Stimulants 2022: Epidemiology, Effects and Treatments

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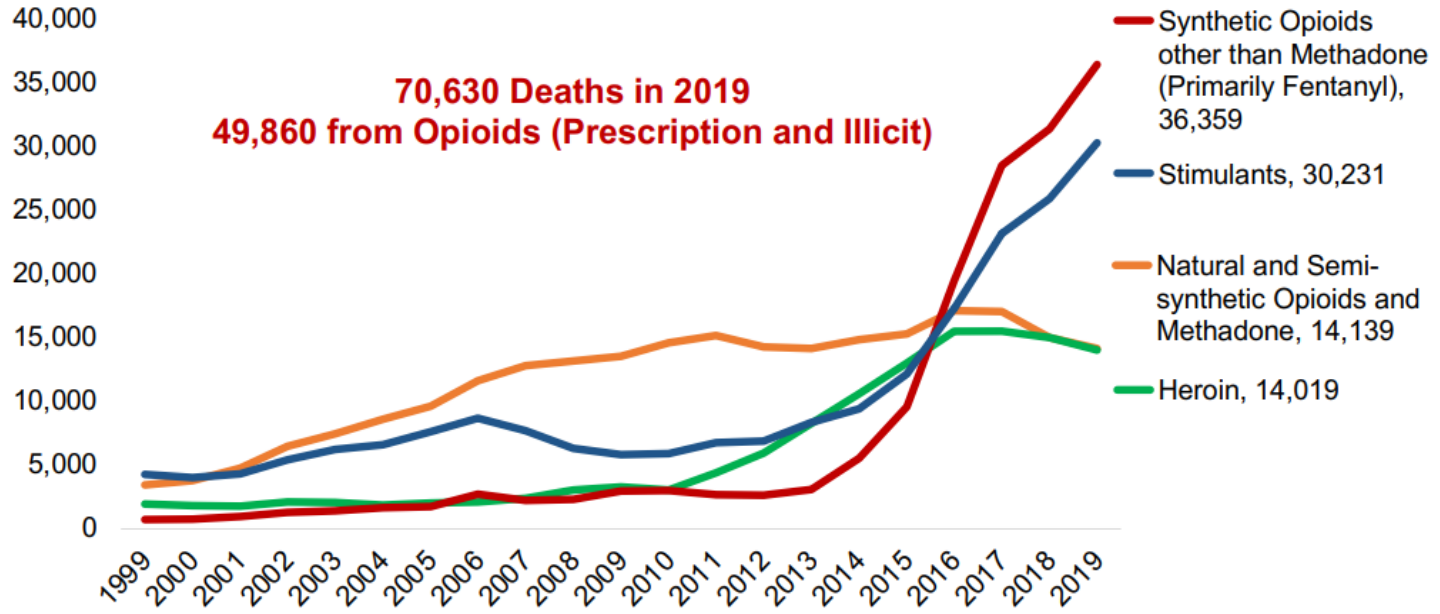
Epidemiology of Methamphetamine and Cocaine use

Evolution of Drivers of Overdose Deaths, All Ages

Analgesics ➡ Heroin ➡ Fentanyl ➡ Stimulants



Source: The Multiple Cause of Death data are produced by the Division of Vital Statistics, National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC), United States Department of Health and Human Services (US DHHS).

Hedegaard H, Miniño AM, Warner M. Drug Overdose Deaths in the United States, 1999-2018. *NCHS Data Brief*. 2020 Jan;(356):1-8. PMID: 32487285.

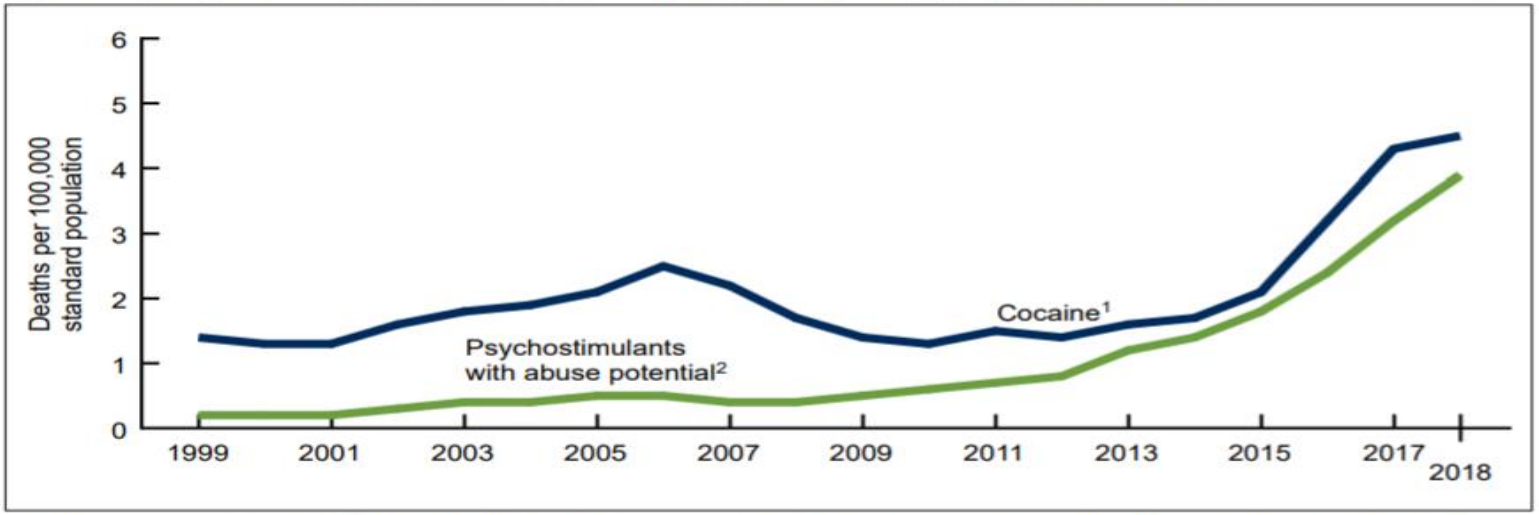
Stimulant overdose rates

- From 2012 through 2018, the age-adjusted rate of drug overdose deaths involving cocaine more than tripled.

- The rate of deaths involving psychostimulants (including methamphetamine) with abuse potential increased nearly 5-fold.

Stimulant overdose rates 1999-2018

Figure 4. Age-adjusted drug overdose death rates involving stimulants, by type of stimulant: United States, 1999–2018

