

Methamphetamine Use Disorder

Ron Cowan, MD, PhD

The University of Tennessee Health Science Center



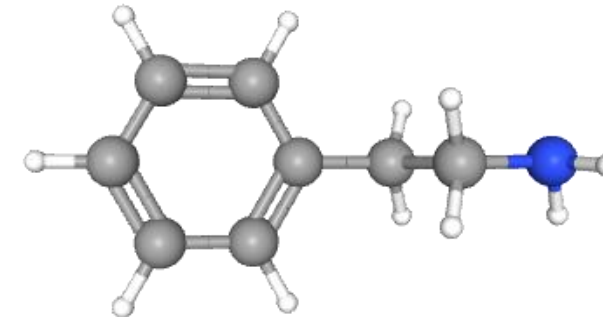
The University of Tennessee Health Science Center—Memphis



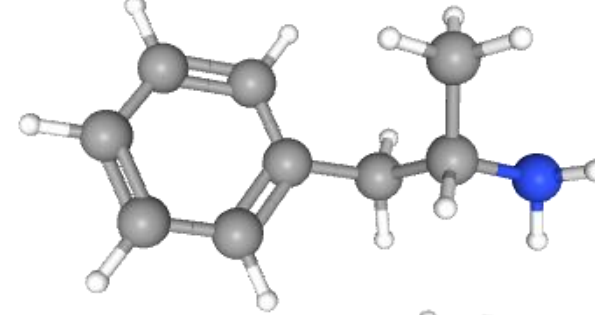
What is methamphetamine?

Methamphetamine history and structure

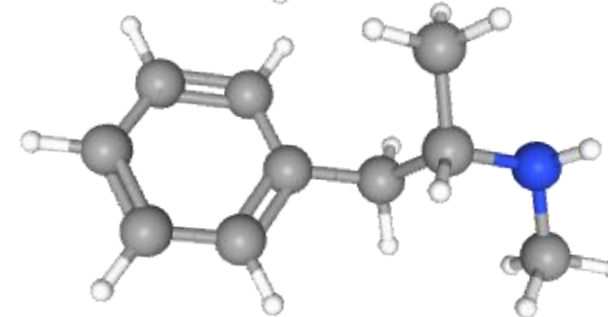
- A psychostimulant (phenylethylamine)
- First known synthesis in late 1800s
- First crystallized in 1919
- FDA approved for attention deficit hyperactivity disorder (ADHD) in age >6 years old
- Schedule II by FDA since 1971



Phenylethylamine



Amphetamine



Methamphetamine

<https://pubchem.ncbi.nlm.nih.gov/compound/10836#section=3D-Conformer>

Forms of methamphetamine



<https://ndarc.med.unsw.edu.au/sites/default/files/ndarc/resources/TR.172.pdf>



<https://www.drugs.com/image/desoxyn-images.html>

Crystal methamphetamine is a form of the drug that looks like glass fragments or shiny, bluish-white

rocks. <https://pubs.nida.nih.gov/publications/drugfacts/methamphetamine>

Description and street names

“NIDA: Methamphetamine is a powerful, highly addictive stimulant that affects the central nervous system.”



Common street names for methamphetamine

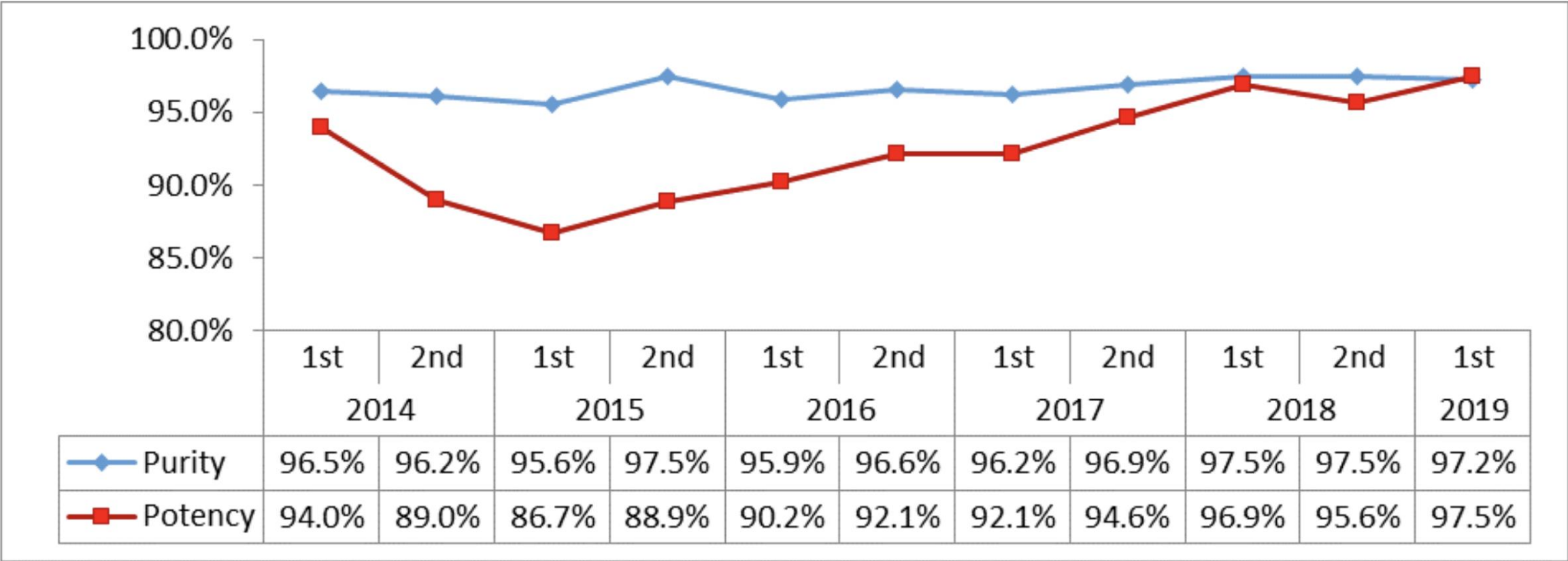
Batu
Bikers Coffee
Black Beauties
Chalk
Chicken Feed
Crank
Crystal
Glass
Go-Fast
Hiropon
Ice
Meth
Methlies Quick

DEA.gov

Poor Man's Cocaine
Shabu, Shards
Speed
Stove Top
Tina
Trash
Tweak
Uppers
Ventana
Vidrio
Yaba
Yellow Bam



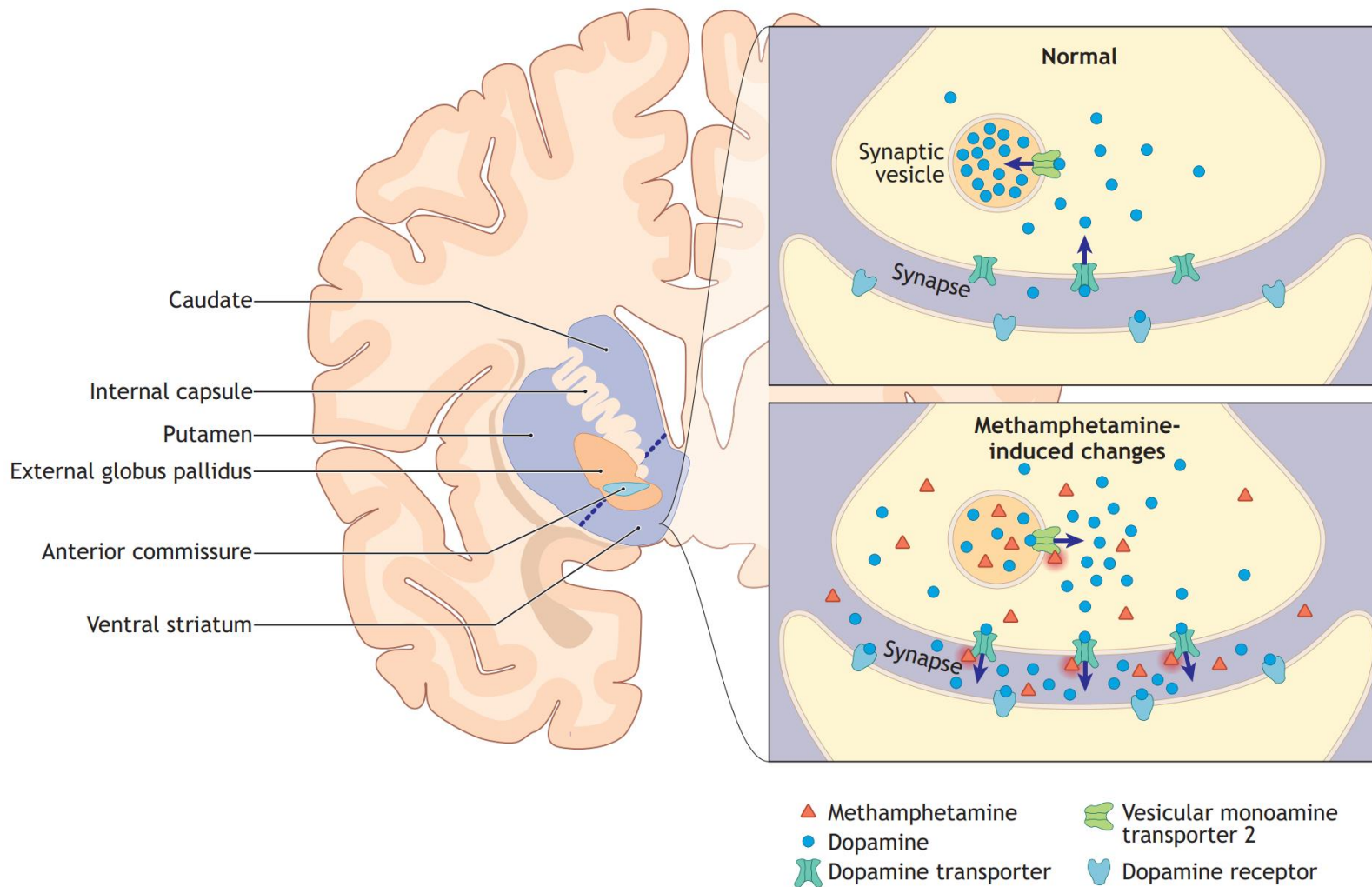
Methamphetamine purity has remained high while potency has gradually increased



Source: DEA Methamphetamine Profiling Program

Methamphetamine mechanisms of action

Methamphetamine mechanisms of action

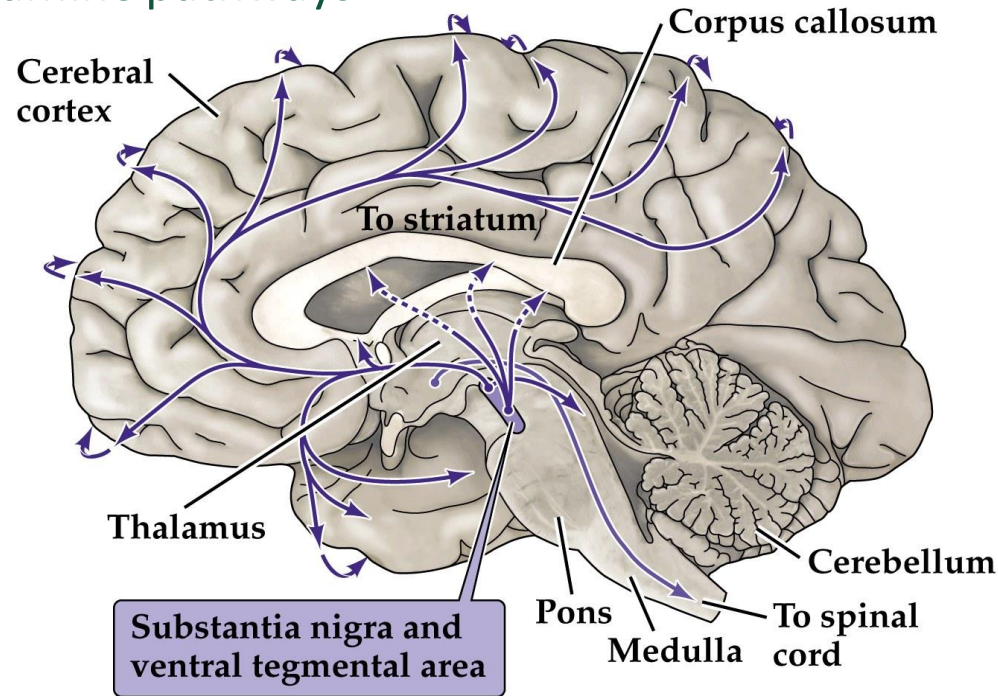


Synaptic actions

- Increases synaptic dopamine, norepinephrine, and serotonin
- Reverses vesicular monoamine transporter 2 (VMAT2)
- Reverses monoamine reuptake transporters
- Inhibits monoamine oxidase (MAO)
- Increases tyrosine hydroxylase

