The Neuroscience of Stimulant Use Disorders

Shannon Robinson, MD
Fellow American Society of Addiction Medicine

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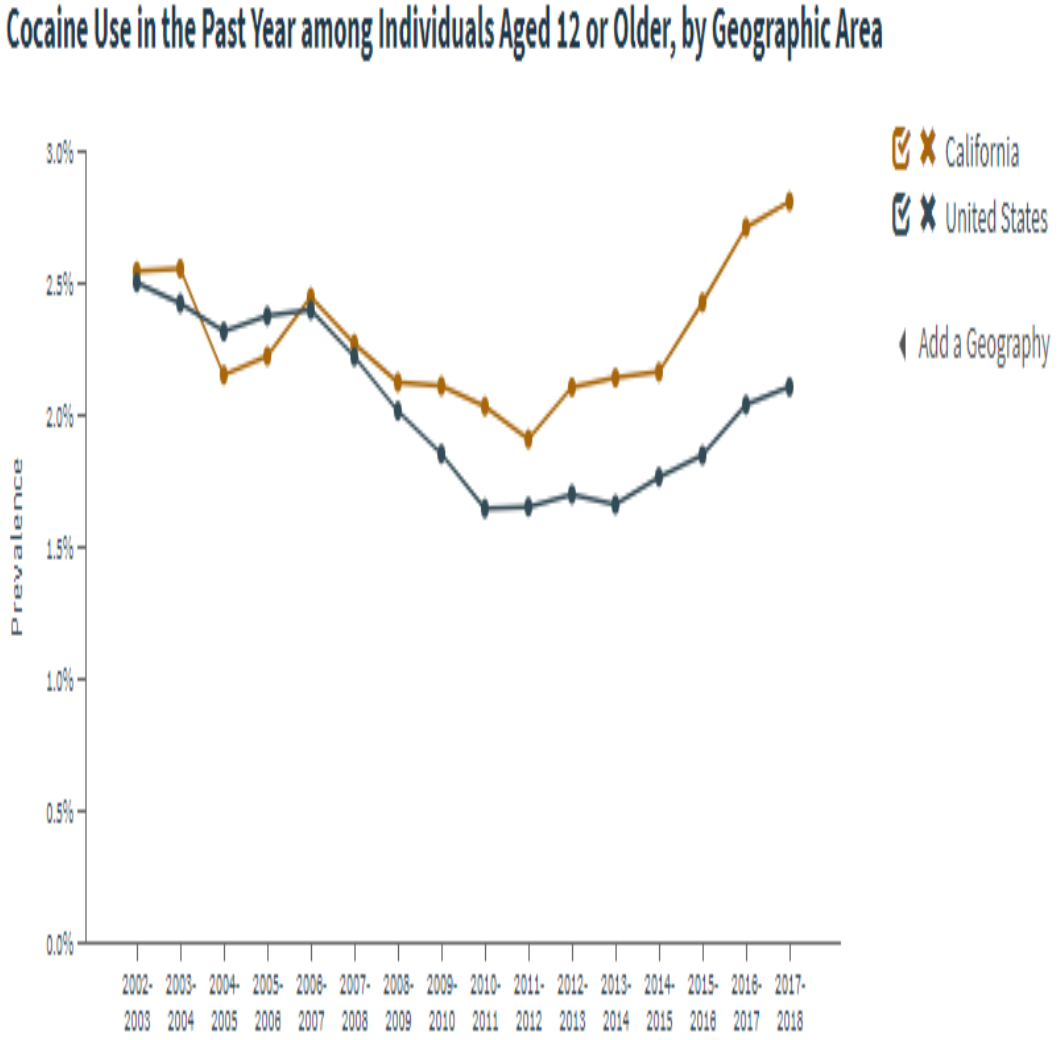
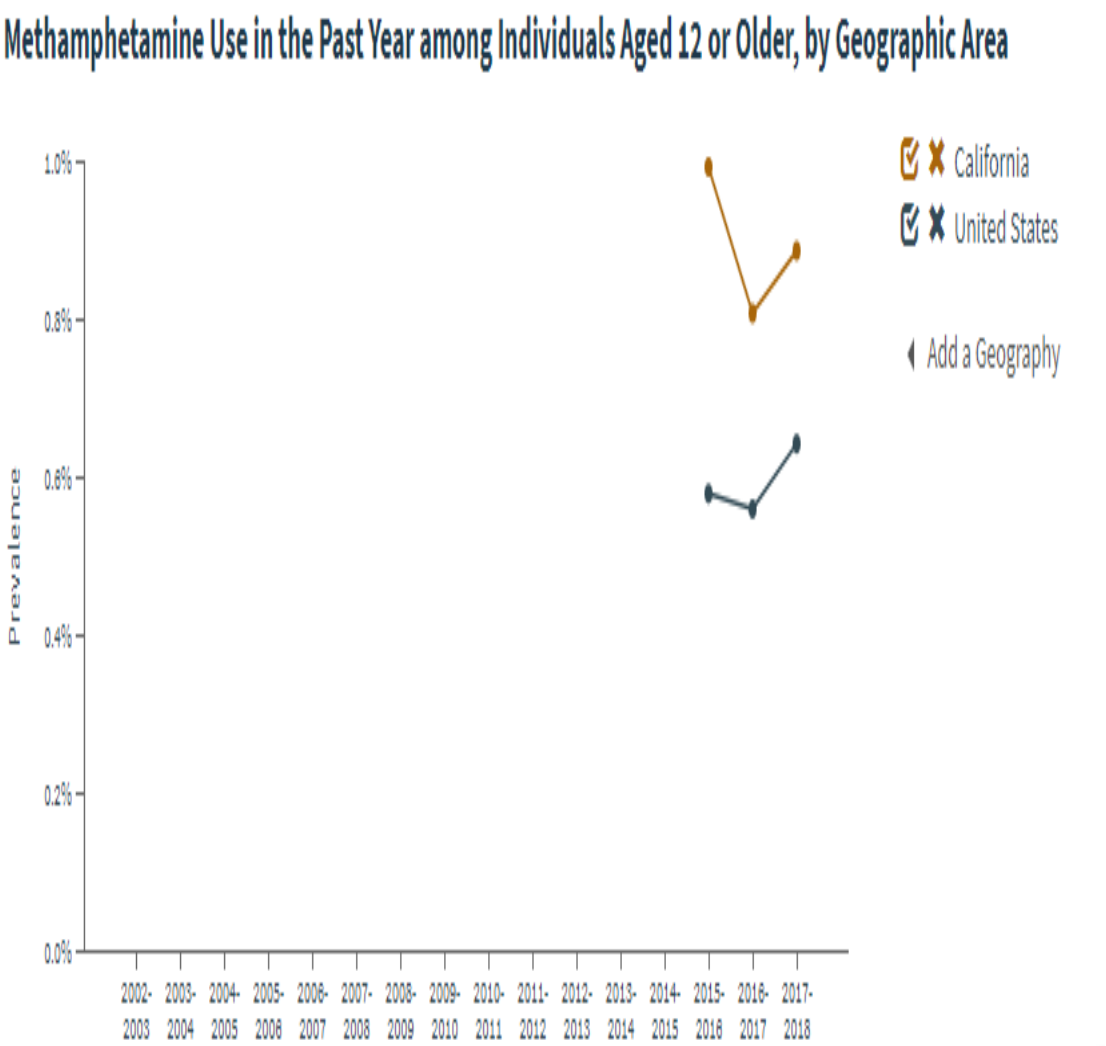
AGENDA

- Types of stimulants
- Effect of stimulants on brain chemistry
- Implications of stimulant on healthcare and criminal justice
- Metabolism of stimulants
- Treatment of Stimulant Use Disorder
  - Psychopharmacology
  - Psychosocial overview