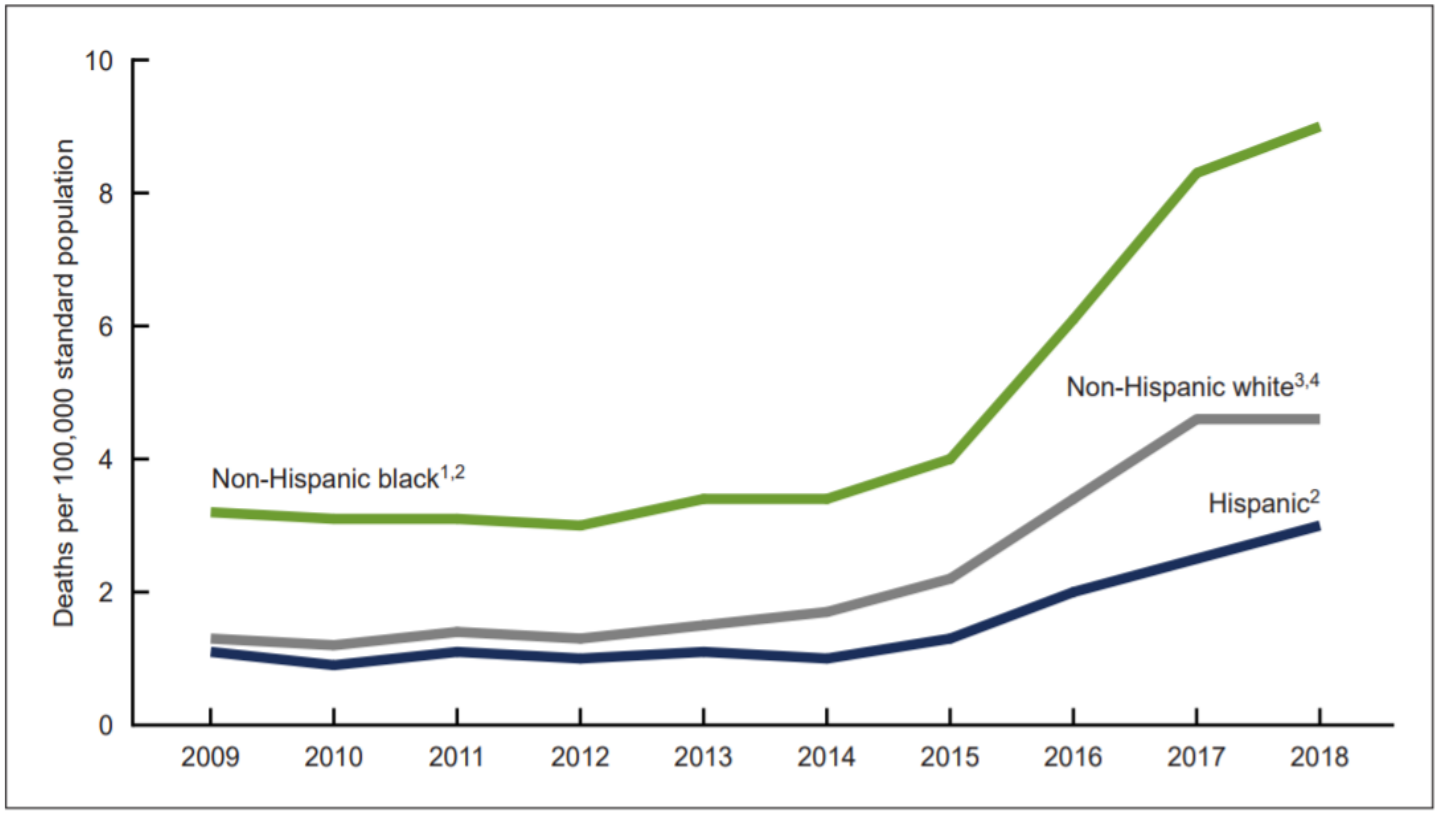


[1]Significant increasing trend from 1999 through 2006, decreasing trend from 2006 through 2012, and increasing trend from 2012 through 2018 with different rates of change over time, $p < 0.05$.
[2]Significant increasing trend from 1999 through 2005, 2008 through 2012, and 2012 through 2018 with different rates of change over time, $p < 0.05$.
NOTES: Deaths are classified using the *International Classification of Diseases, 10th Revision*. Drug-poisoning (overdose) deaths are identified using underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Drug overdose deaths involving selected drug categories are identified by specific multiple-cause-of-death codes: cocaine, T40.5; and psychostimulants, T43.6. Deaths may involve multiple drugs. The percentage of drug overdose deaths that identified the specific drugs involved varied by year, with ranges of 75%–79% from 1999 through 2013 and 81%–92% from 2014 through 2018. Access data table for Figure 4 at: https://www.cdc.gov/nchs/data/databriefs/db356_tables-508.pdf#4.
SOURCE: NCHS, National Vital Statistics System, Mortality.

Increase in drug overdose deaths involving cocaine: United States, 2009-2018 Hedegaard et al., 2020

- The rate of overdose deaths involving cocaine was stable from 2009-2013.
- The rate of overdose deaths nearly tripled from 2013-2018.
- From 2009-2018 the rate of OD deaths involving cocaine was highest in the non-Hispanic black population.
- In 2018 the rate in the non-Hispanic black population was nearly twice that of non-Hispanic whites, and three times that of Hispanics.

Age-adjusted rates of drug overdose deaths involving cocaine by race and Hispanic origin

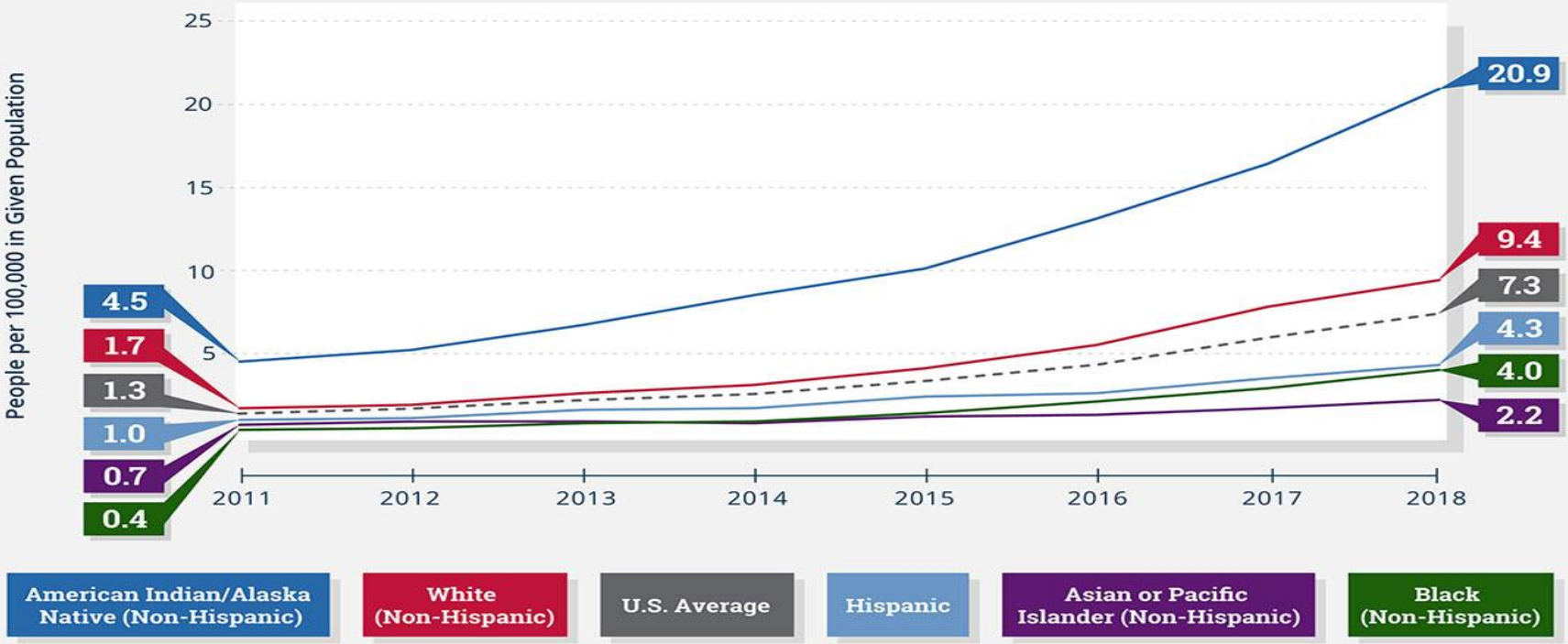


Han B, Cotto J, Etz K, Einstein EB, Compton WM, Volkow ND. Methamphetamine Overdose Deaths in the US by Sex and Race and Ethnicity. J*AMA Psychiatry.* Published online January 20, 2021. doi:10.1001/jamapsychiatry.2020.4321

Increase in methamphetamine overdose deaths by sex, race, and ethnicity

- Data from the 2011-2018 Multiple Cause of Death records
- Looked at age group 25-54 years old (people who use methamphetamine are mostly in this range).
- More than a 5-fold increase from 2011-2018.
- In non-Hispanic American Indians and Alaska Natives deaths more than quadrupled.
- Non-Hispanic Blacks had the sharpest increase (10-fold); this group previously had very low rates of methamphetamine deaths.
- Rates in all groups were higher in men than women; each group increased 5-fold.

U.S. Overdose Deaths Involving Methamphetamine in People Ages 25 – 54*



*Recent national data show that most people who use methamphetamine are between 25 and 54 years old, so investigators limited analysis to this age group.

NIH National Institute on Drug Abuse

drugabuse.gov

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Friedman JR, Hansen H. Evaluation of Increases in Drug Overdose Mortality Rates in the US by Race and Ethnicity Before and During the COVID-19 Pandemic. JAMA Psychiatry. 2022 Mar 2:e220004. doi: 10.1001/jamapsychiatry.2022.0004. Epub ahead of print. PMID: 35234815; PMCID: PMC8892360.