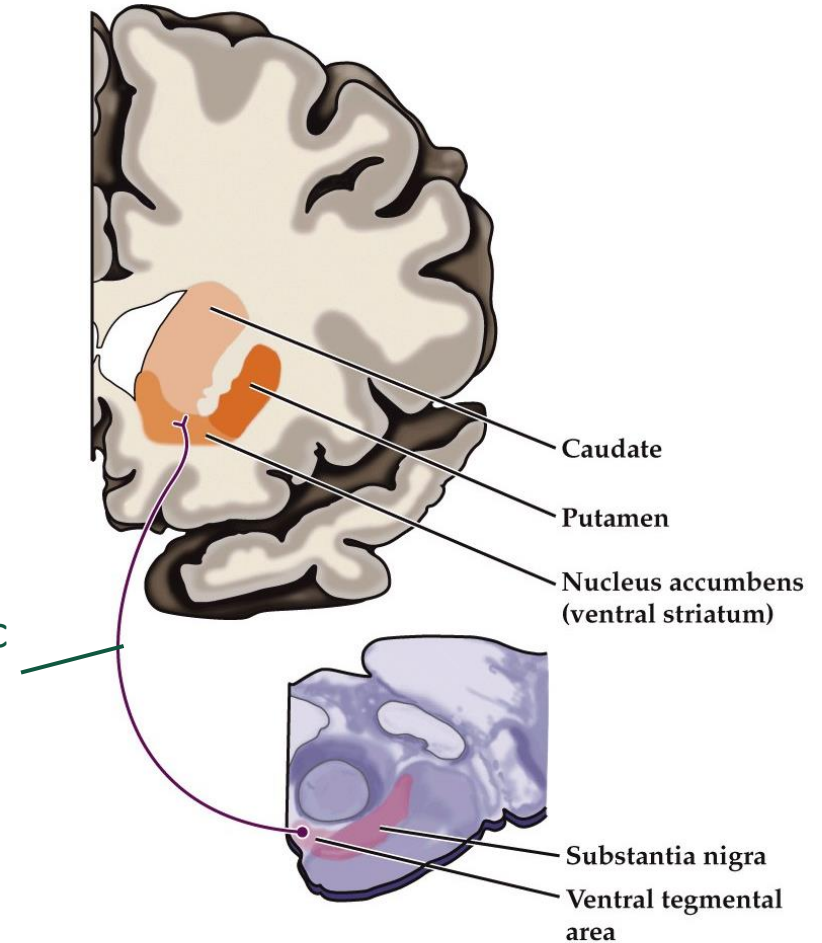
Methamphetamine use disorder results from reinforcement effects at the ventral striatum

Dopamine pathways



NEUROSCIENCE 5e, Figure 6.11 (Part 1)
© 2012 Sinauer Associates, Inc.

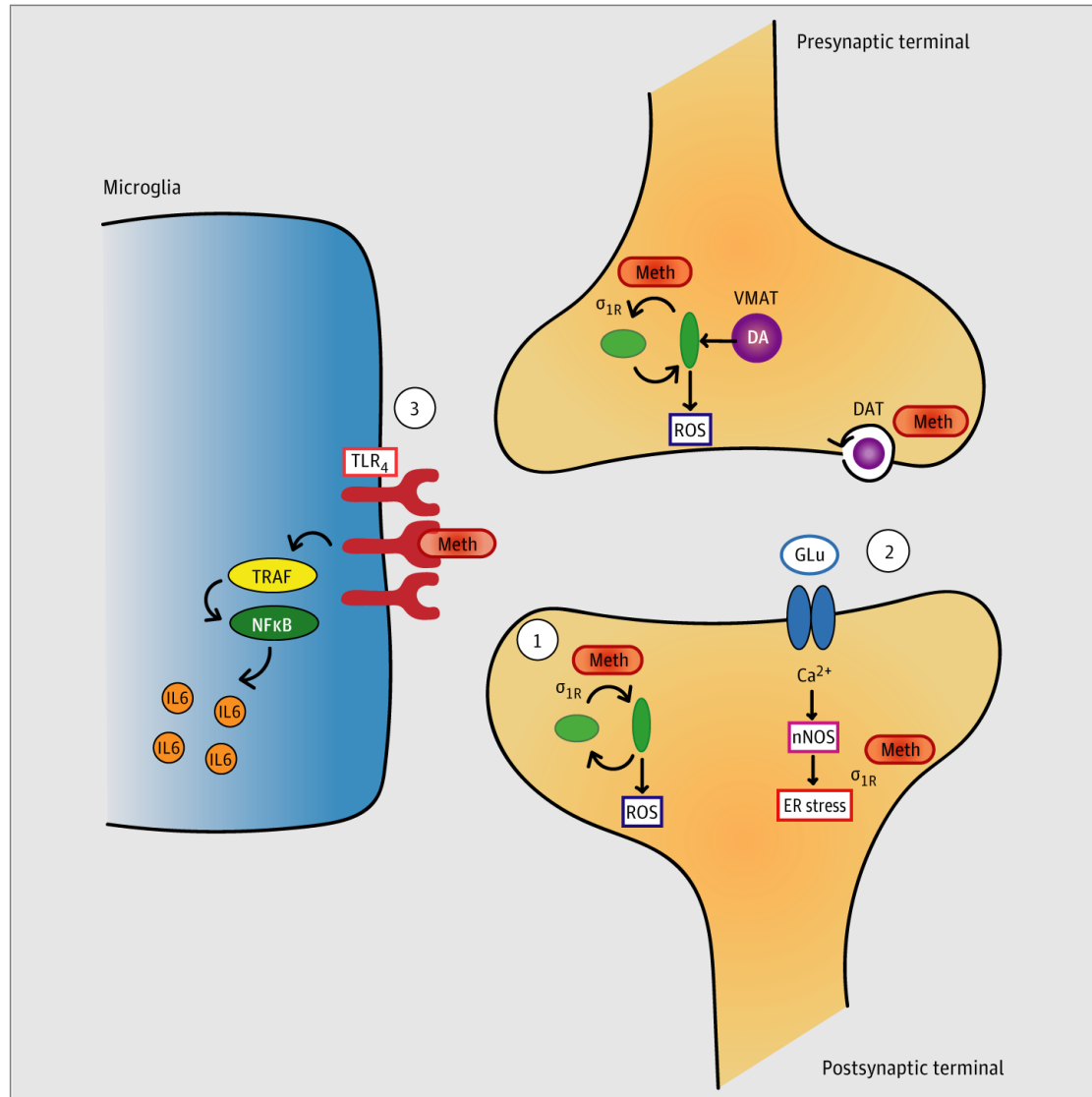
Mesolimbic pathway



NEUROSCIENCE 5e, Figure 29.10 (Part 2)
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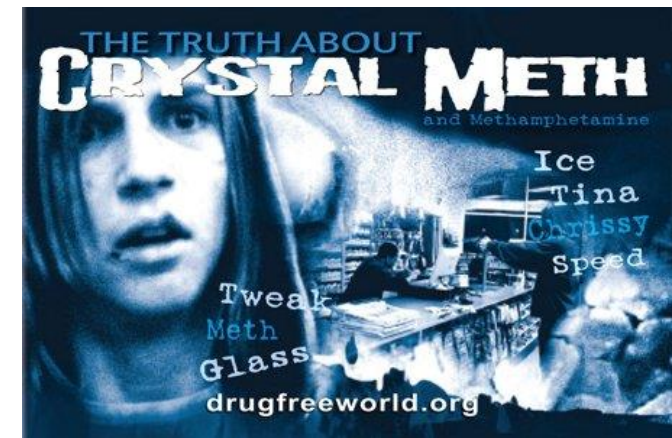
Methamphetamine toxicity

Methamphetamine causes neurotoxicity

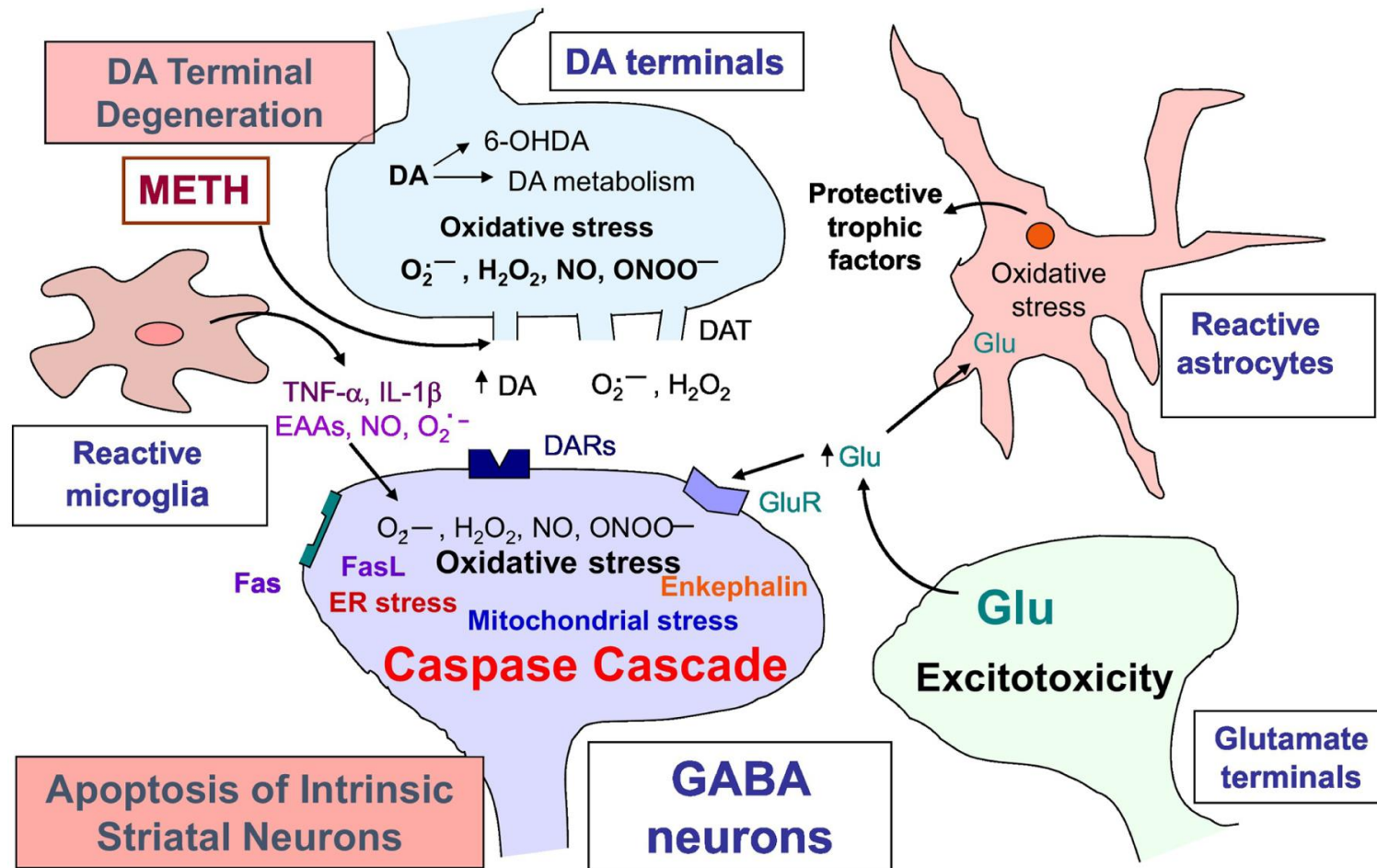


Neurotoxic pathways

- Oxidative stress pathway
- Neurotoxicity/excitotoxicity
- Neuroinflammatory pathway



