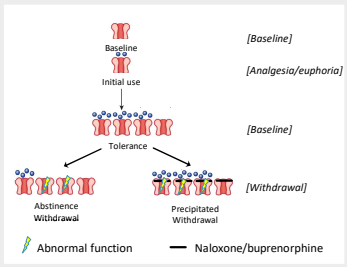
Physical Dependence ~ Withdrawal Severity

- Related to rapidity of development of withdrawal



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Drug Interactions

REVIEW COURSE 2023

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Physiological Drug Interactions

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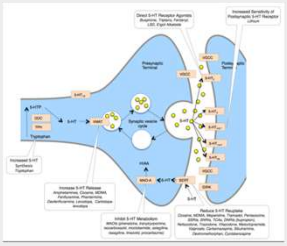
PK/PD Drug Interactions



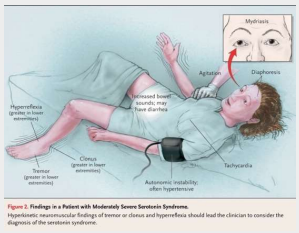


Figure 2. Findings in a Patient with Moderately Severe Serotonin Syndrome.
Hyperkinetic neuromuscular findings of tremor or clonus and hyperreflexia should lead the clinician to consider the diagnosis of the serotonin syndrome.

www.real-psychiatry.blogspot.com
Boyer E. NEJM 2005

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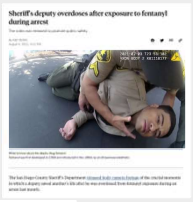
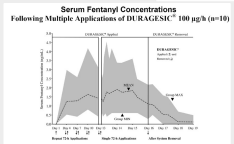
Exposure Pathway





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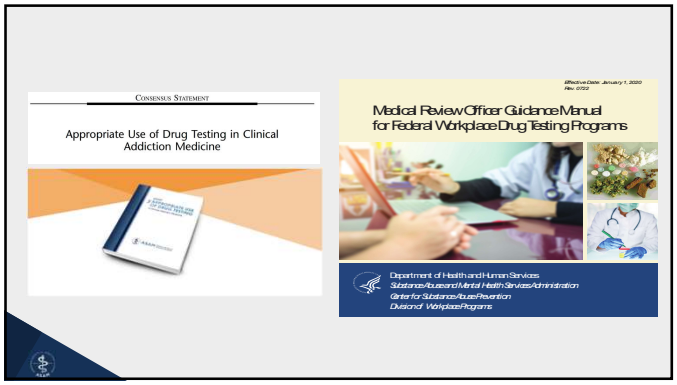

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Philosophical Considerations (for substance use)

- Testing is not meant to "catch" the patient
  - Testing identifies recent use it does NOT identify addiction or impairment
  - A positive finding suggests need to review treatment plan
    - Not to prevent, limit, or punitively change treatment
- Tests must be interpreted in the context of patient self-report and other information from observed behaviors or reliable sources
- Language is important
  - e.g., clean vs dirty, pass/fail

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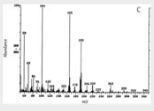
Screening and Confirmatory Tests

Screening (Presumptive) Assays – indicate the presumptive presence of drugs

Highly sensitive

Rapid, inexpensive

Cutoff - Yes/No



Confirmatory (Definitive) Assays – specifically identify the drug detected in the screening assay

Highly specific

Quantitative

Complicated, expensive

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Screening Tests for Drugs of Abuse

- Enzyme immunoassay
  - Based on a substance's structure.
  - Relatively inexpensive, easily automated
- Analytical false positives are possible ("opiate" assay finds hydrocodone)
  - Confirm positive screens in some clinical situations (TBD shortly)
- Analytical false negatives are less common (assay completely misses an analyte)
  - Clinical false negatives occur (doesn't detect a non-morphine opioid)

02/28/2017 23:09	Amphetamines Urine	N	[Not Detect-]	Final

Not Detected * Interpretive Data:
Drug Screen results are provided for medical management only. No chain of custody documentation. Testing does not meet NIDA standards. Positive results are not confirmed.