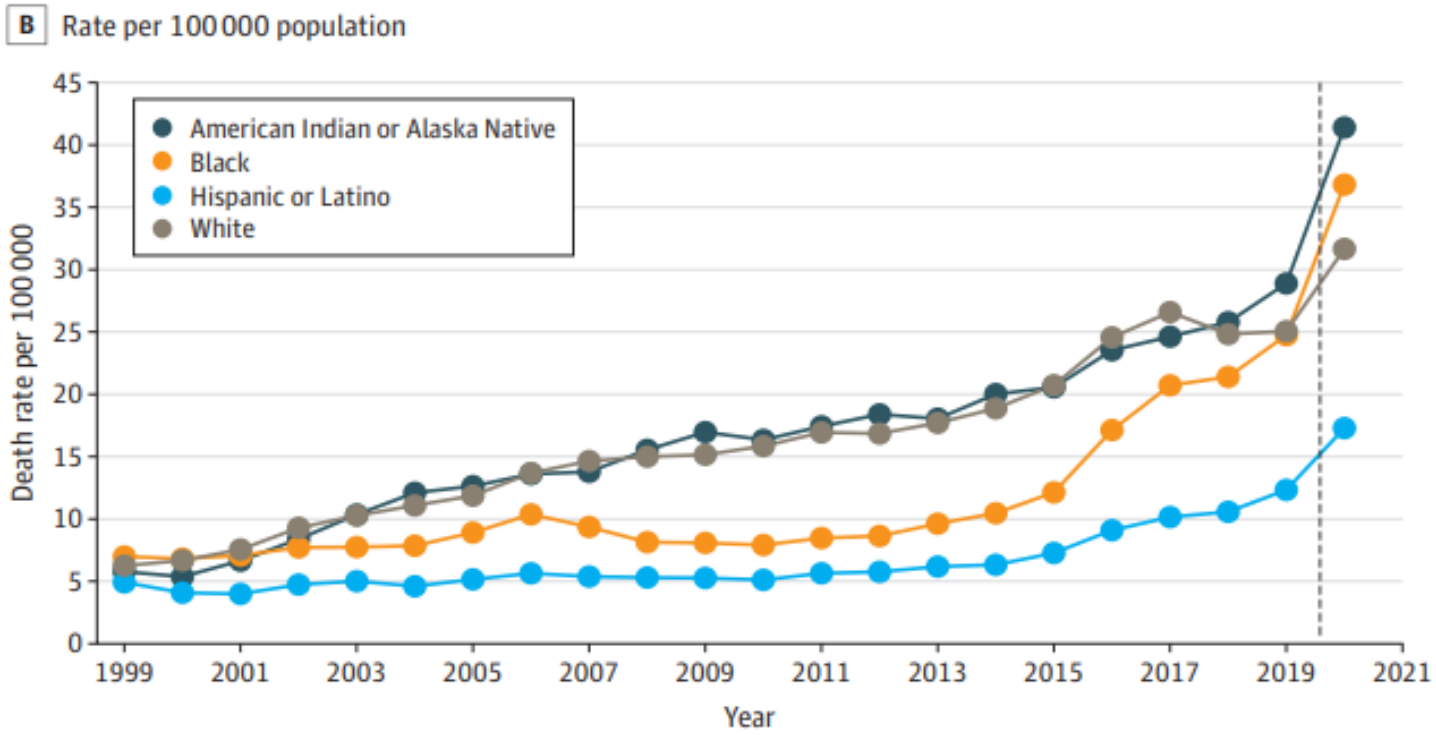
Introduction

- Drug overdose mortality rates have increased sharply in the US since the COVID-19 pandemic began in 2020.
- Since 2015 overdose deaths have been rising most rapidly in the Black and Hispanic communities.
- This study examined increases in overdose mortality rates by race and ethnicity before and during the pandemic.

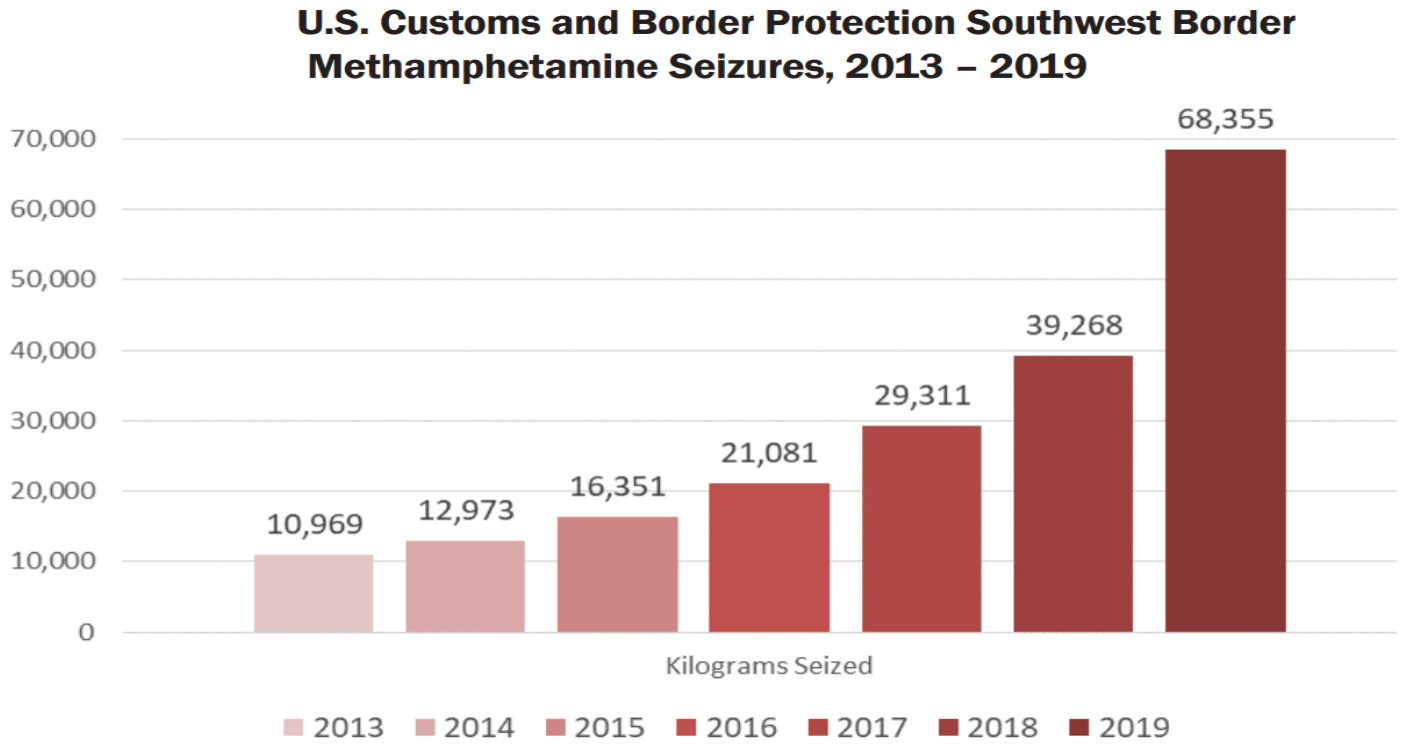
Methods

- Data were form the Centers for Disease Control and Prevention WONDER (Wide-ranging Online Data for Epidemiologic Research) and the National Center for Health Statistics.
- The purpose was to calculate drug overdose death rates per 100,000 population by race and ethnicity for 1999 to 2020.
- Drug overdose deaths were defined using the *International Statistical Classification of Diseases and Related Heatlth Problems*.

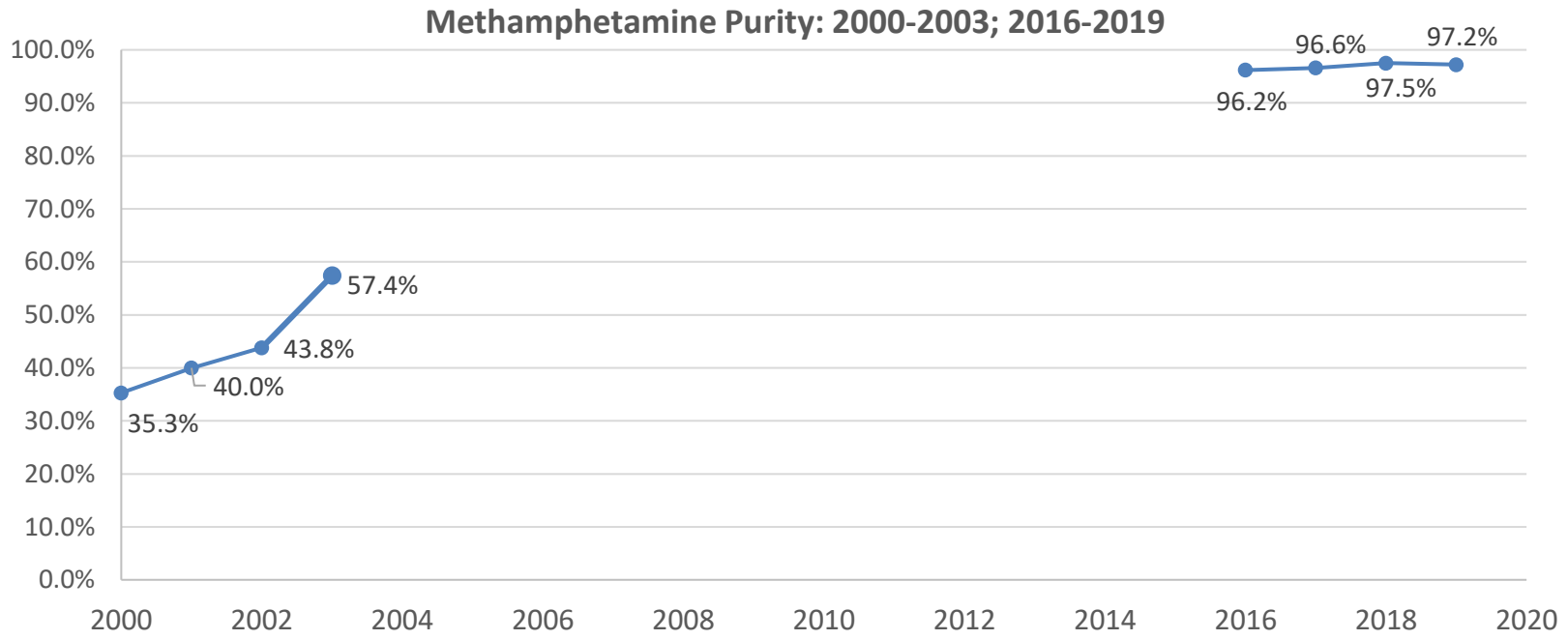
Drug Overdose Mortality per 100,000 Population