STIMULANT USE CONTINUES TO RISE NATIONALLY & LOCALLY





Source: https://pdas.samhsa.gov/saes/state

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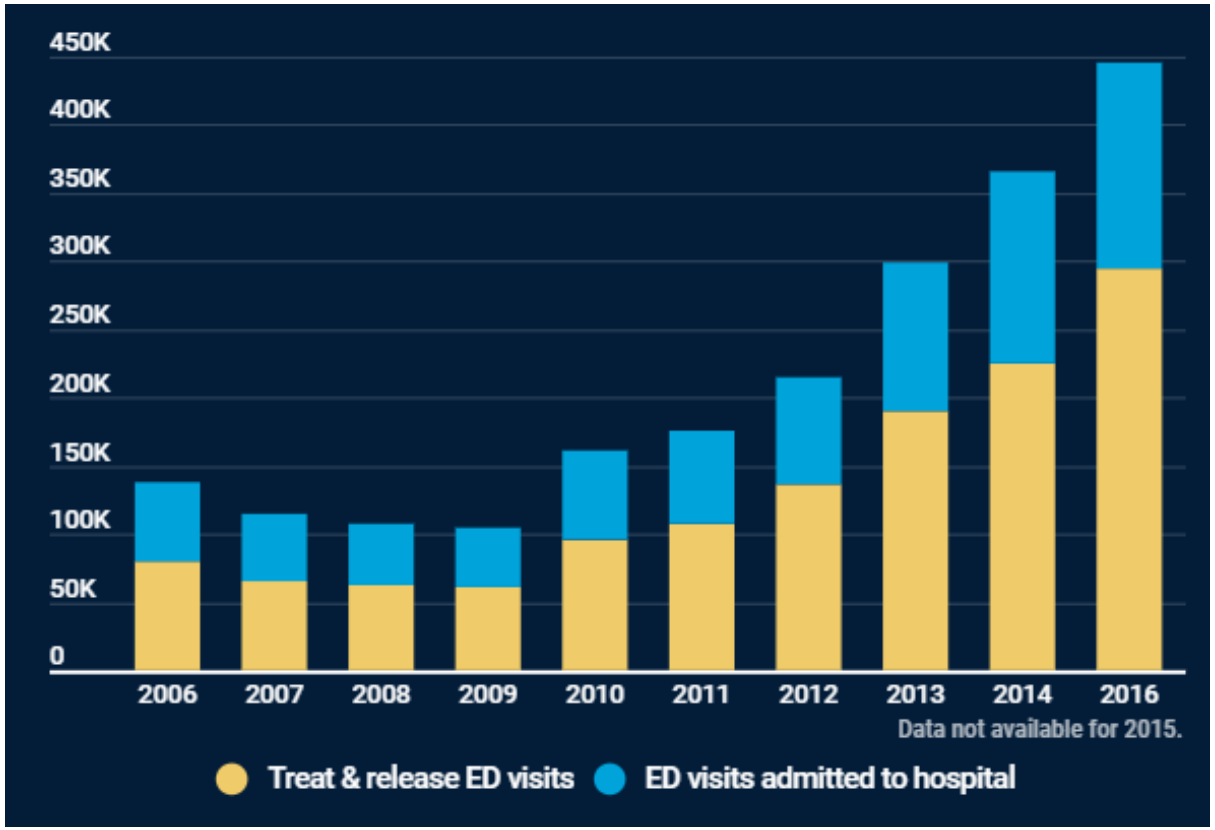
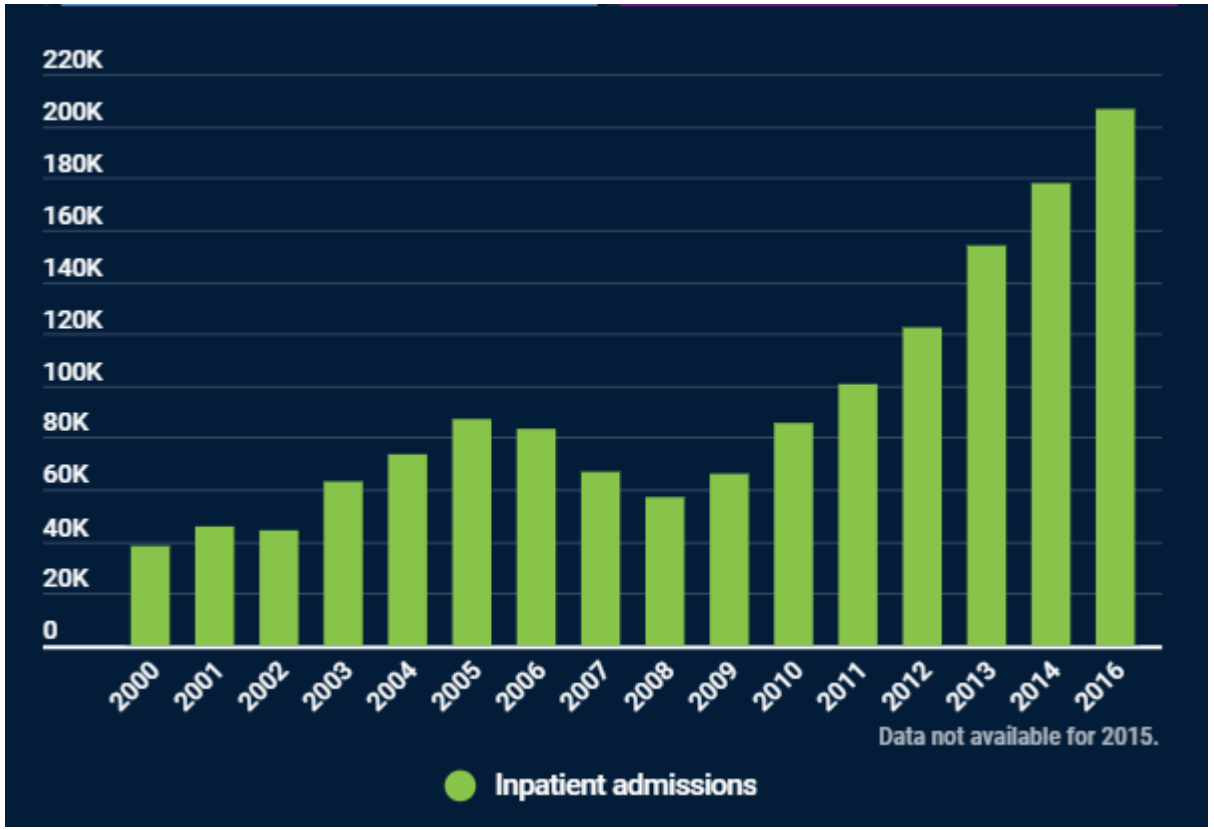
IMPORTANCE: CORRESPONDING TO INCREASE IN METHAMPHETAMINE USE IS INCREASE AN EMERGENCY VISITS & HOSPITALIZATIONS

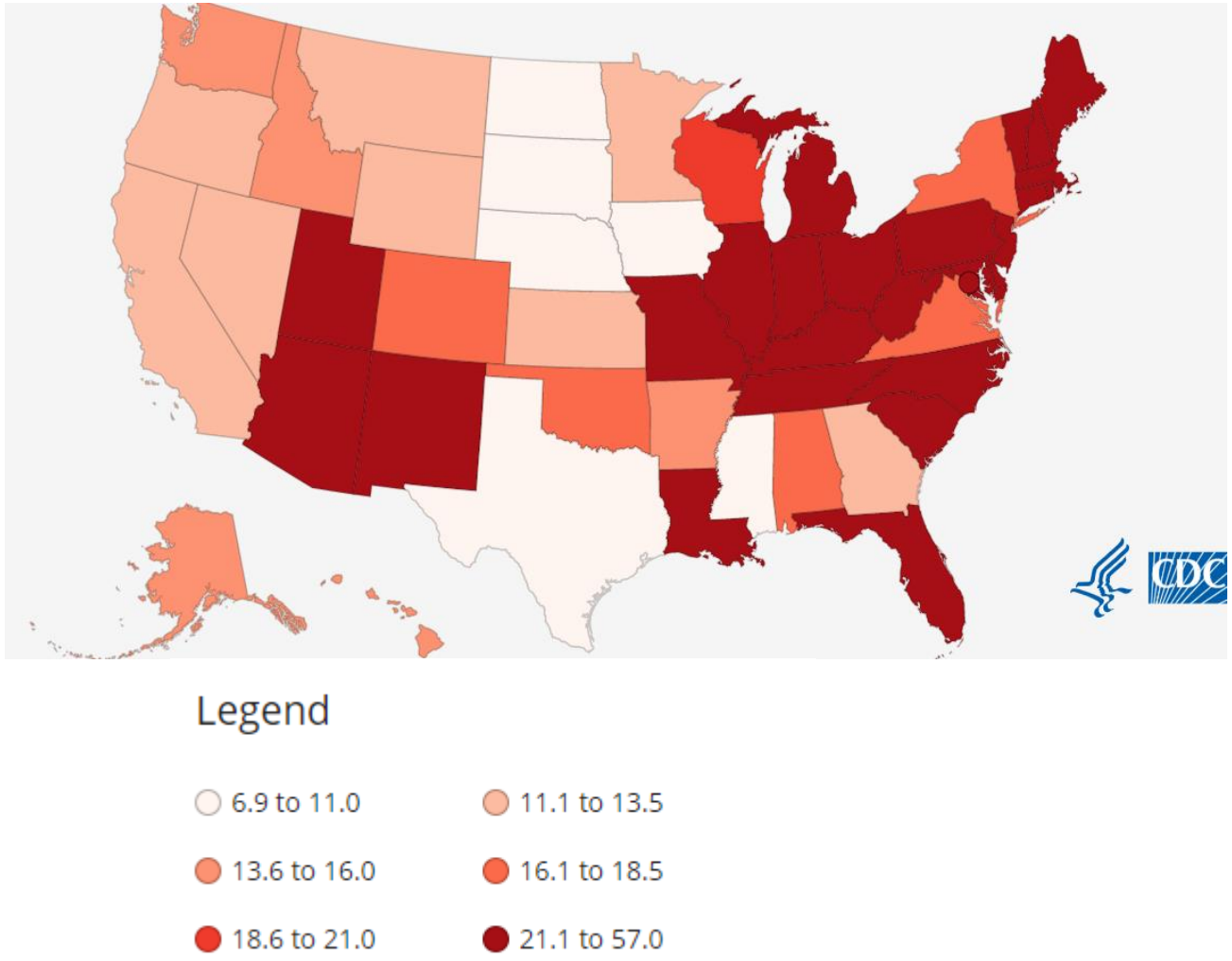




Source: https://www.nihcm.org/categories/beyond-opioids-rapid-increase-in-drug-deaths-involving-stimulants

