ASAM REVIEW COURSE 2023

Pharmacology and Toxicology: Principles, Applications, and Limitations

Lewis S. Nelson, MD, MBA, FASAM
Professor and Chair of Emergency Medicine
Chief, Division of Medical Toxicology and Addiction Medicine
Rutgers New Jersey Medical School

Financial Disclosure

Lewis S. Nelson, MD, MBA, FASAM

- No relevant disclosures

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.

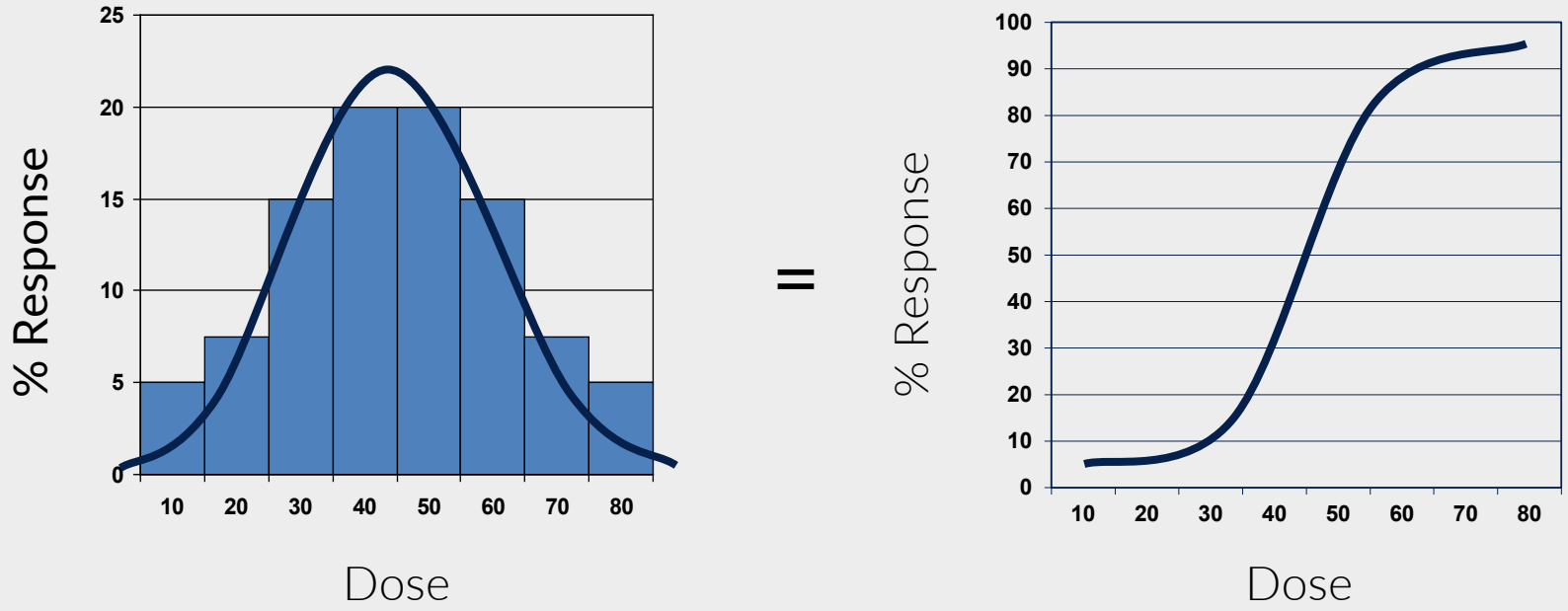
Addiction Medicine IS Pharmacology

- 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

Pharmacokinetics and Pharmacodynamics

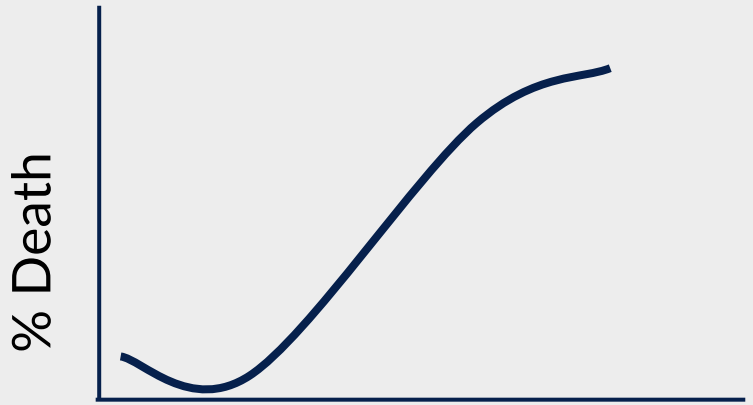
Absorption (Bioavailability)	Distribution	Elimination
Biotransformation	Dose Response (Clinical Effect)	Potency
Drug interaction	Tolerance	Dependence

Dose-Response

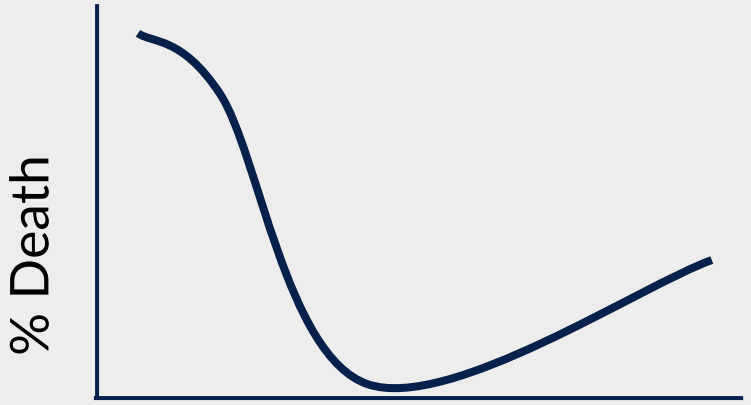


Response = Anything (Blood pressure, Euphoria, Death)

Dose-Response



Ethanol
Vitamins



Oxygen
Water

Response = Death

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

Which has more potent THC?

1980's weed

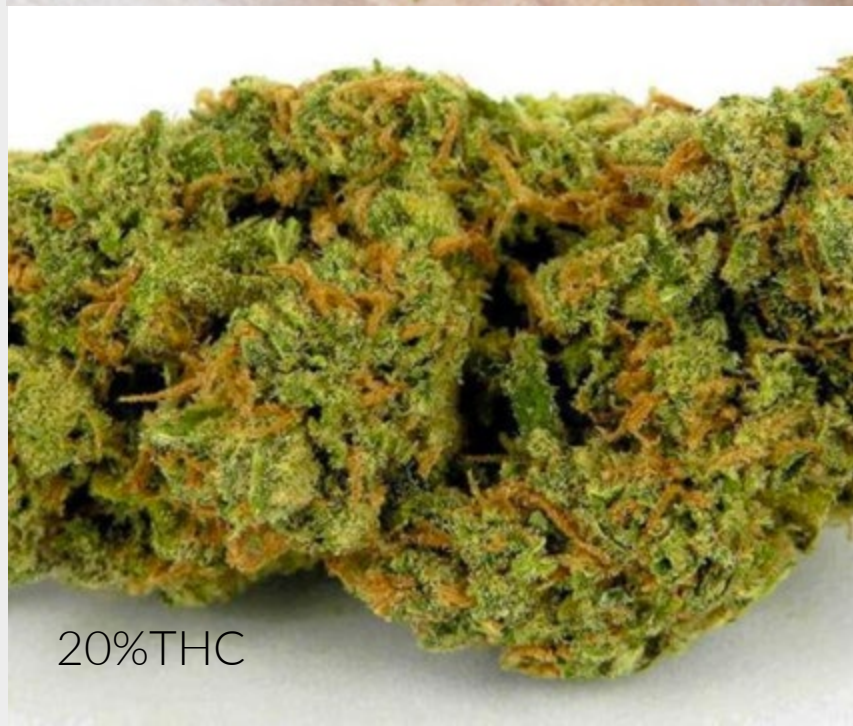
Trick question:

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



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

What is There That is Not Poison?

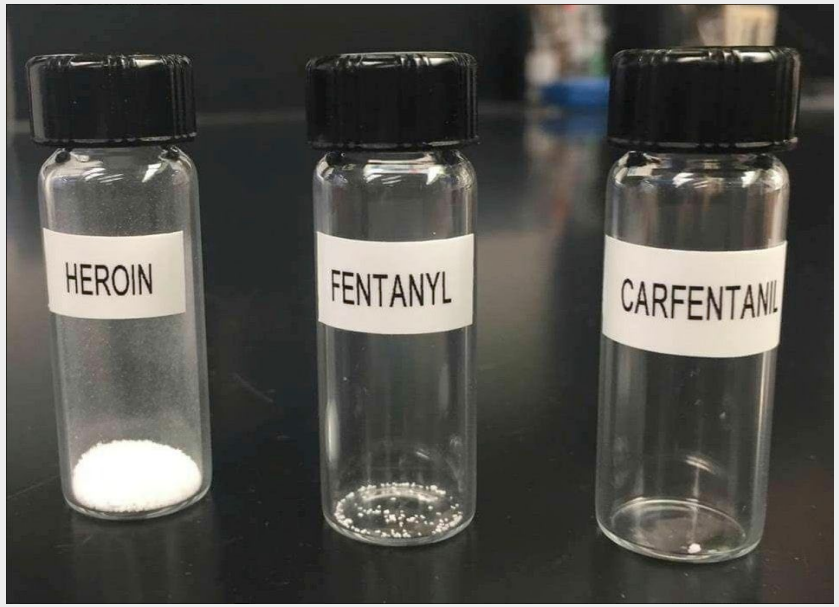
"What is there that is not poison? All things are poison and nothing [is] without poison. Solely the dose determines that a thing is not a poison"

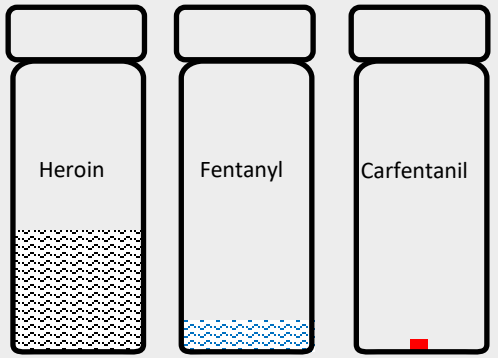
Paracelsus (1493-1541)
in *Third Defense*

"Dose Makes The Poison"

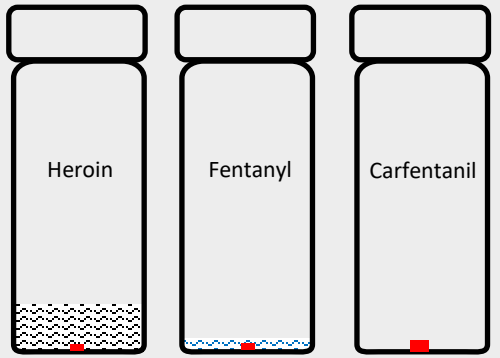
Philip Theophrastus Bombast von Hohenheim
aka PARACELSUS (1493-1541)

Potency doesn’t really matter

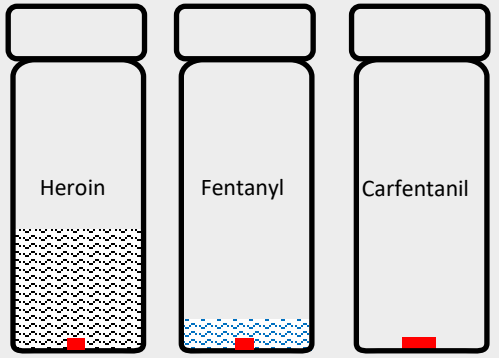




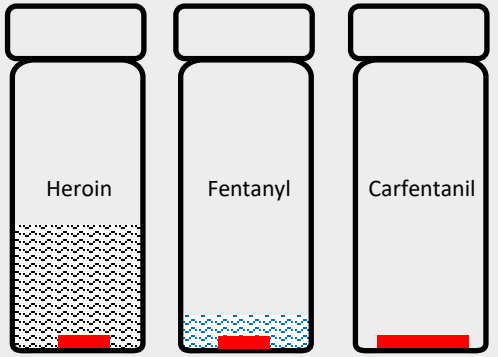
Equi-effective “safe” doses



Equi-effective “safe” doses



Dangerous doses

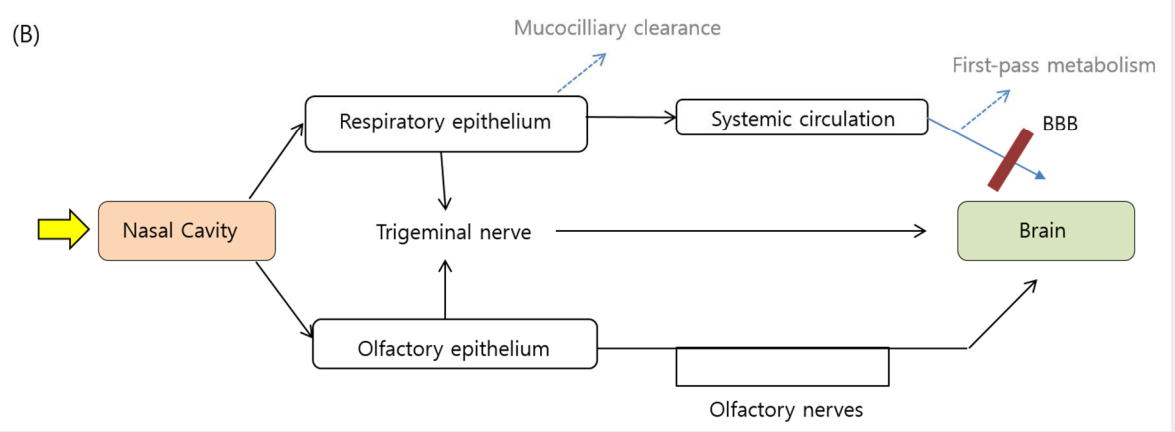


Deadly doses

Absorption

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)