Methamphetamine SW Border Seizures



Methamphetamine Purity 2000-2003 and 2016-2019



Sources: The National Threat Assessment, 2005, National Drug Intelligence Center, U.S. Dept. of Justice
DEA Methamphetamine Profiling Program.
National Drug Threat Assessment, 2020. DEA Methamphetamine profiling program.

A lethal dose

Hansen ER, Carvalho S, McDonald M, Havens JR. A qualitative examination of recent increases in methamphetamine use in a cohort of rural people who use drugs. *Drug Alcohol Depend.* 2021 Dec 1;229(Pt B):109145.

doi: 10.1016/j.drugalcdep.2021.109145. Epub 2021 Oct 28. PMID: 34763138; PMCID: PMC8665094.

Results: Individual factors

- Participants found the MA high attractive (energy, focus, and confidence).
  - "…gave me the confidence and courage to do things I normally didn't wanna do."
- Participants used MA to treat health concerns including attention difficulties, mood disorders, emotional trauma.
  - "It was, you know, the best to me, the best thing ever. I got PTSD from my childhood, and when I sleep I have nightmares. So meth kept me awake, and I didn't have them nightmares, and I was better. I thought I was better, I was numbing my pain."

Results: Individual factors

- Was a way some treated chronic pain.
  - A 39-year-old male laborer with a history of chronic back pain said: “When we’ve got a big day at work, I’ll take me a couple hits that morning, work all day, daylight to dark or whatever we have to do.”
- Helped to suppress withdrawal symptoms and opioid cravings.
  - “Meth will stop withdrawal; did you know that? For anything. It stops it for any kind of drugs—Xanax, Neurontin, pain pills, Suboxone. So, a lot of people have used meth to get off Suboxone.”

Results: Interpersonal factors

- Initiation of MA was often facilitated by members of the participants drug network.
- Many were given MA without knowing what it was.
  - "I was 15 when I first tried meth. I saw one of my friends that I had not seen in a while and she tells me that she had 'ice cream.' I didn't know what it was. And my person that I got weed off was out, so I gave her $20. I was looking for weed, but as soon as I took my first hit of meth I was like, 'Oh my god' because I fell in love."
- MA was increasingly available everywhere.

Results: Community factors

- Participants uniformly described how MA is now the easiest illicit substance to acquire.
  - "Meth already took over. Meth is on every corner, every street, every straight stretch you see."
  - "You don't even hear about selling Lorcets or Percocets anymore. Opioids are gone except for people who that actually take them for real pain."
- Participants consistently described how the ubiquity made MA affordable, especially compared to non-medical prescription opioids (NMPOs), marijuana, and benzodiazepines.

Co-use of Opioids and Stimulants

Baker R, Leichtling G, Hildebran C, Pinela C, Waddell EN, Sidlow C, Leahy JM, Korthuis PT. "Like Yin and Yang": Perceptions of Methamphetamine Benefits and Consequences Among People Who Use Opioids in Rural Communities. *J Addict Med.* 2021 Jan-Feb 01;15(1):34-39. doi: 10.1097/ADM.0000000000000669. PMID: 32530888; PMCID: PMC7734765.

Introduction

- Rural residents initiate drug use at younger ages.
- They are more likely to use methamphetamine (MA).
- They are more likely to engage in riskier drug use behavior.
- This study explores perceptions of methamphetamine use among people who use opioids in rural communities impacted by high rates of opioid overdose.

Theme 1: Environmental Factors Foster Use

- Early exposure: first use in early or mid-adolescence.
  - "I was 12 years old…I was at my friend's house…he brought out white dope (meth) and gave it to all of us. I snorted it, and my life has never been the same ever since then."
- Availability and low cost.
  - "The price of meth has gone down…It's hard to even give it away because everybody wants to do heroin instead…I would prefer to do heroin, but people give meth away these days pretty much."
- Lower stigma relative to heroin.
  - "Meth is very popular. Heroin isn't as popular; people have this stigma that it's the devil's drug, a bad drug."

Theme 2: Perceived benefits of MA

- Opioid withdrawal relief.
  - "If I couldn't find opiates, then I found out that you could use meth and it would help (with opioid withdrawal) a little bit. So I started substituting that with meth."
  - "It gives you more energy and you feel a little bit better. You don't feel so sick."
- Reducing opioid use and using MA to quit using opioids.
  - "We quit – me and my mom – doing heroin and started doing meth, pretty much. That's how we came off it."
- Opioid overdose reversal.
  - "In our eyes, we all think that if you have meth in your shot of heroin, you're not going to die just because it's that helper that's going to keep your heart going…"

Theme 2 (cont.)

- Enhancement of functioning.
  - "I don't shoot MA to get high…I use it as a tool so that I can work my 10 ½ hour day with it and go home and still be a husband and do what I need to do…"
- Pleasurable effects.
  - Using heroin and MA either sequentially or simultaneously produced a more enjoyable high.
  - "It's a yin and yang kind of thing…they go well together."