IMPORTANCE: OVERDOSE DEATHS NATIONALLY AND LOCALLY

Overdose deaths



2018:

Age adjusted OD death rate

Nationally 21/100,000

California 13/100,000

West Virginia 52/ 100,000 (highest rate)

South Dakota 6.9/100,000 (lowest rate)

Number of ODs

Nationally 67,367 ODs

California 5,348 ODs (highest #)

Florida 4,698 ODs (second highest #)

Opioid involved ODs

Nationally 70%

California 45%

Cocaine involved OD death rate

Nationally 4.5

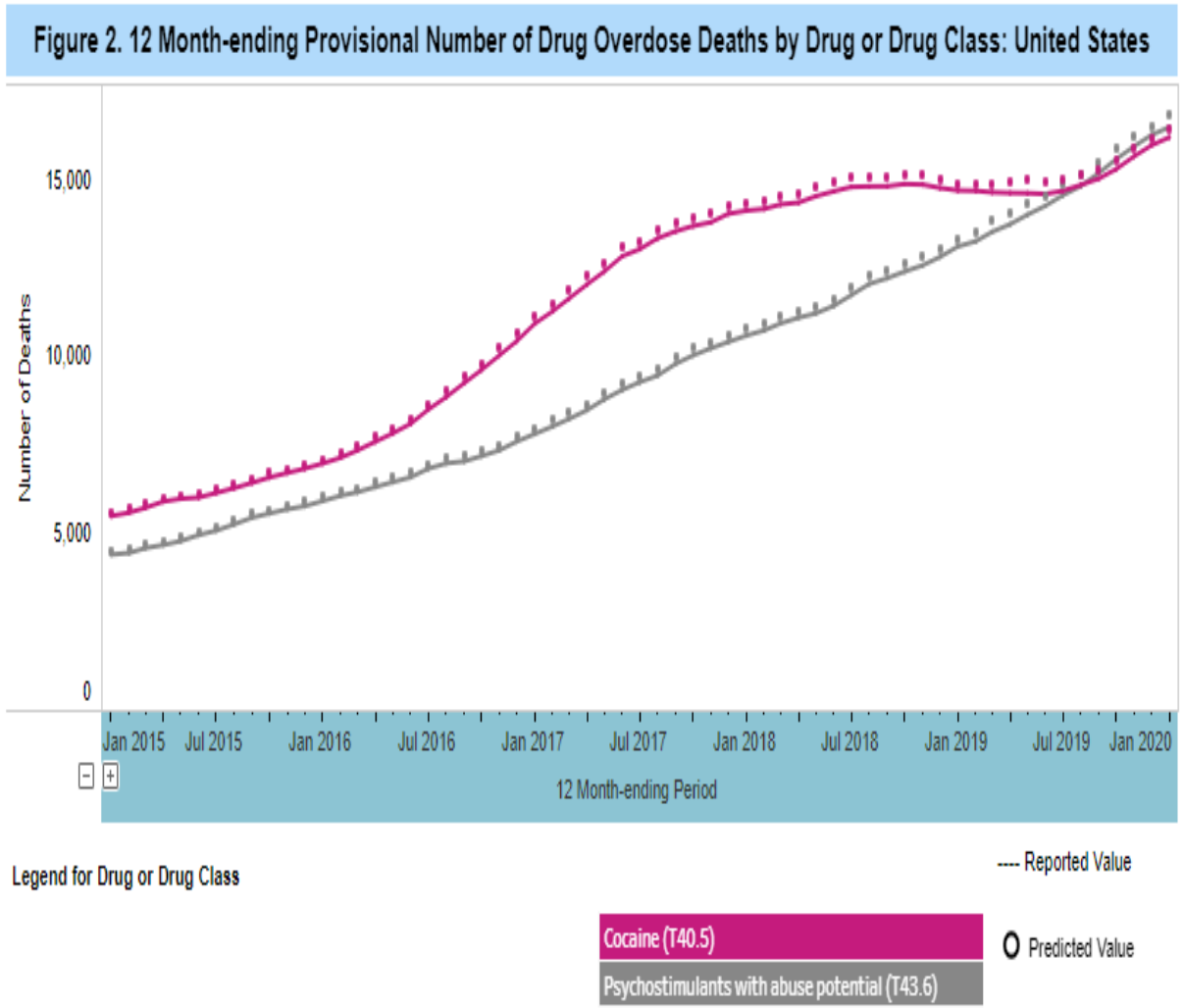
California 1.9

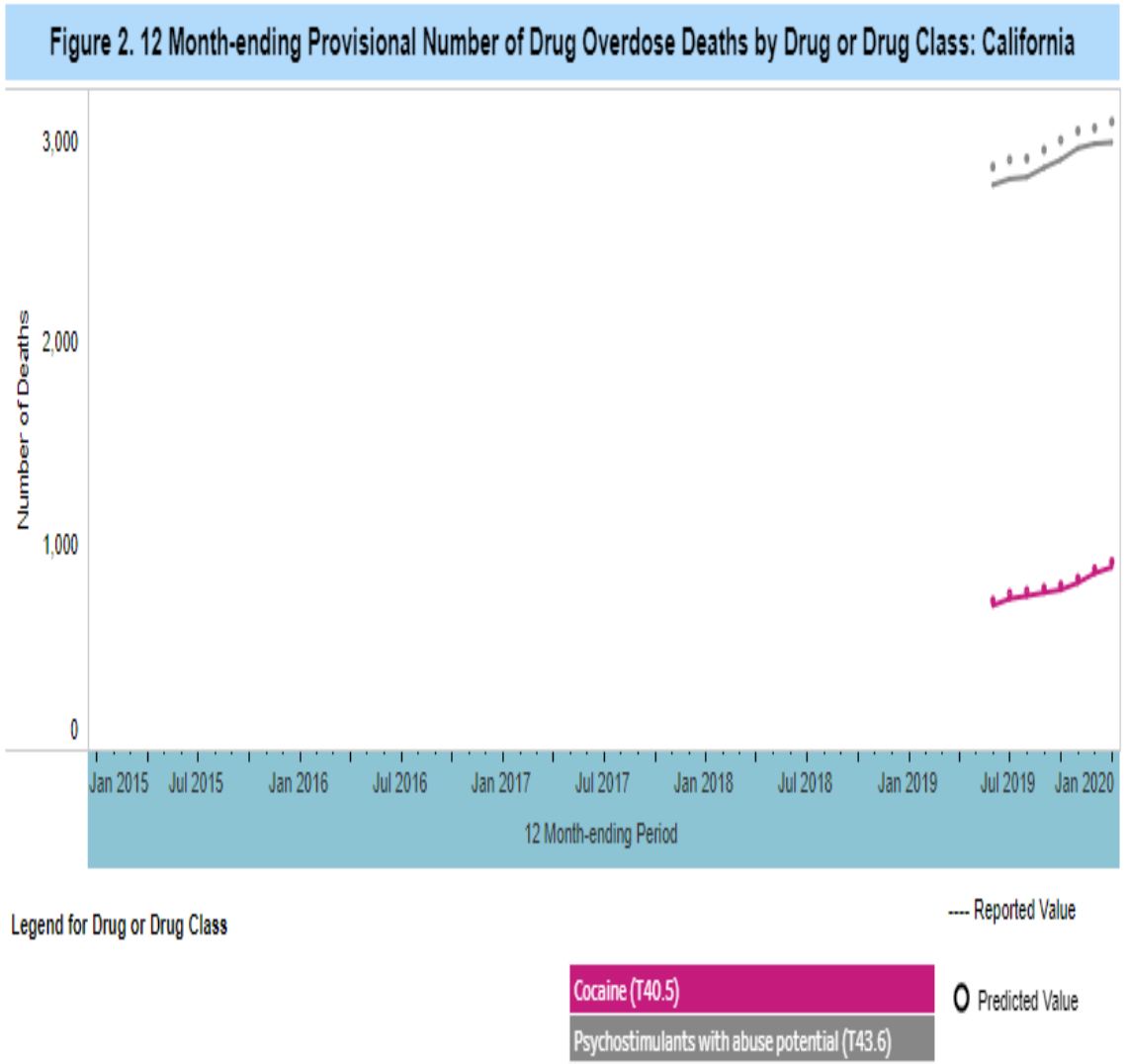