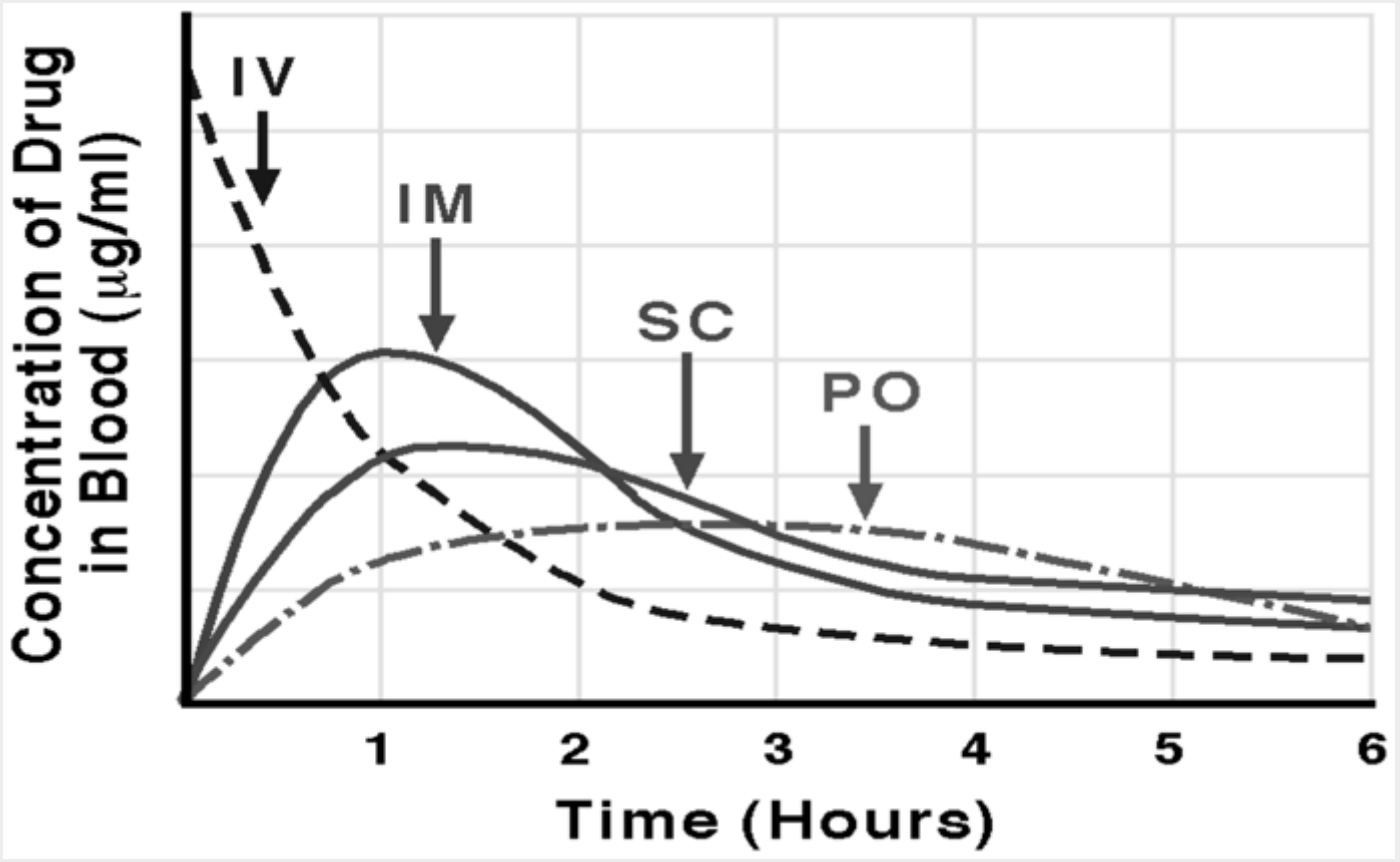
Hong, S. Pharmaceutics 2019;11:540

Bioavailability

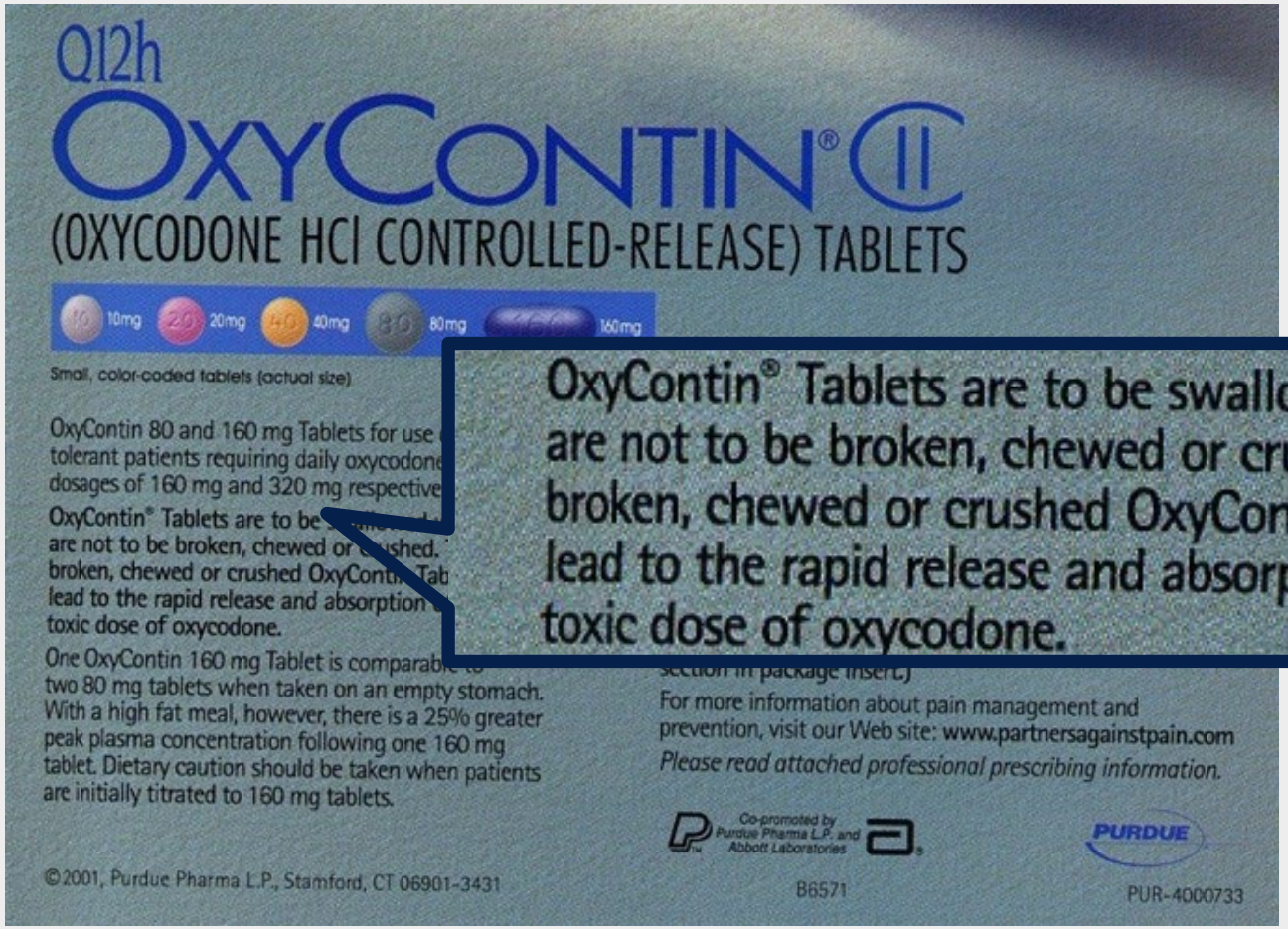
- The amount of unchanged drug reaching systemic circulation after administration is the bioavailability (F).
- F depends upon:
  - Route (IV is 100%)
  - Site specific membrane permeability
  - Drug transporter activity (p-glycoprotein)
  - First-pass metabolism (oral)

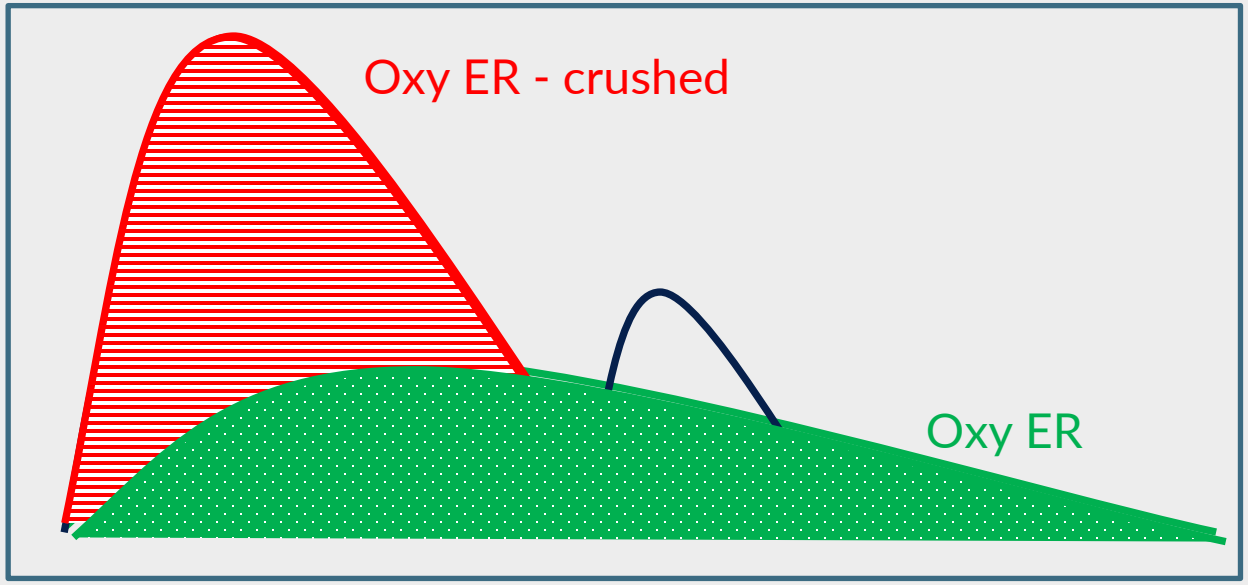
	Route		
	Oral	**Sublingual**	**Buccal**
Buprenorphine	10%	30%	50%
	Oral	**Sublingual**	**Intranasal**
Naloxone	1%	20%	50%
	Oral		
Morphine	33%		
Oxycodone	75%		

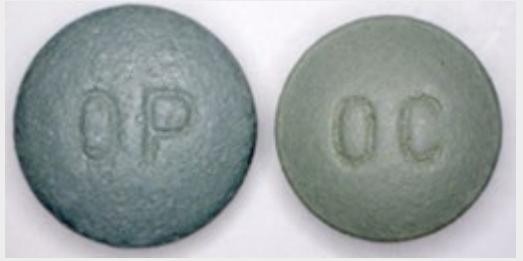
Area Under the Curve (AUC)



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


Q12h
OxyContin® CII
(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS
10mg
20mg
40mg
80mg
160mg
Small, color-coded tablets (actual size)
OxyContin 80 and 160 mg Tablets for use
tolerant patients requiring daily oxycodone
dosages of 160 mg and 320 mg respective
OxyContin® Tablets are to be
are not to be broken, chewed or
broken, chewed or crushed OxyContin Tab
lead to the rapid release and absorption
toxic dose of oxycodone.
One OxyContin 160 mg Tablet is comparable
two 80 mg tablets when taken on an empty stomach.
With a high fat meal, however, there is a 25% greater
peak plasma concentration following one 160 mg
tablet. Dietary caution should be taken when patients
are initially titrated to 160 mg tablets.
For more information about pain management and
prevention, visit our Web site: www.partnersagainstpain.com
Please read attached professional prescribing information.
Co-promoted by
Purdue Pharma L.P. and
Abbott Laboratories
PURDUE
©2001, Purdue Pharma L.P., Stamford, CT 06901-3431
B6571
PUR-4000733
OxyContin® Tablets are to be swallowed whole, and are not to be broken, chewed or crushed. Taking broken, chewed or crushed OxyContin Tablets could lead to the rapid release and absorption of a potentially toxic dose of oxycodone.



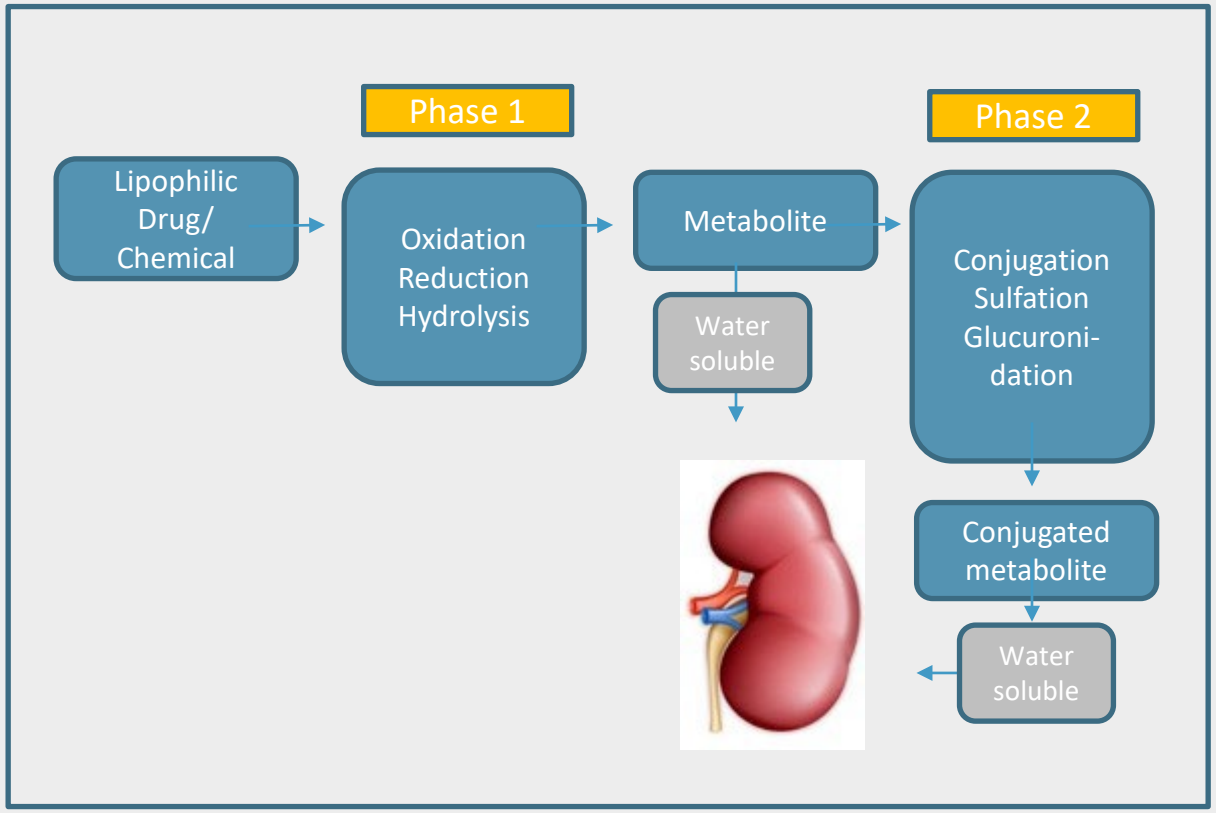


How to Abuse **OP OxyContin**, How to Get High **OP OxyContin** - Bluelight

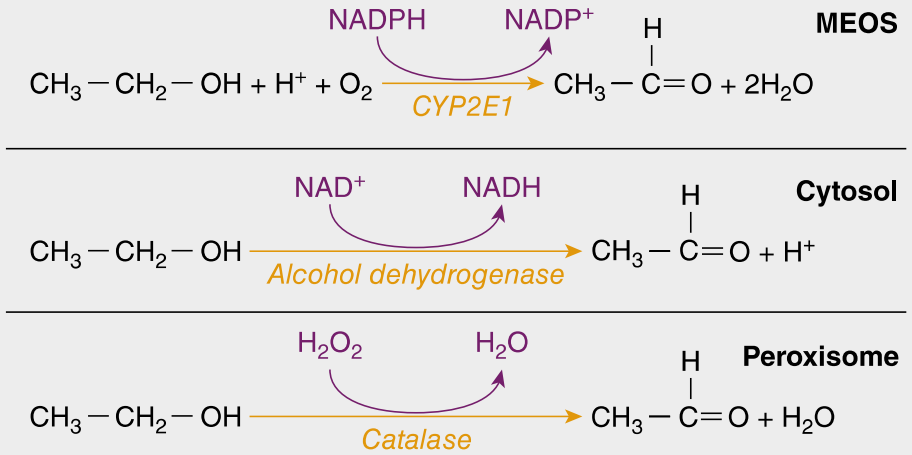
www.bluelight.org/.../526671-How-to-Abuse-**OP-OxyContin**-How-to-Get-High-**OP-OxyContin**

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 ...

Biotransformation



Ethanol Metabolism

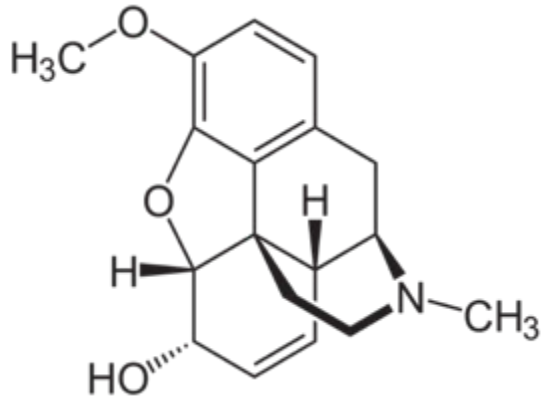


Goldfrank's Toxicologic Emergencies, 11th

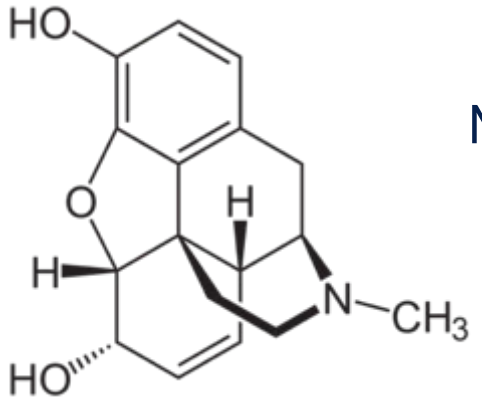
Activation through Biotransformation

- 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

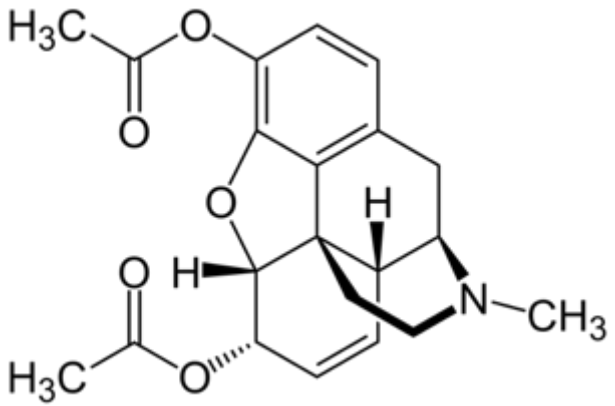
Fun pharm fact: *heroin does not bind to the mu receptor. Metabolism occurs in the CSF.*



Codeine



Morphine



Heroin

Biotransformation

TABLE 11–1 Characteristics of Different Cytochrome P450 Enzymes[26,33,123]

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[a]	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%		

[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.

Goldfrank's Toxicologic Emergencies, 11th

Biotransformation

Genetically based alterations in gene product function.