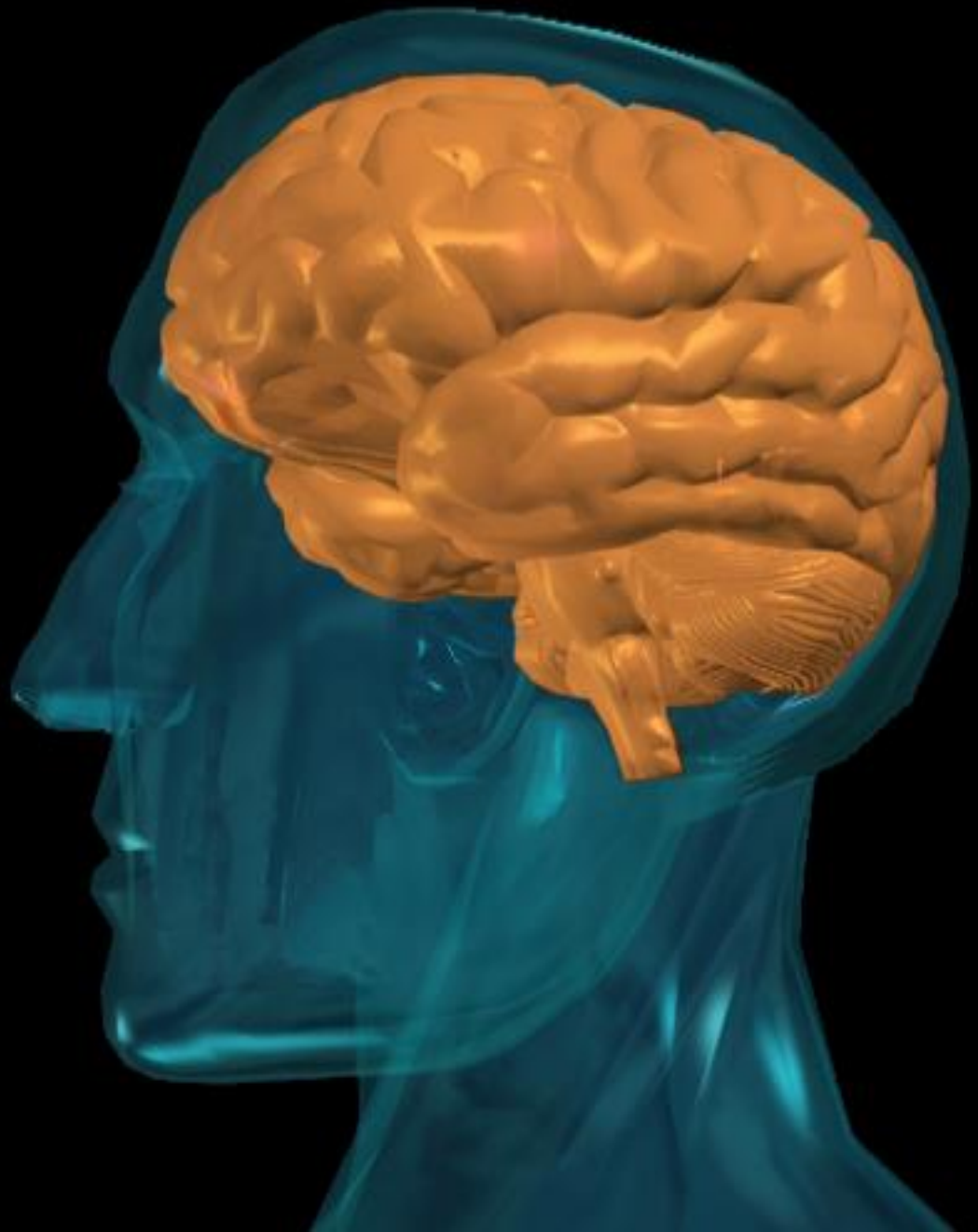
Theme 3: Perceived Consequences of MA

- Discharge from treatment.
  - "I like the people at the methadone clinic but…some of the new policies about if you use meth then you get kicked out. After a couple UAs you get kicked out."
  - "My wife got kicked out of the methadone clinic…she started getting sick…opioid withdrawal…I went out and started buying heroin…then we both started using the heroin, and here we are…"
- Fentanyl adulteration risk.
  - "Because of the opioids that are mixed in with the MA now, it's more of a draw to it."

Discussion

- Use of MA to cope with opioid withdrawal is concerning and reflects a need for education on MA overdose risk.
- 29.8% of rural residents compared to 2.2% of urban residents live in a county without a buprenorphine provider.
- Treatment services including MOUD should not base
- enrollment on abstinence.
- There is a need for evidence-based treatment for polysubstance use.
- Factors that need to be addressed include transportation barriers, community stigma, and social norms around drug use.

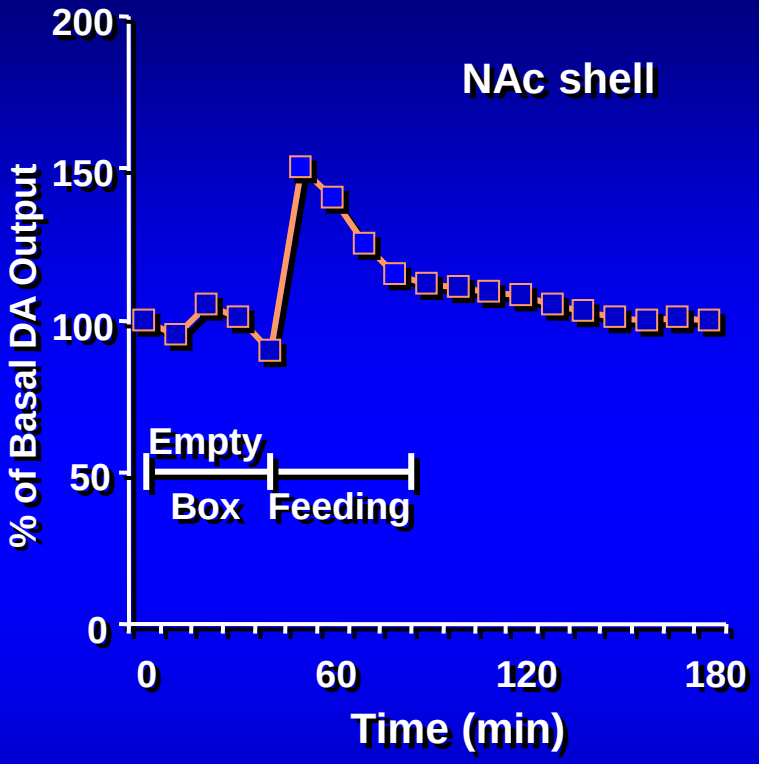
Stimulant Effects



Prolonged Methamphetamine Use Changes The Brain In Fundamental and Long-Lasting Ways