Psychostimulants involved OD death rate

Nationally 3.9

California 6.6

STIMULANT OVERDOSE DEATHS CONTINUE TO RISE NATIONALLY & LOCALLY





Source: https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm#dashboard

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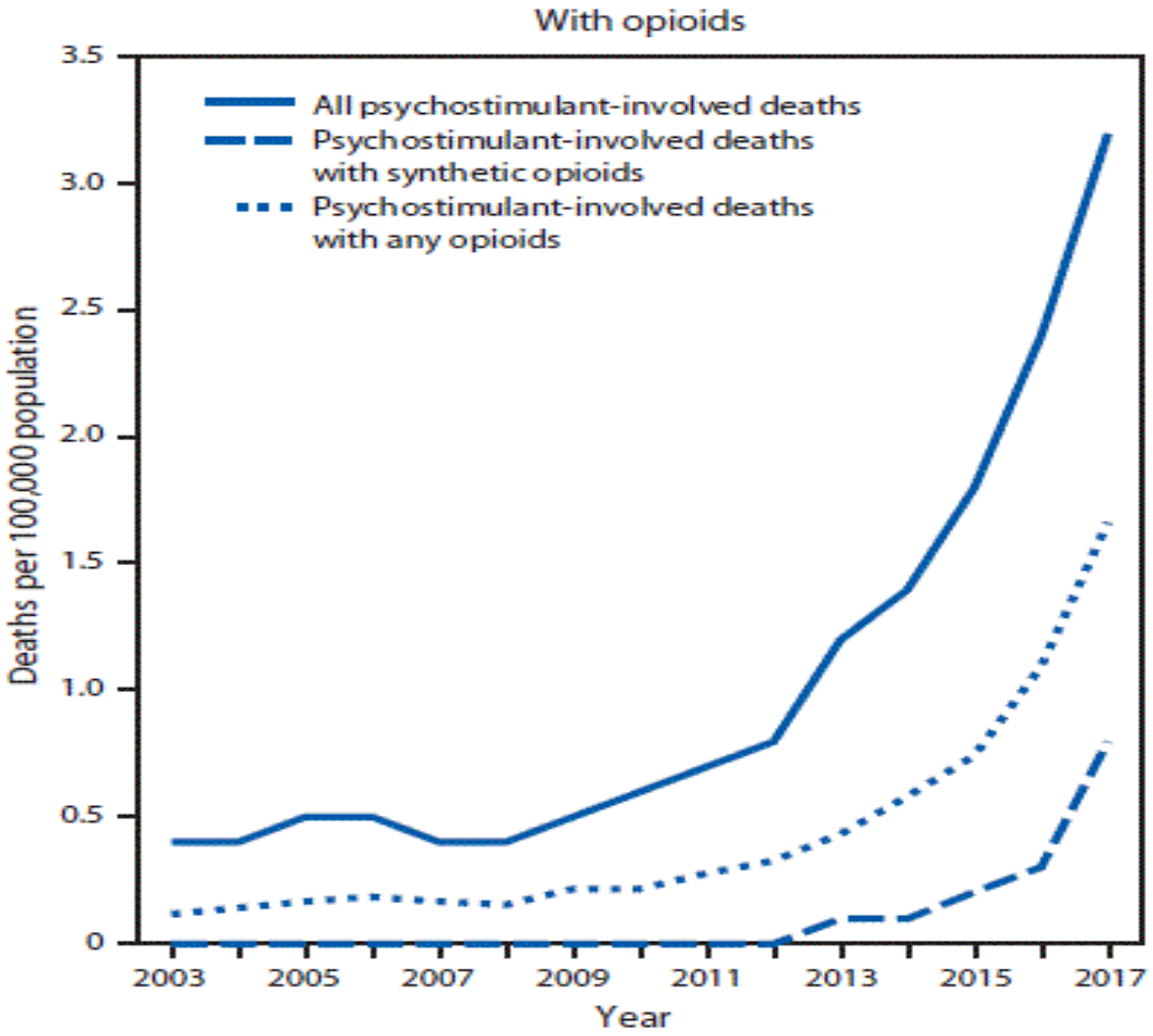
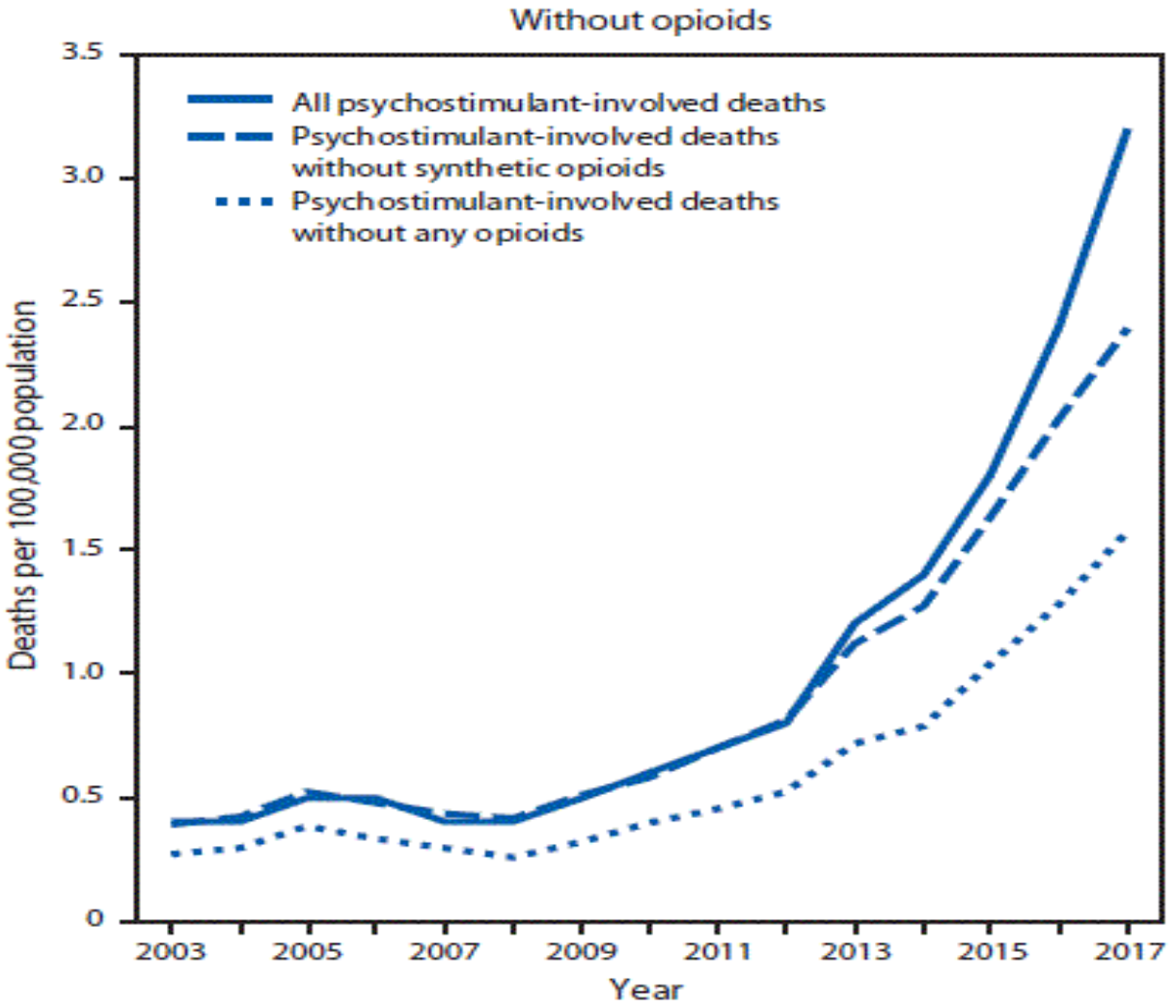
AGE ADJUSTED STIMULANT OD RATES 2003-2017 UNITED STATES WITH AND WITHOUT OPIOIDS





Source: National Vital Statistics System, Mortality File. https://wonder.cdc.gov/.

