

Addiction & Opioids

Mario San Bartolome, MD, MBA, MRO, FASAM

Medical Director
Substance Use Disorders



Your Extended Family.

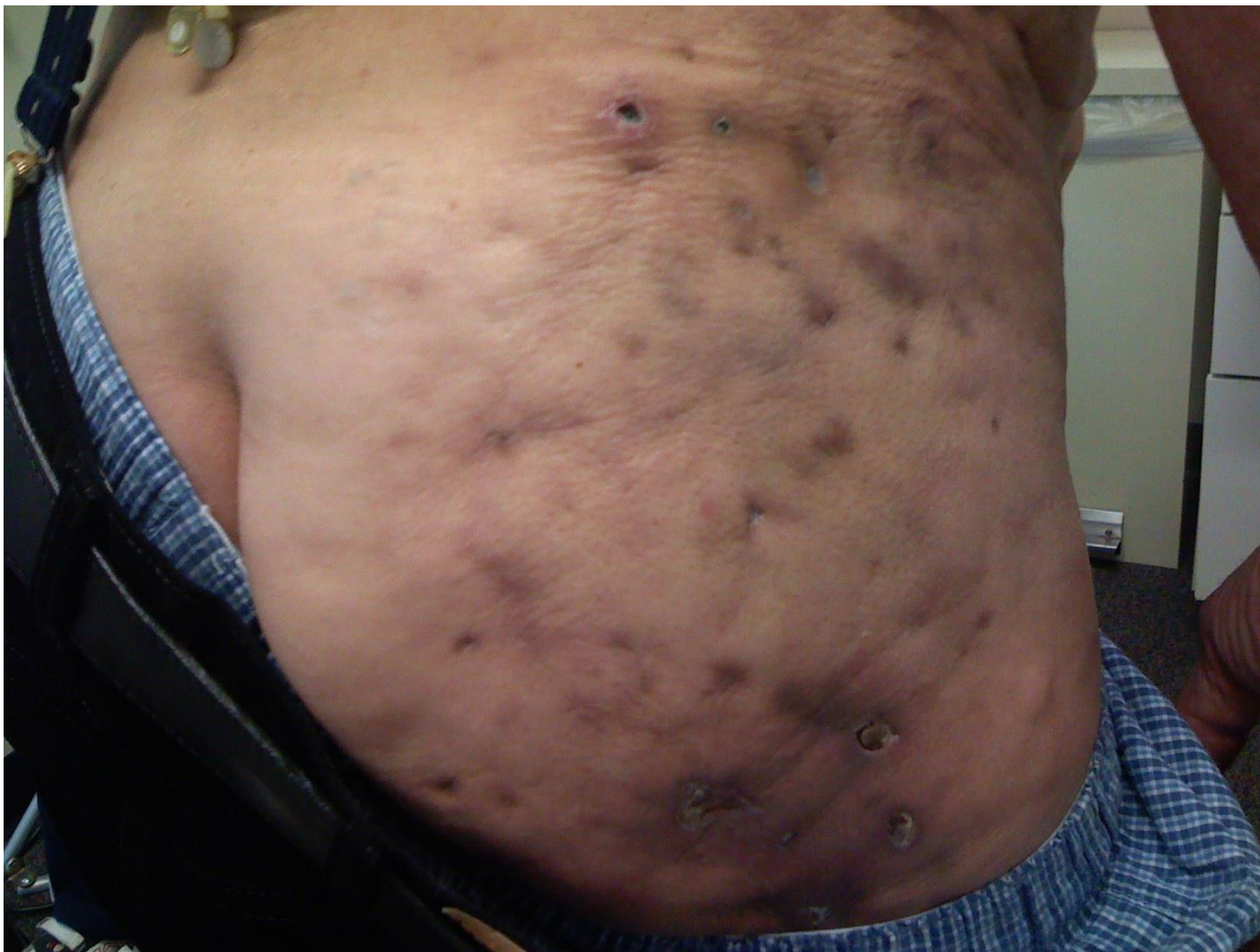
Objectives

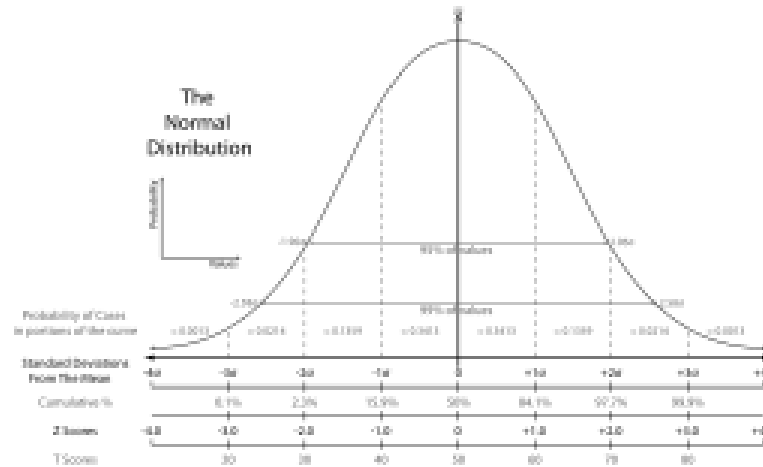
1. To understand the medical model of addiction.
2. To understand how OUD is diagnosed.
3. To understand the purpose of the PDMP CURES system and principles of safe opioid prescribing from the *CDC Guideline for Prescribing Opioids for Chronic Pain*
4. To understand the concept of “harm reduction” and be able to name one medication that is used to treat OUD that accomplishes harm reduction.



None

Case: Joe (not real name)





Facts and Figures

...WHY IT MATTERS

Important Statistics

- 52,404 lethal drug overdoses in 2015 (In 2016 up to 65,000)
- 20,101 deaths related to Rx Opioids
- 12,990 deaths related to heroin
- Estimated cost of Rx drug epidemic is \$78.5 Billion
- Estimated cost of Addiction in US: over \$700 Billion
- 20.4 million adults needing treatment
- 2.3 million received treatment (11%)
- 30% of Americans have some form of acute or chronic pain



Key figures about the opioid epidemic

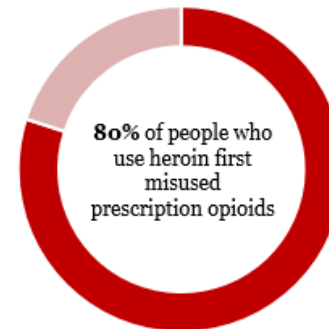
Most people who use heroin initially used prescription opioids

Today, **21-29%** of patients prescribed opioids for chronic pain misuse them



4-6% of people who misuse prescription opioids transition to **heroin**

Of the patients who misuse prescribed opioids, **8-12%** develop an opioid use disorder



Drug overdose is the leading cause of accidental deaths in the U.S.

Every day, an estimated **91 Americans** die due to overdosing on opioids, and a recent study suggests that opioid-related deaths are **drastically underreported**

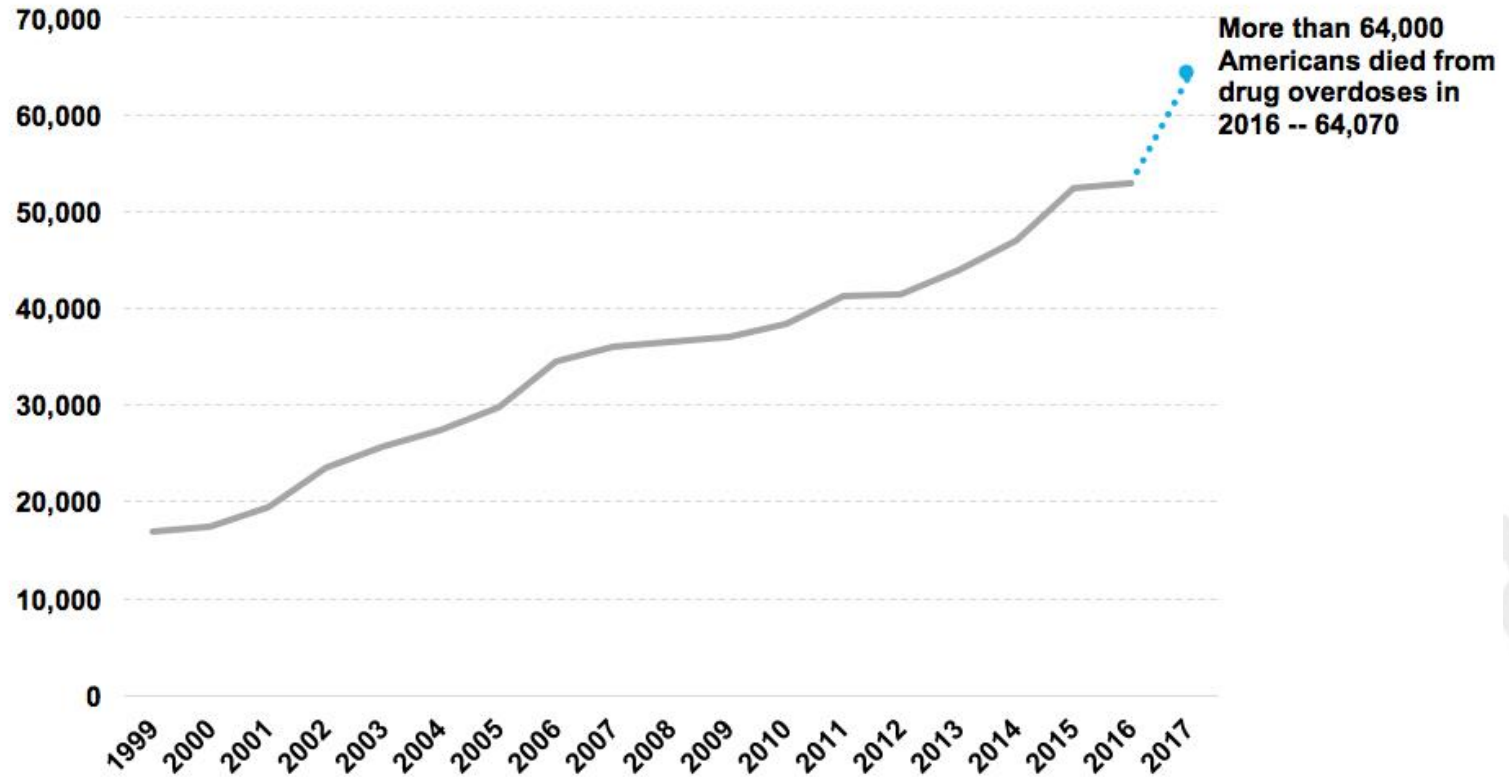
The CDC estimates that prescription opioid misuse costs the United States **\$78.5 billion** each year

- This includes the cost of health care, lost productivity, addiction treatment and criminal justice involvement

Sources: "Opioid Crisis," NIDA, June 2017; "Public Opinion on the Use and Abuse of Prescription Opioids," KFF, November 2015; [Schallhorn](#) "Trump declares opioid epidemic national emergency – here's what that means," Fox News, August 14, 2017.