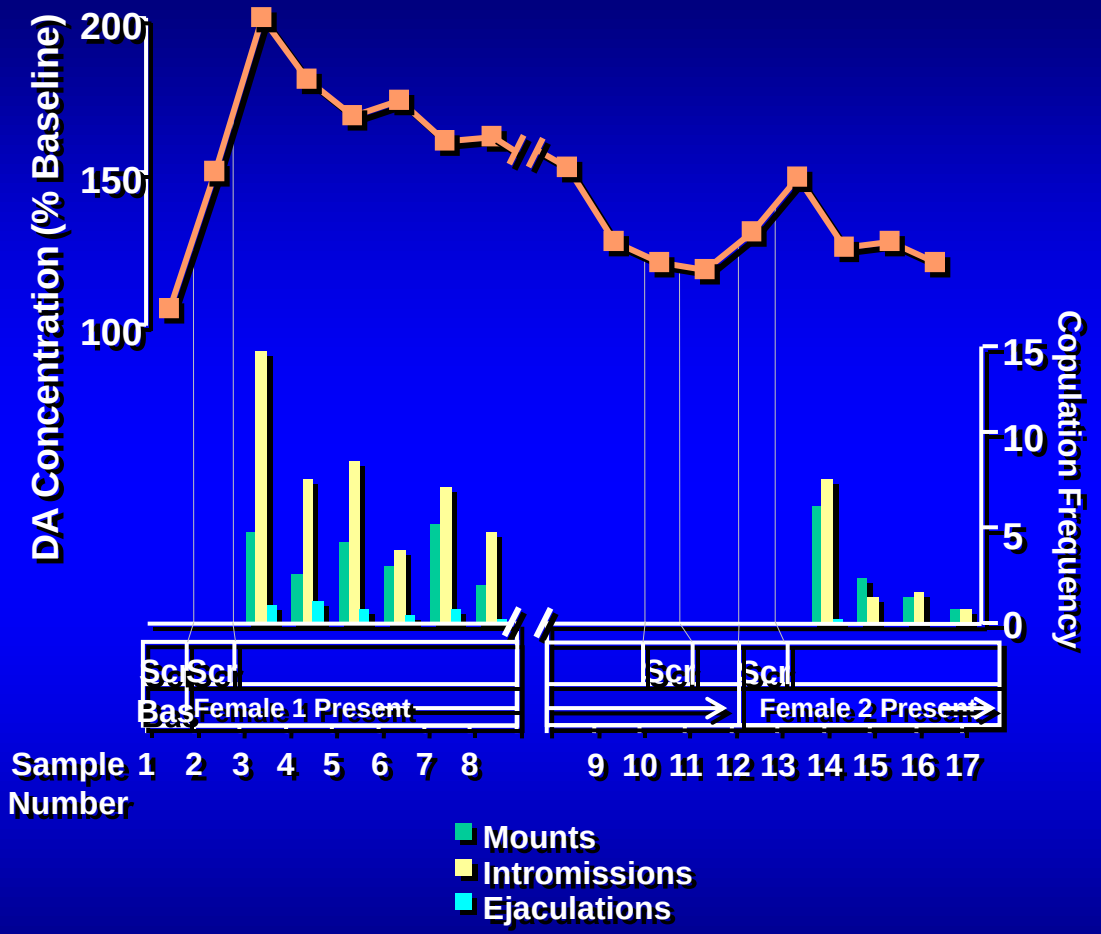
Natural Rewards Elevate Dopamine Levels

FOOD



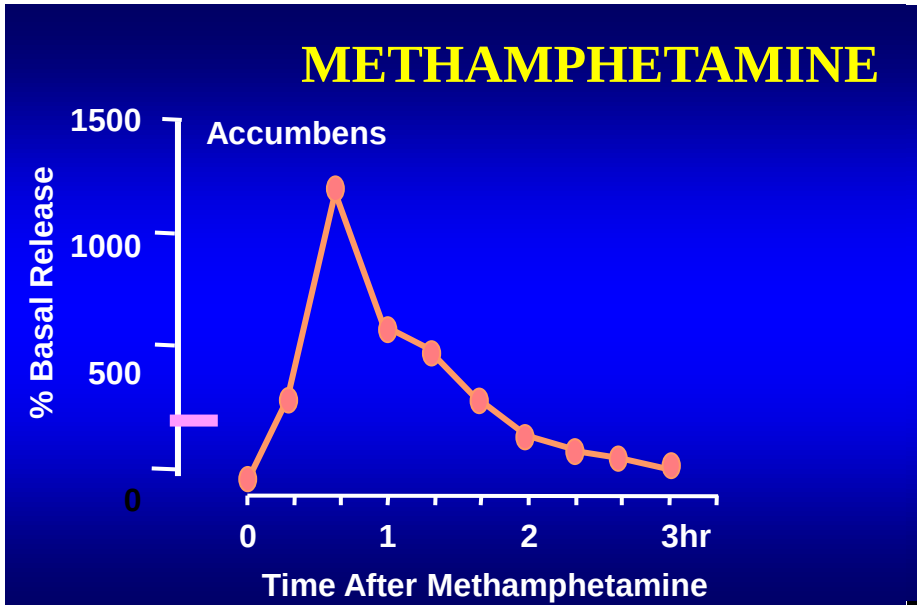
Source: Di Chiara et al.