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"Drugs of Abuse" Screening

NIDA/SAMHSA 5
- Opiates
- Amphetamines
- Cocaine
- Marijuana
- Phencyclidine

Analyte	Screen, ng/mL	Confirmatory, ng/mL
Opiates	2,000	2,000
Cannabinoid	50	15
Amphetamine	500	250
Cocaine	300	150
Phencyclidine	25	25

NIDA-9 (Extended)
- Opiates
- Amphetamines
- Cocaine
- Marijuana
- Phencyclidine
- Barbiturates
- Benzodiazepines
- Methadone
- Propoxyphene

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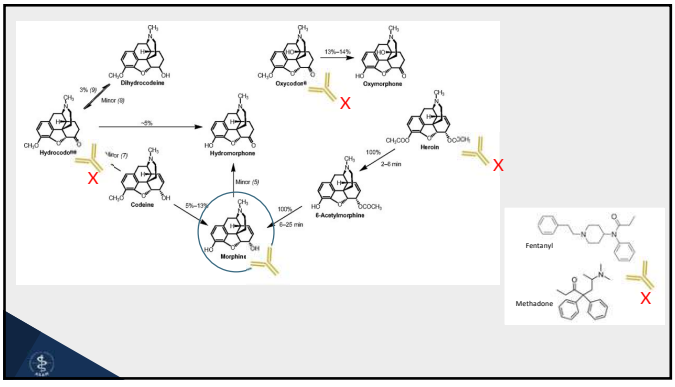

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The "Opiate" Assay: Not So Good for "Opioids"

	Online DAT opiates IF assay	EMIT II+ opiate assay[2]	TDx/TDx-flex opiate opiate assay[3]	Architect/ Aeroset	AxSym opiate[4]	CEDIA opiate[4]	DRI opiate[4]	DRI oxycodone[4]
Morphine	100	100	100	100	100	100	100	<20
Codeine	134	98	>3.6	167	>3.6	125	167	>20
Ethyl morphine	101		<10		>100			
Diacetyl morphine (heroin)	82					53	86	<33
6-Acetylmorphine	78	69	>20	67	<30	81	79	<200
Dihydrocodeine	69	103	>3.6	106	>3.6	50	67	<100
Morphine-3-glucuronide	54	48	>57	47	>57	81	50	<11
Morphine-6-glucuronide			>5.7		<8.6	47	100	
Hydrocodone	28	121	>8.0	158	>12	48	18	<133
Hydromorphone	21	60	>4.4	54	>6.7	57	75	<333
Norcodeine	2						6	>10
Normorphine							6	>10
Oxycodone	0	12	>1.1	11	<1.7	3.1	1.9	100
Oxymorphone		1.5	<10	0	<15	1.9	0.7	103
Noroxycodone								<0.1
Noroxymorphone								<0.1
Meperidine	0	<0.6	<2.0	0	<3.0	0.2	0	
Levallorphan		<4	<6.0	13	<6.0			
Levorphanol		29	>6.0	27	>6.0		2.1	<50
Nalorphine		3	<20	2.3	<30			
Naloxone	0	0.04	<20	0	<30		0	<50
Isiapriminе	0					1.6		
Ranitidine						0	0	
Thebaine	25		<20		<30		<15	
Naltrexone	0						0	<20
Fentanyl			<60		<60			

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TABLE 7–4 Performance Characteristics of Common Urine Drug Screening Immunoassays[a]

Drug/Class	Detection Limits (ng/mL)[b]	Confirmation Limits (ng/mL)[b]	Detection Interval[c]	Comments
Amphetamines/ methamphetamine	500	500	1–2 days (2–4 days)	Decongestants, ephedrine, (–)-methamphetamine, selegiline, and bupropion metabolites are reported to give false-positive test results with some assays; MDA, MDEA, and MDMA are variably detected.
Barbiturates	200		2–4 days	Phenobarbital detection interval is up to 4 weeks.
Benzodiazepines	100–300		1–10 days	Benzodiazepines vary in reactivity and potency. Hydrolysis of glucuronides increases sensitivity. False-positive test results are reported with oxaprozin.
Cannabinoids	50	15	1–2 days (1 month)	Screening assays detect inactive and active cannabinoids; confirmatory assay detects inactive metabolite THCA. Duration of positivity is highly dependent on screening assay detection limits.
Cocaine	150	100	2 days (1 wk)	Screening and confirmatory assays detect inactive metabolite BE. False-positive test results caused by cross-reactive compounds are unlikely.
Opiates Codeine/morphine Hydrocodone/hydromorphone Oxycodone/oxymorphone 6-Acetylmorphine	2,000 300 100 10	2,000 100 50 10	1–2 days (1 week)	Semisynthetic opioids derived from morphine show variable cross-reactivity. Fully synthetic opioids (eg, fentanyl, meperidine, methadone, tramadol) have minimal cross-reactivity. Quinolones are known to cross-react with some assays.
Methadone	300		1–4 days	Doxylamine is reported to cross-react with some assays.
Phencyclidine	25	25	4–7 days (1 month)	Dextromethorphan, diphenhydramine, ketamine, and venlafaxine is reported to cross-react with some assays.