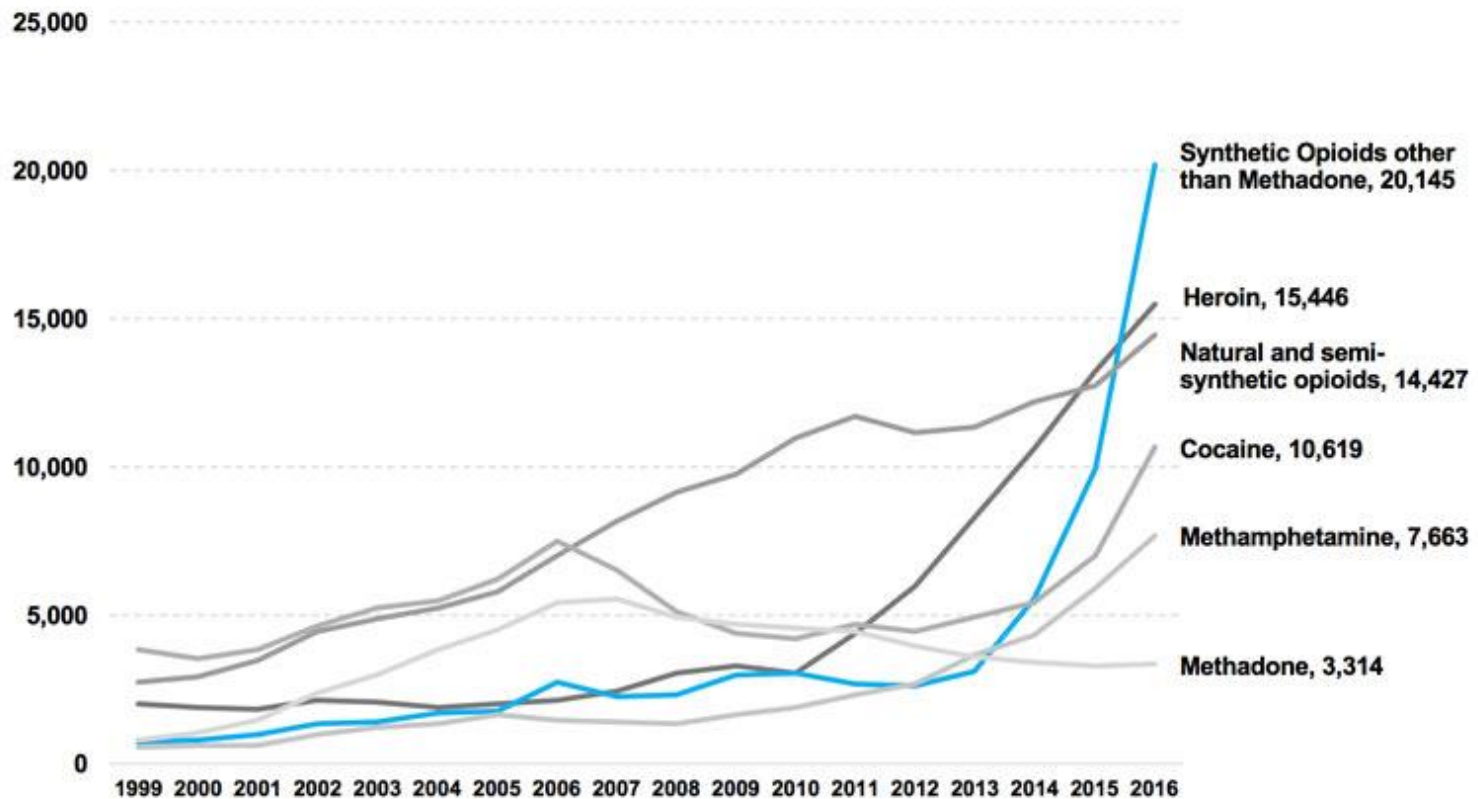
National Journal Presentation Center. Opioid Crisis Deep Dive. Jan 22, 2018.

Total U.S. Drug Deaths



U.S. Drug Deaths* - More than 64,000 Americans died from drug overdoses in 2016, including illicit drugs and prescription opioids--nearly double in a decade. Source: CDC WONDER

Drugs Involved in U.S. Overdose Deaths, 2000 to 2016



Drugs Involved in U.S. Overdose Deaths - Among the more than 64,000 drug overdose deaths estimated in 2016, the sharpest increase occurred among deaths related to fentanyl and fentanyl analogs (synthetic opioids) with over 20,000 overdose deaths. Source: CDC WONDER

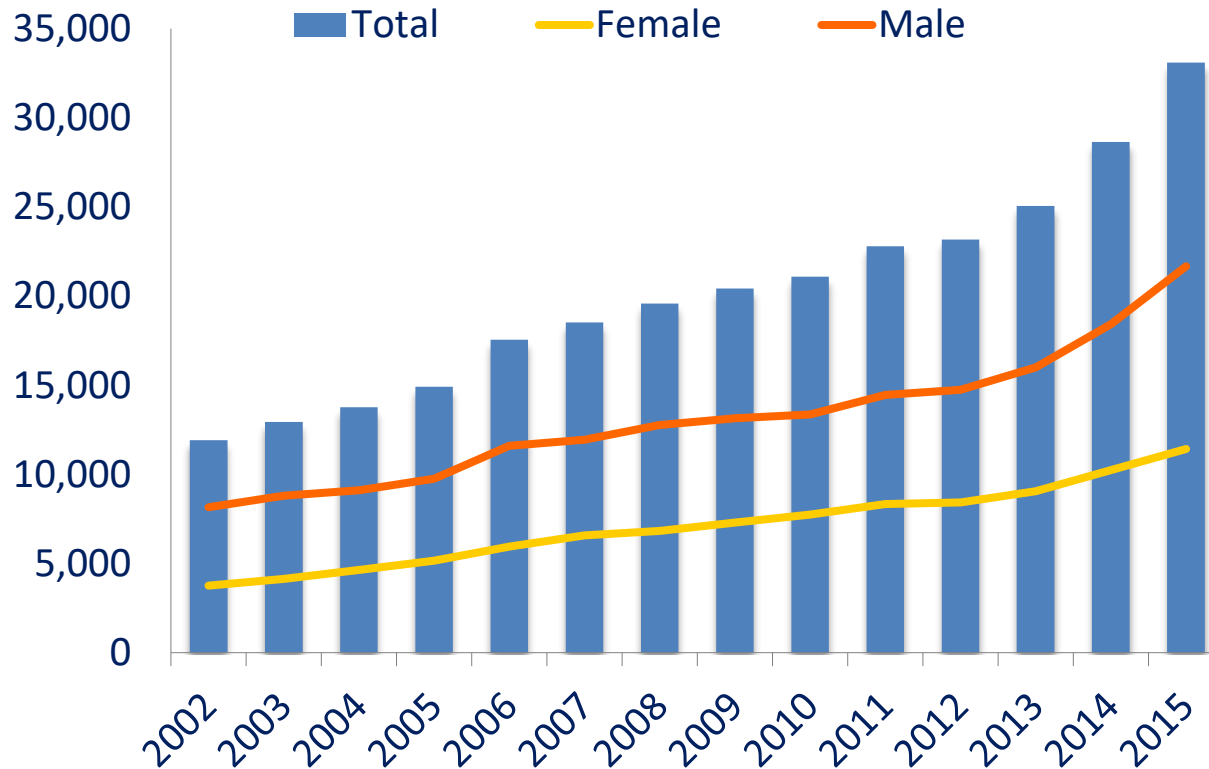
National Overdose Deaths



National Institute
on Drug Abuse



Number of Deaths Involving Opioid Drugs

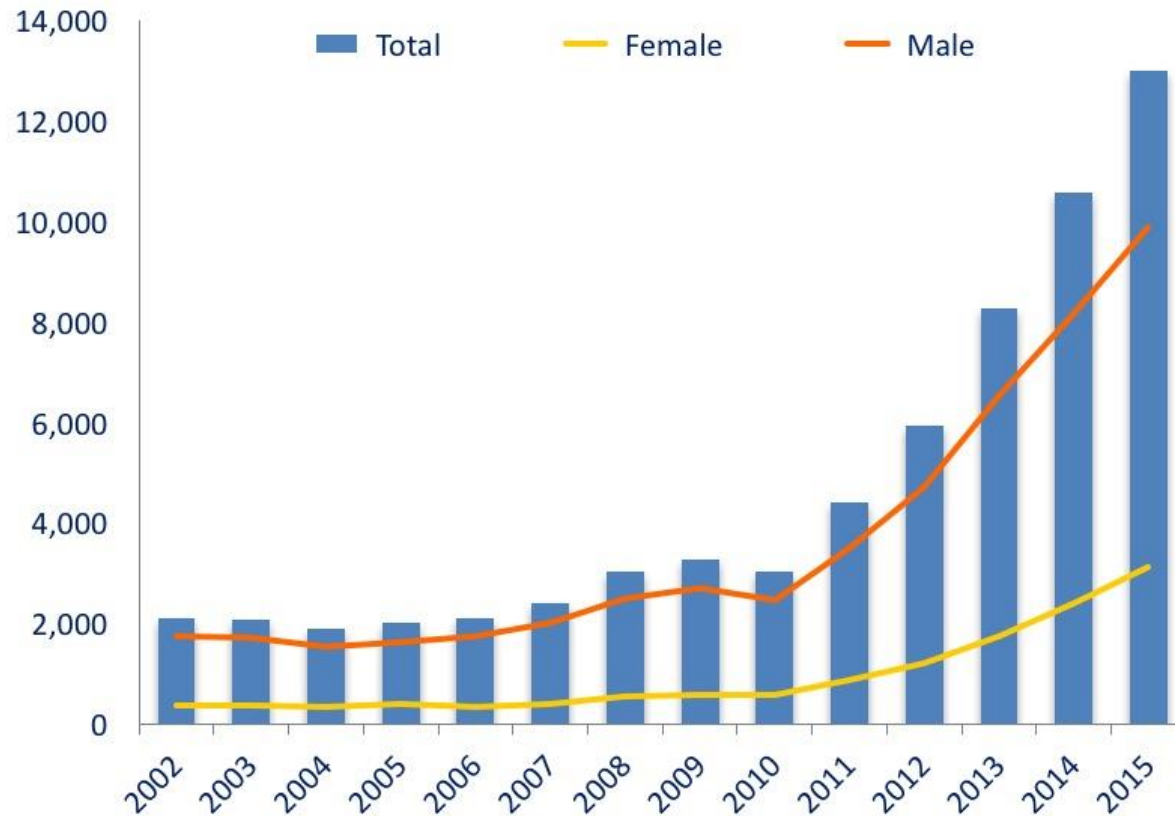


Source: National Center for Health Statistics, CDC Wonder



National Overdose Deaths

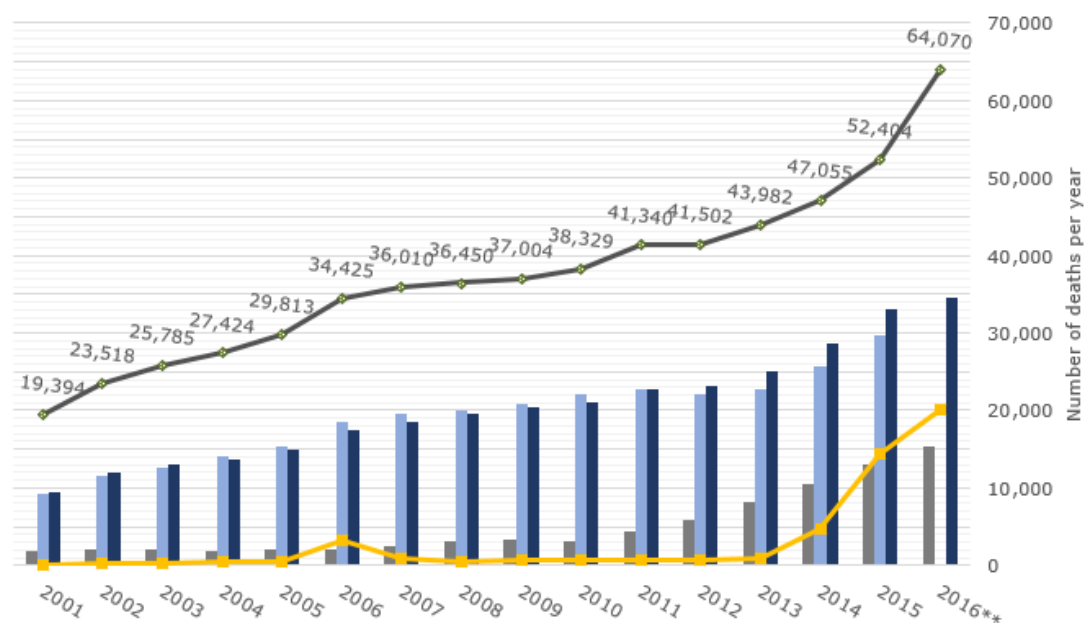
Number of Deaths Involving Heroin



Source: National Center for Health Statistics, CDC Wonder

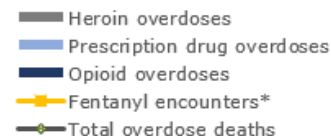
Deaths due to fentanyl overdoses have increased by 540% in the past three years, exceeding those due to heroin