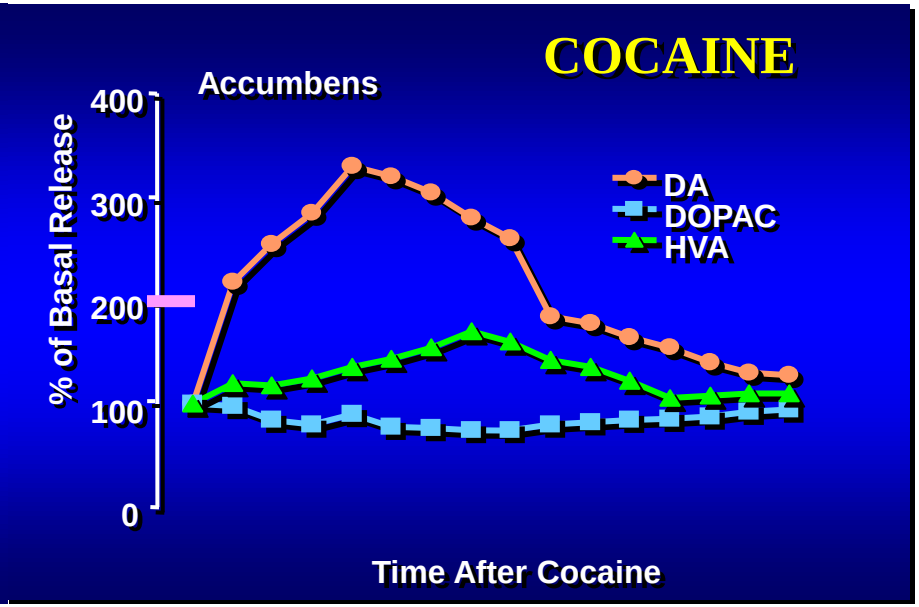
SEX

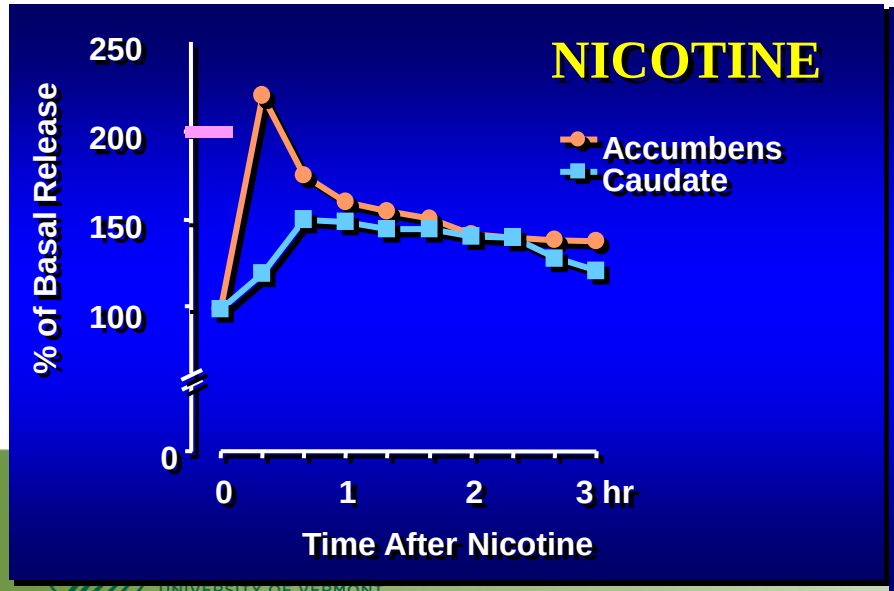


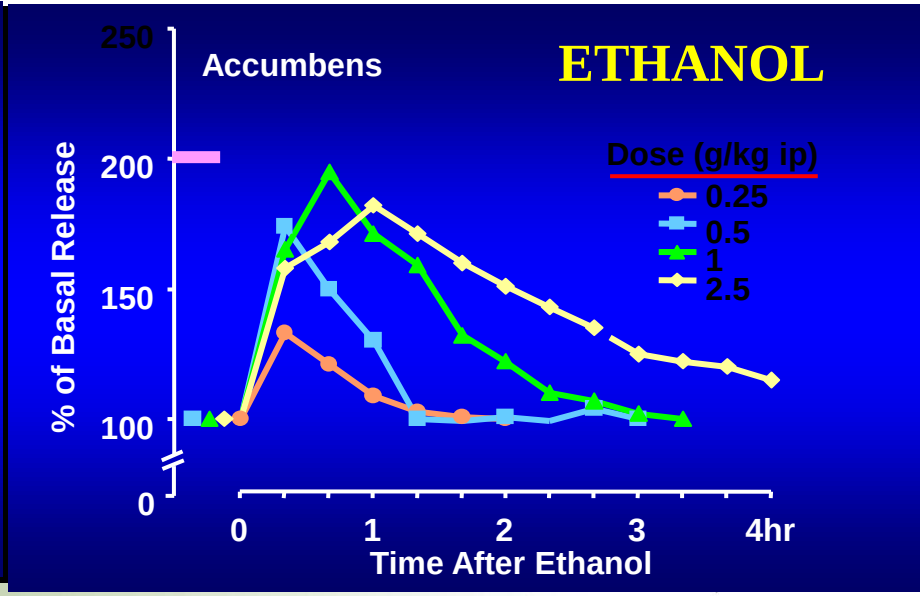
Source: Fiorino and Phillips

Effects of Drugs on Dopamine Release









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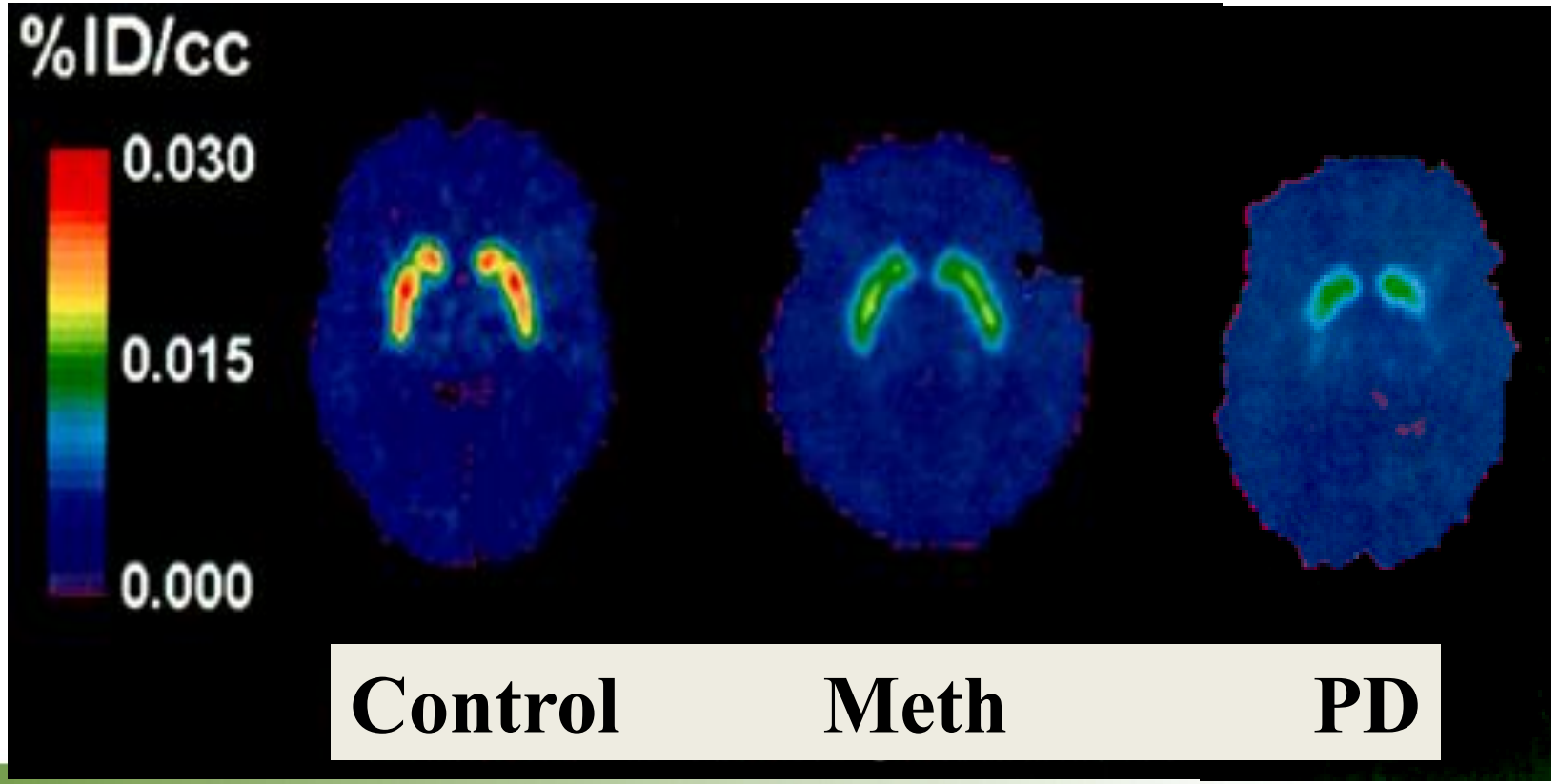
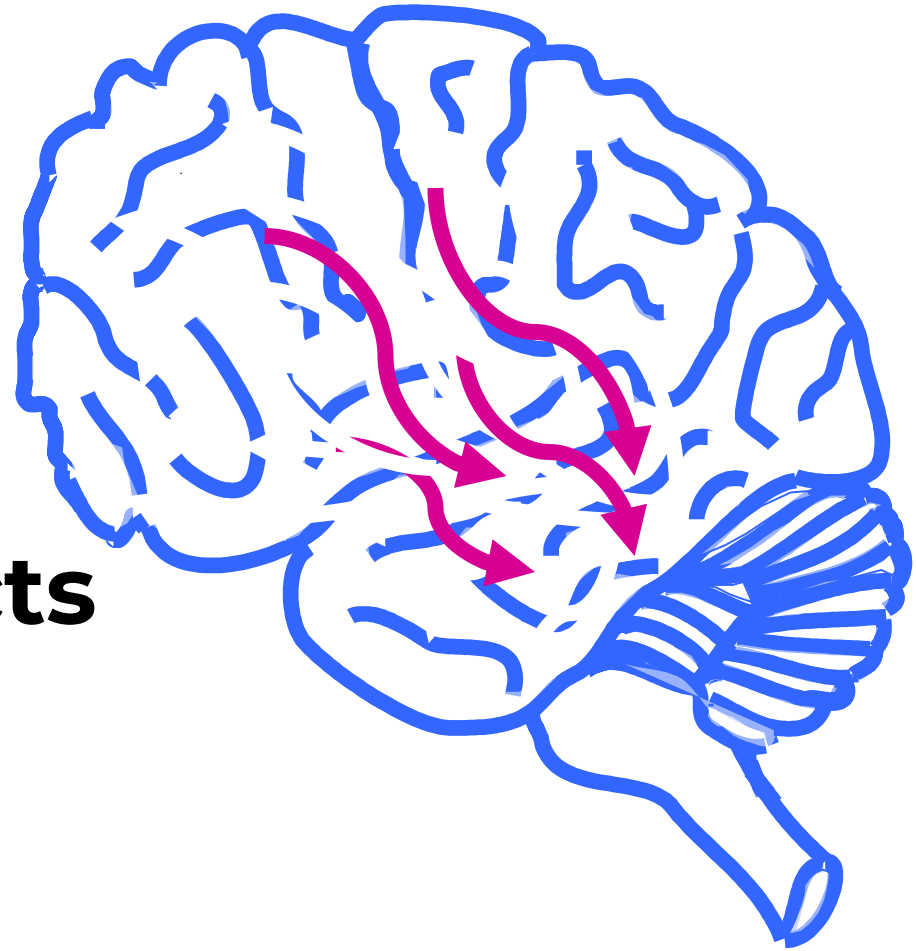
Source: Shoblock and Sullivan; Di Chiara and Imperato

Decreased dopamine transporter binding in METH users resembles that in Parkinson's Disease



Source: McGann U.D.. et al.,Journal of Neuroscience, 18, pp. 8417-8422, October 15, 1998.

Cognitive and Memory Effects



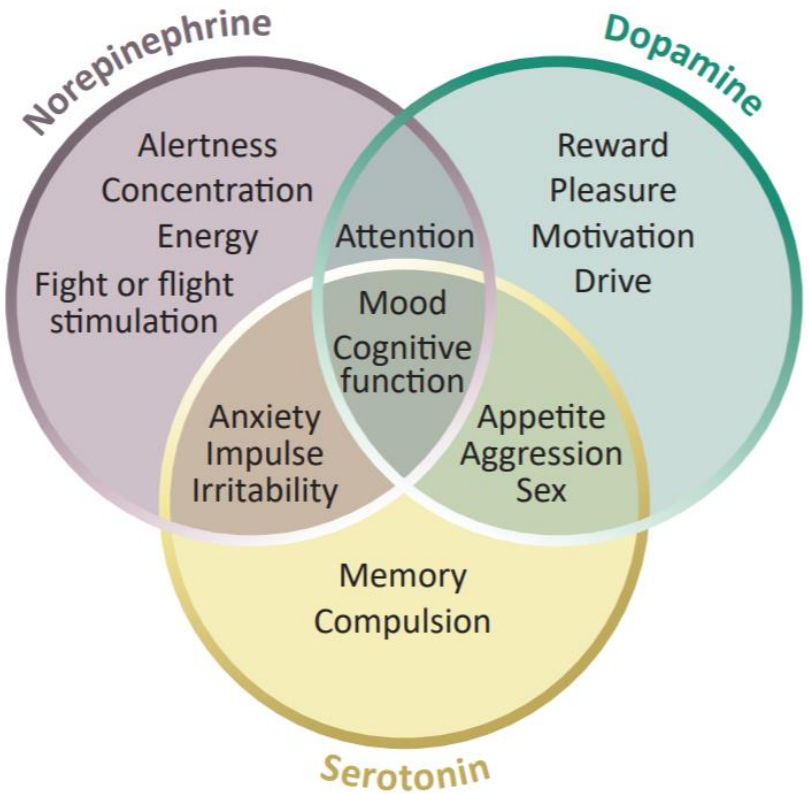
Paulus, M. P. and Stewart, J.L. ,
Neurobiology, Clinical Presentation and Treatment of Methamphetamine Use Disorder:
A Review. *JAMA Psychiatry*, 77:959-966.
doi:10.1001/jamapsychiatry.2020.02462020

Neurotoxicity

- Excessive dopamine resulting in damaged cell structures
- Cell death
- Activation of dopamine D3 receptors resulting in hyperthermia
- Disruption of the blood-brain barrier
- Overall, the altered brain state is consistent with degenerative central nervous system diseases.

Behavioral Effects of Neurotransmitters

FIG. 1 Behavioural effects mediated by the three main neurotransmitters



Cognitive Effects

Soon after cessation of methamphetamine use:

- Poor performance on motor and processing tasks
- Poor performance on verbal fluency and attention

After prolonged abstinence:

- Poor learning efficiency and comprehension
- Poor visual-spatial processing
- Slow processing and psychomotor speed

Cognitive Effects

- It is estimated that more than 2/3 of those with methamphetamine use disorder show cognitive impairment.
- Impairment is associated with older age, longer duration of use, injection route of administration and greater frequency of use.
- Impairment may limit ability to follow through with treatment, comprehend advice and direction in treatment as well as generally achieve good treatment outcomes.