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IMPORTANCE: ETHNICITY DATA

+ 2019 California OD rate/ 100,000

Race/ Ethnicity	Psychostimulants	Cocaine
Native American	19.8	3.0
African American	11.8	9.2
Caucasian	9.6	2.1
Hispanic	4.8	1.2
Asian/ Pacific Islander	1.6	.5
California	6.6	1.9

+ Demographic data should influence education efforts

WHAT ARE STIMULANTS?

- Cocaine
- "Psychostimulants with abuse potential"
  - Pseudoephedrine, ephedrine & cathinone & cathine
  - Amphetamine
    - Methamphetamine (dextro & levo)
    - MDMA/ecstasy = Molly = methylenedioxy-methamphetamine
    - Dextroamphetamine/ Levoamphetamine
    - Methylphenidate = Ritalin
  - Methylxanthines
    - Caffeine (coffee)
    - Theophyline (tea)
    - Theobromide (chocolate)


Coca plant

Powder cocaine/ methamphetamines


Free Base Cocaine


Ephedra


Khat

Bath Salts


Bath Salts


Bath Salts


Mahuang

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WHAT ARE STIMULANTS MEDICINALLY USED FOR?

- Cocaine- used as a vasoconstrictor and numbing agent
- "Psychostimulants with abuse potential"
  - Ephedra- made into pseudoephedrine and used for allergies and colds
  - Khat used for depression, obesity, fatigue
  - Amphetamines are used for obesity, narcolepsy and ADHD
  - Methylxanthines
    - Caffeine (coffee)
    - Theophyline (tea) used for asthma
    - Theobromide (chocolate)

Every class of stimulants has medicinal uses, but not every stimulant has medicinal uses

Not Used Medically in US:
Cathinone
Cathine

SOME CONSEQUENCES ARE DEPENDENT UPON MODE OF CONSUMPTION

- Smoking
  - Burned lips
  - Throat problems
  - Lung problems- acute (50% of those who smoke cocaine) and chronic
- Injection
  - Skin & heart infections
  - Hepatitis or HIV
- Snorting
  - Sinus infections
  - Holes in nasal septum
  - Nosebleeds
  - Hoarseness

Among those who consume drugs by smoking:

- **1 of 6 users will become dependent on cocaine**
- **1 of 9 users will become dependent on amphetamines**

NOTE:
There is cross tolerance from one class of stimulants to another

EFFECTS ARE DEPENDENT UPON MODE OF CONSUMPTION, HALF LIFE AND DOSE

Onset of Action

- Smoking- drug reaches brain within seconds
- Injection- drugs reaches brain within 5 minutes
- Snorting- drugs reaches brain within 15 minutes
- Oral-drugs reaches brain within 45 minutes

Half Life

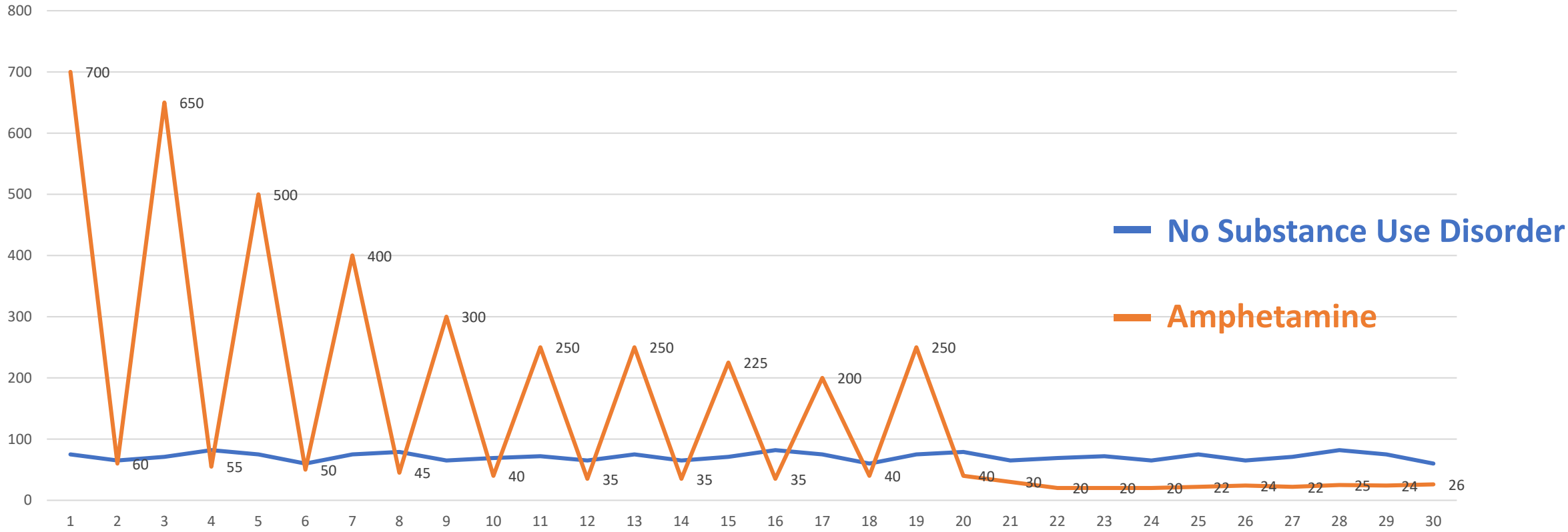
- Cocaine roughly 1h
- Bath Salts roughly 3 hours
- Amphetamine roughly 7 hours
- Methamphetamines roughly 12 hours

<u>Amphetamine:</u>
ADHD 2.5 mg/day to 70mg/ day.
Narcolepsy 5 mg/day to 60 mg/day.
Illicit use of amphetamines can be up to 1 g per DAY.

<u>Methamphetamine:</u>
ADHD approved but not commonly used.
5 mg/day to 25 mg/ day.

NEUROBIOLOGY OF ADDICTION

https://www.youtube.com/watch?v=bwZcPwlRRcc&feature=youtube



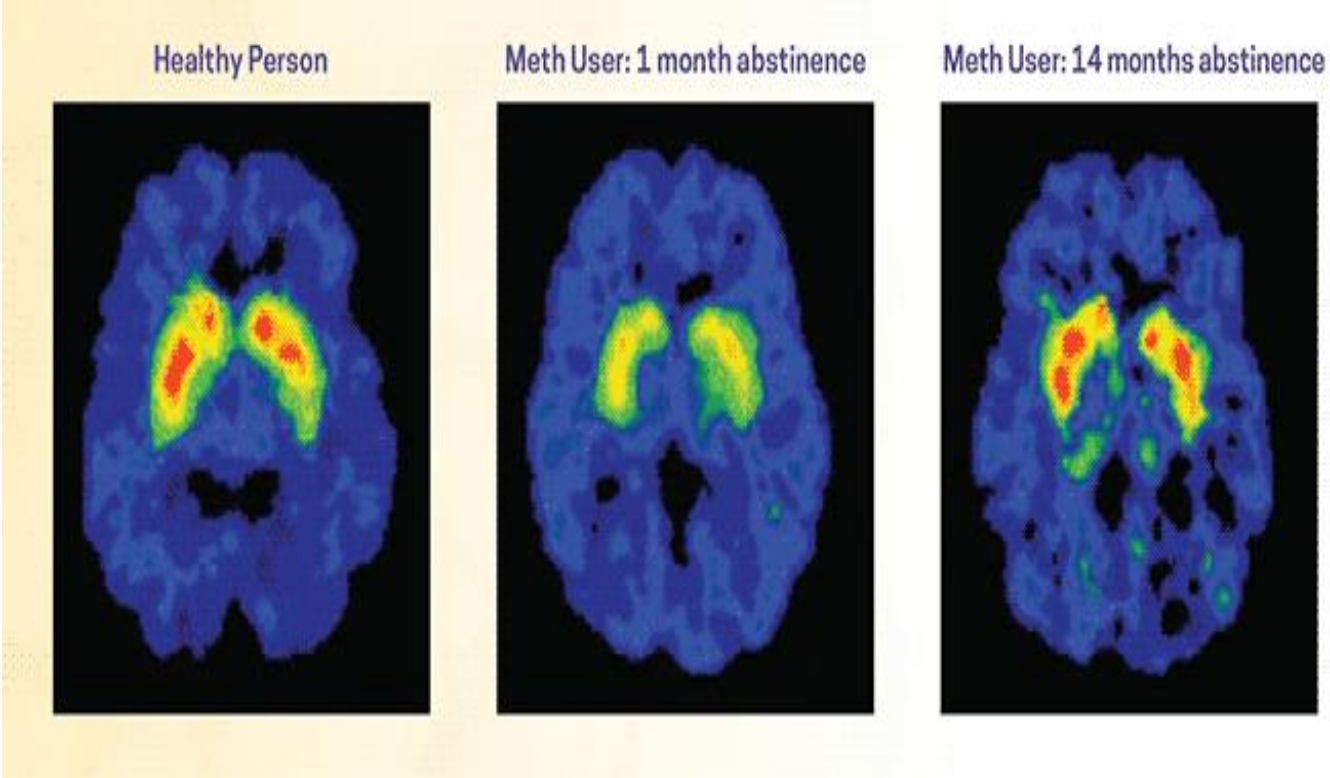
Dopamine levels vs. Episodes of amphetamine use

Source: Volkow (2015) Cell, 162 (4), 712-25.