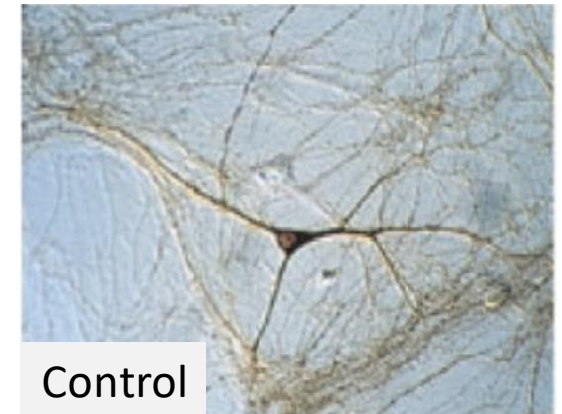
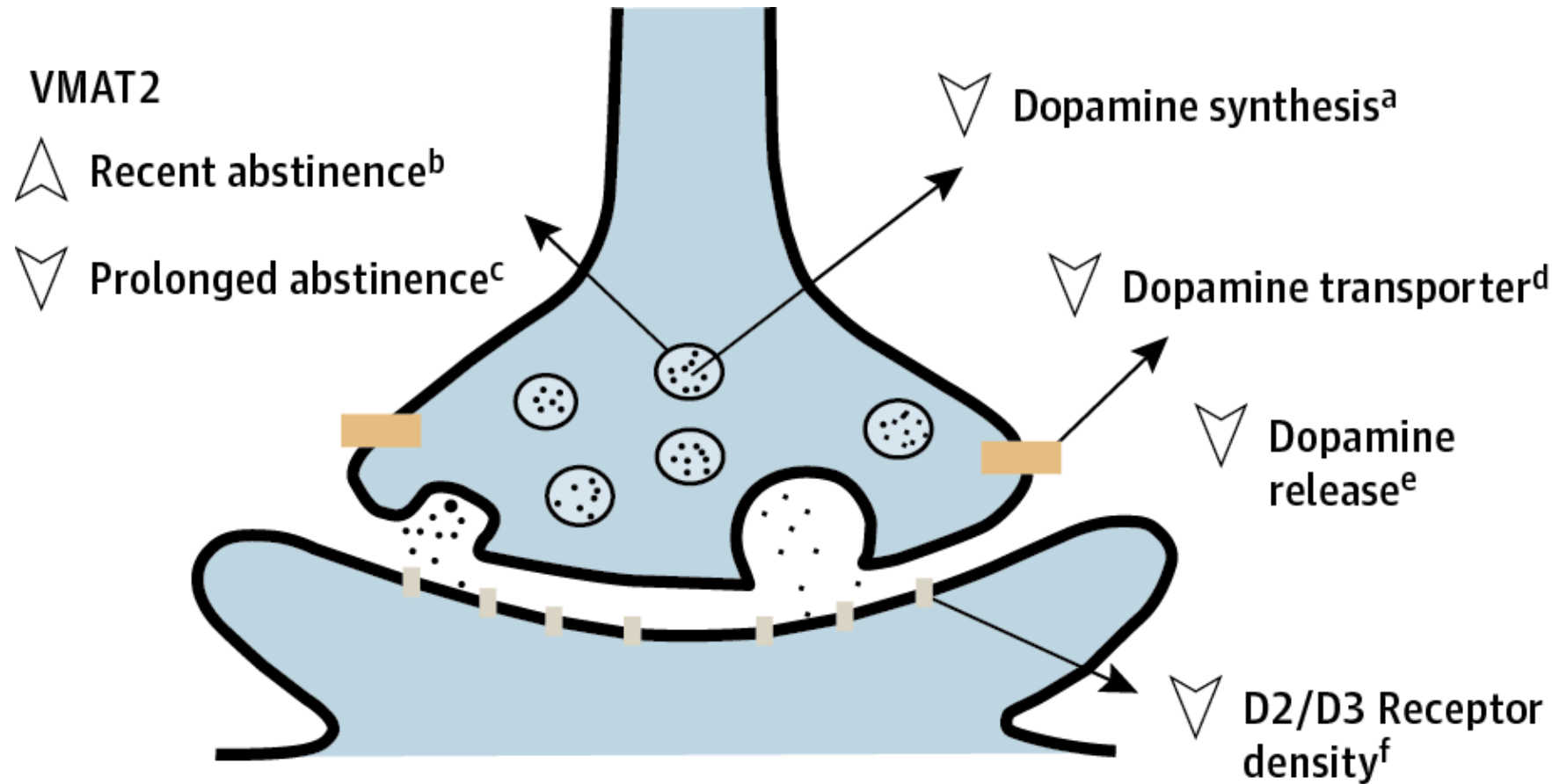
Methamphetamine causes neurotoxicity



Neuronal Effects

- Dopamine terminal degeneration
- Serotonin terminal degeneration
- Neuronal apoptosis
- Neuronal autophagy

Dopaminergic alterations in stimulant users

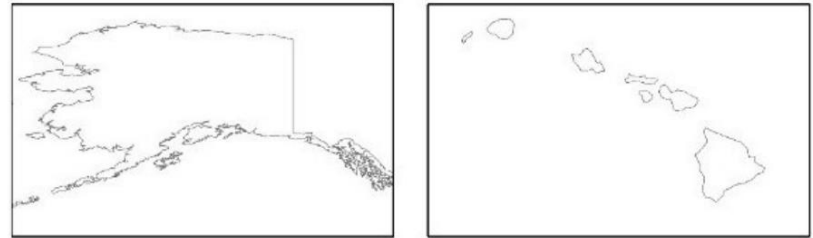
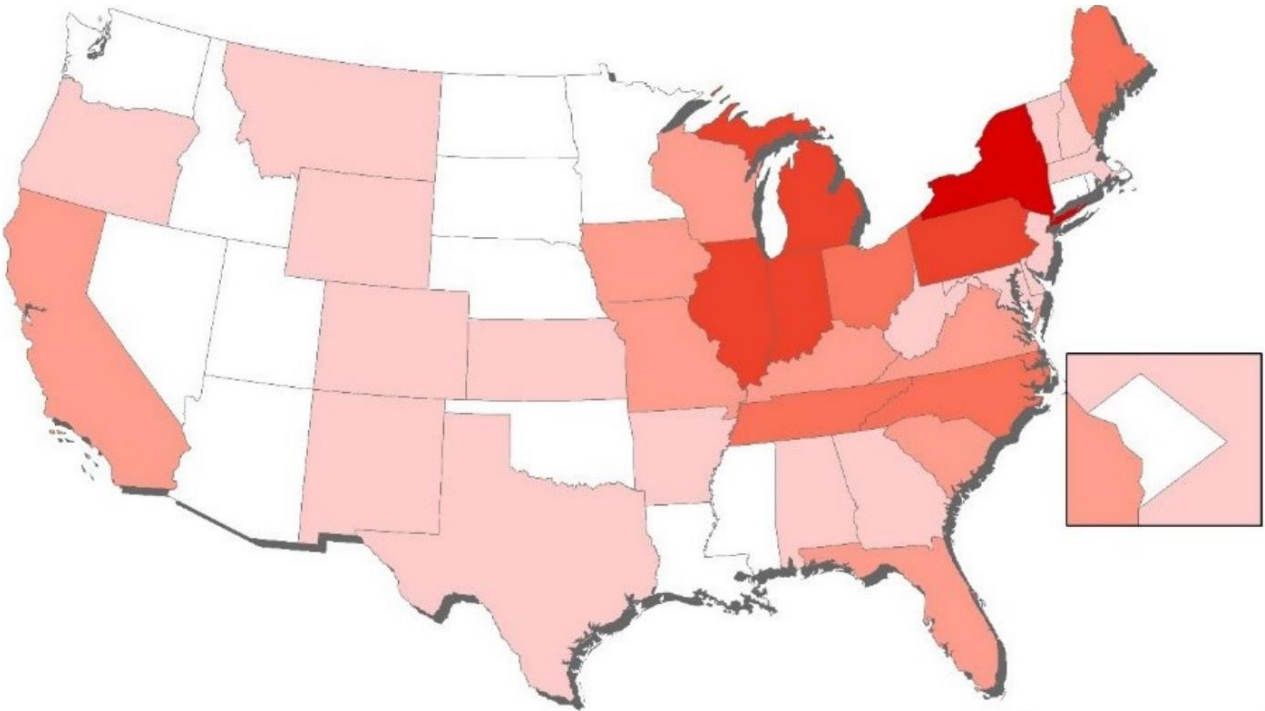
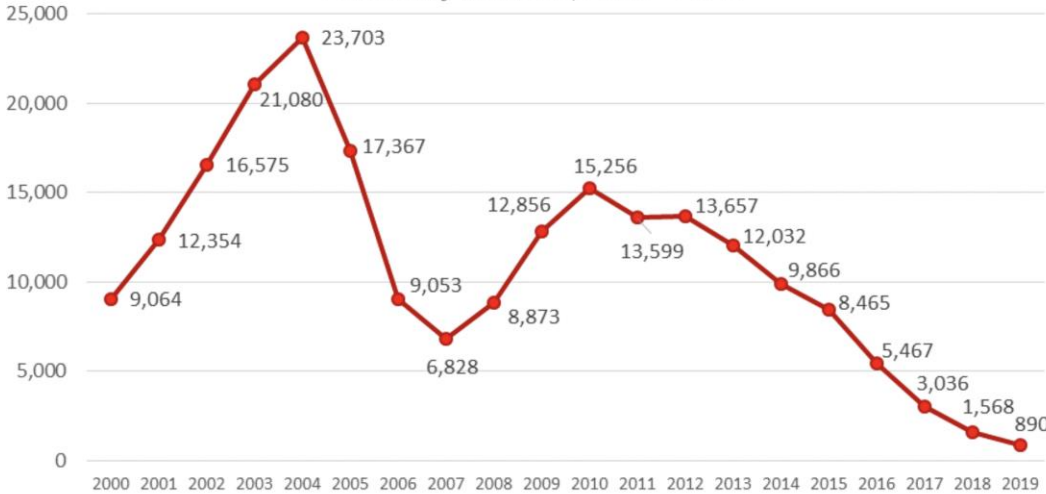


Methamphetamine-Induced Degeneration of Dopaminergic Neurons Involves Autophagy and Upregulation of Dopamine Synthesis
Journal of Neuroscience 15 October 2002, 22 (20) 8951-8960.