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

TABLE 11–1 Characteristics of Different Cytochrome P450 Enzymes[26,33,123]

		2B6	2C9	2C19	2D6	2E1	3A4
		2%–5%	5%–29%	1%–4%	1%–4%	6%–17%	15%–37%
		None	Minor	Minor	Minor	Minor	70%
		Kidney	Small intestine, nasal mucosa, heart	Small intestine, nasal mucosa, heart	Small intestine, kidney, lung, heart	Lung, small intestine, kidney	Much in sm…stine; some in kidney, n…ucosa, lung, stomach
Percent of metabo-lism 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.

Methadone

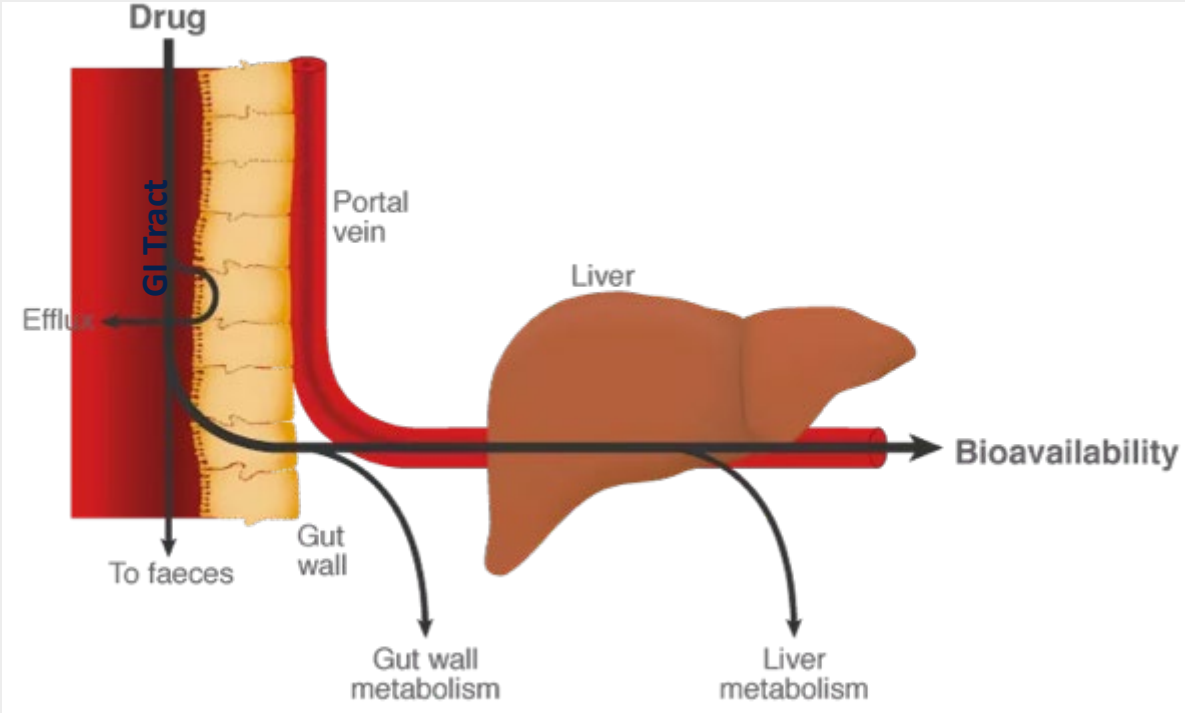
- Primarily responsible for metabolism
- Some HIV meds induce 3A4
- Variability (despite minimal polymorphism) complicates induction

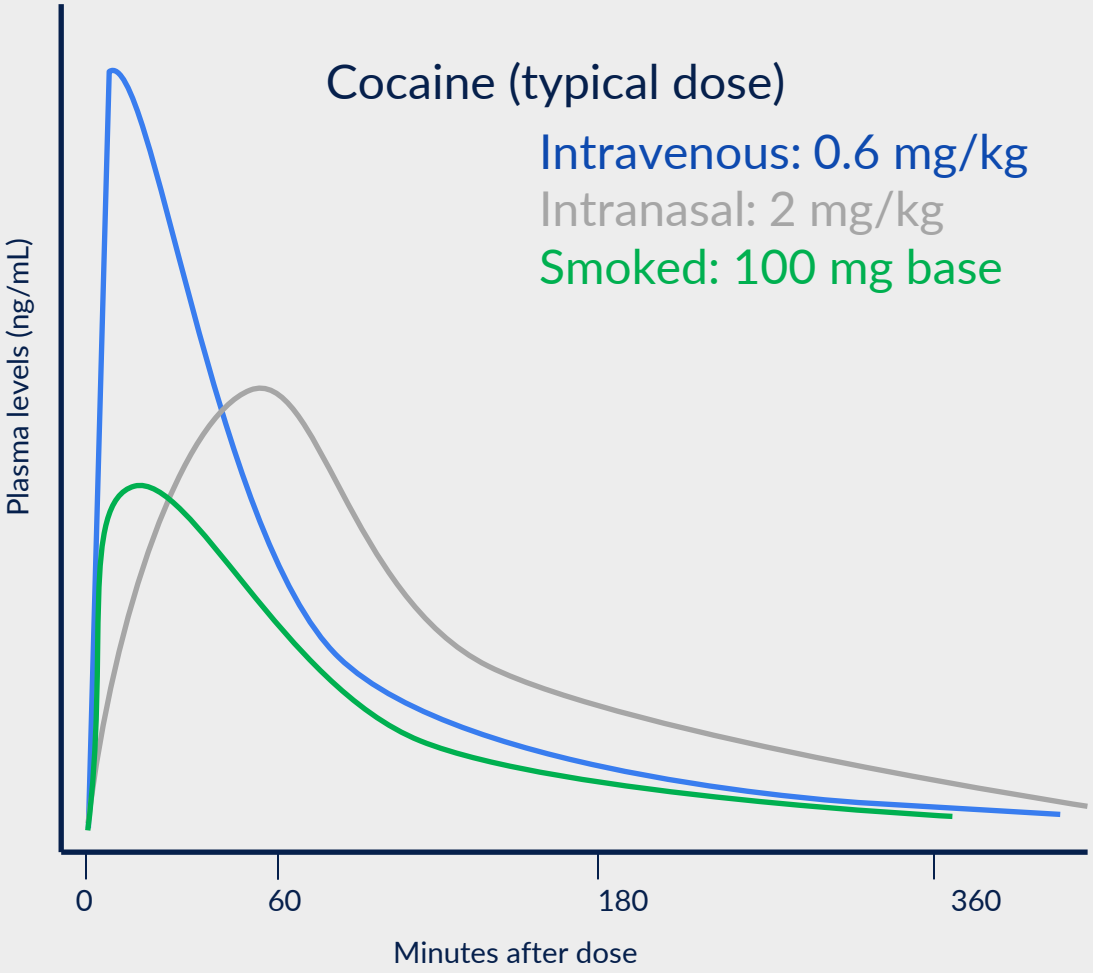
Goldfrank's Toxicologic Emergencies, 11th

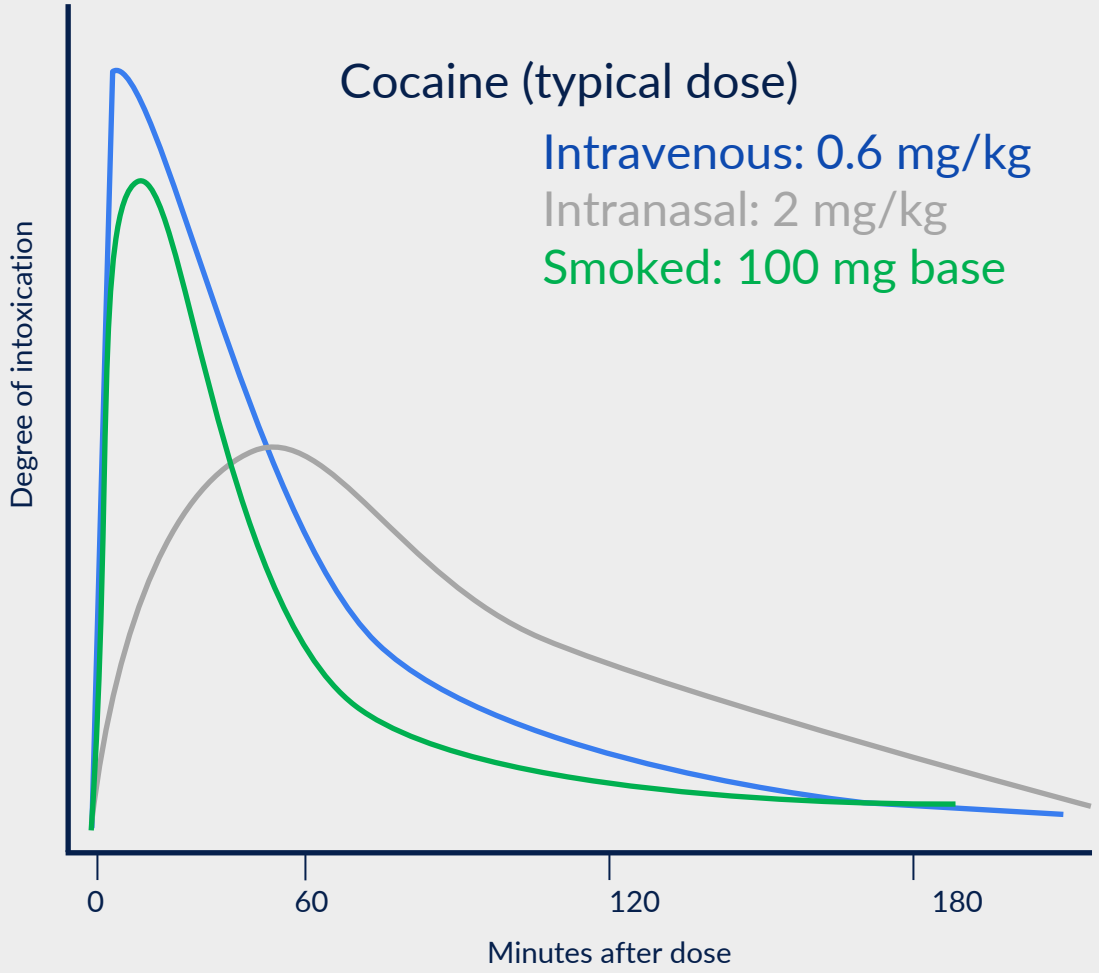
Distribution

First Pass Hepatic Metabolism

Bypass first pass







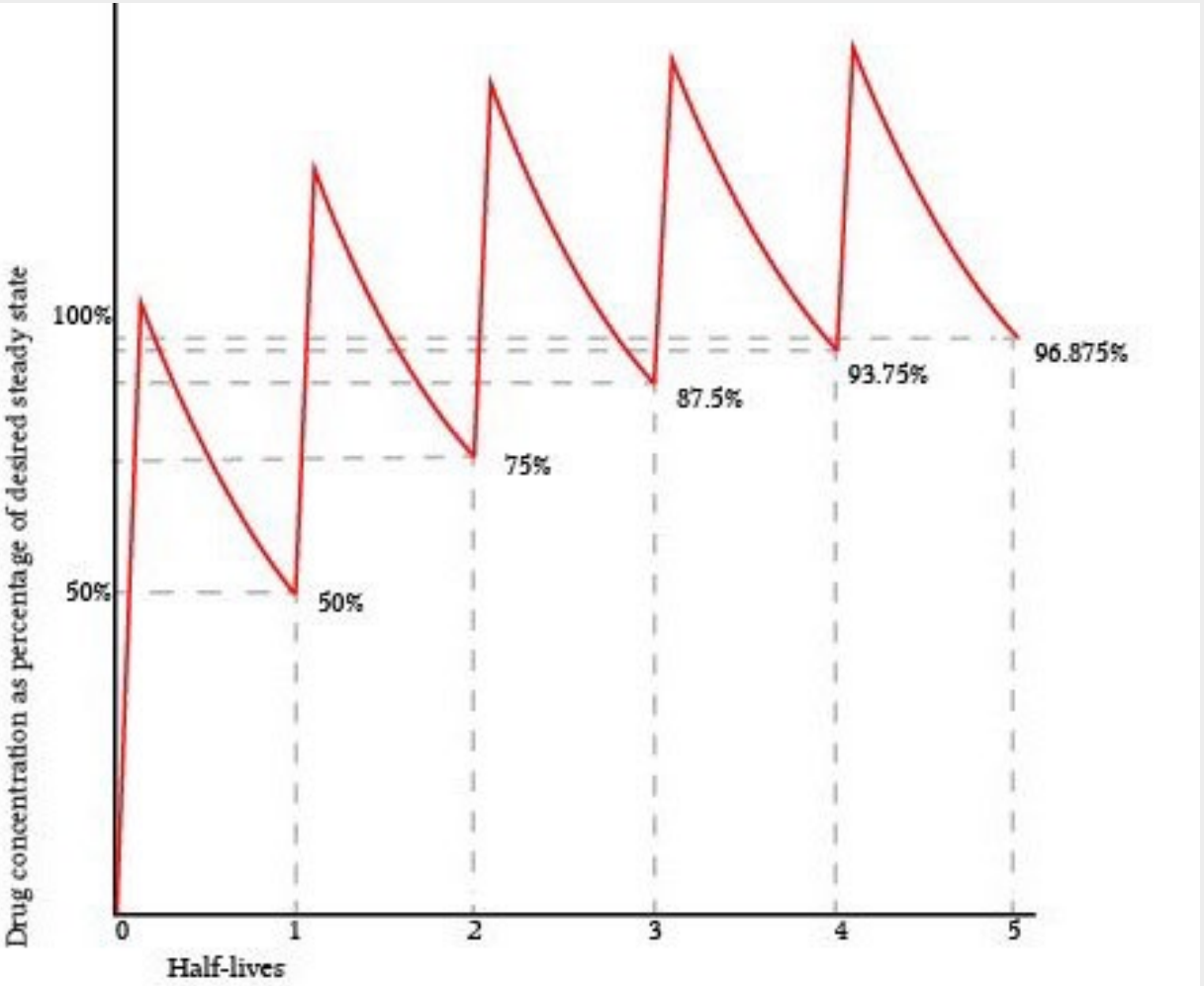
C_{max} and T_{max} depend on route of administration and dose

(C_{max}: IV → *Nasal* → *Smoked*)
(T_{max}: IV = *Smoked* → *Nasal*)

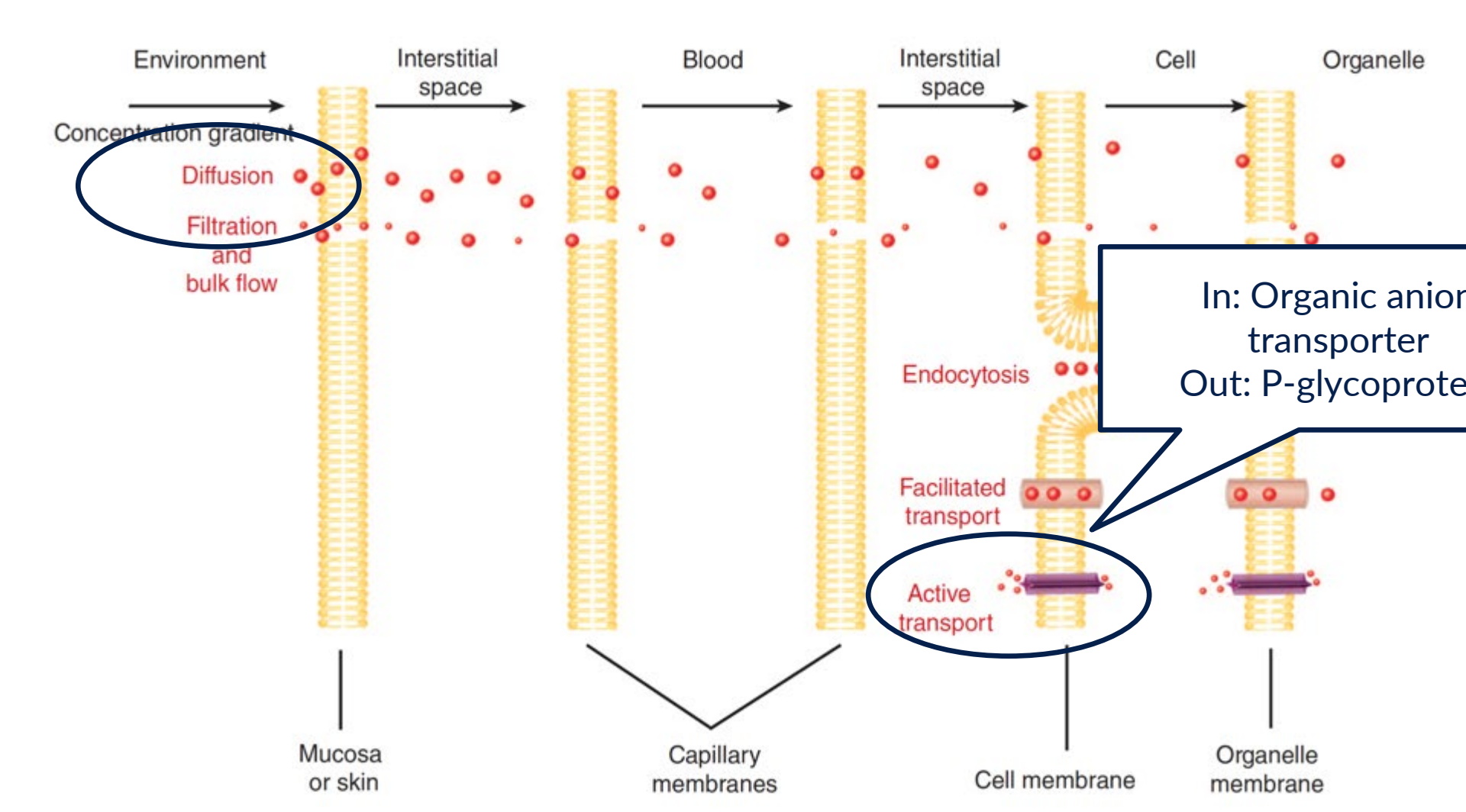
Subjective 'high' (0-100) by route
(*IV* → *Smoked* → *Nasal*)

NIDA Research Monograph 1992, 120

Steady State



- 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)



Goldfrank's Toxicologic Emergencies, 11th

P-Glycoprotein

Loperamide the OTC fentanyl (reason for no CNS activity) [A...
www.bluelight.org/vb/archive/index.php/t-217933.html
Aug 21, 2005 - 50 posts - 30 authors
I have found many commonly available items (herbal extracts, supplements or food items) which are **p-glycoprotein inhibitors**, but inhibition at ...