A breakdown of drug overdose deaths, by year

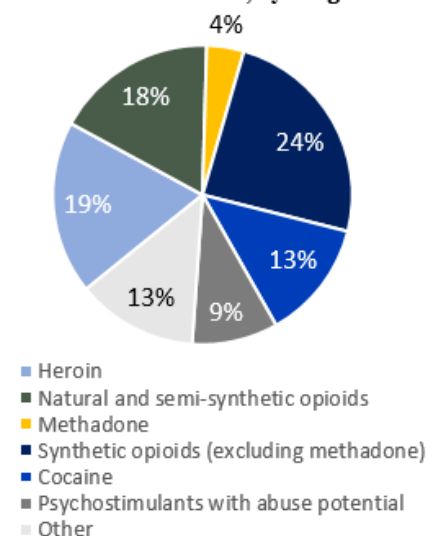


* According to the CDC, there is strong evidence of an association between reported fentanyl encounters and fentanyl-involved overdose deaths

** Prescription drug overdose data is not yet available for 2016, and data listed is provisional and based on data available for analysis as of August 6, 2017



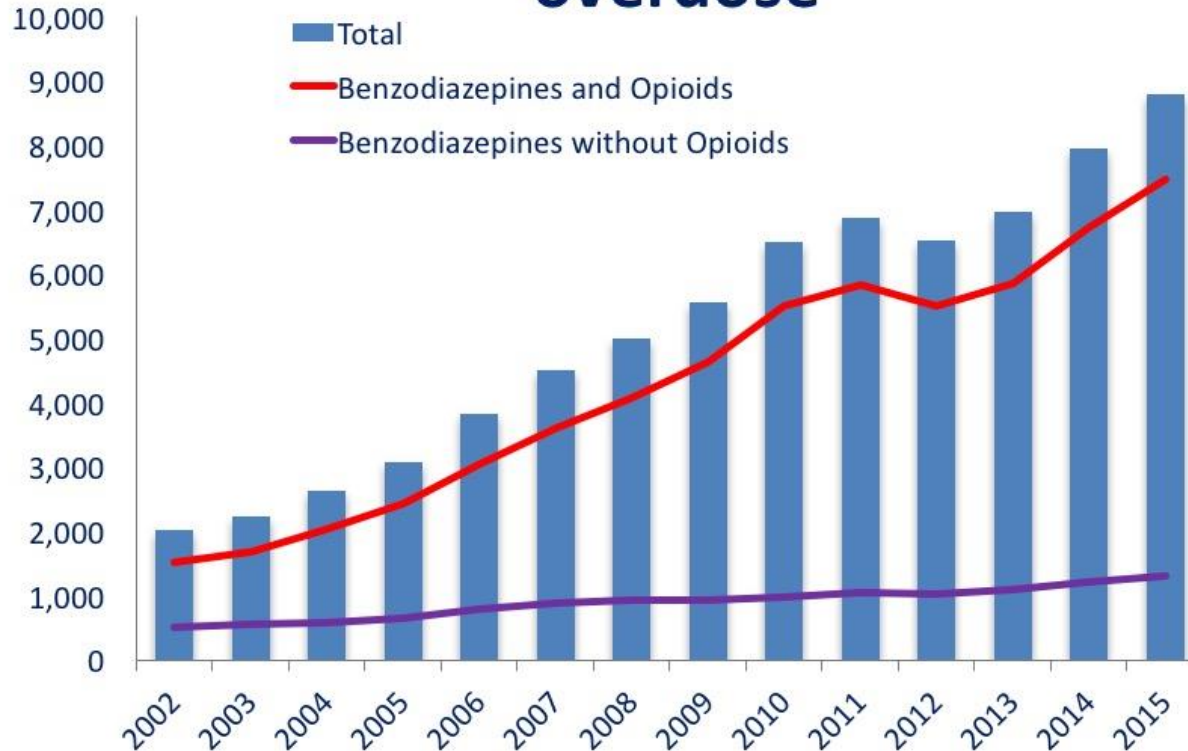
Overdoses in 2016, by drug



Sources: "Drug overdose data," CDC, 2016; Josh Katz, "The First Count of Fentanyl Deaths in 2016: up 540% in Three Years," The New York Times, September 2, 2017