Please note this an HMA proprietary slide.

NEUROBIOLOGY OF ADDICTION RECOVERY TAKES TIME

- Prolonged drug use changes the brain in long lasting ways
- Changes are both functional and structural
- Return to normal takes over 1 year



These images showing the density of dopamine transporters in the brain illustrate the brain's remarkable ability to recover, at least in part, after a long abstinence from drugs—in this case, methamphetamine. [51]

Source: The Journal of Neuroscience, 21(23):9414-9418. 2001

- Monoamines include
  - Dopamine- reward and motivation system
  - Norepinephrine- fight or flight
  - Serotonin- mood, cognition

Receptor Affinity	Dopamine	Norepinephrine	Serotonin
Cocaine	High	High	Moderate
Amphetamine	High	High	Low

EFFECT OF STIMULANTS ON BRAIN CHEMISTRY

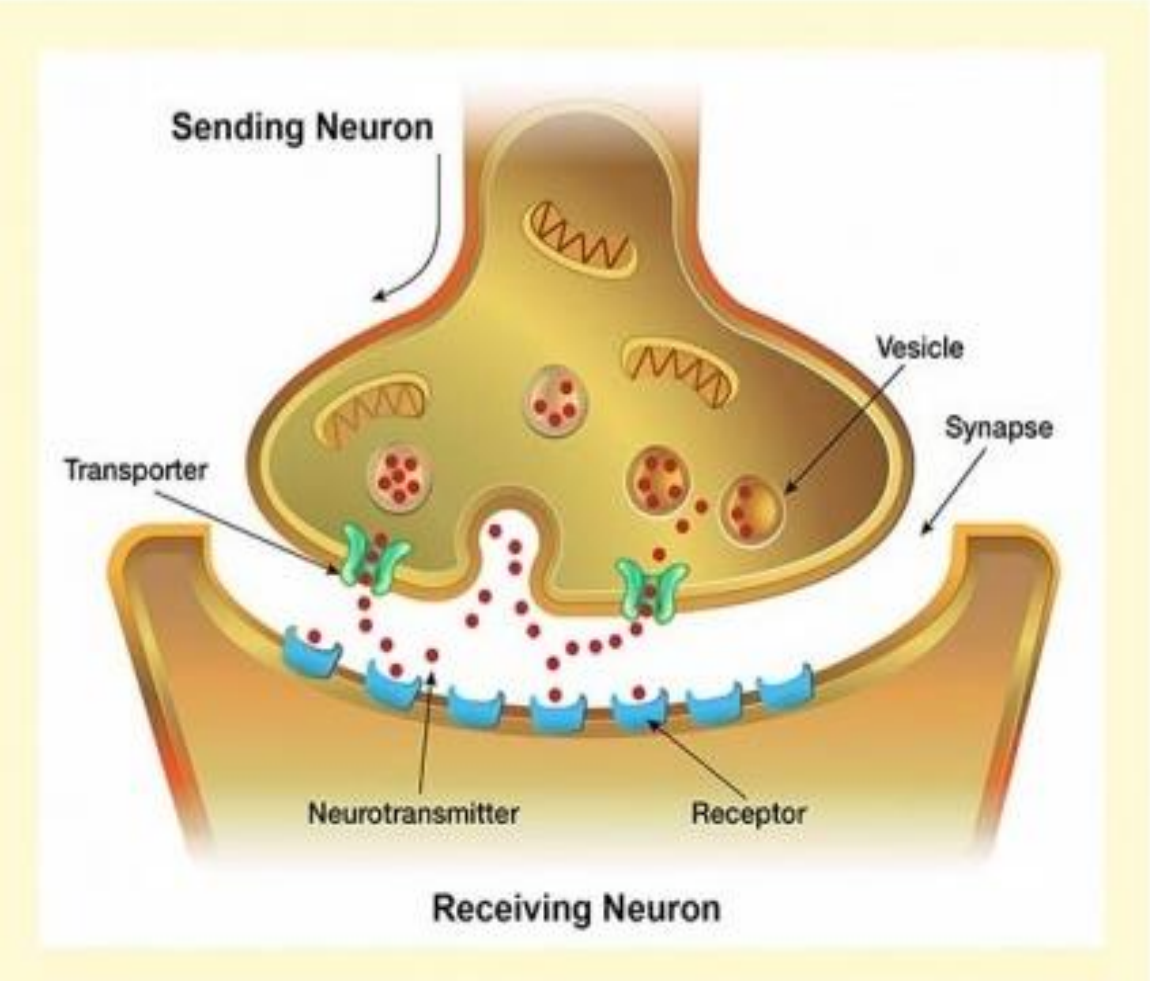
Cocaine
Reuptake Blocker

INDIRECT agonist of

- dopamine
- norepinephrine
- serotonin

BLOCKS

- monoamine reuptake
- sodium channels



Amphetamines
Releaser

INDIRECT agonist of

- dopamine
- norepinephrine
- serotonin

INHIBITS

- metabolism of monoamines
- vesicular storage

REVERSES reuptake

Photo Source: https://www.drugabuse.gov/news-events/nida-notes/2017/03/impacts-drugs-neurotransmission

ACUTE EFFECTS OF STIMULANT INTOXICATION IS RELATED TO DOPAMINE, NOREPINEPHRINE & SEROTONIN

- Increased
  - alertness/ vigilance, concentration, mental acuity
  - energy, locomotion
  - sensory awareness & sexual desire
  - self confidence, grandiosity, anxiety, irritability, paranoia
  - heart rate & blood pressure, irregular heartbeat, vasoconstriction
  - breathing rate, temperature, pupil size & blood sugar
  - electrical activity, seizures
- Euphoria
- Toxic effects on muscles
- Abnormal movements
  - Dystonia, tremors, streotypy
- Decreased
  - brain blood flow & glucose metabolism
  - appetite & sleep
  - judgment & complex multi-tasking
  - defecation and urination

EFFECTS OF STIMULANT INTOXICATION IS RELATED TO DOPAMINE, NOREPINEPHRINE & SEROTONIN

Amphetamines & Violence:

+ Review of 28 studies
+ Amphetamine use compared to no amphetamine use
+ 2-fold increase in violence
+ Risk of violence associated with
    + Frequent use
    + Psychotic symptoms
    + Psychosocial problems
    + Impulsivity
    + Other drug or alcohol use

Source: Foulds et al. 2020

Treatment of Intoxication:

+ Talk down the client in a calm environment
+ Treat agitation with benzodiazepines

Importance for public safety officers:

- Severe agitation may require injections
- Restraints can be counter productive
    - people will fight against the
    - increasing damage to muscles
    - further increasing temperature
- There are no reversal agents

EFFECTS OF STIMULANT INTOXICATION IS RELATED TO DOPAMINE, NOREPINEPHRINE & SEROTONIN

Overdose:

+ Hypertensive (HTN) crisis
+ Cardiac arrythmia
+ Myocardial infarction (MI)
+ Cerebrovascular Accident (CVA)
+ Psychosis

Treatment of Overdose

+ Treat HTN with alpha and/ or beta blockers
+ Treat arrythmias with anti-arrhythmics
+ Treat vasoconstriction with nitroglycerin
+ Treat psychosis with antipsychotics

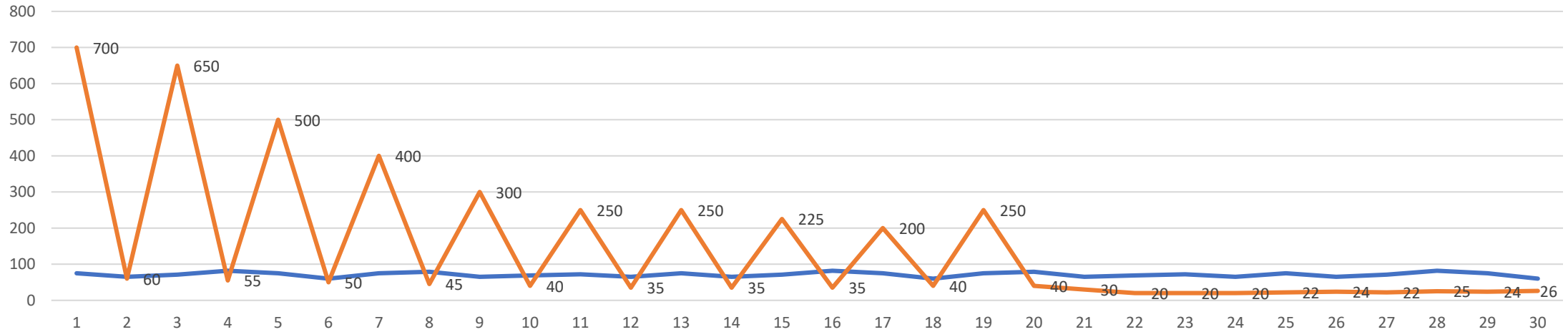
EFFECTS OF STIMULANT INTOXICATION IS RELATED TO DOPAMINE, NOREPINEPHRINE & SEROTONIN