Immodium, BBB, and PGp inhibition [Archive]	8 posts	Jan 12, 2013
(**Loperamide**/cimetidine/quinine) Veteran. Wasn't a ...	13 posts	Oct 2, 2012
Forcing **Loperamide** through the BBB [Archive] - Page 2	30 posts	Jun 21, 2011
Forcing **Loperamide** through the BBB [Archive]	50 posts	May 23, 2006

More results from www.bluelight.org

Loperamide and P-glycoprotein inhibition: assessment of ...
www.ncbi.nlm.nih.gov/... National Center for Biotechnology Information
by J Vandenbossche - 2010 - Cited by 12 - Related articles
Loperamide and P-glycoprotein inhibition: assessment of the clinical relevance. ... coadministration of **loperamide** with a **P-glycoprotein inhibitor** or substrate.

Combinations - **Loperamide** Potentiation + **p-glycoprotein** in...
www.drugs-forum.com › ... › DRUG-FORUMS › Opiates & Opioids
Mar 2, 2012 - 3 posts - 2 authors
SWIM is going to be performing an experiement with **Loperamide**, he is ... SWIM is aware of the dangerous of **inhibiting p-glycoprotein** but is not ...

Addiction - metabolite of **loperamide** is possible PGP ...	4 posts	Feb 28, 2013
Combinations - Cheap Opiate High-potential ...	22 posts	Dec 27, 2012
Experiences - **Loperamide** Report	22 posts	Jan 16, 2012
Blood brain barrier permeation	17 posts	Dec 4, 2010

More results from www.drugs-forum.com

Pepper **Inhibits P-Glycoprotein** (just add **loperamide**??) [Ar...

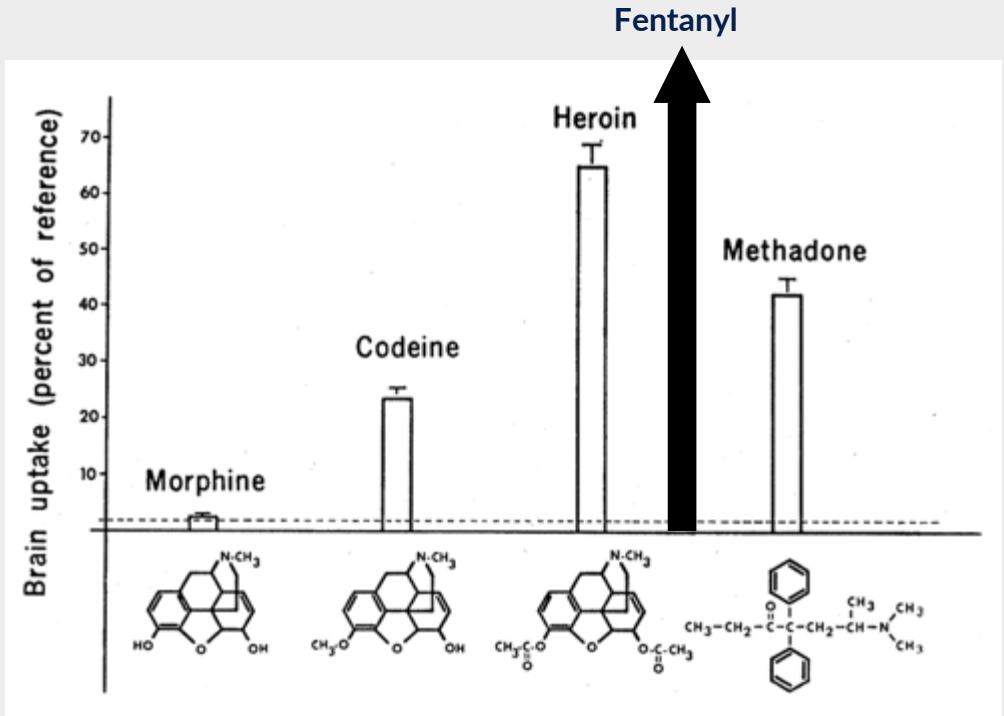
"Street pharmacologists" understand these principles

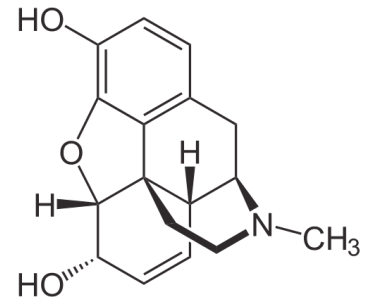
Loperamide and p-glycoprotein inhibitors

Lipophilicity

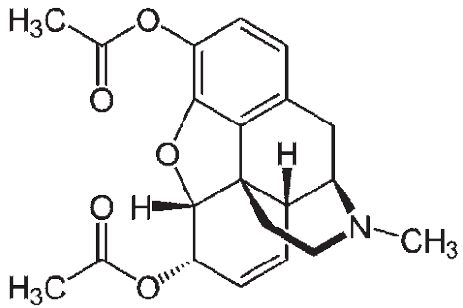
Lipophilicity = Reward = Abuse liability

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

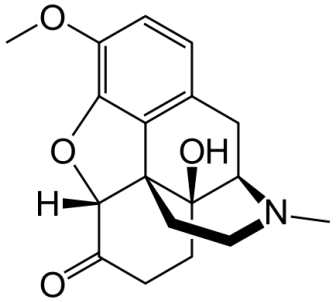




Morphine



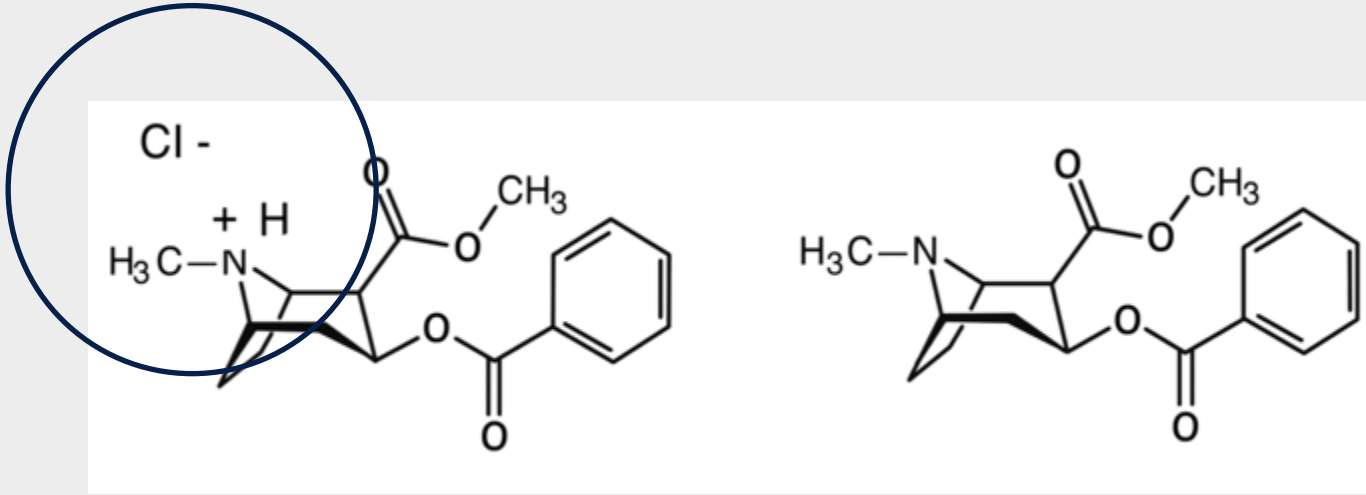
Heroin (diacetyl morphine)



Oxycodone

Oldendorf WH. Science. 1972

Addiction Medicine IS Pharmacology



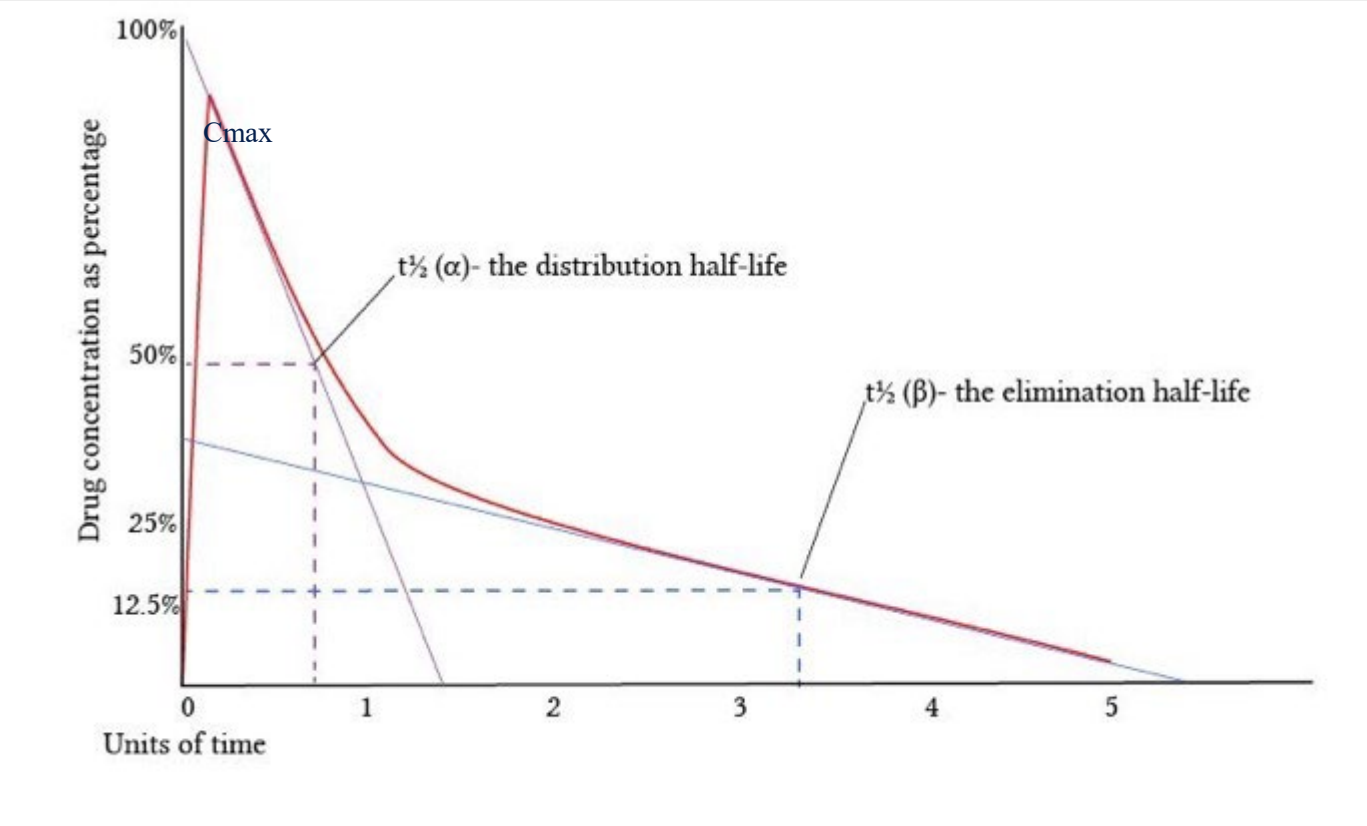
Cocaine hydrochloride
(salt)

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

Elimination

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

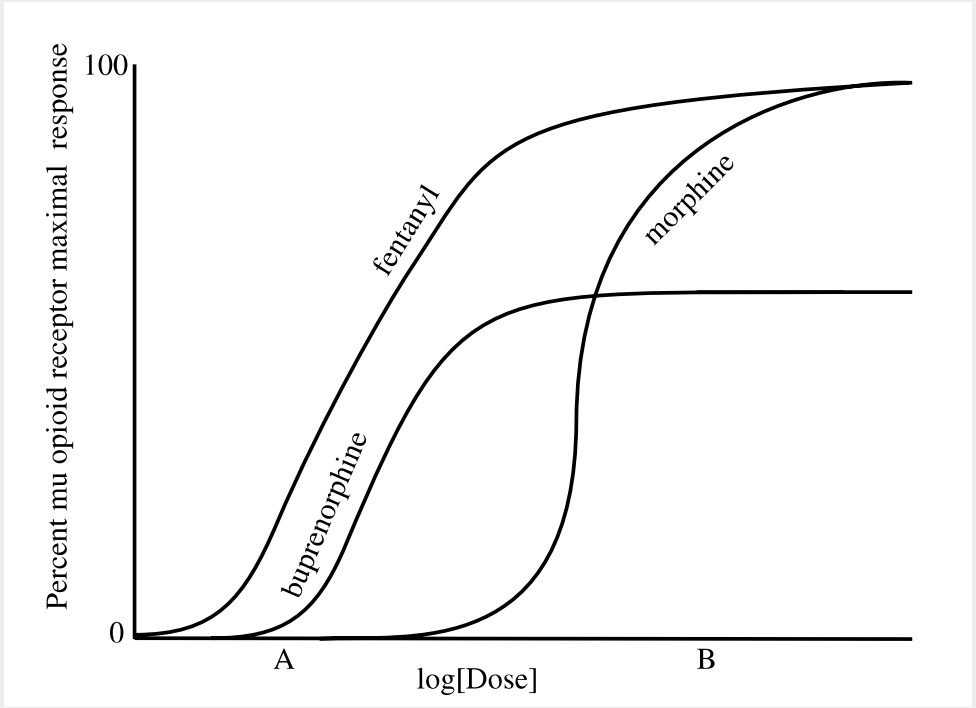
Drug	Half life (distrib)	Half life (redistrib)	Half life (term)	LogP
Fentanyl	2 min	12 min	480 min	4.05
Methadone	120 min	---	1440 min	3.93