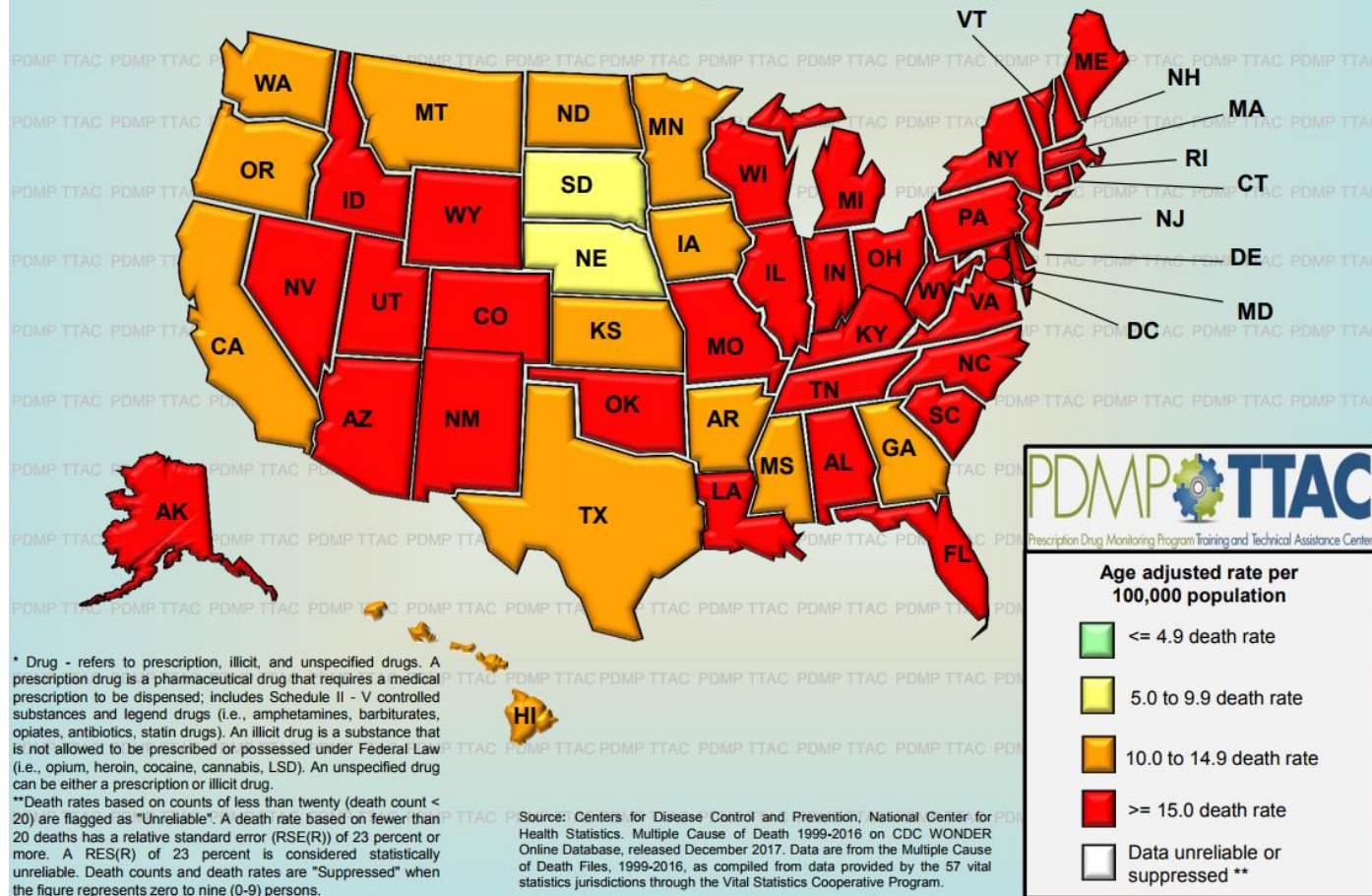


Opioid involvement in benzodiazepine overdose

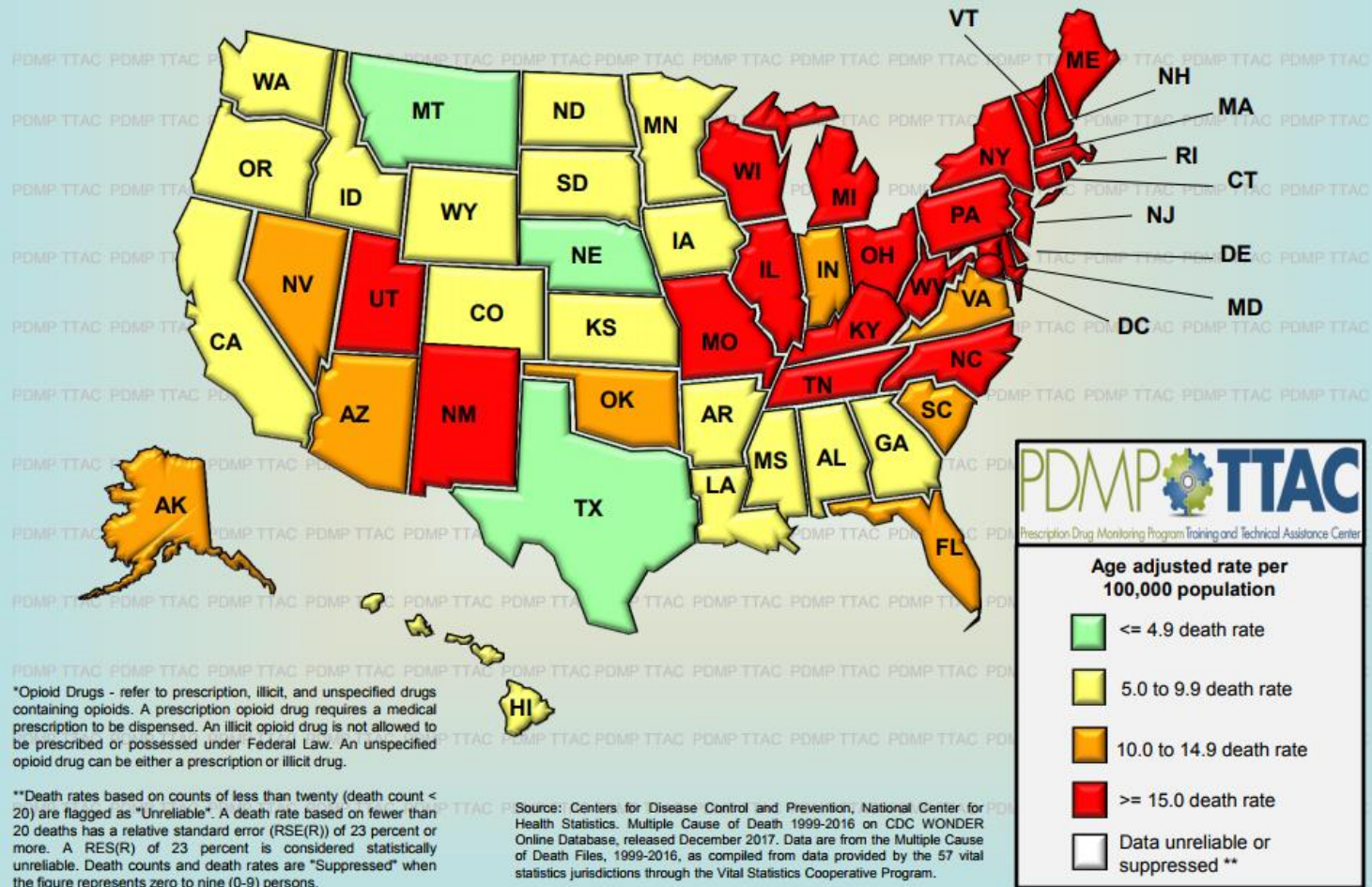


Source: National Center for Health Statistics, CDC Wonder

2016 Death Rates for Drug* Overdose by State



2016 Death Rates for Opioid Drug * Overdose by State



National Ranking of 1999 - 2016 Average Death Rates for Opioid Drug Overdose

Rank	State	Deaths	Population	Age Adjusted Rate	Rank	State	Deaths	Population	Age Adjusted Rate
1	West Virginia	6,030	32,969,943	19	27	Colorado	5,999	87,520,147	6.7
2	Utah	5,855	47,101,624	13.5	28	Michigan	11,412	179,175,401	6.4
3	New Mexico	4,531	35,591,378	13.2	29	Virginia	8,952	139,832,729	6.3
4	Nevada	6,076	45,337,347	13.1	30	New York	20,666	347,668,398	5.8
5	Rhode Island	2,314	19,028,324	12.2	31	Pennsylvania	12,698	226,120,660	5.8
6	Maryland	12,093	102,112,259	11.6	32	New Jersey	8,948	156,731,084	5.7
7	New Hampshire	2,636	23,374,853	11.4	33	South Carolina	4,232	80,204,580	5.3
8	Massachusetts	13,217	117,373,383	11.2	34	Wyoming	510	9,717,004	5.3
9	Kentucky	7,879	76,506,661	10.4	35	Montana	844	17,392,834	5.1
10	Oklahoma	6,652	65,958,887	10.3	36	Arkansas	2,427	51,115,387	5
11	Ohio	19,226	206,878,661	9.5	37	Georgia	7,621	167,104,718	4.5
12	District of Columbia	990	10,821,657	9.1	38	Idaho	1,151	26,808,882	4.5
13	Maine	2038	23,678,068	8.9	39	California	29,217	657,732,064	4.4
14	Washington	10,578	117,319,695	8.8	40	Indiana	4,860	114,672,389	4.3
15	Delaware	1,296	15,642,558	8.5	41	Hawaii	1,032	23,820,385	4.2
16	Tennessee	9,419	110,944,821	8.5	42	Kansas	1,972	50,399,794	4.1
17	Connecticut	5,211	63,428,300	8.3	43	Minnesota	3,695	93,869,577	3.9
18	Vermont	895	11,177,520	8.1	44	Texas	16,988	433,541,733	3.9
19	Arizona	8,397	109,191,391	7.9	45	Iowa	1911	54,240,721	3.7
20	North Carolina	12,960	163,935,950	7.9	46	Louisiana	2,917	81,497,954	3.6
21	Missouri	7,849	105,641,925	7.6	47	Alabama	2689	84,016,831	3.3
22	Oregon	5,063	67,122,422	7.5	48	South Dakota	416	14,407,304	3.1
23	Florida	23,742	328,270,645	7.4	49	Mississippi	1373	52,684,994	2.7
24	Alaska	870	12,360,948	6.8	50	North Dakota	295	12,151,986	2.5
25	Illinois	15,540	228,431,026	6.8	51	Nebraska	690	32,356,691	2.2
26	Wisconsin	6,758	100,761,896	6.8	Total		351,630	5,435,746,389	6.5

Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2016 on CDC WONDER Online Database, released December 2017. Data are from the Multiple Cause of Death Files, 1999-2016, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program.

Perinatal Addiction

Between 2000 and 2009, opioid use increased from 1.19 per 1,000 hospital births to 5.63 per 1,000 hospital births in the US



Neonatal Abstinence Syndrome (NAS)

Between 2000 and 2009, NAS has increased from 1.20 per 1,000 hospital births per year to 3.39 per 1,000 hospital births per year.





ACUTE



Description	Acute	Chronic
Cause	Normal response to injury or medical condition	Often unknown or unrelated to medical findings
	Signal of tissue damage or underlying medical condition	Pain is often not a signal of harm
Duration	Short term	Lasts longer than three months
	Pain reduces as body heals	Pain often continues even after healing
Treatment	Often responds to traditional medical treatment	Minimal or no response to traditional medical treatment
Quality of life	Does not affect long-term quality of life	Often interferes with quality of life including sleep, work, recreational activities
	May or may not affect mood	Often accompanied by depression, anger and frustration.

CHRONIC



Multimodal Approach



Goals...

- Restore function
- Reduce pain
- Improve QOL
- Cultivate well-being

Systematic reviews: multidisciplinary treatment of chronic pain is more cost-effective than single modality options

Flor H et al. *Pain* 1992, Roberts AH et al. *Clin J Pain* 1993,
Patrick LE et al. *Spine* 2004, Kamper SJ et al. *Cochrane Review* 2014

Pain Experience

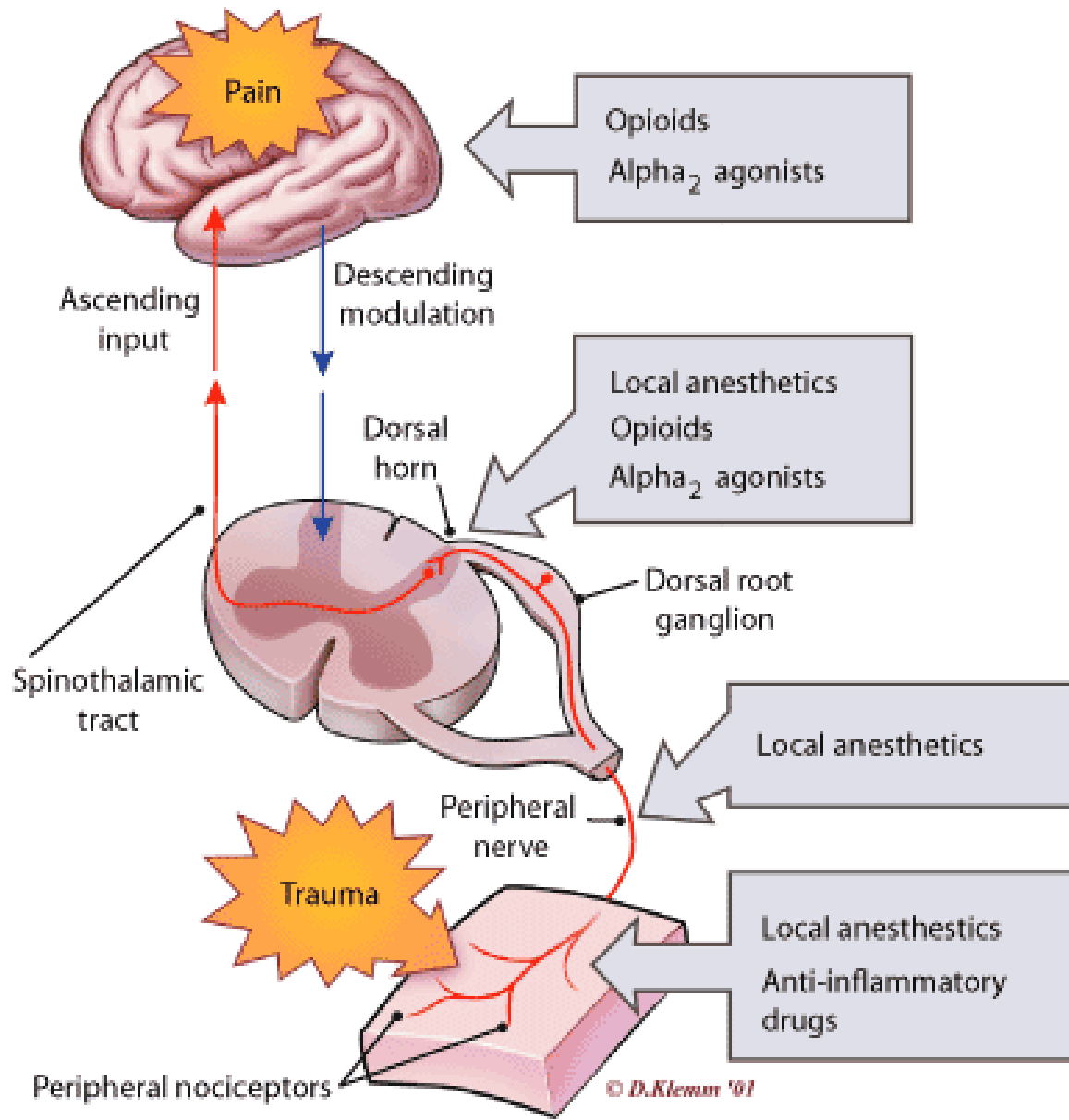
- Patients with active opioid use disorders (OUD)...
 - have less pain tolerance than peers in remission or matched controls
 - have less pain tolerance than siblings without an addiction history
- Patients with an OUD on opioid agonist treatment (i.e. methadone, buprenorphine) have less pain tolerance than matched controls
- What came first?...decreased pain tolerance or OUD

Martin J (1965), Ho and Dole V (1979), Compton P (1994, 2001)

Opioids—A Little History

- Derived from opium poppy
- Used for thousands of years
- Morphine (named after Morpheus, the Greek God of Dreams)
- Effective Painkiller
- Morphine used extensively during Civil War
- 1830 Jean-Pierre Robiquet isolated codeine from opium.
- “First Opium War”-by 1830’s British dependence on opium resulted in warships being sent to coast of China to response to China’s attempt to suppress traffic.
- 1874, in an attempt to find a less addictive form of morphine→heroin
- 1905 US congress banned opium
- 1937 Max Bockmuhl synthesized methadone in an attempt to look for less addictive drug than morphine and heroin.
- 1984 Vicodin
- 1995 OxyContin
- 1999 Percocet
- And so on...







*In the past, addiction was
about
drugs*

*The new definition of addiction is
about
brains*

Latin: *addictus*



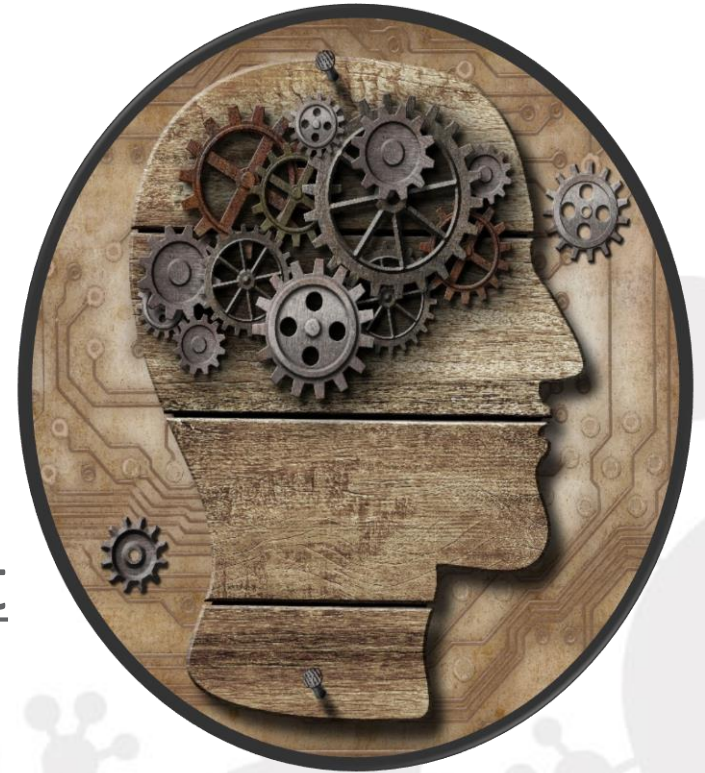
Roman law meant a debtor was awarded as a slave to his creditor

Addiction

Addiction is a **primary, chronic** disease of brain **reward, motivation, memory** and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual **pathologically pursuing** reward and/or relief by substance use and other behaviors.