Origins of US methamphetamine

US domestic amphetamine production has declined since 2010

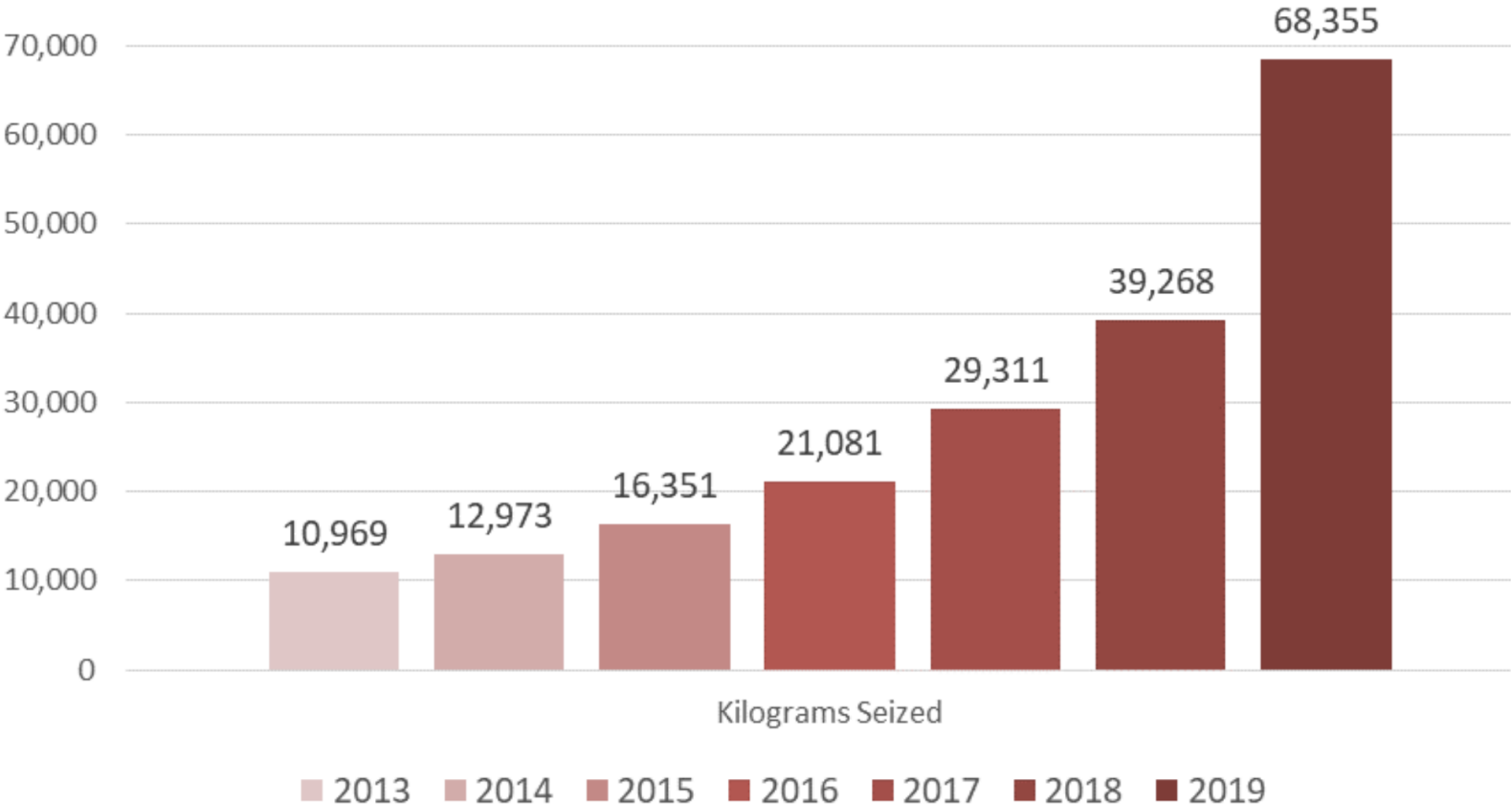
Figure 14. Number of Domestic Methamphetamine Laboratory Incidents, 2000 – 2019



Source: El Paso Intelligence Center, National Seizure System

Methamphetamine seizures at the Southwest Border are increasing

Figure 16. U.S. Customs and Border Protection Southwest Border Methamphetamine Seizures, 2013 – 2019



Most US methamphetamine is synthesized in Mexico using precursors from China and India



Precursors are shipped from China and India to Mexico



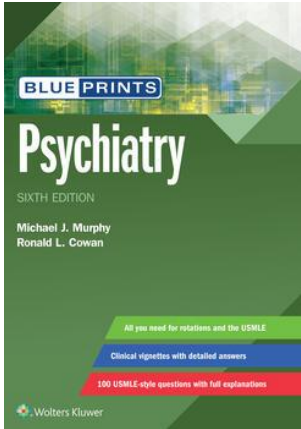
Domestic methamphetamine production peaked in 2004

Mexican transnational criminal organizations (TNCOs) control wholesale distribution

Mexican and domestic criminal groups control retail distribution

Methamphetamine Use Disorder

Methamphetamine use disorder is classified as a stimulant use disorder in the DSM-5



Criteria for substance use disorder include 2 or more of the symptoms below resulting from substance use that cause impairment or distress within a 12-month period.	
Domain	Symptom/Behavior
Impaired control	Using more than planned
	Loss of control/inability to cut down
	A great deal of time is spent with the substance
	Craving
Social impairment	Interference with role
	Continued use despite consequences
	Giving up other activities
Risky use	Using substance when physically dangerous
	Continued use in the presence of a physical or psychological problem
Pharmacological	Tolerance
	Withdrawal

Stimulant use disorder

Specify if:

- **In early remission:** After full criteria for stimulant use disorder were previously met, none of the criteria for stimulant use disorder have been met for at least 3 months but for less than 12 months (with the exception that Criterion A4, “Craving, or a strong desire or urge to use the stimulant,” may be met).

- **In sustained remission:** After full criteria for stimulant use disorder were previously met, none of the criteria for stimulant use disorder have been met at any time during a period of 12 months or longer (with the exception that Criterion A4, “Craving, or a strong desire or urge to use the stimulant,” may be met).

Specify if:

- **In a controlled environment:** This additional specifier is used if the individual is in an environment where access to stimulants is restricted.

Stimulant Use Disorder

Specify severity:

- **Mild:** Presence of 2–3 symptoms
- **Moderate:** Presence of 4–5 symptoms
- **Severe:** Presence of 6 or more symptoms

Specify drug type:

- Amphetamine-type substance
- Cocaine
- Other or unspecified stimulant

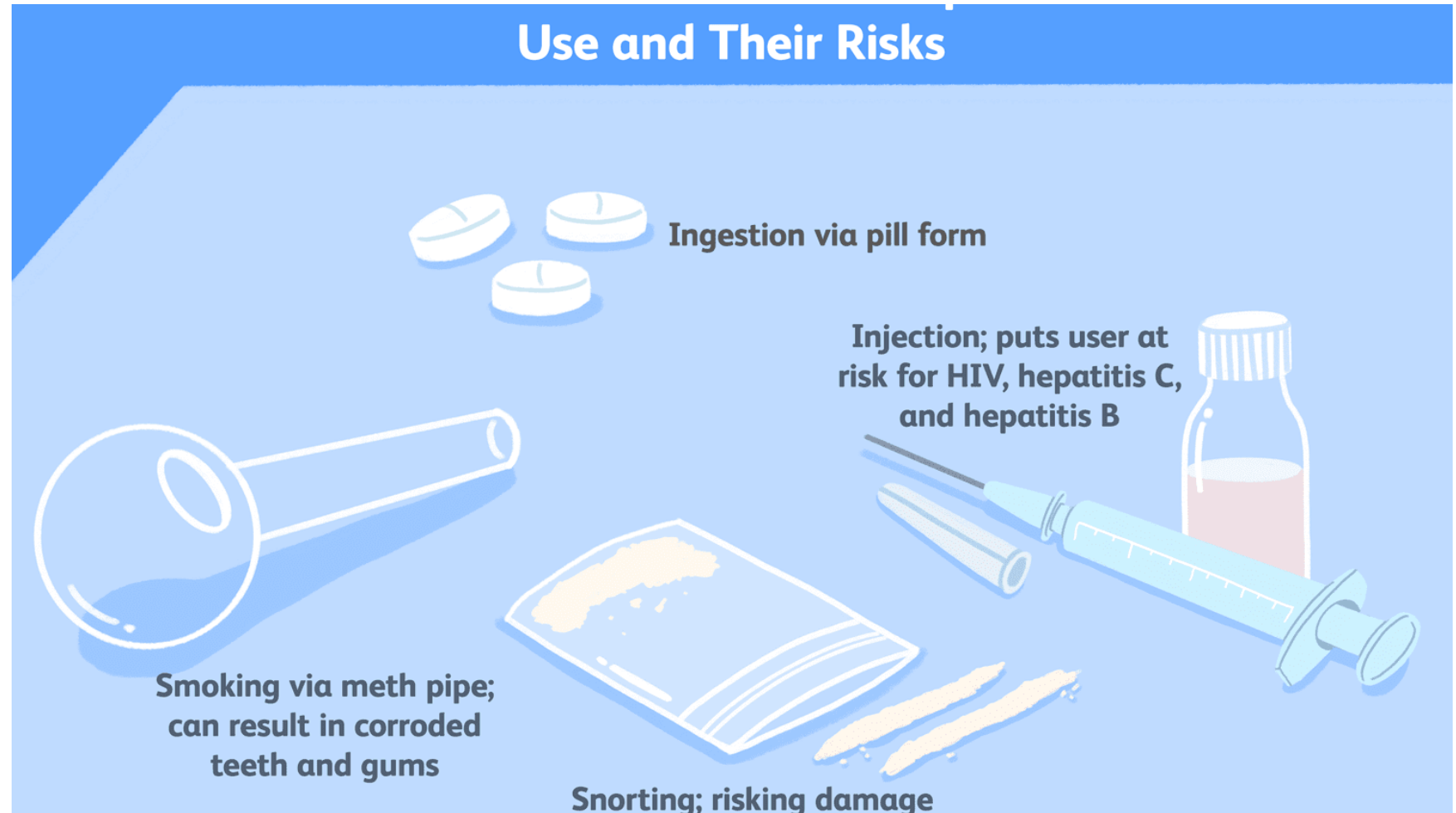


Methamphetamine use and overdose

Methamphetamine is used in a variety of ways

Methods of use

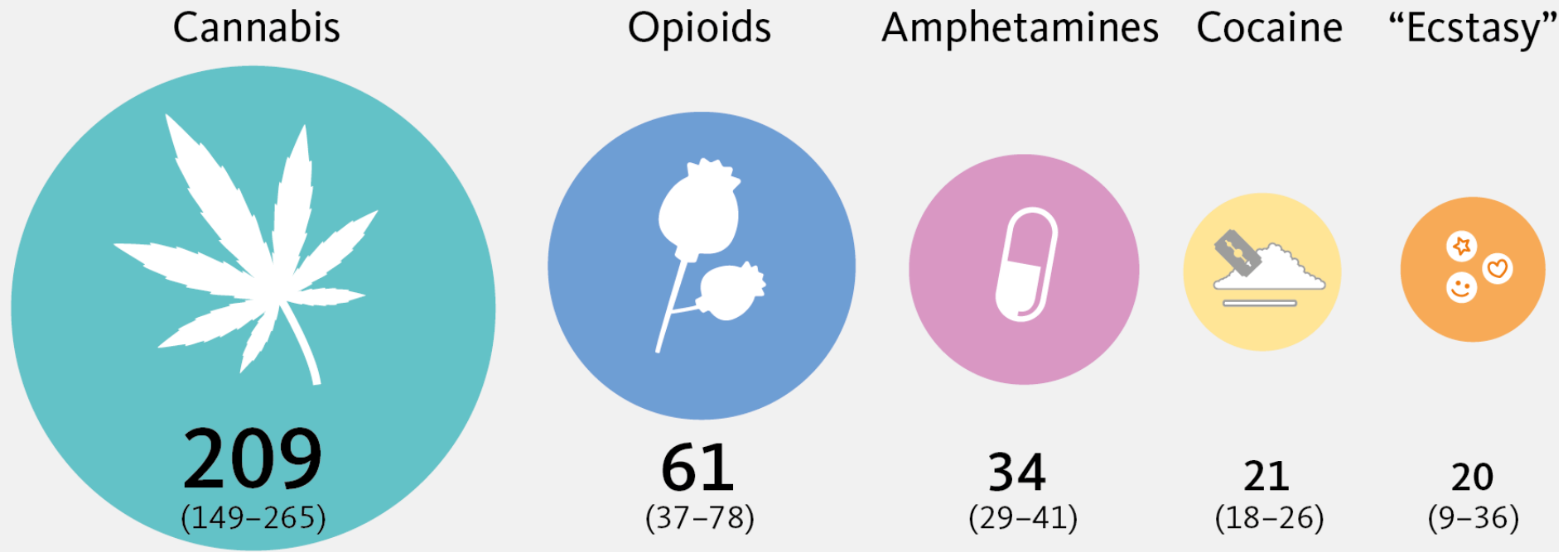
- Smoking
- Snorting
- Injection
- Oral



2 million people in the US and 30 million worldwide use methamphetamine



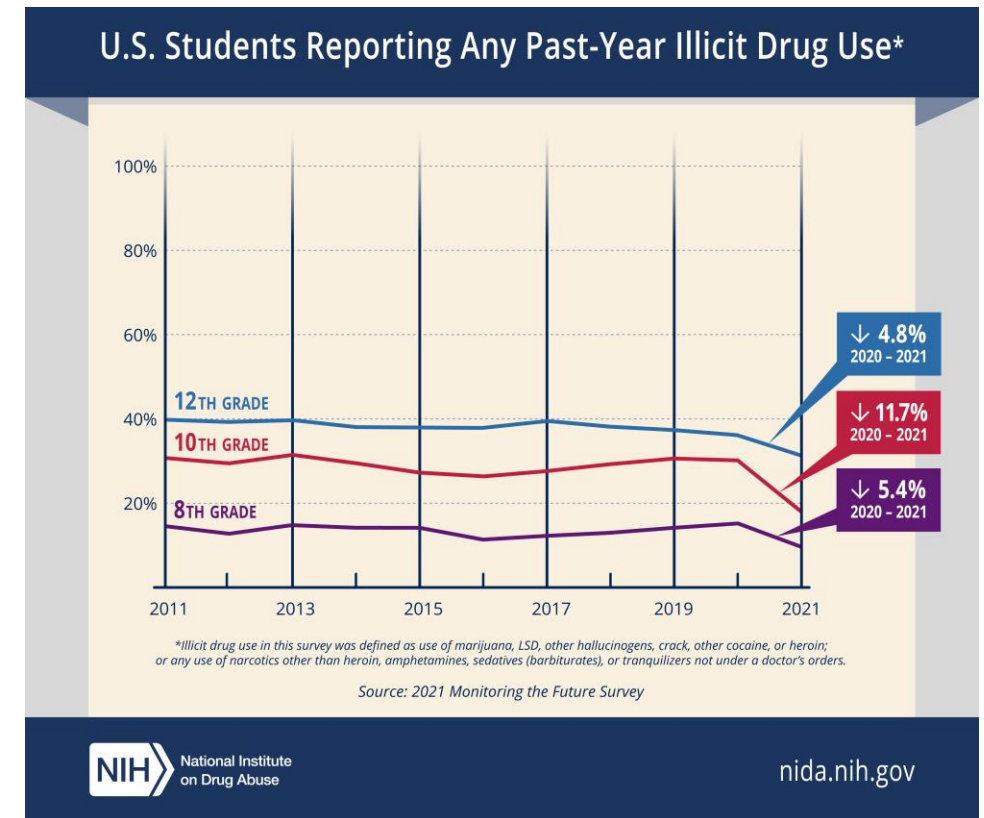
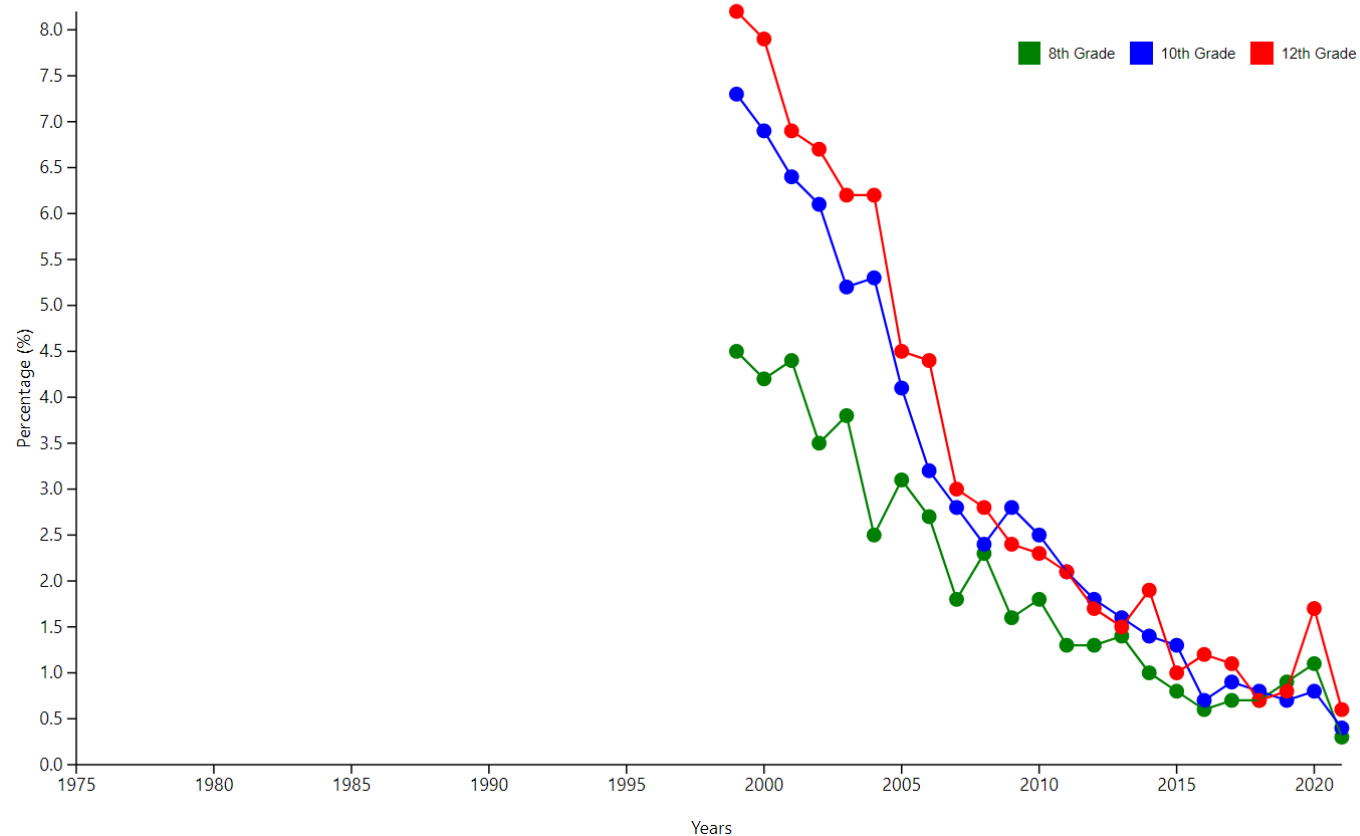
GLOBAL ESTIMATES OF THE NUMBERS OF DRUG USERS IN MILLIONS (2020)



SAMHSA: 500 people each day try meth for the first time.

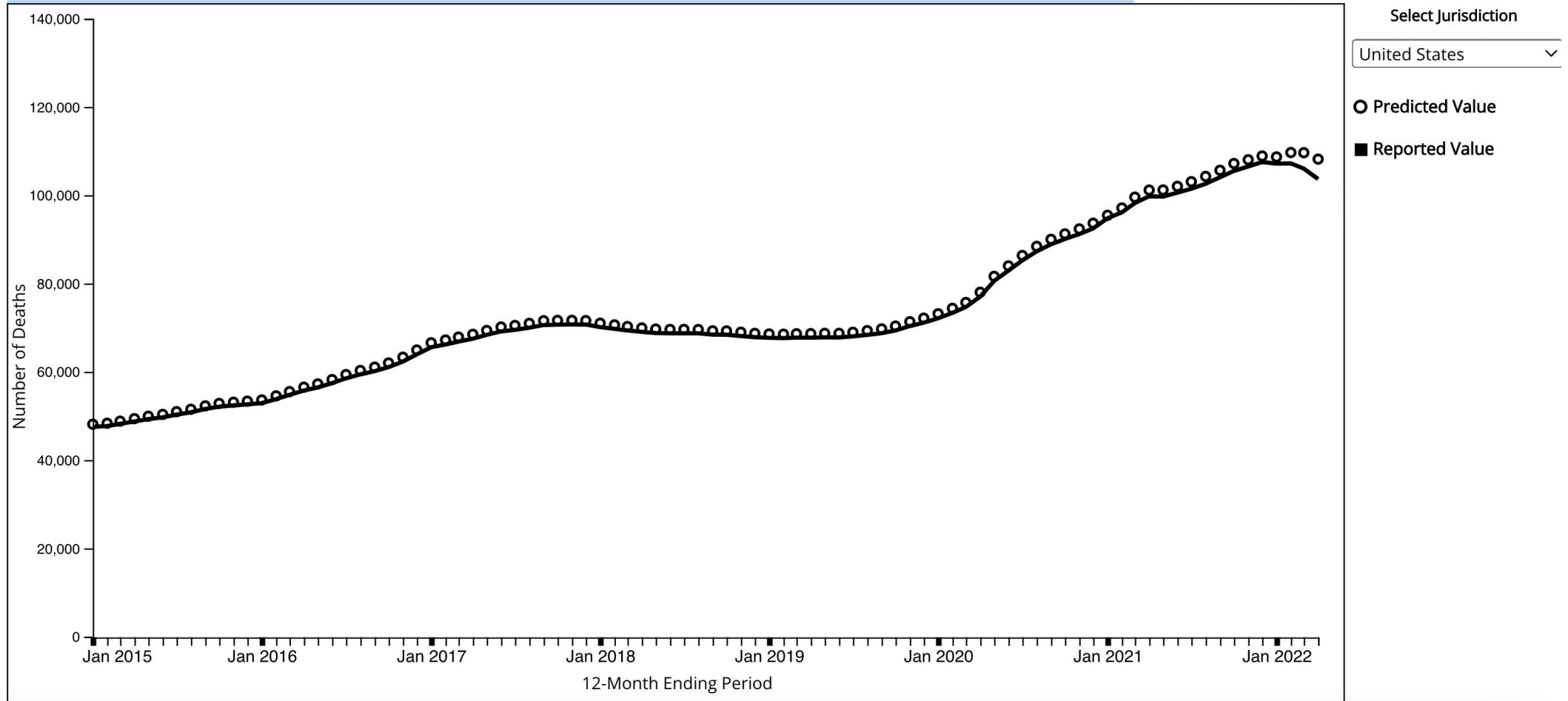
Rates of use of methamphetamines and all drugs have been declining in US school age groups