Note: all half-lives have ranges, not shown

Receptor Pharmacology

Efficacy

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

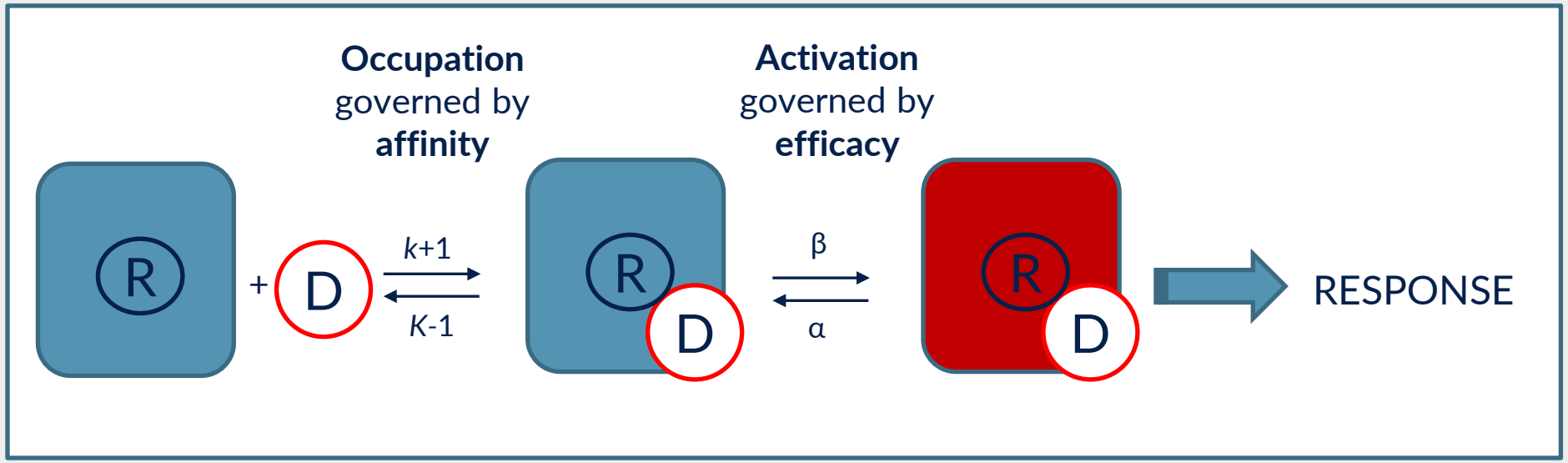


Affinity

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

Receptor kinetics
On-off

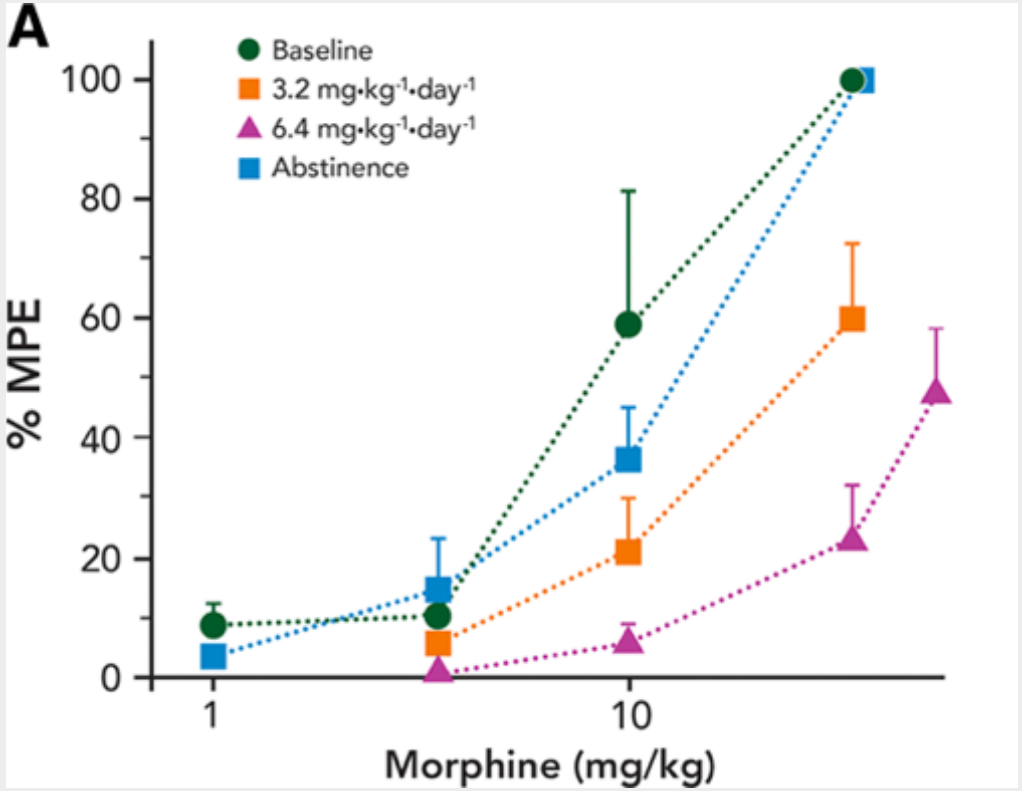


Pharmacodynamics

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

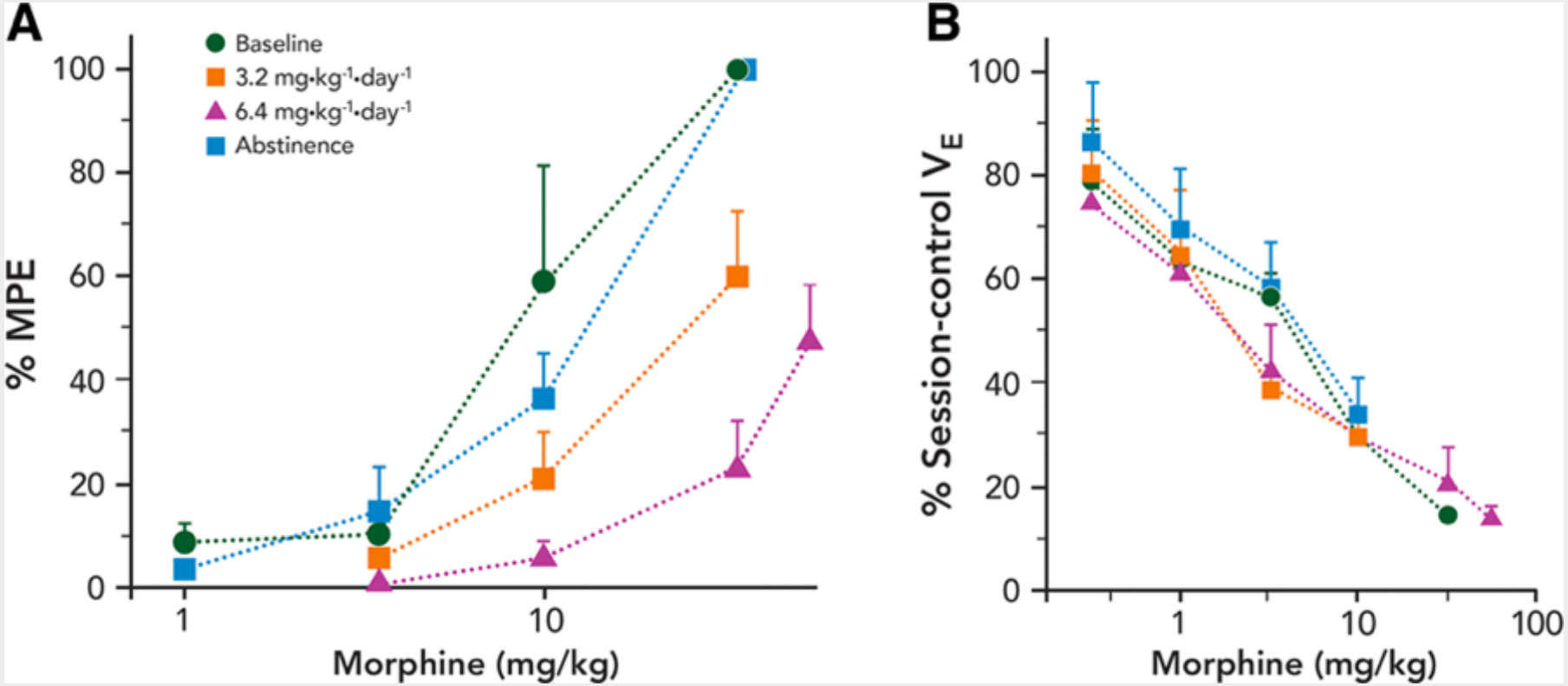
Analgesia



Differential Tolerance

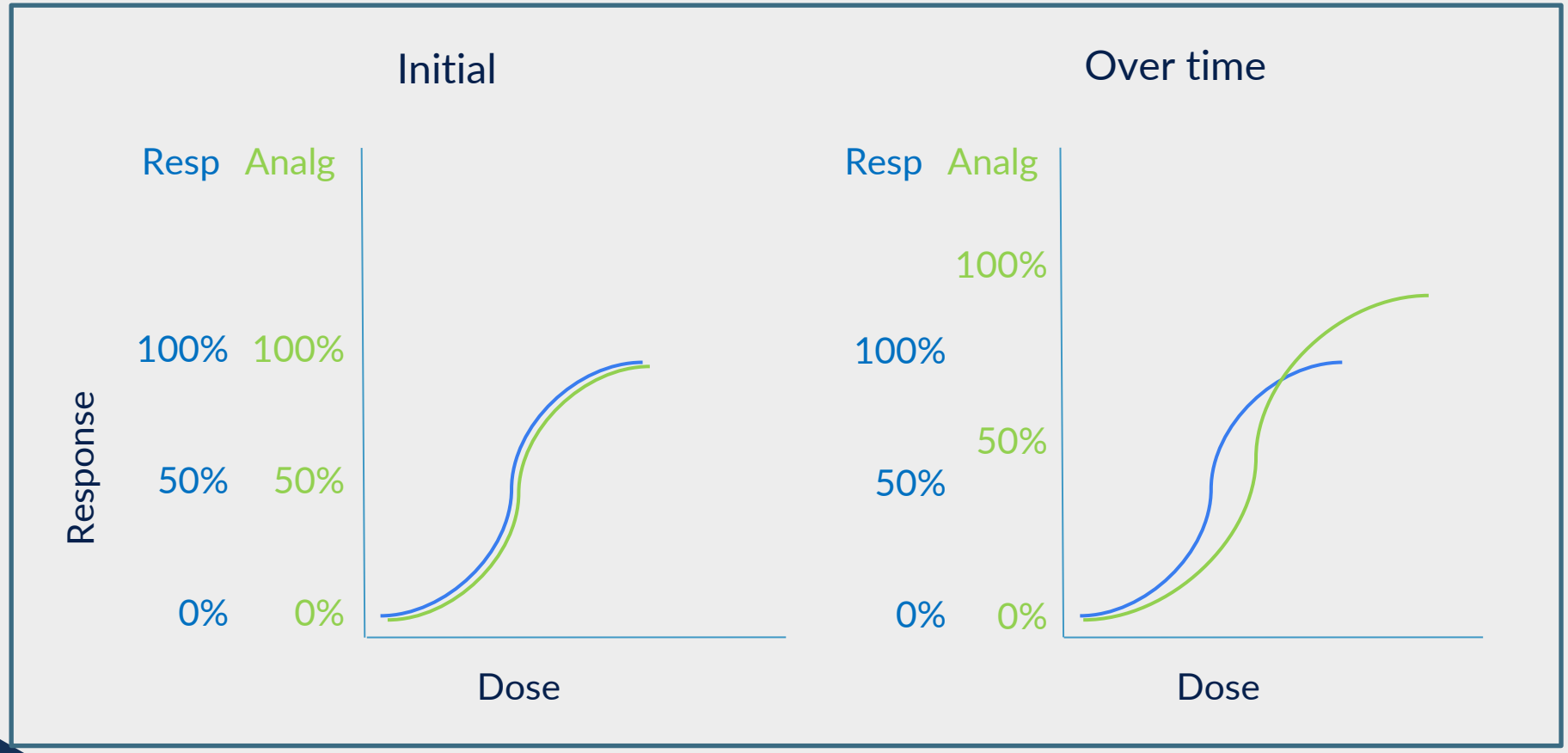
Analgesia

Respiratory depression



Hayhurst. Anesthesiology 2016;124:483-8

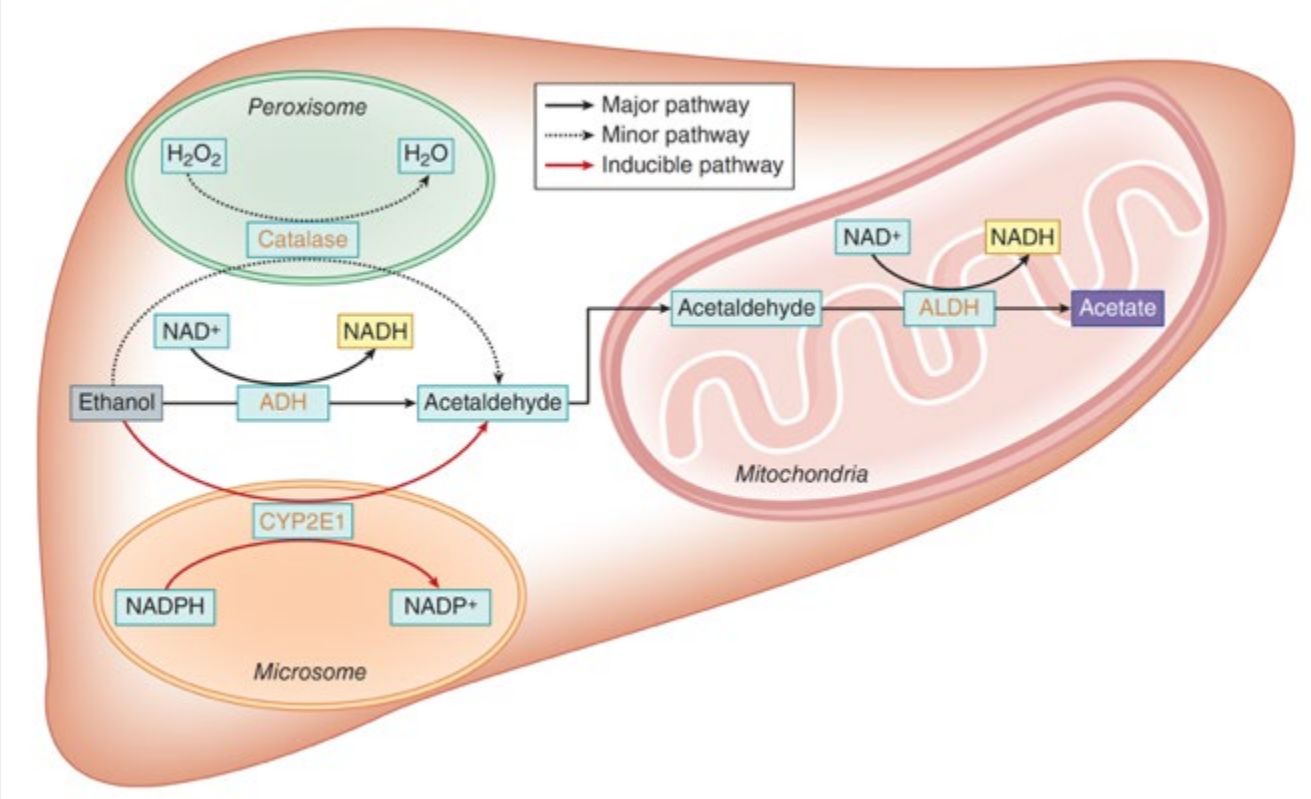
The Paradox of Differential Tolerance



Tolerance to analgesia is rapid
Tolerance to respiratory depression is slow

Pharmacokinetic Tolerance

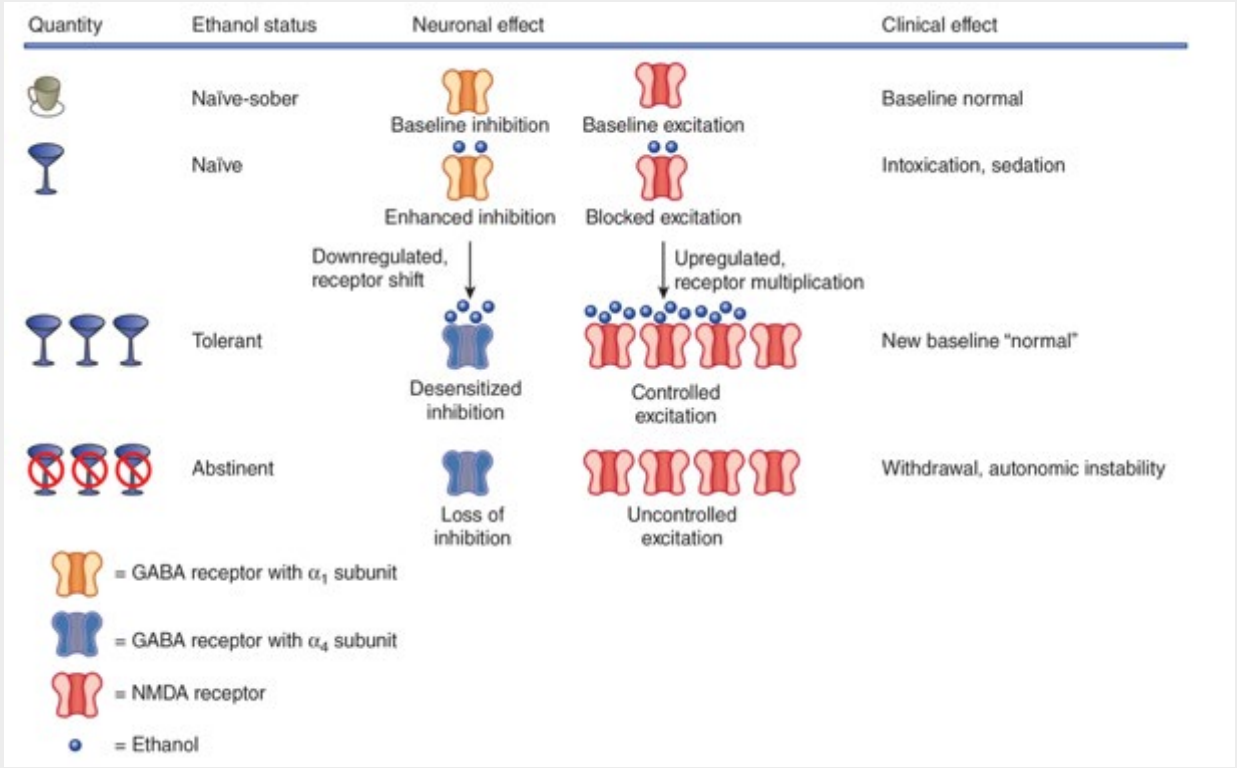
- A consequence of increased metabolism after a drug is repeatedly administered
- Results in less drug being available at the receptor for drug activity.
- Ethanol
  - Although ADH is not inducible, CYP2E1 is
  - Accounts for more rapid elimination of alcohol in heavy, chronic users