[a]Performance characteristics vary with manufacturer and may change over time. For the most accurate information, consult the package insert of the current kit or contact the manufacturer. [b]Substance Abuse and Mental Health Services Administration cutoff concentrations.[1] Are shown for amphetamine/methamphetamine, cannabinoids, cocaine, opiates, and phencyclidine immunoassays. Other commercial immunoassay cutoffs are also listed. Other cutoffs may be set by individual laboratories. [c]Values are after typical use; values in parentheses are often heavy or prolonged use.
BE = benzoylecgonine; MDA = methylenedioxyamphetamine; MDEA = methylenedioxyethylamphetamine; MDMA = methylenedioxymethamphetamine; THCA = tetrahydrocannabinolic acid.

Goldfrank's Toxicologic Emergencies, 11th Edition

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Positive Opioid Screen

- You are evaluating your long-standing patient who tests positive for "opiates" on routine testing. The patient assures you they have not used any drugs.
- (Analytical) true positive
  - Clinical false positive
  - Not an (analytical) false positive
- Note
  - Unclear which opioid
  - Does not correlate with impairment
  - Cannot tell route, time of use, or amount used

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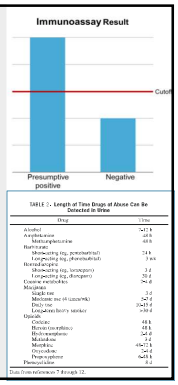
Interpretation of a Negative Opioid Screen

- Patient is not using
  - Diversion away
- Clinical false negative
  - Collection/Lab error
  - Wrong assay used
    - e.g.: "Opiate" assay for oxycodone
  - Cutoffs are often used
  - Detection periods are short



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The Gold Standards for Confirmation

- Gas Chromatography/Mass Spectrometry
  - Gold standard for confirmation
  - Chemical "fingerprint" of drugs
  - Sensitive and specific
  - Legally defensible
- Liquid Chromatography/Tandem Mass Spectrometry (LC/MS/MS)
  - Emerging Standard for Confirmation
  - Less sample preparation

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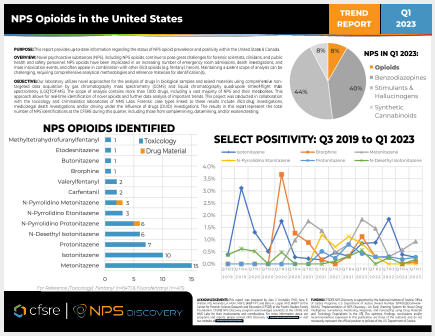

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Buprenorphine analysis

- Can only generalize about expected levels
  - No credible way to say "X" dose should give "Y" level
  - Patients tend to stay within a certain range over time unless dose change
    - Trending helpful and can detect aberrancy
- Adulterated specimen
  - Bup without metabolite (always)
  - Bup >1000 ng/mL, even with metabolite (suggestive)
- Higher Bup levels than Norbup levels due to:
  - Dosing shortly before urine test
  - CYP 3A4 inhibitor or substrate which slows conversion to metabolite

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Matrix Considerations

- Window of detection
- Time to obtain results (availability of POCT)
- Ease of collection (need for trained personnel, collection facilities)
- Invasiveness/unpleasantness of collection
- Availability of the sample (e.g., renal health, shy bladder, baldness, dry mouth)
- Susceptibility of the sample to tampering

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Drugs and metabolites are concentrated in urine
Can compare to creatinine


Drugs are found in much lower concentrations
Easy to observe


Drugs and metabolites incorporated into hair
Concentrations of drugs low with sporadic use