Methamphetamines: Trends in Lifetime Prevalence of Use in Grades 8, 10, and 12

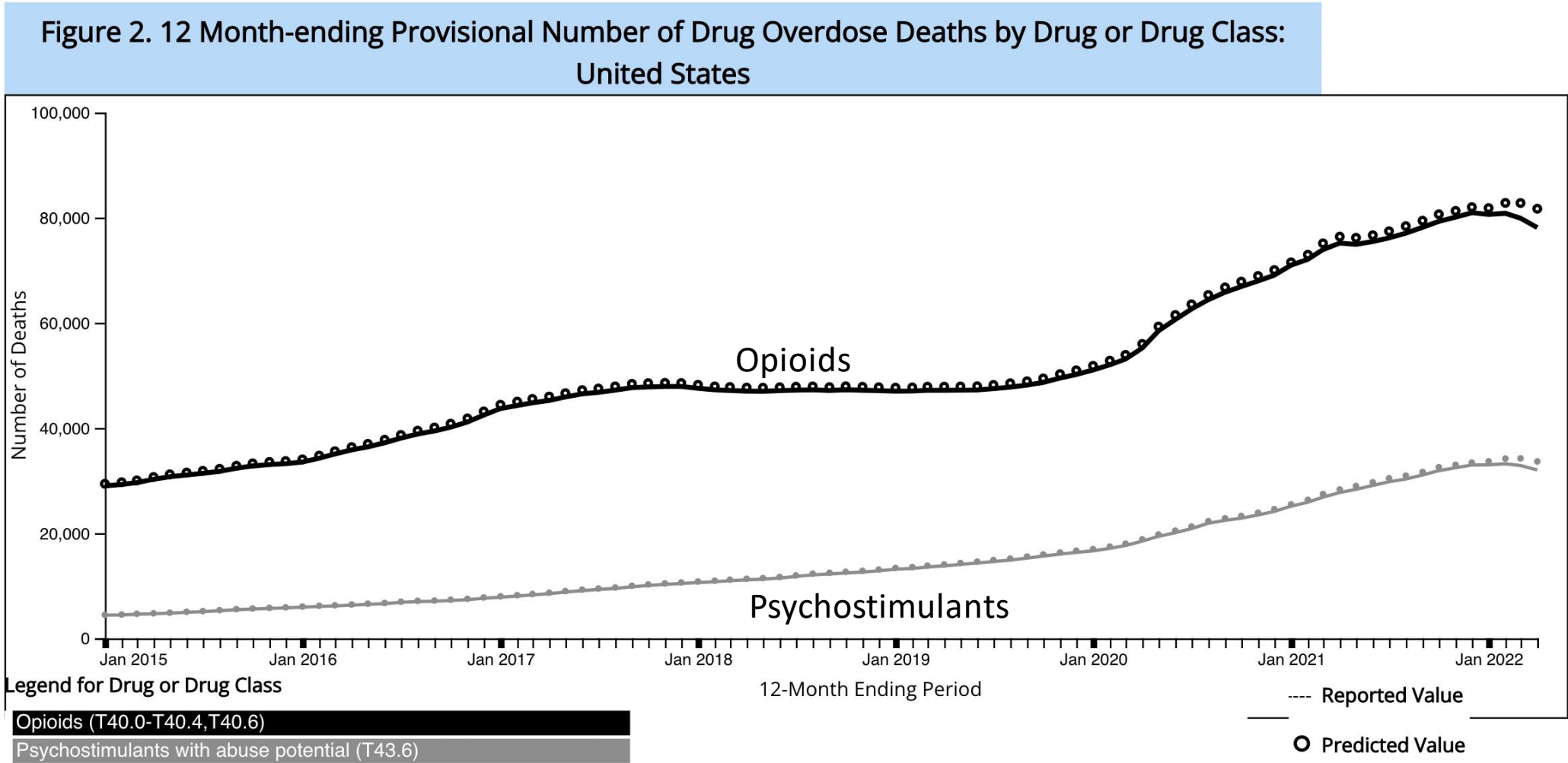


Over 100,000 people in the US died from overdose of any drug in the past 12 months

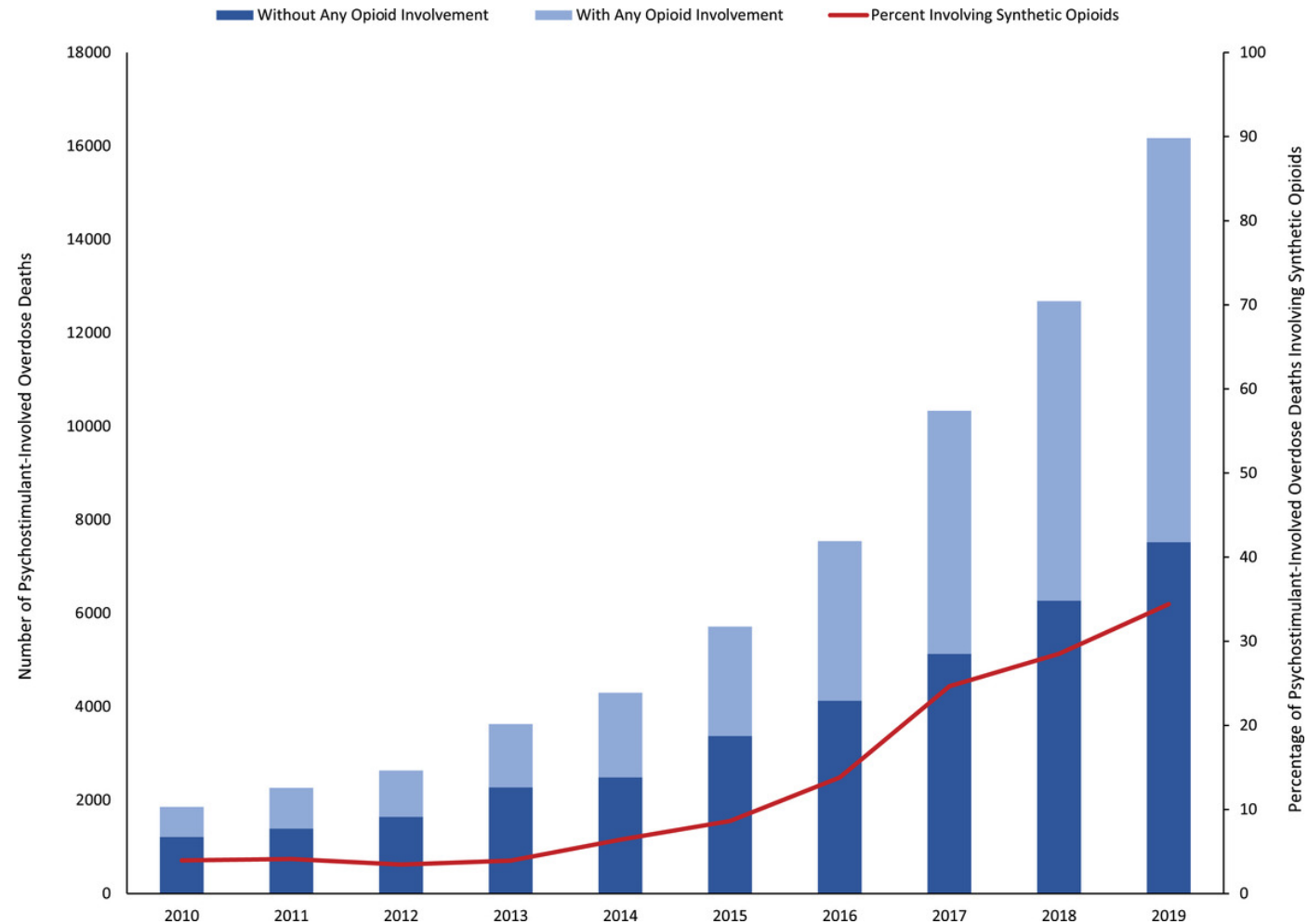
Figure 1a. 12 Month-ending Provisional Counts of Drug Overdose Deaths: United States



Most overdose deaths are due to opioids but psychostimulant overdose deaths, mostly methamphetamine, are increasing

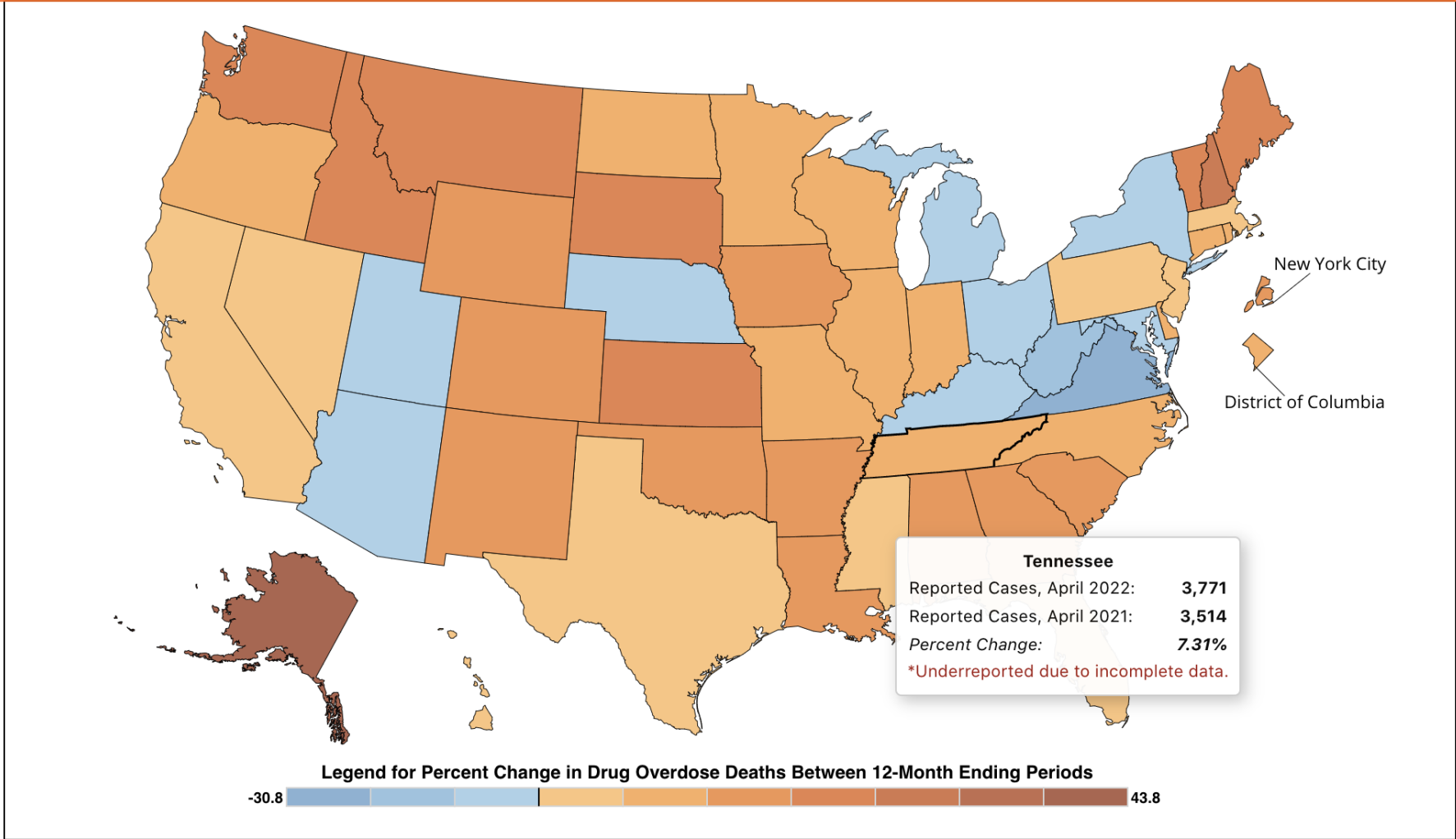


About half of psychostimulant overdose deaths involve opioids, often fentanyl



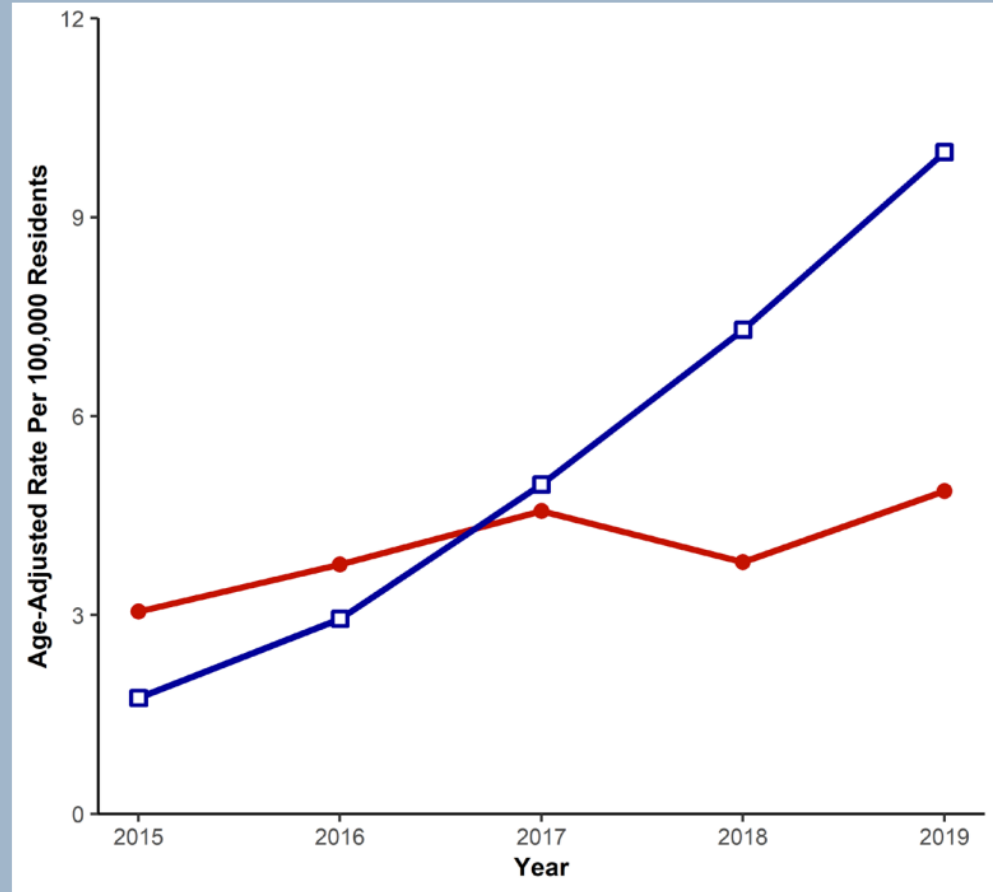
Overdose deaths to any drug rose 7% in Tennessee