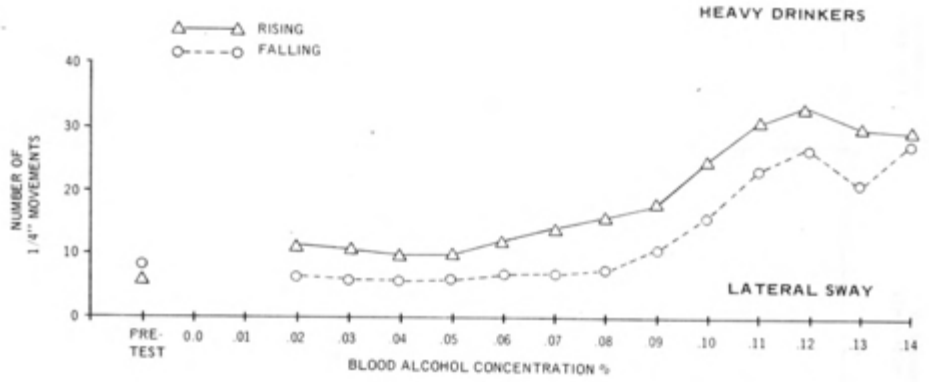
Goldfrank's Toxicologic Emergencies, 11th

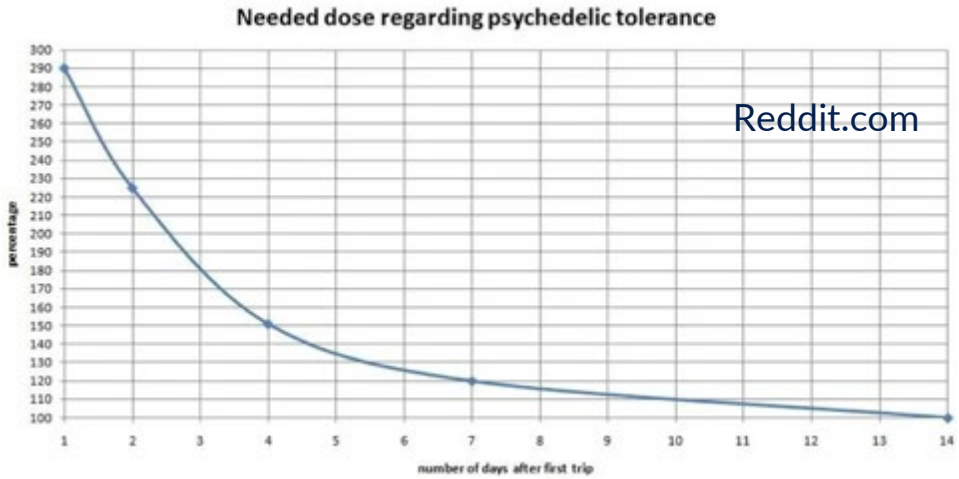
Pharmacodynamic Tolerance

- 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

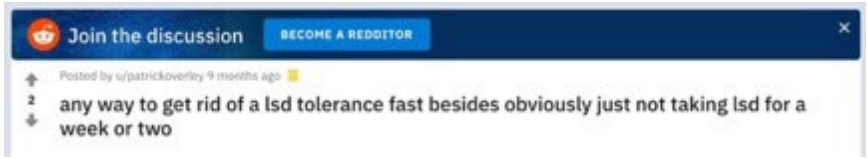


Goldfrank's Toxicologic Emergencies, 11th





Reddit.com



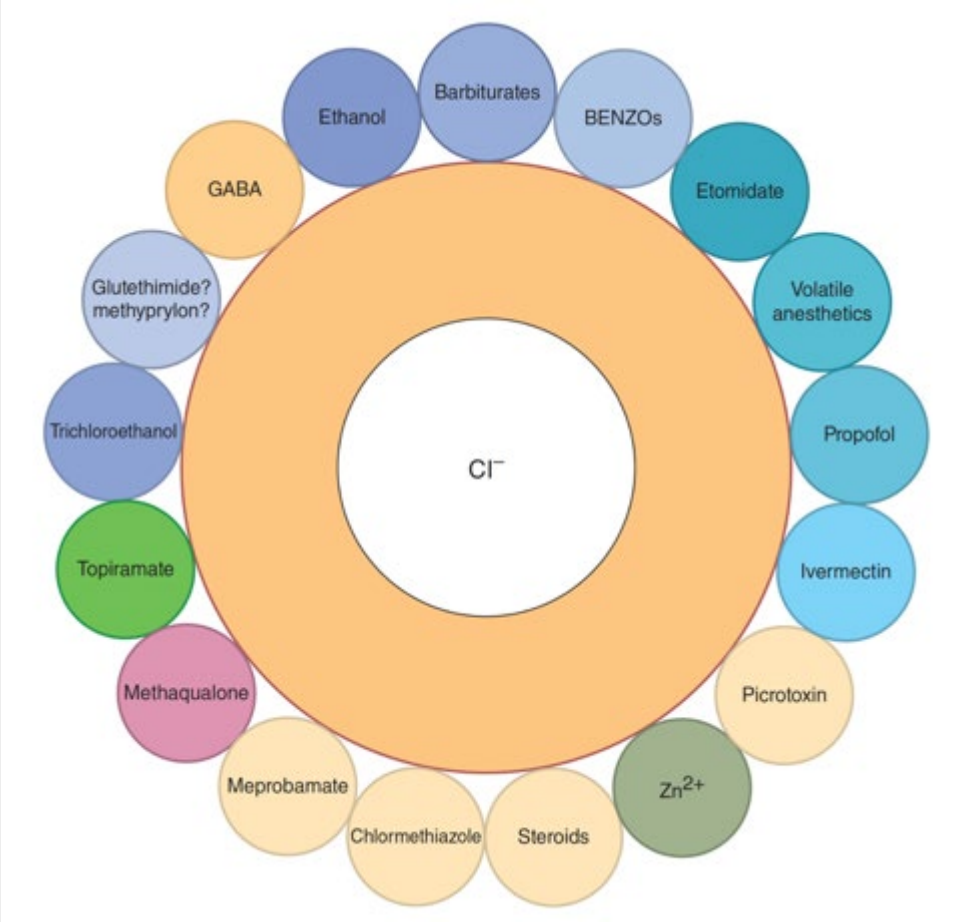
Other Clinical Examples of Tolerance

- 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

Conditioned Tolerance

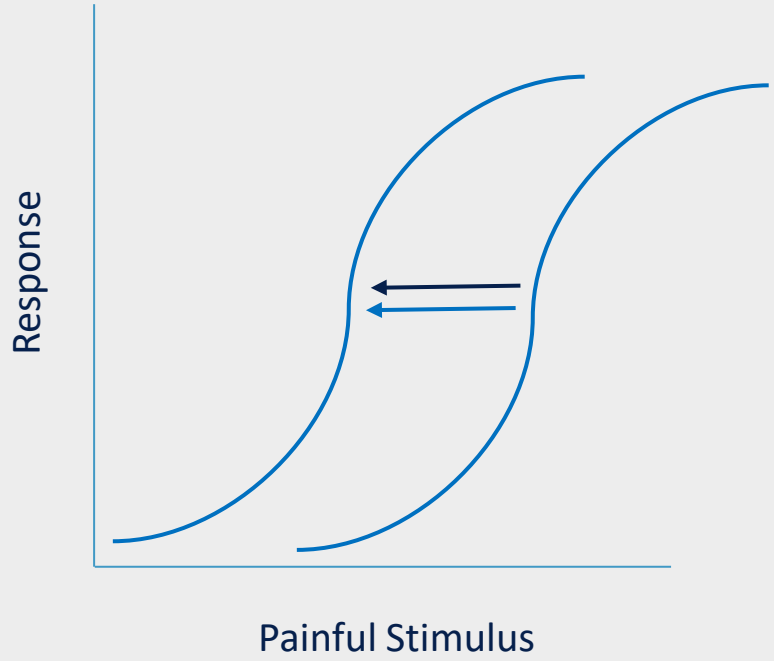
Cross-Tolerance

- 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.



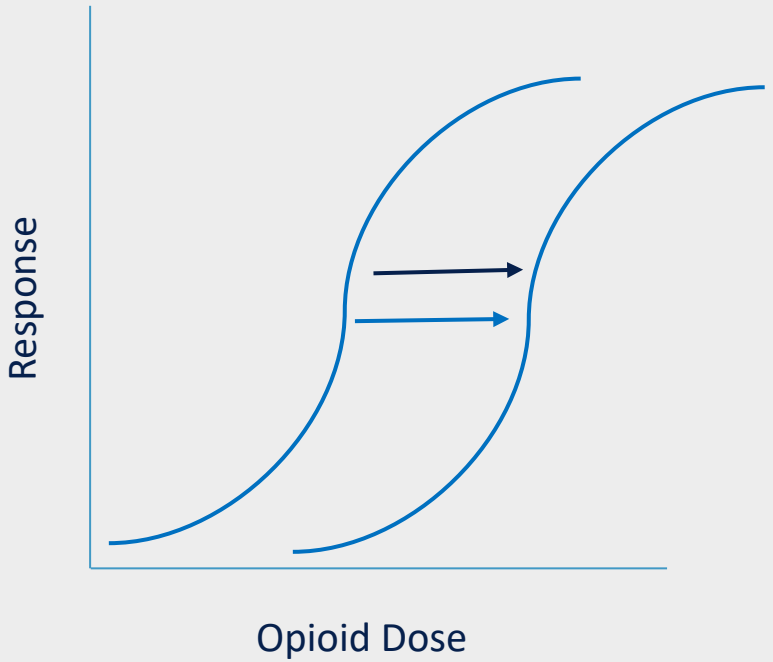
Goldfrank's Toxicologic Emergencies, 11th

Opioid-induced Hyperalgesia



Lowering of the pain threshold

Opioid Tolerance

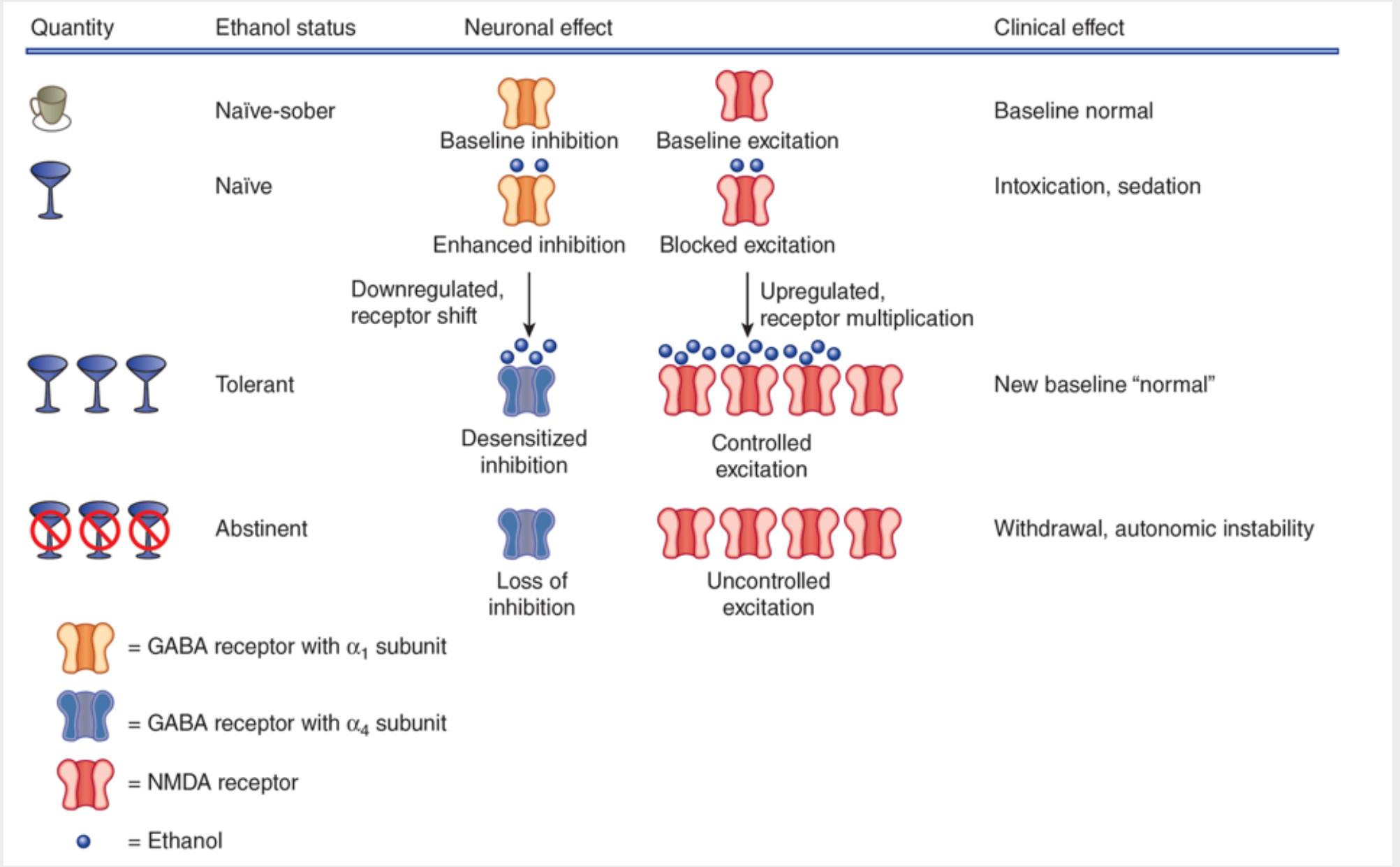


Decreased efficacy of the opioid

Superficially clinically indistinguishable

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



Goldfrank's Toxicologic Emergencies, 11th

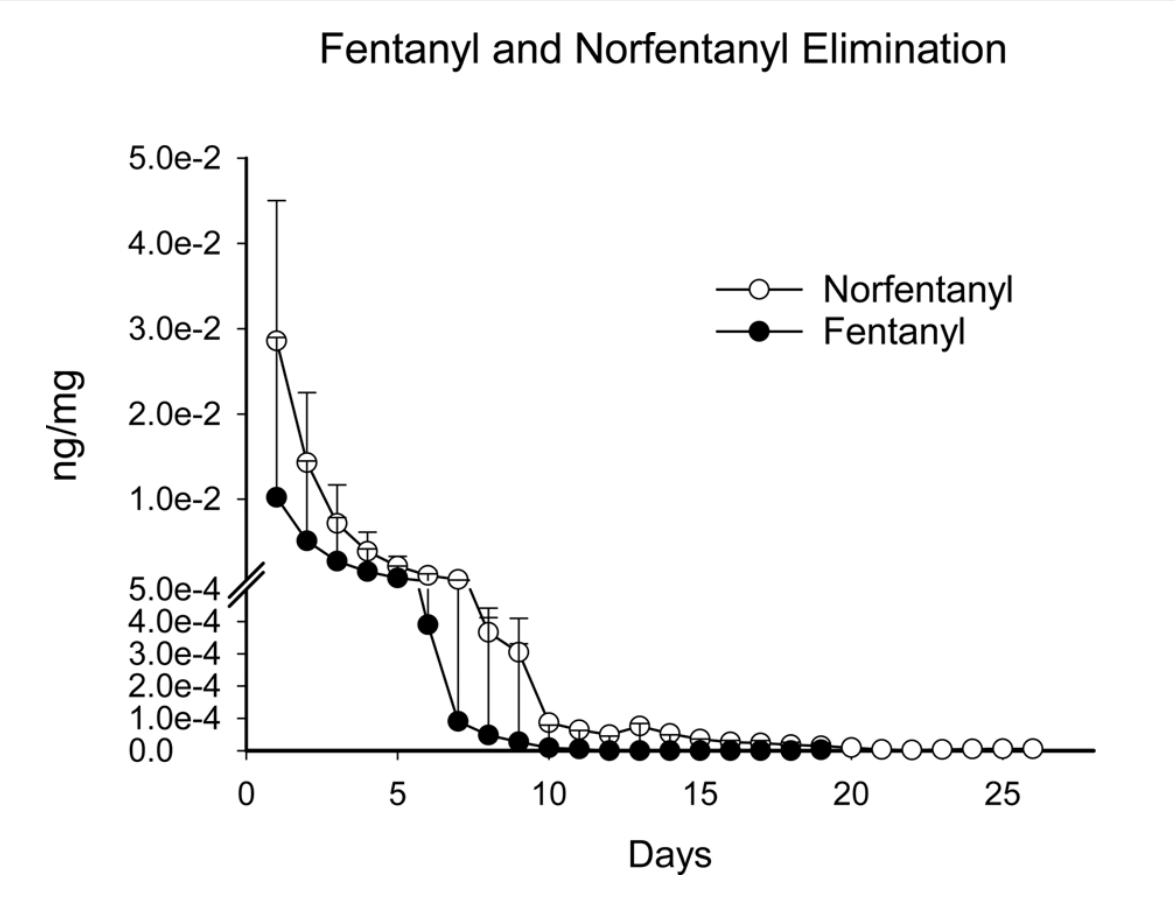
Physical Dependence ~ Withdrawal Severity