Prospective collection, 1-2 weeks
Inter and intraindividual variability


Invasive and expensive to test
More direct relationship to impairment


Easy to collect and observe
Essentially limited to ethanol

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TABLE 4. Comparing Testing Characteristics Across Matrices

	Blood	Breath	Oral Fluid	Urine	Sweat	Hair
General detection period	<24 hours [2] 1–8 hours [25] 1–48 hours [26]	~1 hr per standard drink	<24 hours [2] 12–24 hours [27] 1–36 hours [28] 5–48 hours [29] 12–48 hours [25]	1.5–4 days [29] 1–3 days [25,26,30]	Continuous, usually 1–4 weeks [2,26]	7–90 days [2] 7–100 days [26]
POCT/On-site immunoassay available	Yes, primarily used for alcohol	For alcohol	Yes	Yes	No	No
Primarily detects	Parent drug compound; blood alcohol concentration	Parent drug compound; blood alcohol concentration	Parent drug compound	Drug metabolite	Parent drug compound	Parent drug compound
Best use in treatment setting	Determination of acute impairment or intoxication for alcohol	Determination of acute impairment or intoxication for alcohol	Short-term detection in ongoing treatment	Intermediate-term detection in ongoing treatment	Medium-term prospective monitoring	Long-term monitoring; 3-month drug use history
Ease of collection	Requires staff trained in phlebotomy	Easily collected	Easily collected	Requires specialized collection facility (restroom)	Easily collected	Easily collected
Intrusiveness of collection	High for intravenous access	Low	Low	High	Low	Low
Resistance to tampering	High	High	High, but some uncertainty	Low	High, but some uncertainty	High when chemically untreated
Retesting same sample	Difficult	Generally not possible	Difficult	Possible	Possible depending on patch used	Easy

ASAM Appropriate Use of Drug Testing in Clinical Addiction Medicine, 2017

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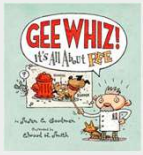
Specimen validity testing



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Where Can I Get Help with Interpretation?

- Medical or forensic toxicologist
- Staff at the testing laboratory
- A physician with MRO certification

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References

- Nelson LS, Howland MA, Lewin NA, Smith SW, Goldfrank LS, Hoffman RS. Goldfrank's Toxicologic Emergencies, 11th Edition. New York, McGraw Hill, 2019.
- Hayhurst CJ, Durieux ME. Differential Opioid Tolerance and Opioid-induced Hyperalgesia: A Clinical Reality. Anesthesiology. 2016;124(2):483-488.
- Oldendorf WH. Some Relationships Between Addiction and Drug Delivery to the Brain. NIDA Research Monograph 120: Bioavailability of drugs to the brain and the blood brain barrier. 1992.
- ASAM Appropriate Use of Drug Testing in Clinical Addiction Medicine, 2017

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What property of fentanyl accounts for its enhanced psychoactive effects compared to morphine?

A. Charge
B. Lipophilicity
C. Molecular weight
D. Potency

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A patient started on opioids requires increasing doses of medication to get adequate pain relief. At the same time, painful stimuli elicit more pain that they previously did. What does this represent?

A. Hyperalgesia
B. Pharmacodynamic tolerance
C. Pharmacokinetic tolerance
D. Withdrawal

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Which of the following drug screening tests is associated with the lowest rate of false positive results?

A. Amphetamine
B. Cocaine
C. Opioids
D. Phencyclidine

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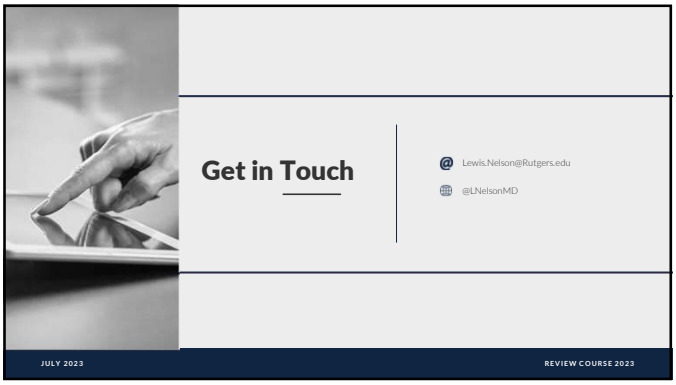

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