Figure 1b. Percent Change in Reported 12 Month-ending Count of Drug Overdose Deaths, by Jurisdiction: April 2021 to April 2022



Psychostimulant deaths have been increasing in Tennessee

Age-Adjusted Rates for Stimulant Overdose Deaths in TN, 2015-2019



Legend

- Cocaine
- Psychostimulants (including methamphetamine)

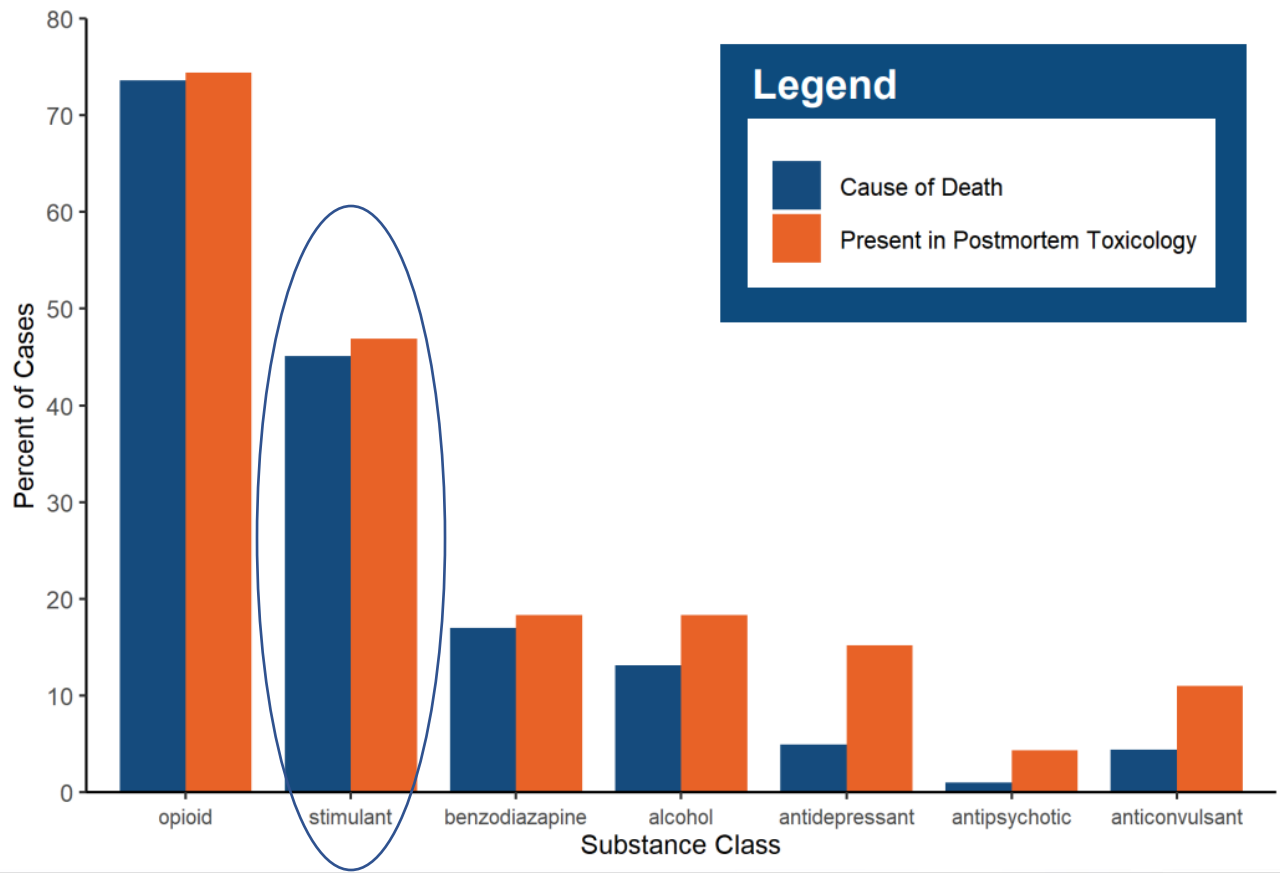
Analysis by the Office of Informatics and Analytics, TDH (last updated November 12, 2020). Limited to TN residents.

Data Source: TN Death Statistical File.



Stimulants, including methamphetamine, are the second most common cause of overdose death in Tennessee

**Major Drug Classes Involved in SUDORS
Drug Overdose Deaths in TN, 2019 (n= 1,475)²⁷**

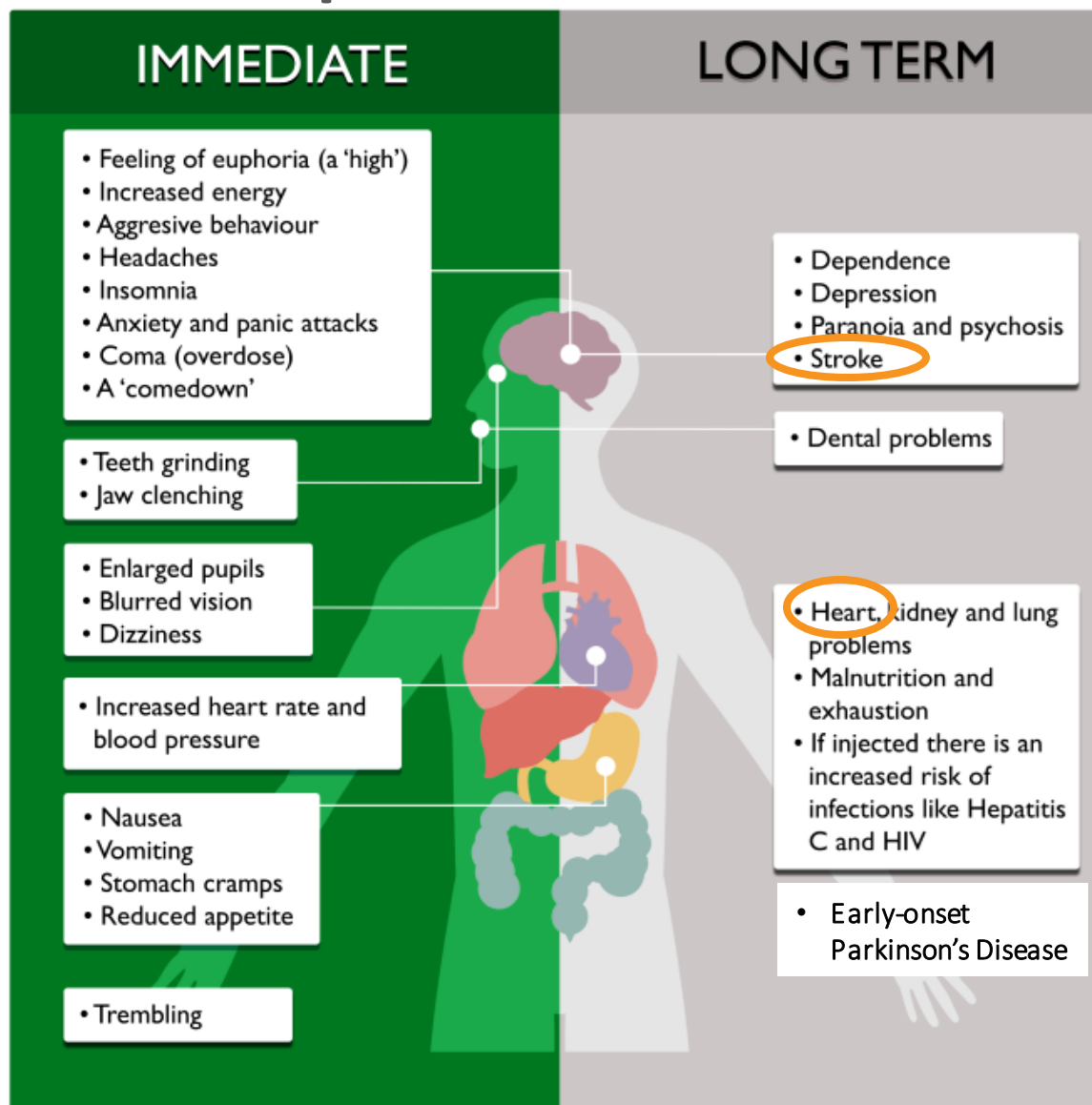


What are the consequences of
methamphetamine use?

Effects of methamphetamine use

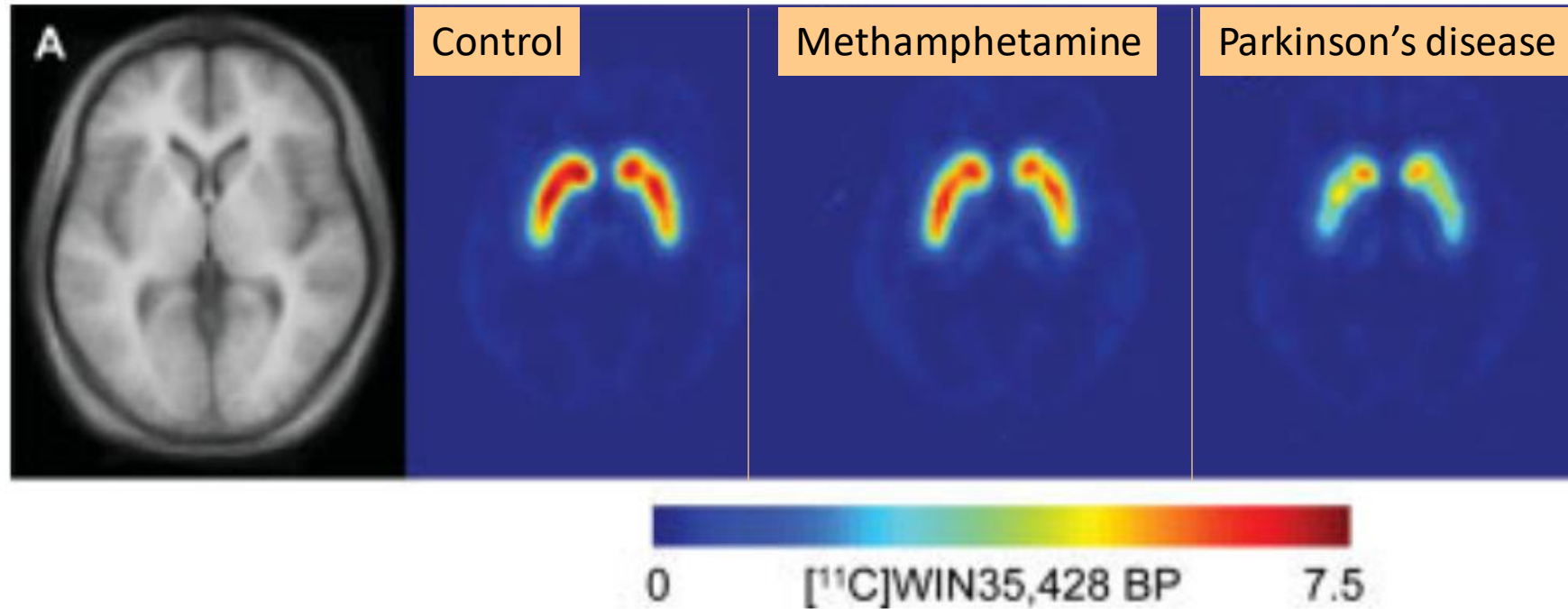


Rusk County Sheriff's Office Drug Unit



Rusk County Sheriff's Office Drug Unit

Dopamine reuptake transporters (DAT) are reduced in abstinent methamphetamine users