- 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,*], J. Gregory Hobelmann[a,b], George A. Oyler[c], Eric C. Strain[a]

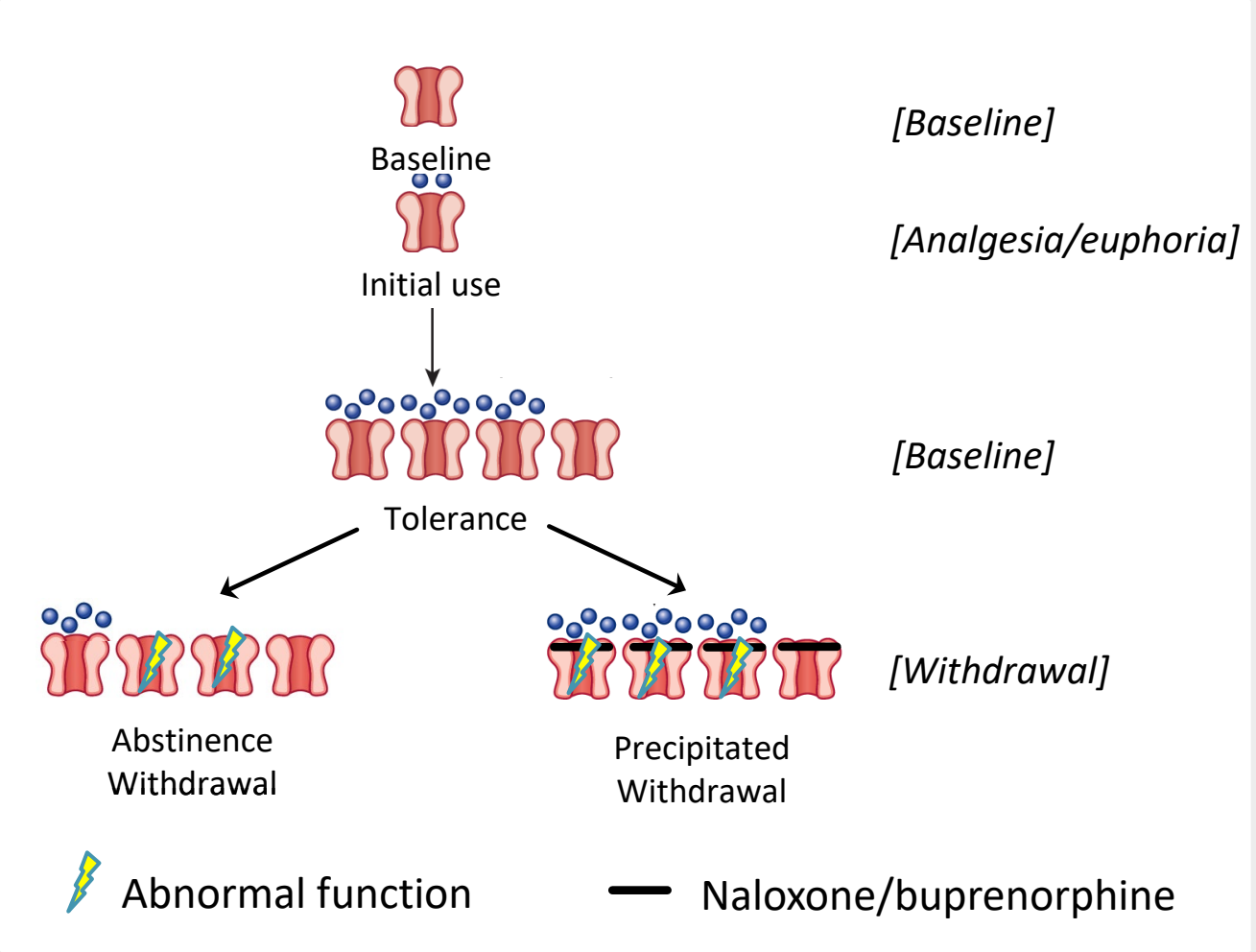
[a] Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, 21224, USA
[b] Ashley Addiction Treatment, Havre de Grace, MD, 21078, USA
[c] Department of Chemical and Biomolecular Engineering, Johns Hopkins University, Baltimore, MD, 21218, USA



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

Physical Dependence ~ Withdrawal Severity

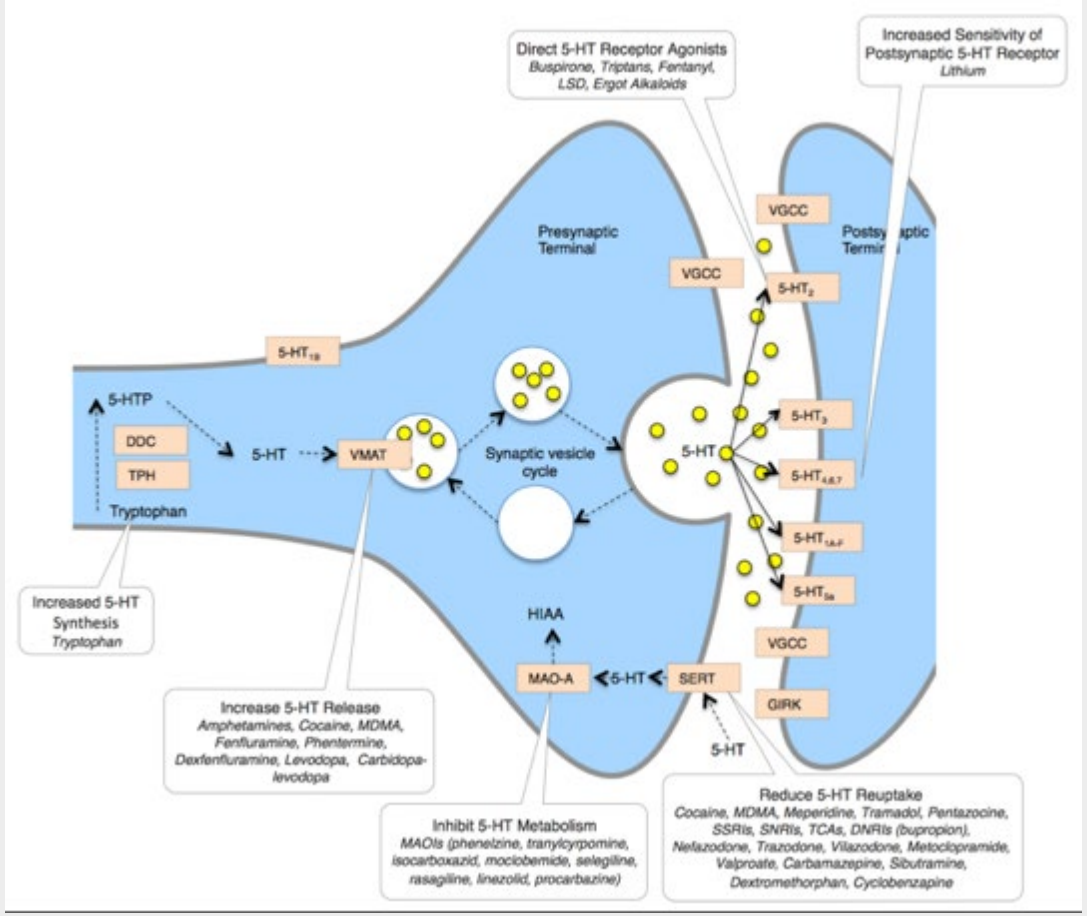
- Related to rapidity of development of withdrawal



Drug Interactions

Physiological Drug Interactions

PK/PD Drug Interactions



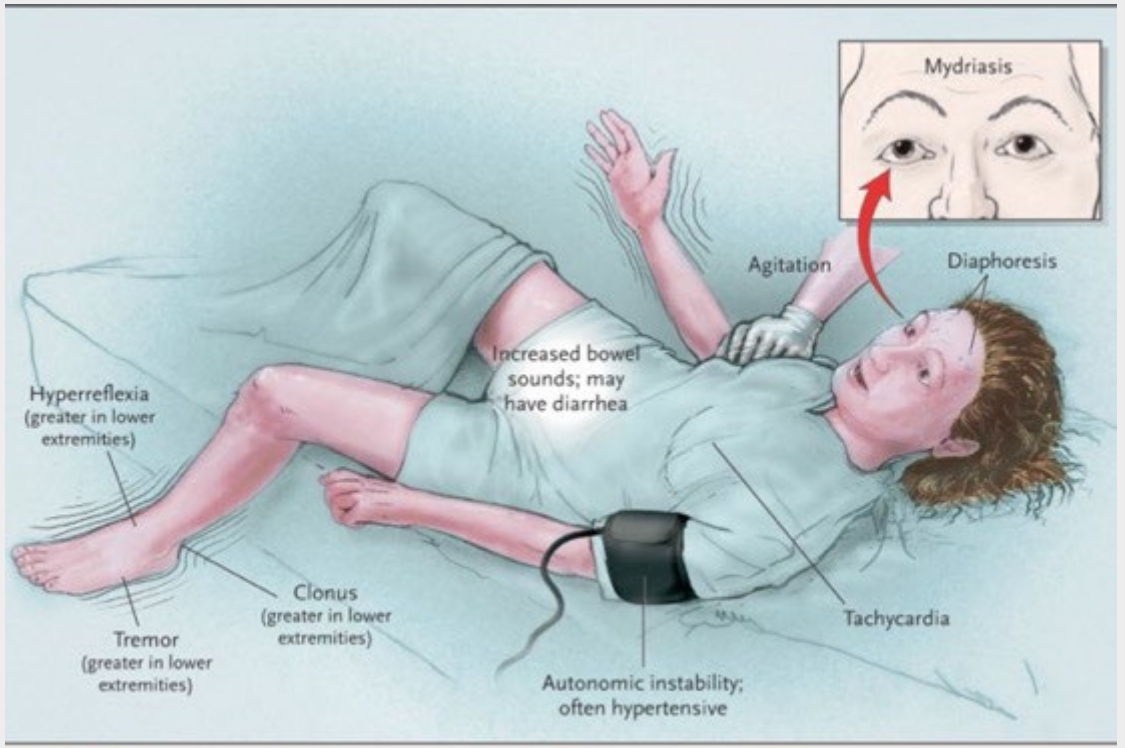


Figure 2. Findings in a Patient with Moderately Severe Serotonin Syndrome.
Hyperkinetic neuromuscular findings of tremor or clonus and hyperreflexia should lead the clinician to consider the diagnosis of the serotonin syndrome.

www.real-psychiatry.blogspot.com

Boyer E. NEJM 2005

Exposure Pathway

DRUGS · Published January 28

Men had enough fentanyl to kill entire population of New York City, New Jersey combined, police say

By Travis Fedschun, | Fox News

Jesus Carrillo-Pineda, 31, and Daniel Vasquez, 28, were sentenced Friday in New Jersey's largest seizure of fentanyl. (New Jersey State Police)

Sponsored Content

[Pics] Fishermen Discover Something Unusual Sitting on a Lone Iceberg. When...
Science Glory

New Solar Tech Saving Homeowners A Fortune
Sunrun

Ad Content by Outbrain

More from Fox News

Trump rips into Obama for 'lies',...
Fox News Politics

Kavanaugh to skip traditional walk...
Fox News Politics

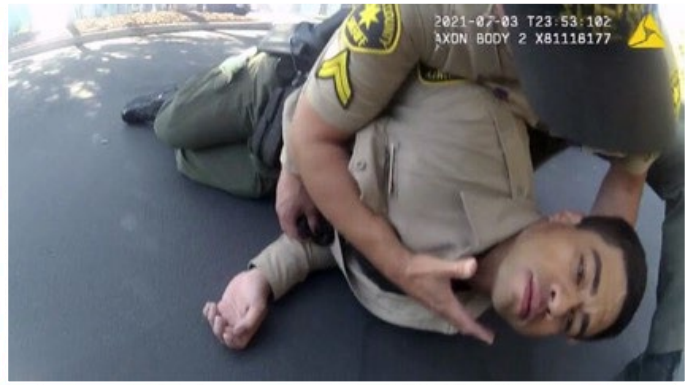
Bernie Sanders ripped for...
Fox News Politics

British couple arrested for...
Fox News World

Sheriff's deputy overdoses after exposure to fentanyl during arrest

The video was released to promote public safety.

By ABC NEWS
August 6, 2021, 4:51 PM



What to know about the deadly drug fentanyl
Fentanyl was first developed in 1959 and introduced in the 1960s as an intravenous anesthetic.

The San Diego County Sheriff's Department released body camera footage of the crucial moments in which a deputy saved another's life after he was overdosed from fentanyl exposure during an arrest last month.

FEBRUARY 3, 2023

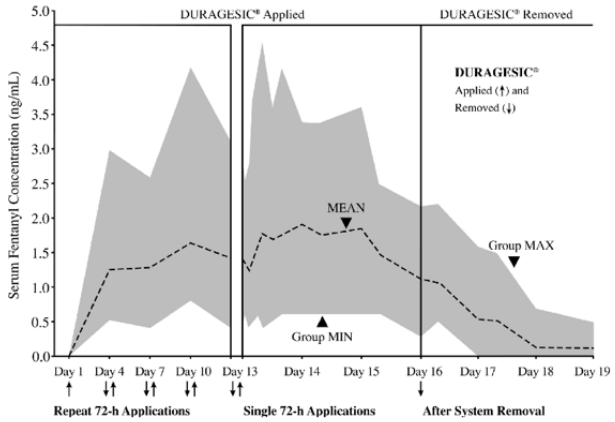
BROWN, COLLEAGUES INTRODUCE BIPARTISAN BILL TO PROTECT FIRST RESPONDERS FROM EXPOSURE TO FENTANYL AND OTHER DANGEROUS DRUGS

Bipartisan, Bicameral Legislation Will Help State and Local First Responders Protect Themselves

SHARE TWEET EMAIL PRINT

WASHINGTON, D.C. – U.S. Senator Sherrod Brown (D-OH) introduced the ***Protecting First Responders from Secondary Exposure Act,*** bipartisan, bicameral legislation that aims to help state and local governments purchase containment devices to safely store dangerous drugs and preserve them for evidentiary use, and provide first responders training to reduce their risk of secondary exposure to lethal substances. The bill would establish the first federal program to

Serum Fentanyl Concentrations Following Multiple Applications of DURAGESIC® 100 µg/h (n=10)



CONSENSUS STATEMENT

Appropriate Use of Drug Testing in Clinical Addiction Medicine

Effective Date: January 1, 2020
Rev. 0722

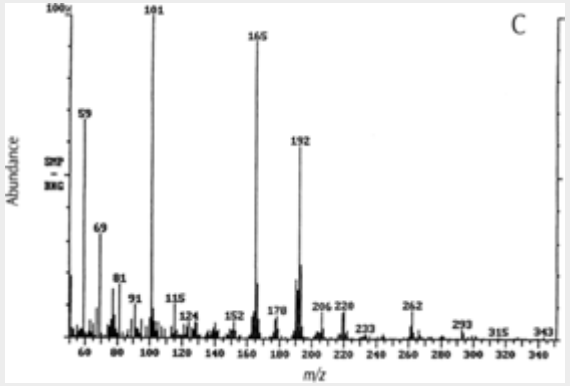
Medical Review Officer Guidance Manual for Federal Workplace Drug Testing Programs

Department of Health and Human Services
Substance Abuse and Mental Health Services Administration
Center for Substance Abuse Prevention
Division of Workplace Programs

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

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

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.				