Cerebrovascular and cardiovascular disease

Leading causes of death with methamphetamine use disorder

- Strokes on rise, most often with young men
- Strokes are primarily hemorrhagic

Cardiovascular Disease associated with methamphetamine use:

- Pulmonary hypertension
- Cardiac arrhythmia
- Cardiomyopathy

Smid, M., Metz and Gorden. (2019). Stimulant Use in Pregnancy: *An Under-Recognized Epidemic Among Pregnant Women*, Clin Obstet Gynecol. *62*(1), 168–184.

Stimulant Use in Pregnancy
Smid et al., 2019

Meta-analysis of 31 studies found cocaine use during pregnancy increased risk of:

- pre-term delivery,
- low birth weight,
- small for gestational age, (Gouin, 2011).

Meta-analysis of 8 studies found methamphetamine use during pregnancy was associated with:

- earlier gestational age at delivery,
- lower birth weight,
- smaller head circumference (Kalaitzopoulos, 2018).

Infants with prenatal exposure to methamphetamine exhibit jitteriness, drowsiness, and respiratory distress suggesting withdrawal.

Cocaine and methamphetamine are excreted in breastmilk and contraindicate breastfeeding.

Stimulant Use in Pregnancy
Smid et al., 2019

- Long-term follow-up of 204 methamphetamine exposed maternal-child pairs and 208 unexposed pairs (Derauf et al., 2007).
- At one month, 33% methamphetamine-exposed mothers did not have custody compared to 2% of unexposed.
- At age 3 years, heavy prenatal methamphetamine use (≥ 3days per week) was associated with anxiety/depression and attention problems.
- At age 7.5 years, methamphetamine-exposed children had poorer cognitive function.
- UCLA Study of 4-5 year olds found impoverished vocabulary and poorer fluency with language

Dental Effects

- Rampant caries and tooth fracture most common (Shaner, 2002; 2006)
- Periodontal disease
- Mechanisms:
  - Poor oral hygiene
  - Xerostomia (dry mouth)
    - Alpha 2 receptor stimulation inhibits saliva
    - Dehydration from appetite suppression and increased psychomotor activity
  - Soft drink consumption
  - Bruxism
  - Acidic content of MA (controversial)
  - Corrosive contaminants of MA (smoking)

Shetty V, Mooney LJ, Zigler CM,

Belin TR, Murphy D, Rawson R. The relationship between methamphetamine use and increased dental disease. *J Am Dent Assoc*. 2010 Mar;141(3):307-18. doi: 10.14219/jada.archive.2010.0165. PMID: 20194387; PMCID: PMC2947197.

Results

- Prevalence of dental or oral disease was high in MA users (41.3%).
- MA users had significantly more missing teeth than matched controls (4.58 vs 1.96 missing, $p<.001$).
- MA users were significantly more likely to report oral health problems ($p<.001$).
- IV use of MA was significantly more likely to be associated with missing teeth than smoking MA.

Dermatological Effects

- Pruritis from vasoconstriction
- Cutaneous ulcers and excoriations from skin picking (formication, “meth bugs”)
- Abscesses (“skin popping” confers greatest risk)
- Cellulitis
- Burn injuries

Rawson, R.A., Washton, A.M., Domier, C.P., & Reiber, C. (2002). Drugs and sexual effects: Role of drug type and gender. *Journal of Substance Abuse Treatment 22*(2), 103-108

Acute Management Strategies

Methamphetamine Presentations to an Emergency Department: Management and Complications

Isoardi et al., 2019

- 329 patients (378 presentations) in 2016
- ED in Brisbane, Australia
- Clinical effects:
  - Behavioral disturbance, 78%
  - Tachycardia, 56%
  - Hypertension, 42%
  - Hyperthermia, 5%

Clinical management of individuals who use stimulants: *Acute Psychosis*

- Symptoms of acute psychosis: Auditory hallucinations, and visual (flashing lights, peripheral artifacts), olfactory, and tactile sensations. In addition, powerful paranoia and persecutory delusions are extremely common, along with ideas of reference, stereotypy and compulsive acts, blunt affect, poverty of speech, delirium, and violence.
- Stimulant-induced psychosis is generally transient and may require use of either a benzodiazepine or an antipsychotic, both of which should be discontinued when acute symptoms have resolved. Risperidone and olanzapine are less likely to cause extrapyramidal symptoms and their sedative properties may ameliorate psychomotor agitation. Monitor for hyperthermia and dehydration when antipsychotics are used in patients with acute stimulant intoxication.

Clinical management of individuals who use stimulants: *Intoxication*

- Symptoms include: Euphoria, hyperexcitability, hypersexuality, increased locomotor activity, agitation, and psychotic symptoms, including paranoia and hallucinations. Objective findings of hypertension, tachycardia, and arrhythmias that present on EKGs of users reflect sympathetic overdrive.
- Acute agitation from MA intoxication is most often the condition that leads users to seek medical attention, and "talking down" the patient in a calm environment is the first course of action. Addressing possible cocaine/MA toxicity may involve emetics or lavage to remove MA pills. Benzodiazepines may be effective in acute management of agitation and distress and may reduce seizure potential in patients

Zhao J, Kral AH, Simpson KA, Ceasar RC, Wenger LD, Kirkpatrick M, Bluthenthal RN. Factors associated with methamphetamine withdrawal symptoms among people who inject drugs. *Drug Alcohol Depend.*

2021 Apr 10;223:108702. doi: 10.1016/j.drugalcdep.2021.108702. Epub ahead of print. PMID: 33894459.

Introduction

- Methamphetamine (MA) withdrawal is characterized by depression, fatigue, sleep disturbance, increased appetite, depression, and anxiety.
- Symptoms can persist 4 weeks.
- There is a significant impairment in daily functioning.
- Withdrawal can pose a barrier to harm reduction practices.
- Recent studies have identified increasing rates of methamphetamine (MA) injection.
- This study looks at the prevalence, frequency, and severity of MA withdrawal symptoms in a cohort of PWID.

Results

- Drug use past 30 days
  - Median frequency: 173 times
  - Median number of injections: 112 times
- MA withdrawal in past 6 months
  - 53% of PWID reported withdrawal
  - 25% reported weekly symptoms
  - 20% reported very or extremely painful symptoms

Discussion

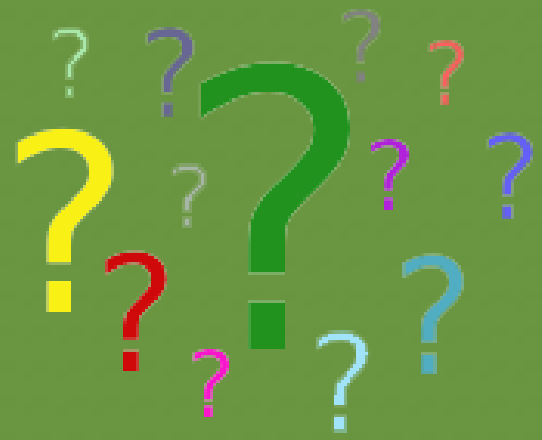
- Tranquilizer use which is associated with MA withdrawal may be reflective of self-medication of anxiety and sleeplessness in withdrawal.
- MA withdrawal symptoms are common among PWID and are associated with receptive syringe sharing.
- Receptive syringe sharing is associated with rushed injecting in public settings with increased risk of overdose and other adverse outcomes.
- Safe supply and syringe services programs targeting people who inject MA are indicated.

Clinical Management of Individuals who use Stimulants : *Withdrawal*

- Stimulant withdrawal symptoms consist of severe fatigue, cognitive impairment, feelings of depression and anxiety, anergia, confusion, and paranoia. For the majority of patients experiencing acute withdrawal/early-phase abstinence, most symptoms resolve within 2 to 10 days.
- Rest, exercise, and a healthy diet may be the best management approach for most people in withdrawal. Those with heightened agitation and sleep disturbance may respond to benzodiazepines, but acute depression and anhedonia associated with early abstinence generally resolve without intervention.

Current status of Treatment Approaches for Methamphetamine Use Disorder

- **Contingency management unanimously (7 systematic reviews and meta-analyses) found to have best evidence of effectiveness**.
- Other approaches with less but clear evidence of support: Cognitive Behavioral Therapy (CBT) and Community Reinforcement Approach (CRA).
- Approach with evidence for treatment of a broad variety of SUD: Motivational Interviewing (MI).
- Approach with recent studies showing benefit to methamphetamine users: Physical Exercise (PE) (e.g., Rawson et al., 2015).



QUESTIONS
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