Definition-Life-Process Model

- Addiction is not a disease
- Habitual Response
 - Gratification
 - Security
- Understood in the context
 - Social Relationships
 - Experiences



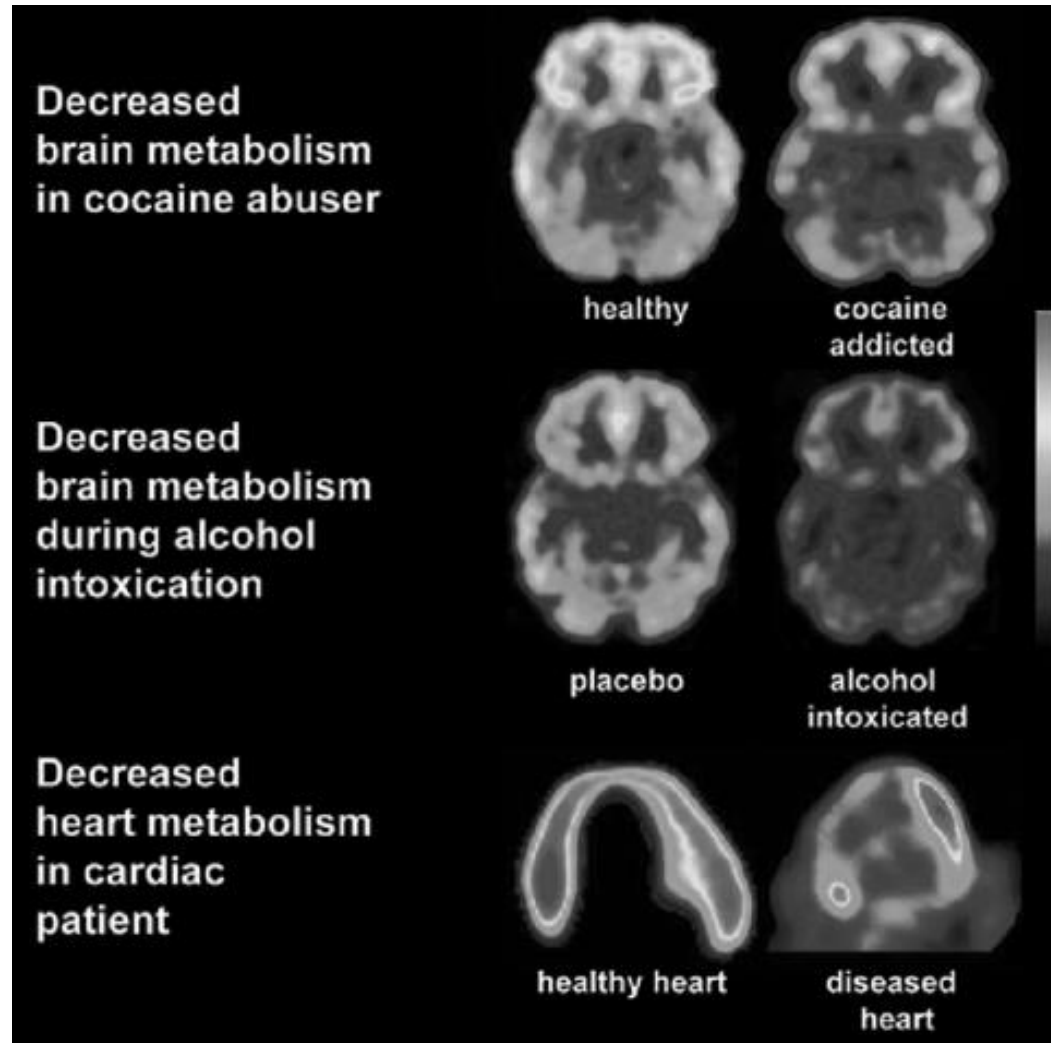
“...a disease is a cluster of symptoms and /or signs with a more or less predictable course.”

The cluster may be associated with physical abnormality or may not.

Page x, Psychiatric Diagnosis, 1st Ed, 1994, Woodruff, Goodwin, Guze



Neuroimaging



Volkow ND, Kim SW, Wang GJ, et al. Acute alcohol intoxication decreases glucose metabolism but increases acetate uptake in the brain. *Neuroimage* 2013;64:277-283

The Face of a Meth User – 10 years



age 28



age 29



age 30



age 31



age 32



age 33



age 34



age 35



age 36



age 37

Dead at age 38

Co-Morbidities

- **Mental Health Disorders** (major depressive disorder, bipolar disorder, psychotic disorders and personality disorders)
- **Communicable Diseases**
 - Viral Hepatitis (B & C)
 - HIV
 - **Sexually Transmitted Infections**
- **Other ID**
 - Endocarditis
 - Abscesses and bacteremia
 - Botulism
- **Trauma**
 - Domestic Violence
 - Physical/Sexual Abuse
 - Altercations
- **Pregnancy/Neonate**
 - Abruptio placentae, Neonatal Abstinence Syndrome, Fetal Alcohol Syndrome, Low birth weight, Stillbirths



DSM V: Opioid Use Disorder

- ✓ ***Tolerance**
- ✓ ***Withdrawal**
- ✓ **Use in larger amounts or duration than intended**
- ✓ **Persistent desire to cut down**
- ✓ Giving up interests to use opioids
- ✓ **Great deal of time spent obtaining, using, or recovering from opioids**
- ✓ Craving or strong desire to use opioids
- ✓ Recurrent use resulting in failure to fulfill major role obligations
- ✓ **Recurrent use in hazardous situations**
- ✓ Continued use despite social or interpersonal problems caused or exacerbated by opioids
- ✓ **Continued use despite physical or psychological problems**

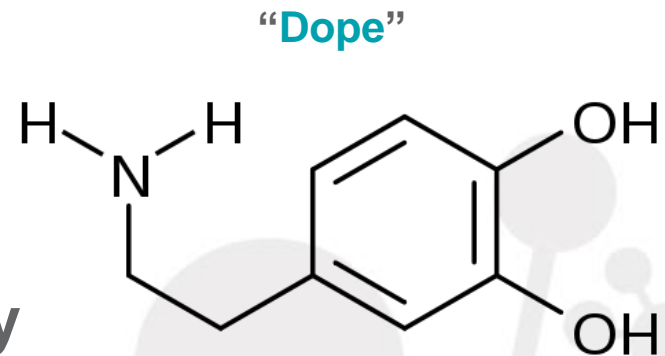
***This criterion is not considered to be met for those individuals taking opioids solely under appropriate medical supervision**

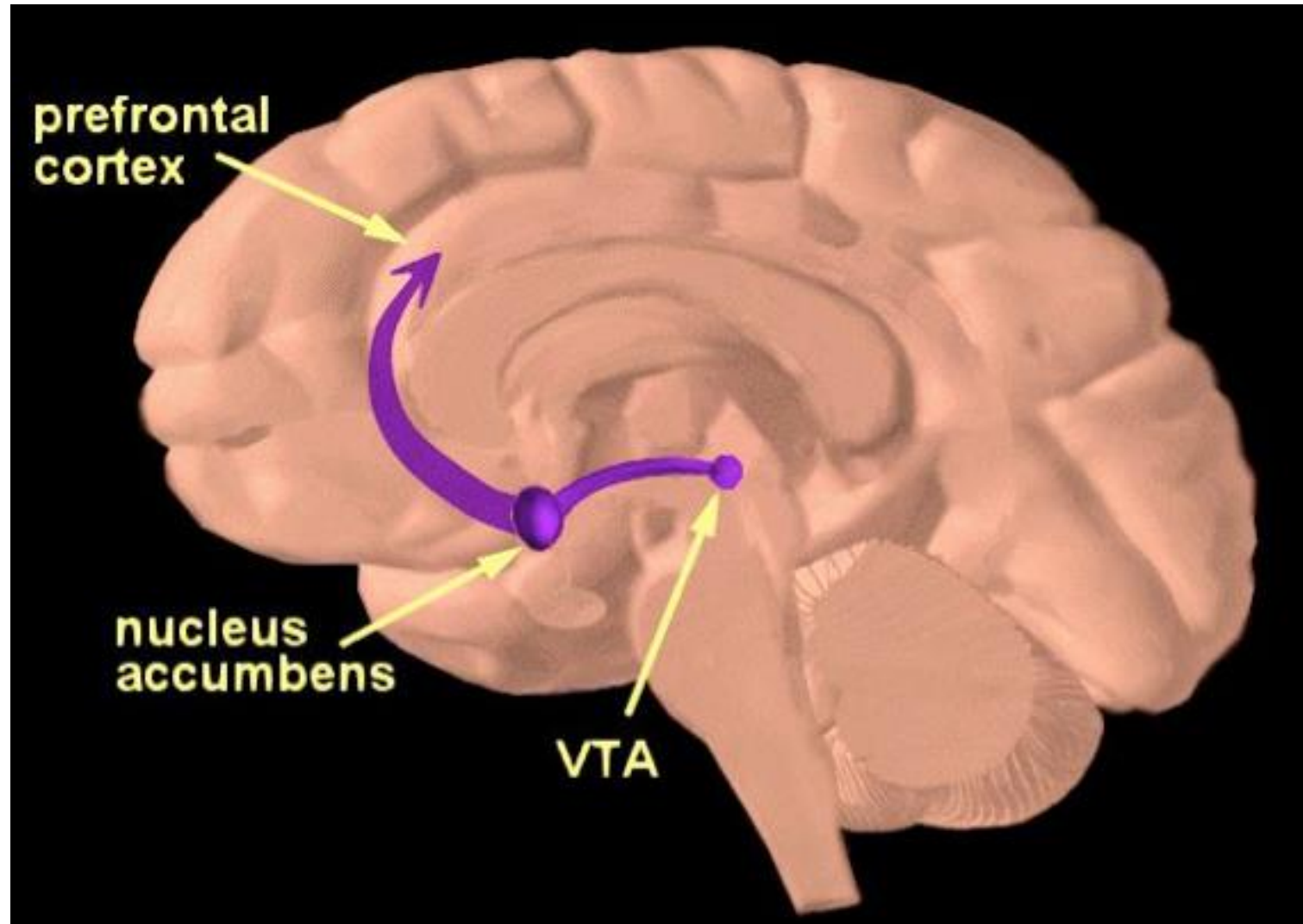
Mild OUD: 2-3 Criteria
Moderate OUD: 4-5 Criteria
Severe OUD: ≥ 6 Criteria

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.)

Getting “Addicted” and the Pleasure Reward Pathway

- The Reward pathway in the brain is activated by activities we find pleasurable.
- The common reward pathway in the brain for all pleasurable activities involves the neurotransmitter **Dopamine**