Symptoms Preceding Death

+ Collapse
+ Breathing difficulty
+ Hyperthermia
+ Chest pain
+ Palpitations
+ Cough
+ Coughing up blood

LONG TERM PSYCHOLOGICAL EFFECTS OF CONTINUAL USE OF ILLICIT STIMULANTS

+ Tolerance to euphoria and appetite suppression
+ Loss of ability to concentrate & severe memory loss*
+ Loss of ability to feel pleasure without drug



+ Paranoia and psychosis (hallucinations & delusions)
+ Insomnia and fatigue
+ Irritable and angry
+ Depression (suicidal ideation)
+ Impulsive, reckless sexual behavior

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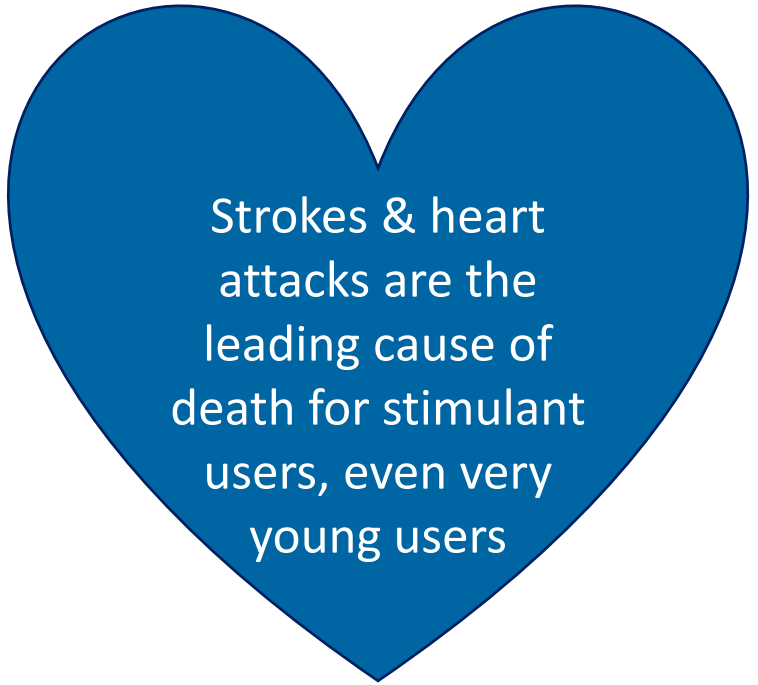
LONG TERM PHYSICAL EFFECTS OF CONTINUAL USE OF STIMULANTS

+ Dry mouth, severe dental decay & gum problems
+ Bruxism
+ Weight loss
+ Increased sweating; oily skin
+ Skin lesions from injection & formication (leading to skin picking)
+ Headaches
+ Seizures
+ Strokes (hemorrhagic) & heart attacks
+ Irregular heart beats
+ Cardiomyopathy
+ Kidney & liver failure
+ Pulmonary hypertension
+ Damaged brain cells
+ Neonatal effects



STIMULANTS AND PREGNANCY

+ Maternal death- pregnancy may increase risk of cardiovascular events
+ Preterm labor
+ Earlier gestational age at delivery
+ Low birth rate
+ Small for gestational age
+ Strokes in utero
+ Secreted in breast milk

Child:
Dysregulated behavior, growth, inhibitory control, attention and abstract reasoning, but these effects appear to be related to gestational age at delivery, psychiatric disorders, other prenatal exposures and quality of postnatal environment. *
Anxiety, depression at 3y**
Worse cognitive function at 7 y**

Source: Gouin 2011- cocaine; Kalaitzopoulos, 2018
*Smid, M. C., Metz, T. D., & Gordon, A. J. (2019). Stimulant Use in Pregnancy: An Under-recognized Epidemic Among Pregnant Women. *Clinical obstetrics and gynecology*, *62*(1), 168–184. https://doi.org/10.1097/GRF.0000000000000418
**Deruf et al. 2007

CESSATION FROM STIMULANTS

- Acute withdrawal: 4 days (no medication intervention recommended)
  - Increased appetite
  - Increased sleep & dreaming
  - Decreased activity & energy
  - Depression & anhedonia
  - Decreased concentration
  - Craving
- Protracted withdrawal up to 10 weeks
- Lingering effects on the brain; may be permanent
  - Psychosis
  - Movement Disorders

AMPHETAMINES CAUSE OXIDATIVE STRESS, NEUROTOXICITY & NEURO INFLAMMATION

- 2/3 of people with amphetamine use disorder have cognitive impairment
- Impairment is associated with
  - Older age
  - Earlier onset of use
  - Longer duration of use
  - Greater frequency of use
- May limit ability to follow through on treatment

Source: Paulus, M (2020) Neurobiology, clinical presentation, and treatment of methamphetamine use disorder a review. JAMA Psychiatry 77(9): 959-66.

AMPHETAMINE LINGERING EFFECTS ON THE BRAIN

- May be permanent even with prolonged abstinence
  - Attention
  - Memory
  - Learning efficiency
  - Visual- spatial processing
  - Processing speed
  - Psychomotor speed
  - Executive dysfunction

- Damage cell structures
  - Mitochondria in neurons & microglia
- Damage DNA
  - Chromosomal alterations
- Inflammation of microglia
- Disruption of blood brain barrier
  - Inflammatory markers in peripheral blood
- Cell death

STIMULANT METABOLISM

- Cocaine ----> norcocaine, ecgonine methyl ester, benzoylecgonine (compound detected in toxicology)
- Cocaine plus alcohol
  - Alcohol inhibits metabolism of cocaine
  - The 2 react and form cocaethylene
    - Also a stimulant
    - 4x the half life
    - Greater cardiac toxicity than cocaine without alcohol
    - Associated with seizures, liver damage, compromised immune system

METHAMPHETAMINE METABOLISM

Amphetamine-Type Stimulants	LOQ (ng/mL)	Detection Time* up to
Amphetamine	25	3 days
Methamphetamine	25	3 days
3,4-Methylenedioxyamphetamine (MDA)	25	2 days
3,4-Methylenedioxymethamphetamine (MDMA)	25	2 days
Phentermine	25	
Ephedrine/pseudoephedrine	25	5 days

+ Selegiline ----> methamphetamine (Vick's inhaler) ----> amphetamine ----> norephedrine…
+ Cathinone ----> norephedrine
+ MDMA ----> MDA
+ Captogen ----> amphetamine and theophylline
+ Pseudoephedrine ----> norpseudoephedrine*
+ Ephedrine ----> phenylpropane*
+ Phentermine ----> hydroxyphentermine