“Drugs of Abuse” Screening

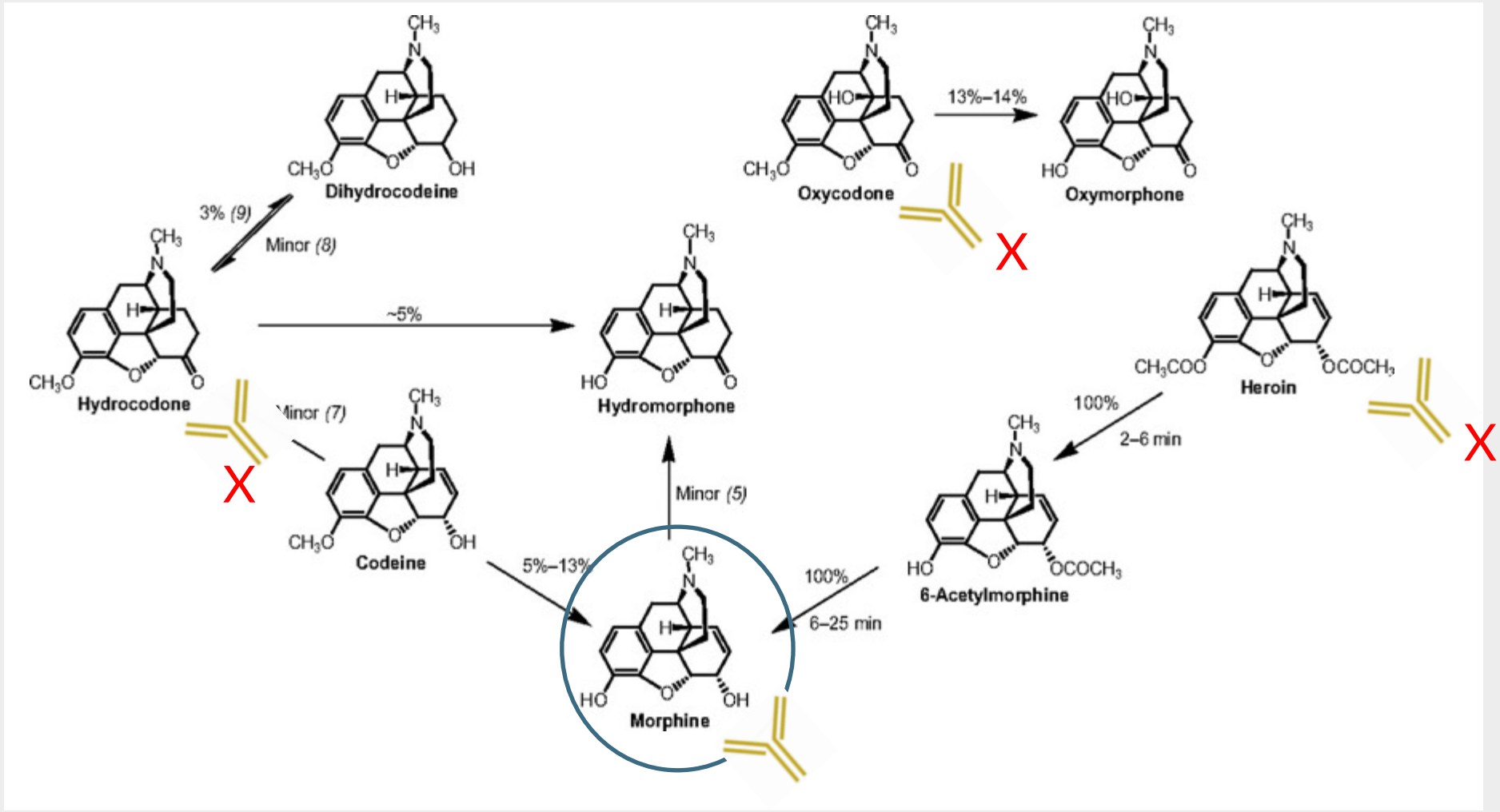
NIDA/SAMHSA 5

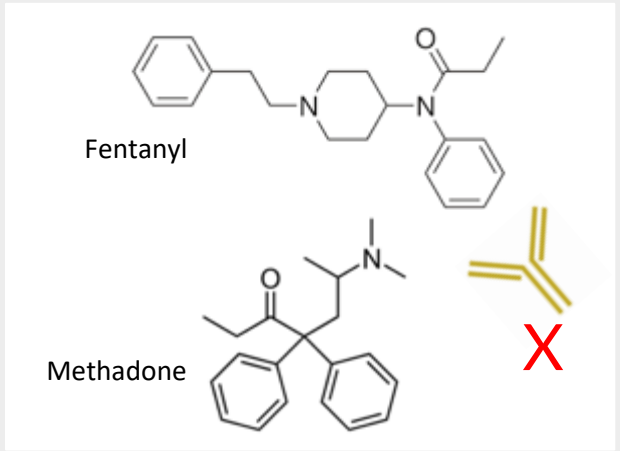
- Opiates
- Amphetamines
- Cocaine
- Marijuana
- Phencyclidine

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


Dihydrocodeine
3% (9)
Minor (8)
Hydrocodone
~5%
Hydromorphone
Oxycodone
13%–14%
Oxymorphone
Heroin
100%
2–6 min
6-Acetylmorphine
Minor (7)
Codeine
5%–13%
Minor (5)
Morphine
100%
6–25 min
X
X
X


Fentanyl
Methadone
X

The “Opiate” Assay: Not So Good for “Opioids”

	Online DAT opiates II[1] assay	EMIT II+ opiate aassay[2]	TDx/TDx-flex opiate opiate assay[3]	Archetict/ Aeroset	AsSym opiate[3]	CEDIA opiate[4]	DRI opiate[4]	DRI oxycodone[4]
Morphine	100	100	100	100	100	100	100	<29
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	7.5	<333
Norcodeine	2							<10
Normorphine							0	<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
Imiprimine	0					1.6		
Ranitidine						0	0	
Thebaine	25		<20		<30		<15	
Naltrexone	0						0	<20
Fentanyl			<40		<60			

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*
Amphetamine/ methamphetamine	500	500	1–2 days (2–4 days)	Decongestants, ephedrine, L-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		1–30 days	Benzodiazepines vary in reactivity and potency. Hydrolysis of glucuronides increases sensitivity. False-positive test results are reported with oxaprozin.
Cannabinoids	50	15	1–3 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			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.
Codeine/morphine	2,000	2,000		
Hydrocodone/hydromorphone	300	100		
Oxycodone/oxymorphone	100	50		
6-Acetylmorphine	10	10		
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 lot or contact the manufacturer. [b]Substance Abuse and Mental Health Services Administration recommendations[10] are shown for amphetamines/methamphetamines, 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 after heavy or prolonged use.

BE = benzoylecgonine; MDA = methylenedioxyamphetamine; MDEA = methylenedioxyethylamphetamine; MDMA = methylenedioxymethamphetamine; THCA = tetrahydrocannabinolic acid.

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

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

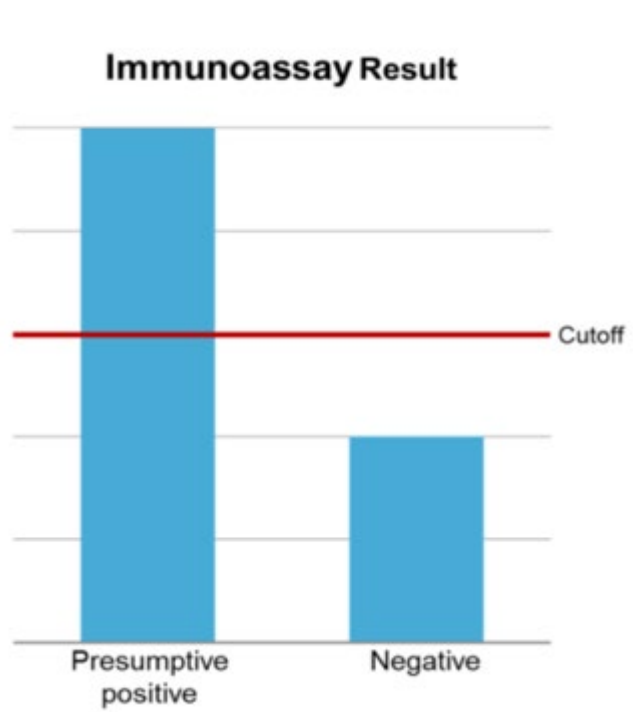
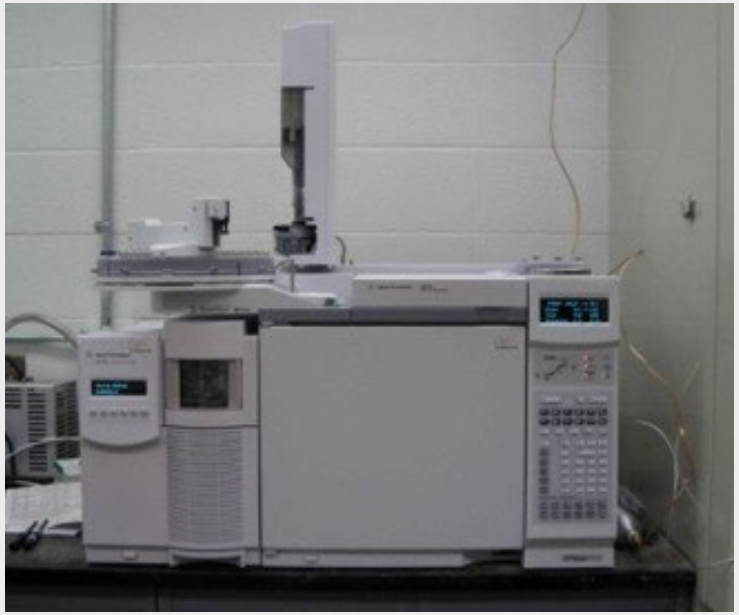


TABLE 2. **Length of Time Drugs of Abuse Can Be Detected in Urine**

Drug	Time
Alcohol	7-12 h
Amphetamine	48 h
Methamphetamine	48 h
Barbiturate	
Short-acting (eg, pentobarbital)	24 h
Long-acting (eg, phenobarbital)	3 wk
Benzodiazepine	
Short-acting (eg, lorazepam)	3 d
Long-acting (eg, diazepam)	30 d
Cocaine metabolites	2-4 d
Marijuana	
Single use	3 d
Moderate use (4 times/wk)	5-7 d
Daily use	10-15 d
Long-term heavy smoker	>30 d
Opioids	
Codeine	48 h
Heroin (morphine)	48 h
Hydromorphone	2-4 d
Methadone	3 d
Morphine	48-72 h
Oxycodone	2-4 d
Propoxyphene	6-48 h
Phencyclidine	8 d

Data from references 7 through 12.



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

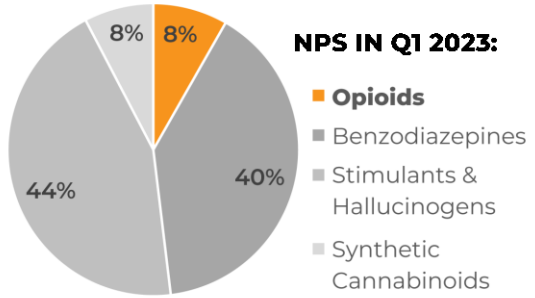
NPS Opioids in the United States

TREND REPORT | Q1 2023

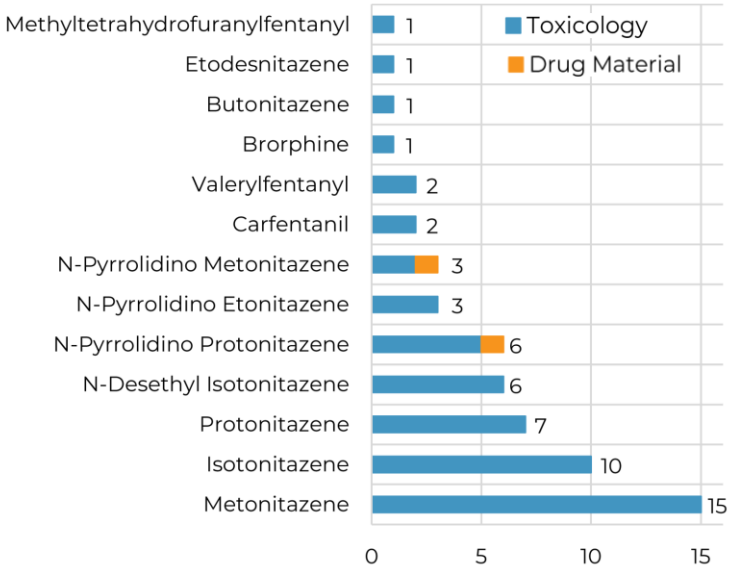
PURPOSE: This report provides up-to-date information regarding the status of NPS opioid prevalence and positivity within the United States & Canada.

OVERVIEW: Novel psychoactive substances (NPS), including NPS opioids, continue to pose great challenges for forensic scientists, clinicians, and public health and safety personnel. NPS opioids have been implicated in an increasing number of emergency room admissions, death investigations, and mass intoxication events, and often appear in combination with other illicit opioids (e.g. fentanyl, heroin). Maintaining a current scope of analysis can be challenging, requiring comprehensive analytical methodologies and reference materials for identification(s).

OBJECTIVE: Our laboratory utilizes novel approaches for the analysis of drugs in biological samples and seized materials using comprehensive non-targeted data acquisition by gas chromatography mass spectrometry (GC-MS) and liquid chromatography quadrupole time-of-flight mass spectrometry (LC-QTOF-MS). The scope of analysis contains more than 1,000 drugs, including a vast majority of NPS and their metabolites. This approach allows for real-time identification of novel opioids and further data analysis of important trends. This project was conducted in collaboration with the toxicology and criminalistics laboratories of NMS Labs. Forensic case types linked to these results include illicit drug investigations, medicolegal death investigations, and/or driving under the influence of drugs (DUID) investigations. The results in this report represent the total number of NPS identifications at the CFSRE during this quarter, including those from sample-mining, data-mining, and/or esoteric testing.

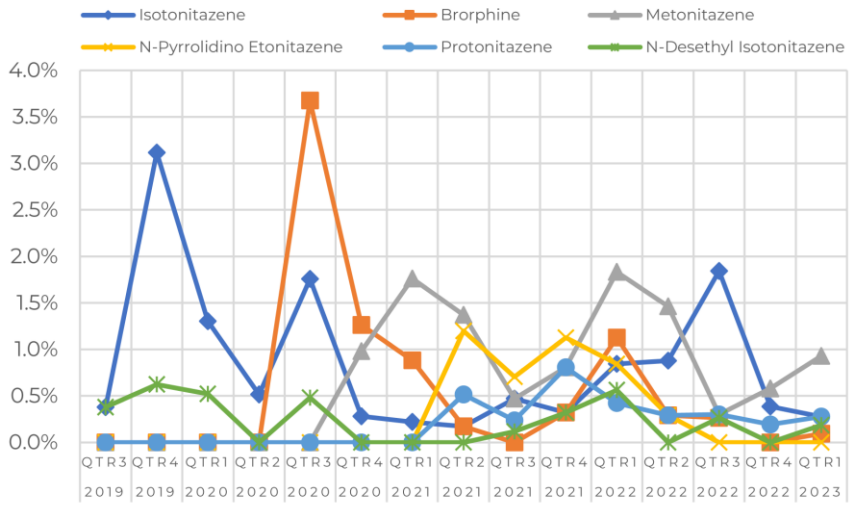


NPS OPIOIDS IDENTIFIED



For Reference [Toxicology]: Fentanyl (n=647) & Fluorotentanyl (n=415)

SELECT POSITIVITY: Q3 2019 to Q1 2023



cfsre | NPS DISCOVERY

ACKNOWLEDGEMENTS: This report was prepared by Alex J. Krotulski, PhD, Sara C. Walton, MS, Amanda LA. Mohr, MSFS, D-ABFT-FT, and Barry K. Logan, PhD, F-ABFT at the Center for Forensic Science Research and Education (CFSRE) at the Fredric Rieders Family Foundation. CFSRE / NPS Discovery program acknowledges scientists at the CFSRE and NMS Labs for their investments and contributions. For more information about our programs and reports, please contact NPS Discovery at npsdiscovery@cfsre.org or visit our website at www.cfsre.org/nps-discovery.

FUNDING: CFSRE / NPS Discovery is supported by the National Institute of Justice, Office of Justice Programs, U.S. Department of Justice (award number 15PNIJ-22-GG-04434-MUMU). "Implementation of NPS Discovery – An Early Warning System for Novel Drug Intelligence, Surveillance, Monitoring, Response, and Forecasting in the Drug Materials and Toxicology Populations in the U.S." The opinions, findings, conclusions, and/or recommendations expressed in this publication are those of the author(s) and do not necessarily represent the official position or policies of the U.S. Department of Justice.

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

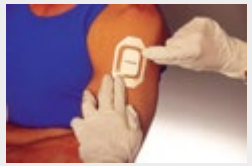
Matrix Considerations

- 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

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

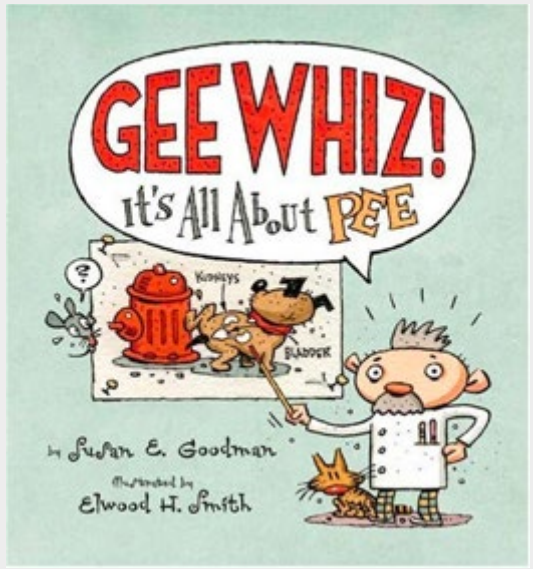
Easy to collect and observe
Essentially limited to ethanol

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

Specimen validity testing



Where Can I Get Help with Interpretation?

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

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

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

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

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

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

Get in Touch

Lewis.Nelson@Rutgers.edu

@LNelsonMD