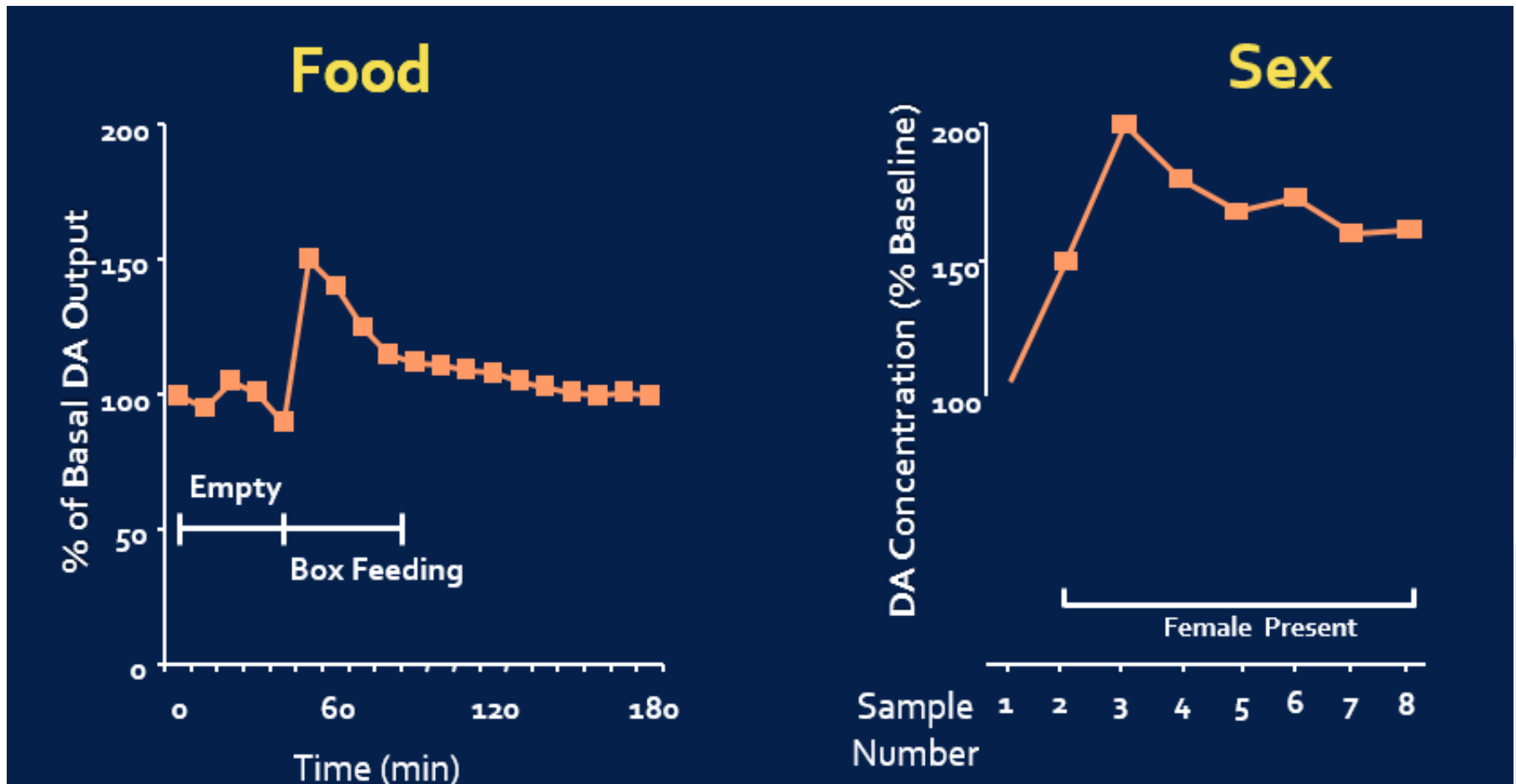


Getting “Addicted” and the Pleasure Reward Pathway



**Drugs that hijack
the natural
pleasure circuitry
of the brain can
become
“addictive.”**

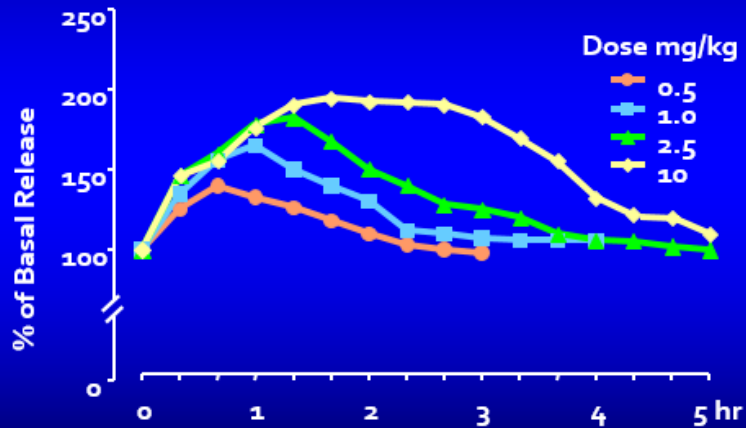
Natural Rewards & Dopamine Levels



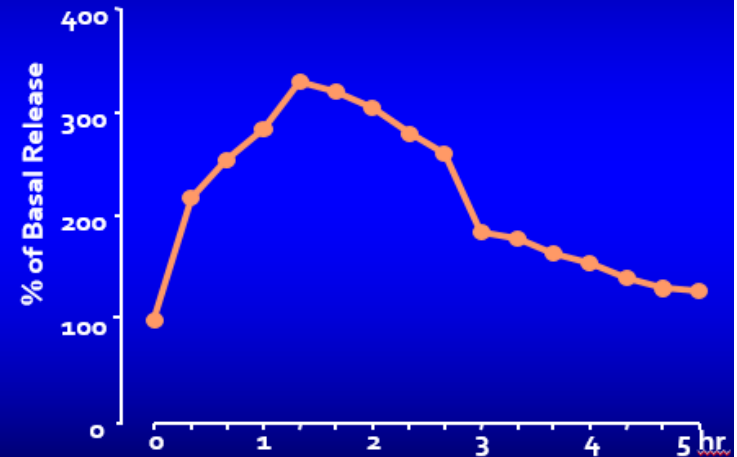
Adapted from Di Chiara et al, Neuroscience, 1999