  ----> nitrophentermine

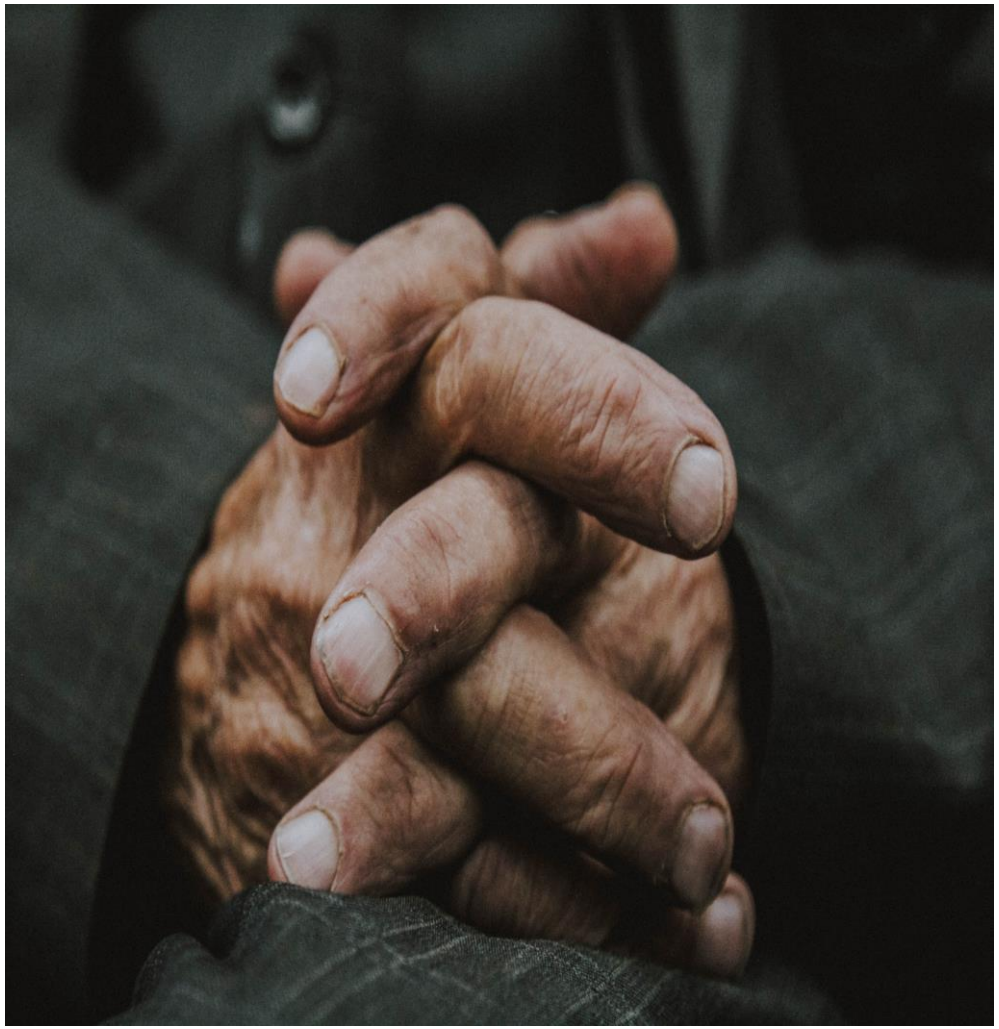
+ Bupropion ----> hydroxybupropion

** pseudoephedrine & ephedrine can be made into methamphetamine in a lab, but this doesn't occur naturally*

DIFFERENTIATING AMPHETAMINES ON CONFIRMATORY TOXICOLOGY

- L and D methamphetamine & amphetamine
  - L isomer (enantiomer)
    - Vicks
    - Preparation H
    - Selegiline
  - D isomer
    - Prescription stimulants
  - Mixture
    - Illegally manufactured stimulants (mostly L)
- Mirror images but not superimposable

Photo source: Unsplash



TREATMENT OF STIMULANT USE DISORDER

- Harm Reduction needed due to IV use & risk of fentanyl contamination
  - Educational materials on psychological & physical effects
  - Fentanyl test strips
  - Syringe Exchange & other clean injection supplies
  - Naloxone and overdose prevention education
  - Quiet rooms to come down
  - Showers & antibiotics for infection prevention & treatment
  - Safe sex practices & condoms
  - Water for hydration
  - Tooth paste and toothbrush
- Increased risks with COVID and Stimulant Use Disorder
  - Harm reduction sites closed
  - Fewer treatment slots
  - Treatment delivery may not be of the same intensity or quality
  - Social distancing prevents rescues
  - Increased risk of serious infection due to lung damage associated with use

Medications have not been found to be consistently effective;
Vaccine trials and other pharmacotherapy trials are underway

- Replacement therapies: cocaine vs amphetamines
- Antidepressants: SSRIs and tricyclic antidepressants not effective
  - Bupropion- risk of seizures; 5 failed trials for amphetamine use disorder
  - Mirtazapine- risk of weight gain; single small study + for amphetamine use disorder in MSM
- Treatment of co-occurring SUD
  - Opioid agonists- increased dose of buprenorphine or methadone shows decreased cocaine use generally
- Naltrexone- + results in multiple small studies amphetamine use disorder and cocaine use disorder
- Antiseizure medications- Topiramate (risks)- + one of two small studies amphetamine use disorder

There are NO FDA approved medications for stimulant use disorders.
Best Practices and Standards of Care do NOT endorse medication for stimulant disorders at this time.

- Motivational Interviewing (MI)
  - Decreased days of stimulant use & amount of stimulant used/ day
- Cognitive Behavior Therapy (CBT)
  - Decreased quantity of stimulant use & frequency/ week
  - Decreased risky sexual behaviors
- Community Reinforcement Approach- see next slide
- Contingency Management- see next slide

STRONG EVIDENCE FOR THESE AS INDIVIDUAL INTERVENTIONS OR IN COMBINATION APPROACHES

- Community Reinforcement Approach (CRA)
  - Decreased addiction severity
  - Decreased drug use (weeks of use, frequency/week, $/week)
  - Increased cocaine abstinence
- Contingency Management (CM)
  - Decreased days of stimulant use
  - Decreased stimulant cravings
  - Decreased HIV risk behaviors
  - Studies:
    - 50% of vets completed 14 sessions in 12 weeks compared to 42% completing 2 sessions in 1 year
    - 2 VA studies: 92% of almost 28,00 tox screens negative & of >69,000 tox screens negative

How does CM Work?

- Select objective target behavior (attendance, abstinence)
  - Define the behaviors
    - Attendance at clinic (med appt, group appt, providing tox)
    - Abstinence from DOC? all illicit drugs? prescribed drugs? alcohol? nicotine?
- Provide immediate, consistent, tangible, desired rewards for target behavior
- Escalate size of reward for consistent behavior
- When target behavior does not occur
  - Withhold the reward
  - Reset size of reward for next occurrence of target behavior
- Example: Fishbowl Method- 250 good jobs, 209 $1, 40 $20, 1 $100

REMEMBER:
Measure objectively & frequently
Don't set the bar too high or low

Average cost: $75-$200/12 weeks

Source: Dominick DePhilippis, Ph.D. Philadelphia CESATE: Center of Excellence in Substance Addiction Tx & Education

CASE

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Ms. Smith presents for her follow up appointment. She is being treated for opioid and amphetamine use disorders. She is on buprenorphine 24mg per day. Ms. Smith regularly attends an intensive outpatient program 3 days per week. Her toxicology test is positive for buprenorphine, norbuprenorphine, methamphetamine and amphetamine.

+ What is the best next step?

A. Increase her medication to target her methamphetamine use

B. Stop her medication because she is using amphetamines

C. Adjust her psychosocial treatment & ensure there is a CM component

D. Add peer support

This question has multiple correct answers
A, C and D are all correct.

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CONTACT US

FOR ANY QUESTIONS OR COMMENTS

MATinCountyCJ@healthmanagment.com

SHANNON ROBINSON
srobinson@healthmanagement.com

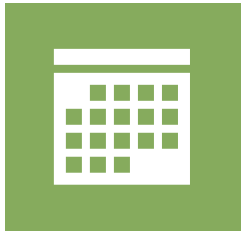
Contact your HMA coach to discuss how to apply today's learnings.

A link to the recording of today's webinar and the slides will be posted on Addictionfreeca.org
Feel free to forward to others on your team.

DHCS

HEALTH MANAGEMENT ASSOCIATES

UPCOMING EVENTS

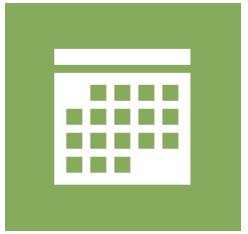


Webinar: Sublocade

October 13 @ 10AM
Shannon Robinson MD,
Katie Dolezal NP
Emilee Wilhelm-Leen MD

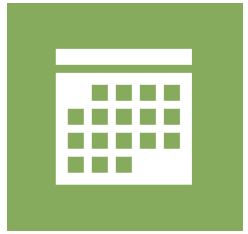
Webinar: Methadone Getting it into your Jails

November 11 @ 9AM
Donna Strugar Fritsch



Webinar: Opioid Withdrawal Clinical Opioid Withdrawal Scale Training

December 3 @ 10AM
Shannon Robinson



Learning Collaborative

December 16 @ 1PM

POLLING QUESTION

Overall, today's webinar was:

+ Very useful
+ Somewhat useful
+ Not very useful
+ Not useful at all

The material presented today was:

+ At the right level
+ Too basic
+ Too detailed

After entering your response, please provide CHAT input on anything you'd like to know more about stimulants and your client work

Before the toxicology webinar next year, please answer the following:

1. The routine urine toxicology test used at the clinic/ facility where I work is a…
   A. preliminary test.
   B. confirmatory test.
   C. preliminary test that is reflexively confirmed.
   D. I am unsure if the test is a preliminary or a confirmatory.

2. Does the routine toxicology test detect buprenorphine? methadone?
3. Does the routine toxicology test differentiate between amphetamine and bupropion?