Adapted from Fiorino and Phillips, J Neuroscience, 1997

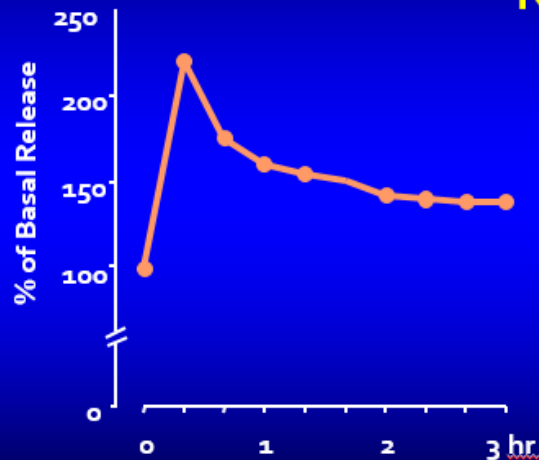
MORPHINE



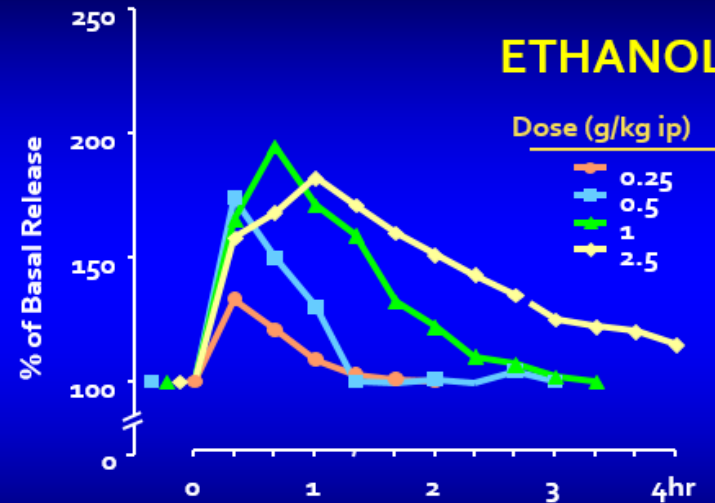
COCAINE



NICOTINE

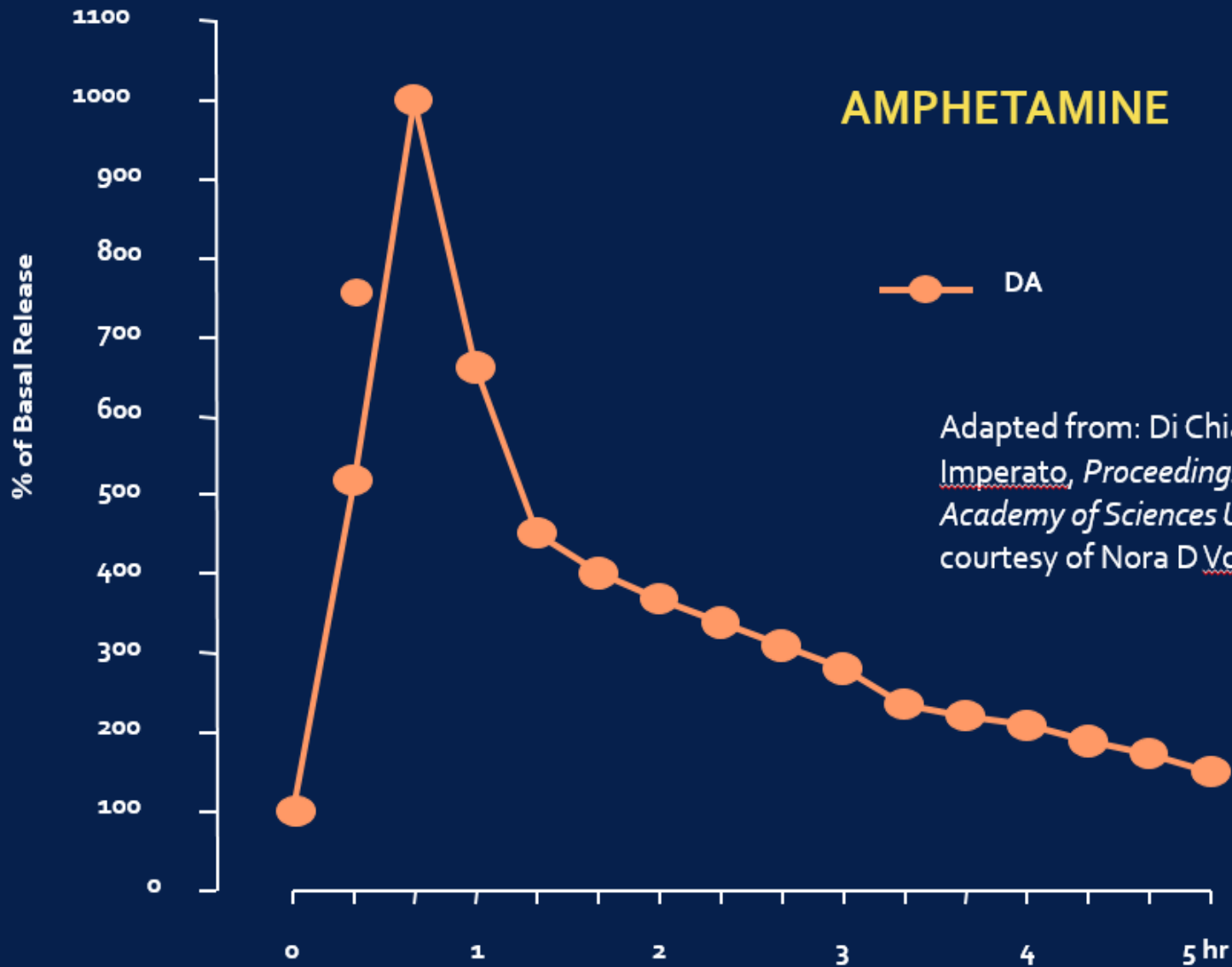


ETHANOL



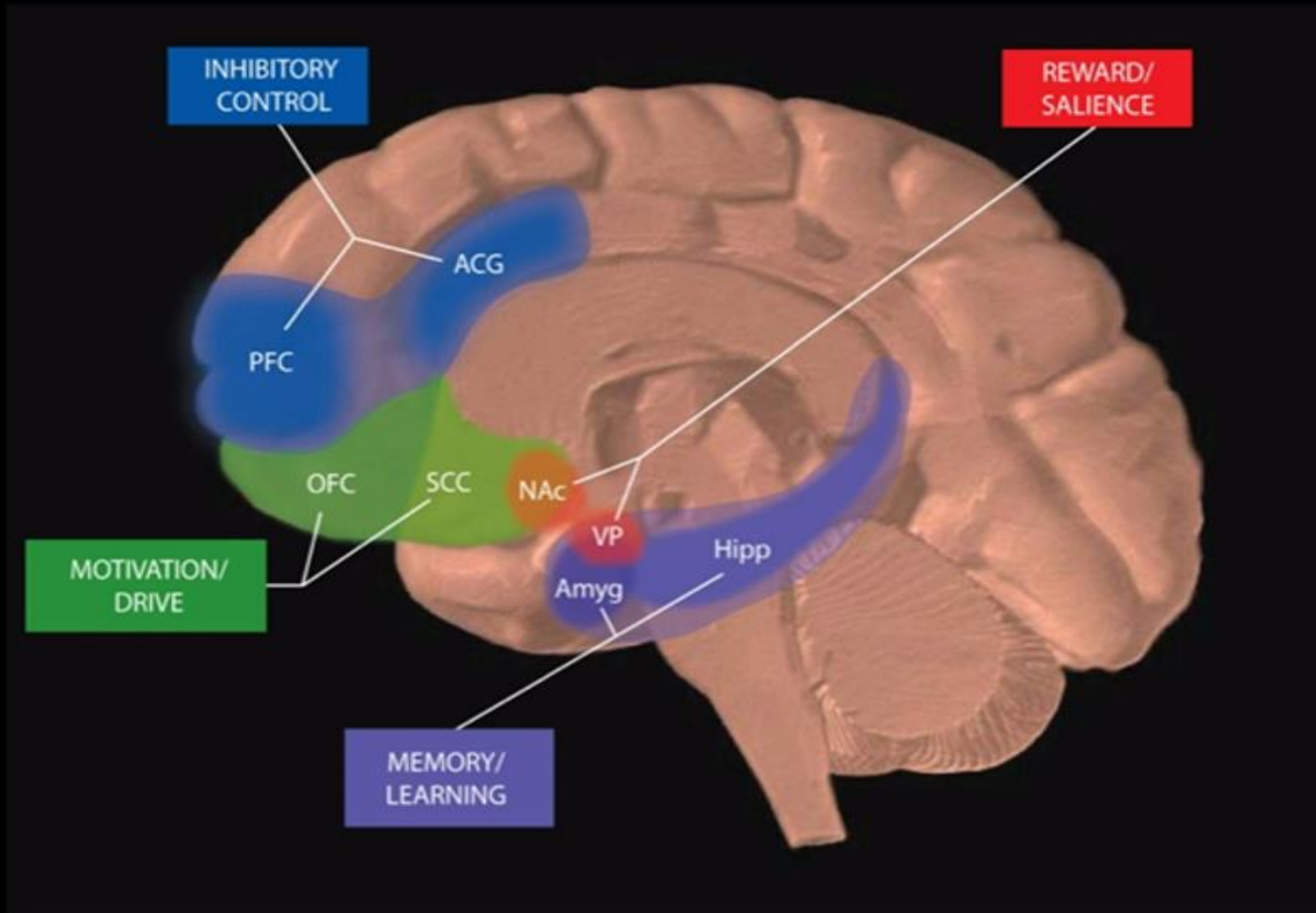
Adapted from Di Chiara and Imperato, Proceedings of the National Academy of Sciences, 1988; courtesy of Nora D Volkow, MD

AMPHETAMINE

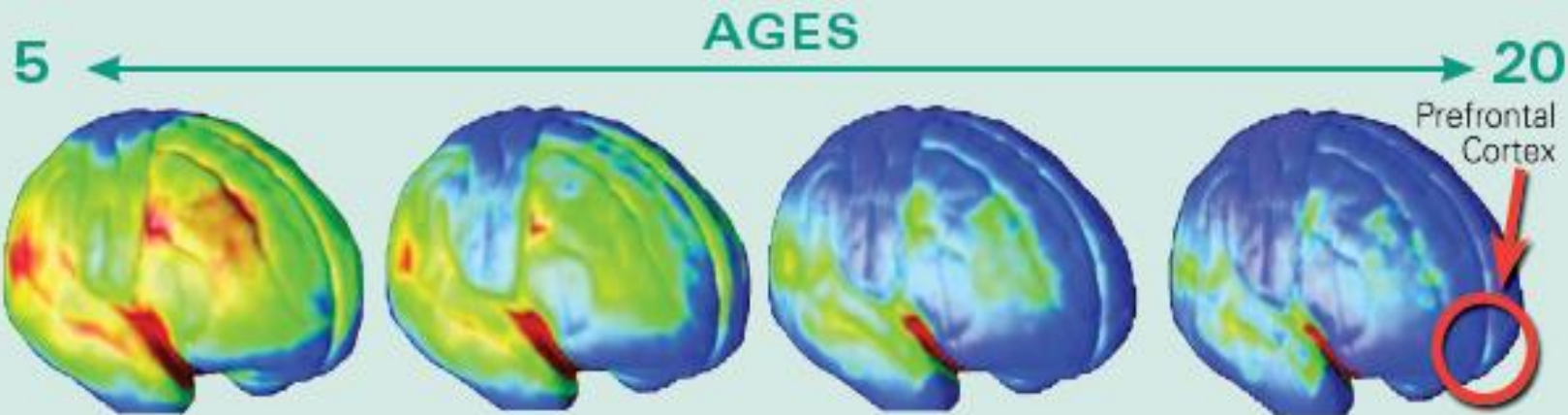


Adapted from: Di Chiara and Imperato, *Proceedings of the National Academy of Sciences USA*, 1988; courtesy of Nora D Volkow, MD.

Circuits Involved In Drug Abuse and Addiction



**Glutamate, GABA, NMDA, Opioid, NACH, ECS
also important**



Blue represents maturing of brain areas.



Adverse Childhood Events

ABUSE



Physical



Emotional



Sexual

NEGLECT



Physical



Emotional

HOUSEHOLD DYSFUNCTION



Mental Illness



Incarcerated Relative



Mother treated violently



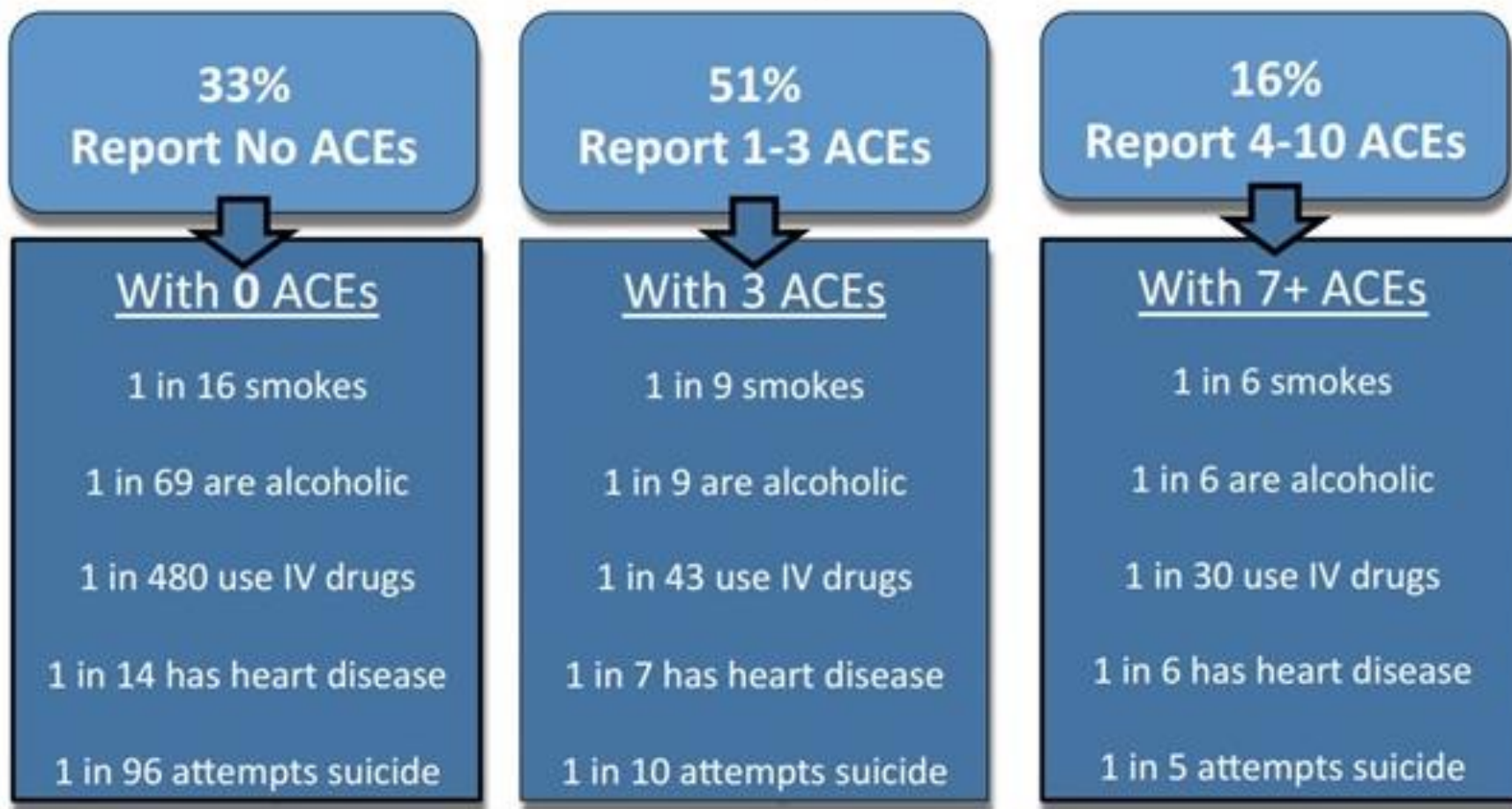
Substance Abuse



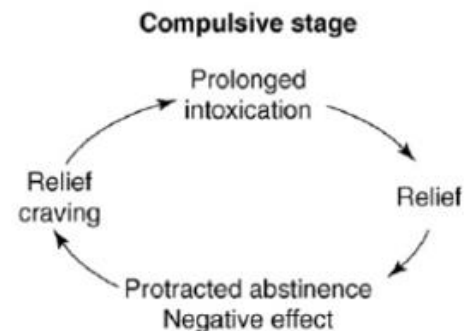
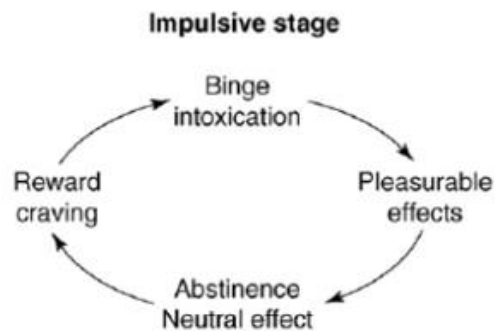
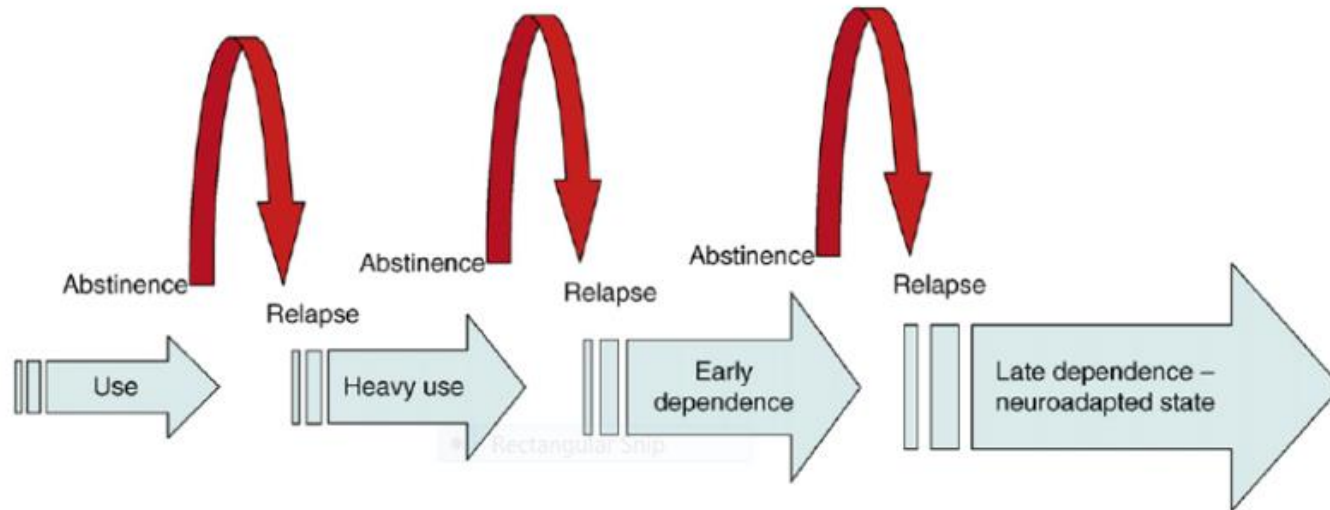
Divorce

Adverse Childhood Events

Out of 100 people...



Transition from Positive to Negatively Reinforced Drug Use



**Positive
Reinforcement**



**Negative
Reinforcement**

From: Koob GF, *Alcohol Clin Exp Res*, 2003, 27:232-243.

Relapse

- **Triggering (Pavlovian conditioning)**
- **Stress**
- **Negative neuropsychiatric adaptation**

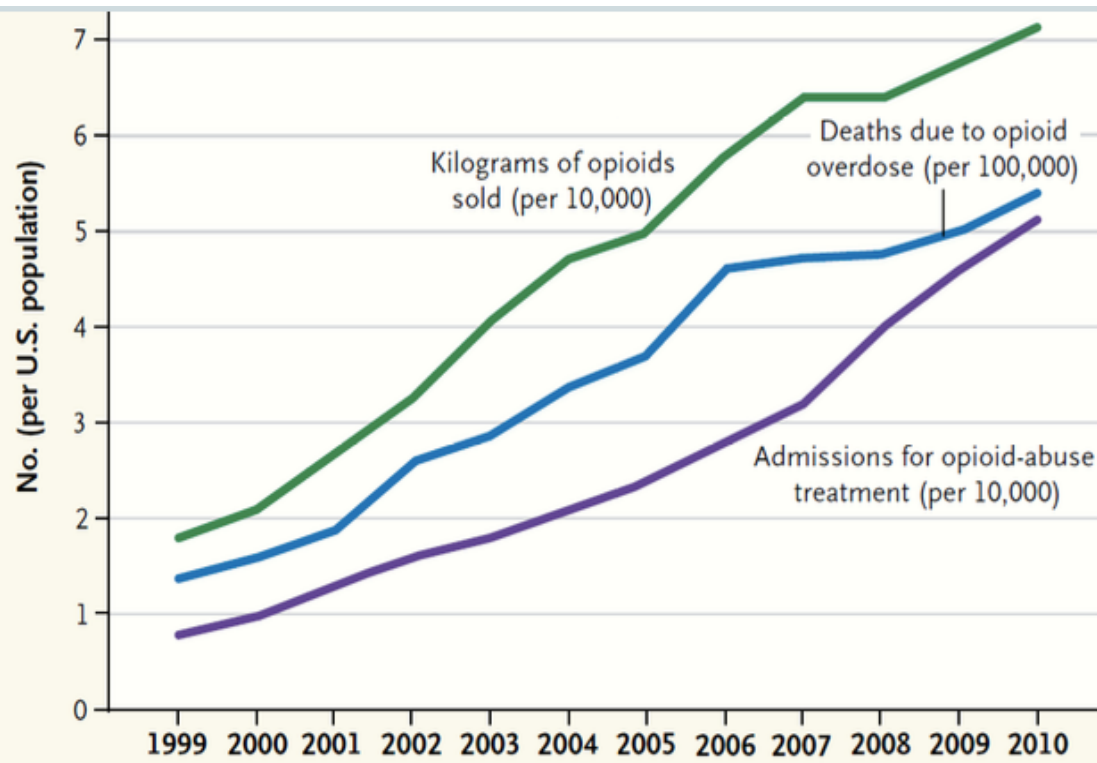
Weiss F, Advances in Neurosci Addiction 2010
Ciccocioppo, Neuropsychopharmacology, 2002
Sinha, Gen Psych, 2006
Goodwin, Compr Psychiatry, 2002



Medication-related Factors	Risk	
Daily dose >100 MME	overdose	addiction
Long-term opioid use (>3 mo)	overdose	addiction
ER/LA opioid formulation	overdose	
Combination opioids + benzodiazepines	overdose	
<2 weeks after starting ER/LA opioid	overdose	



Patient-related Factors	Risk	
Mental health disorder (e.g. depression, anxiety)	overdose	addiction
Substance use disorder (e.g., alcohol, nicotine, illicit)	overdose	addiction
Family history of substance use disorder		misuse
Adolescent		addiction
Age <45		misuse
Age >65	overdose	
Sleep-disordered breathing	overdose	
Legal history (e.g., DUI, incarceration)		misuse
History of sexual abuse		misuse
History of overdose	overdose	



In US, ~5-8 million on chronic opioid Rx for chronic pain

Volkow ND et al. *N Engl J Med.* 2014

Since 2010, there has been a decline in opioid prescriptions yet still remains >3 x higher than in 1999, and is nearly 4 x higher than in Europe

Guy GP et al. Vital Signs: Changes in Opioid Prescribing in the United States, 2006–2015. *MMWR* 2017

Universal Precautions

- **Misuse risk assessment and stratification**
 - ORT - Opioid Risk Tool
 - SOAPP - Screener and Opioid Assessment for Patients with Pain
- **Patient Provider Agreements (PPA)**
 - Informed consent (risks and benefits)
 - Plan of care including medication management
- **Monitor for benefit and risk**
 - Regular face-to-face visits
 - Reports from others
- **Monitor for adherence, addiction, diversion**
 - Urine drug testing
 - Pill counts
 - Prescription Drug Monitoring Program data

*

- APS/AAPM
- American Society of Interventional Pain Physicians
- American Academy of Neurology
- FSMB
- Canadian National Pain Centre
- CDC

Gourlay DL *Pain Med* 2005

Drug Testing

Objective information

- Evidence of therapeutic adherence
- Evidence of use or non-use of illicit drugs
- Discuss urine drug testing openly with patient
- One medical data point to integrate with others
- Urine drug **screens** are usually immunoassays
 - Quick and relatively inexpensive
 - Risk of false positives and negatives
- Unexpected findings can be verified with **definitive testing** using Gas Chromatography (GC) or Liquid Chromatography (LC) and Mass Spectroscopy (MS)

Identify a toxicologist/clinical pathologist for questions regarding unexpected results

Heit HA and Gourlay DL. *J Pain Symptom Manage.* 2004
Christo PJ et al. *Pain Physician.* 2011

PDMP CURES

- Statewide electronic database on dispensed controlled substance prescriptions
- Prescription data available to prescribers (*and delegates in some states*) and pharmacists
- >60% states mandate use before prescribing controlled substances
- Evidence that PDMP use can change prescriber and patient behaviors and initial evidence* that it may be associated with reductions in opioid-related death rates

www.pdmpexcellence.org/sites/all/pdfs/Brandeis_PDMP_Report.pdf

Haffajee RL, et al. *JAMA*. 2015

Haegerich TM et al. *Drug Alcohol Depend*. 2014

*Patrick SW et al. *Health Affairs*. 2016



IMPROVE
OPIOID
PRESCRIBING



PREVENT
OPIOID USE
DISORDER



TREAT OPIOID
USE DISORDER



REVERSE
OVERDOSE

Pharmacologic Therapies

FDA

- Varenicline
- Bupropion
- Nicotine-Replacement Therapy
- Acamprosate
- Disulfiram
- Naltrexone
- Buprenorphine
- Methadone



Symptom Targeted

- Clonidine
- Buspirone
- SSRI / SNRI /TCAs
- Muscle relaxants (not carisoprodol)
- Anticonvulsants (i.e., gabapentin, levetiracetam)
- Sedative Hypnotics (i.e., benzodiazepines & barbiturates)
- Antiemetics (i.e., ondansetron, promethazine)
- Antihistamines (i.e., hydroxyzine)
- Non-narcotic analgesics

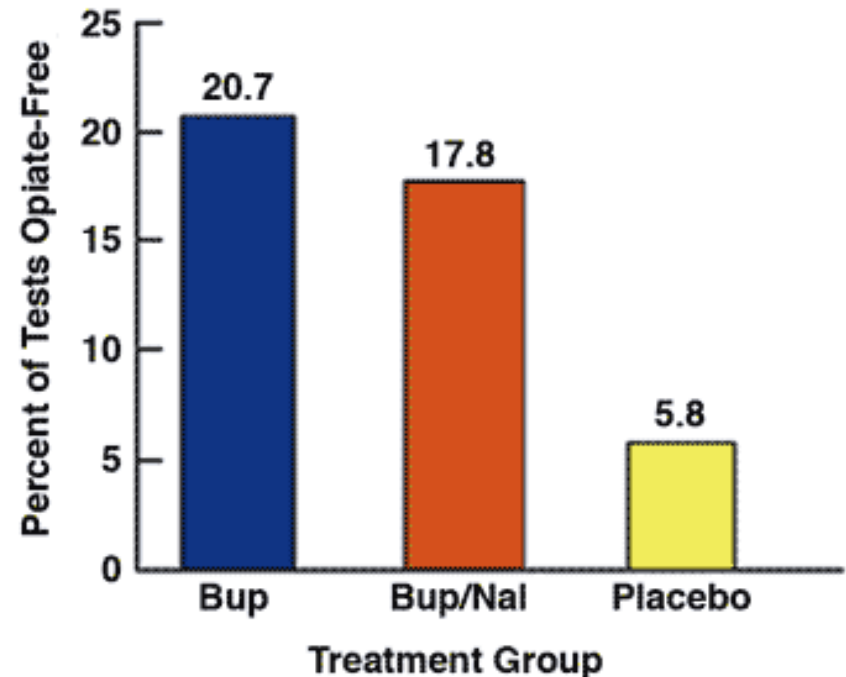
Methadone

- Full Agonist at mu opioid receptor
- Usually dispensed as liquid
- **Requires Opioid Treatment Program**
- May be euphorogenic
- Safety: No ceiling effect, complicated by QTc prolongation
- Long half-life
- Reduces variations in opioid levels
- Protects patient (and fetus) from withdrawal & improves obstetric outcomes
- Allows for anticipation of NAS
- Dose may change during pregnancy
- Barriers: daily dosing at center



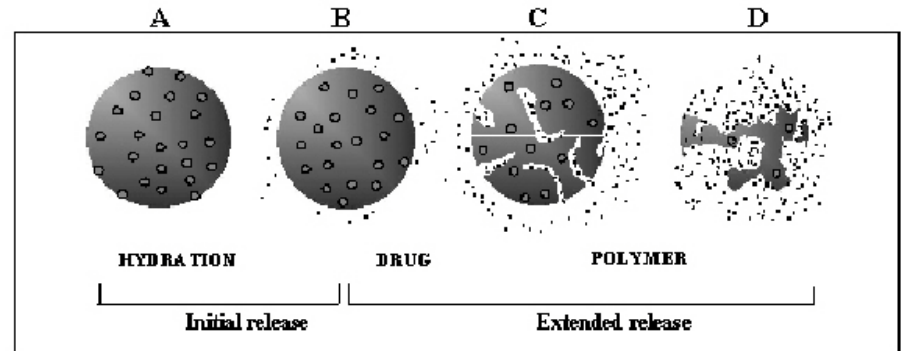
Buprenorphine

- Partial Agonist at mu receptor and antagonist at kappa receptor
- In pregnancy, use monotherapy
- Not significantly euphorogenic
- Safety: Ceiling effect on respiratory depression
- Long half-life
- When properly dosed, blocks other opioids (higher affinity)
- Protects mother & fetus from withdrawal
- Distinct on drug screening
- Higher risk of diversion
- Treatment setting can be in outpatient office: MD/DO, NP, PA with waiver
- Requires “INDUCTION”



Naltrexone

- Opioid antagonist
- Indication: Alcohol and/or Opioid dependence (Cravings management vs blockade)
- Available in oral (daily) and injectable form (Long-Acting, dosed monthly)
- Injectable form expensive but associated with improved compliance
- Low side-effect profile
- Easy to use in Alcohol Dependence
- Can be difficult to use in Opioid Dependence due to precipitated withdrawal risk
- Treatment results in reduced opioid tolerance and **increased** risk of opioid overdose on relapse once blockade wears off



Basic Formulation Components

- Drug
- Polymer
- Released naltrexone

Variables Modulating Release

- Drug load, dissolution
- Polymer chemistry, degradation
- Microsphere porosity, size

Dean, R. The Preclinical Development of Medisorb Naltrexone, a once a month long-acting injection, for the treatment of alcohol dependence. *Frontiers in Bioscience* 10, 643-655, January 1, 2005.

Naloxone





Thank You

Mario San Bartolome, MD, MBA, MRO, FASAM
Medical Director, Substance Use Disorders

Mario.SanBartolome@MolinaHealthcare.com