METH avg. exposure: mean (range)

Number of exposures

1262 (60–3285)

Duration of use (years)

5.56 (0.42–12)

Frequency of use: exposures per month

21.10 (2.08–41.67)

Usual dose (g)

0.5 (0.25–1)

Maximum dose (g)

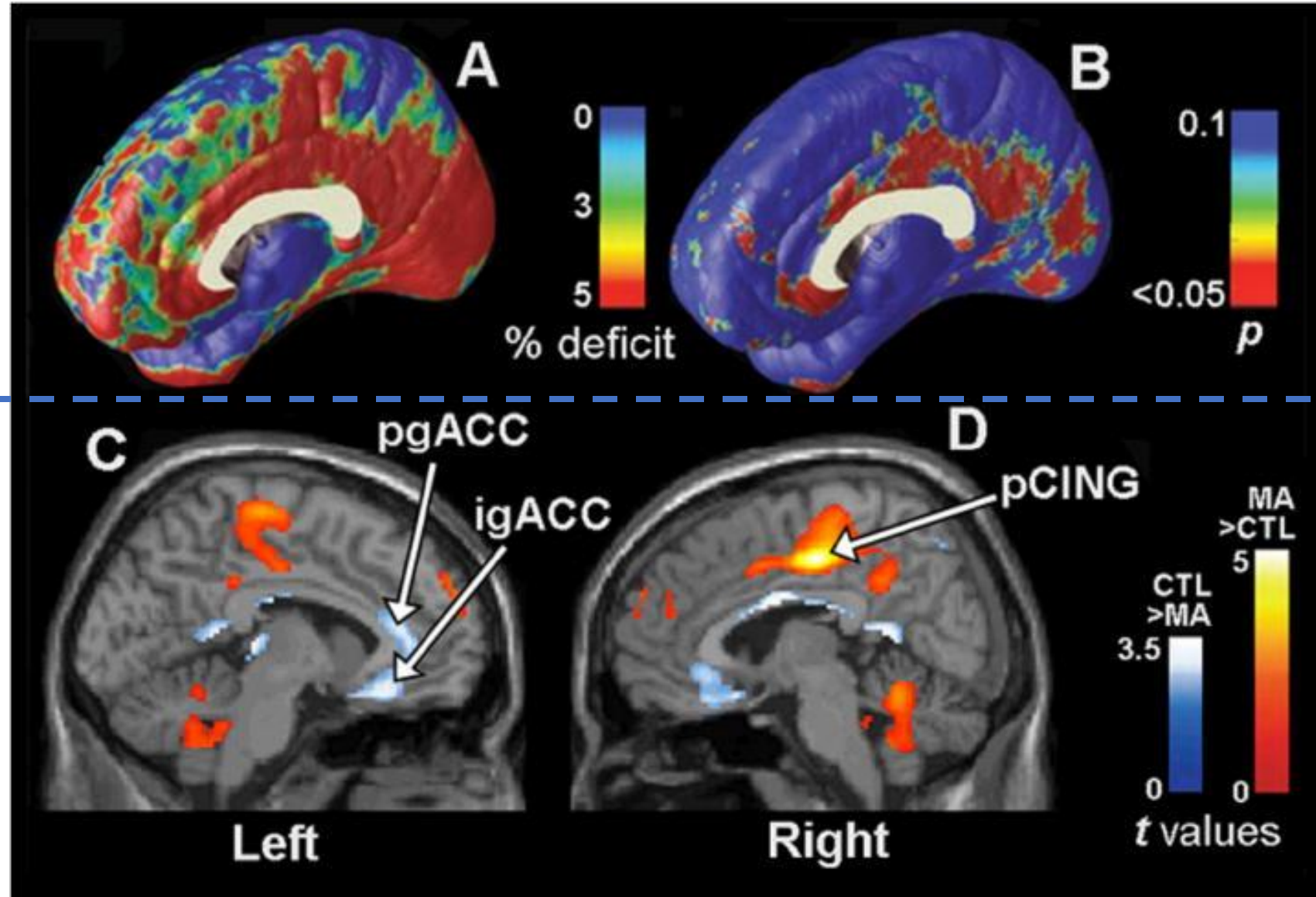
1.71 (0.5–5)

Time since last use (months)

77.43 ± 102.21 (8–300)

Methamphetamine users have altered brain structure and function

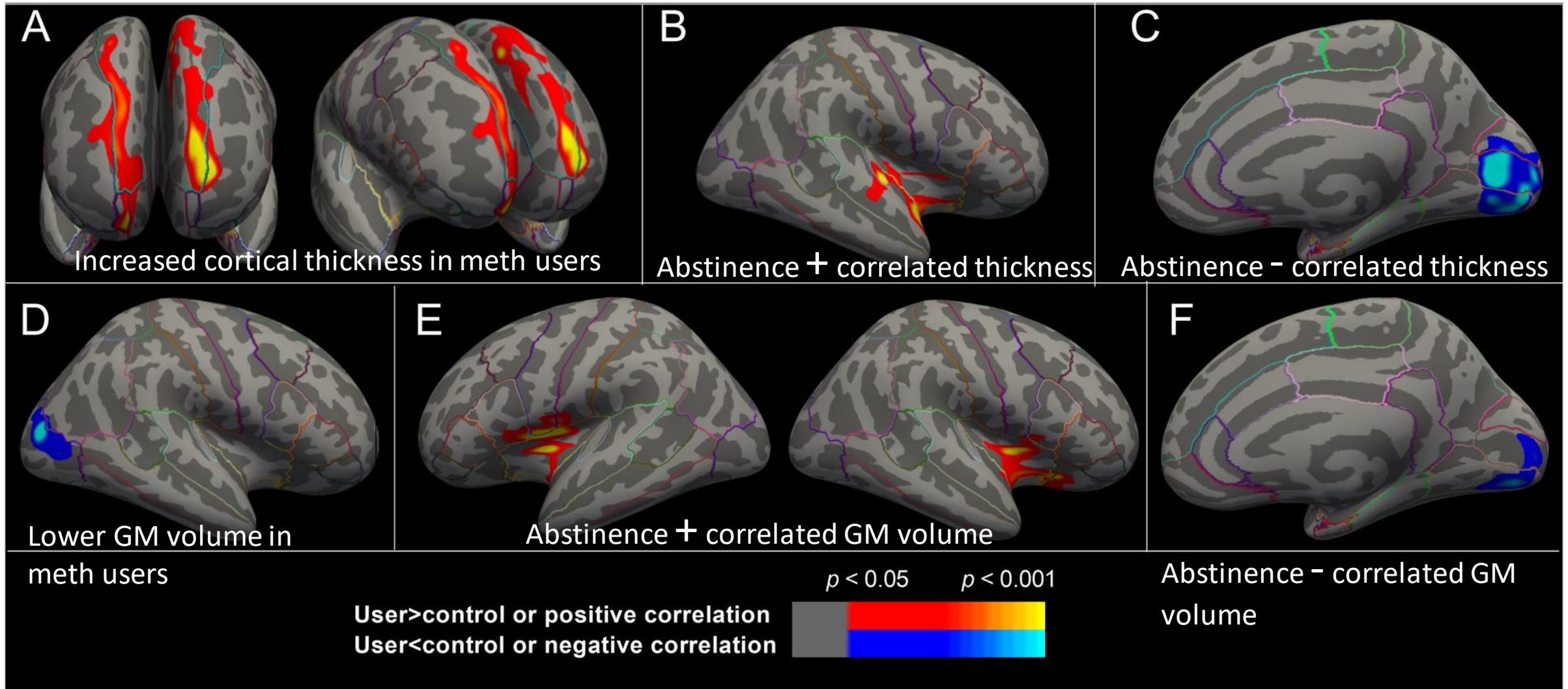
Gray
matter
volume



Glucose
metabolism



Brain gray matter in abstinent methamphetamine users



Methamphetamine users have persistently impaired cognition

Impaired Domains

- Learning efficiency
- Visual-spatial processing
- Comprehension knowledge
- Retrieval fluency
- Processing speed
- Psychomotor speed
- Impulsivity



<https://health.harvard.edu>

How do we treat methamphetamine use disorder?

Treating methamphetamine use disorder

- No FDA approved pharmacotherapies
 - some unapproved medications hold promise
- Psychotherapies and behavioral interventions have the best-established efficacy
 - contingency management may be most effective
- Transcranial Magnetic Stimulation (TMS) has shown some promise



Mostly failed trials for multiple drug classes

No clear effects on abstinence

Bupropion monotherapy

Sertraline

Atomoxetine

Imipramine

Aripiprazole

Gabapentin

Modafinil

Baclofen

Naltrexone monotherapy

Ondansetron

Varenicline

Riluzole

N-acetyl cysteine

PROMETA (flumazenil,
gabapentin, hydroxyzine)

Pharmacological treatment

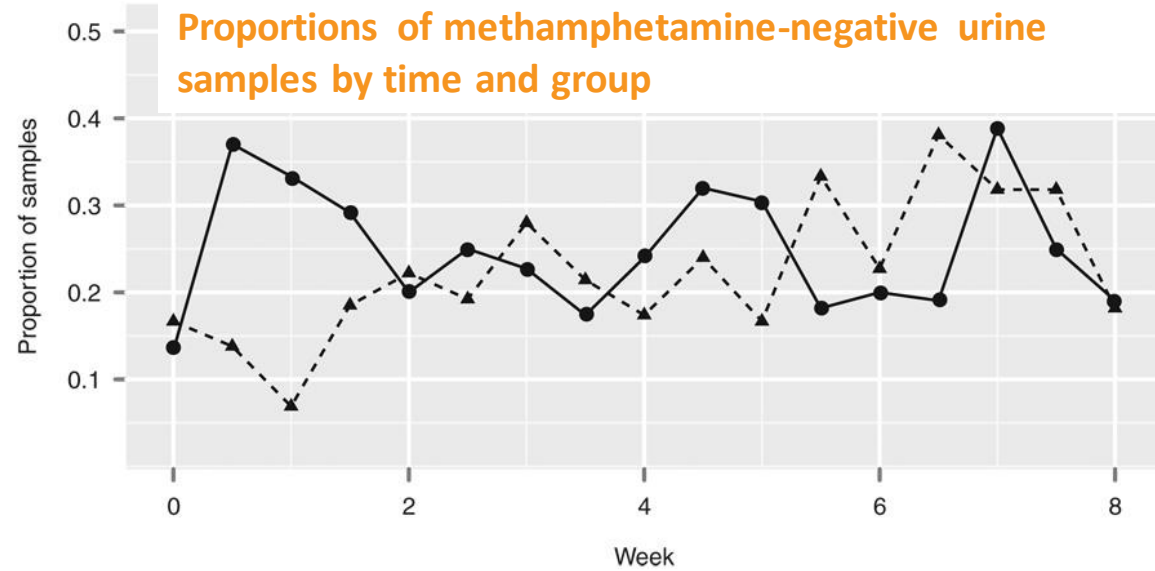
Dopamine agonist medications/psychostimulants

Dextroamphetamine SR—effective at reducing craving and some withdrawal symptoms. No effect on use.

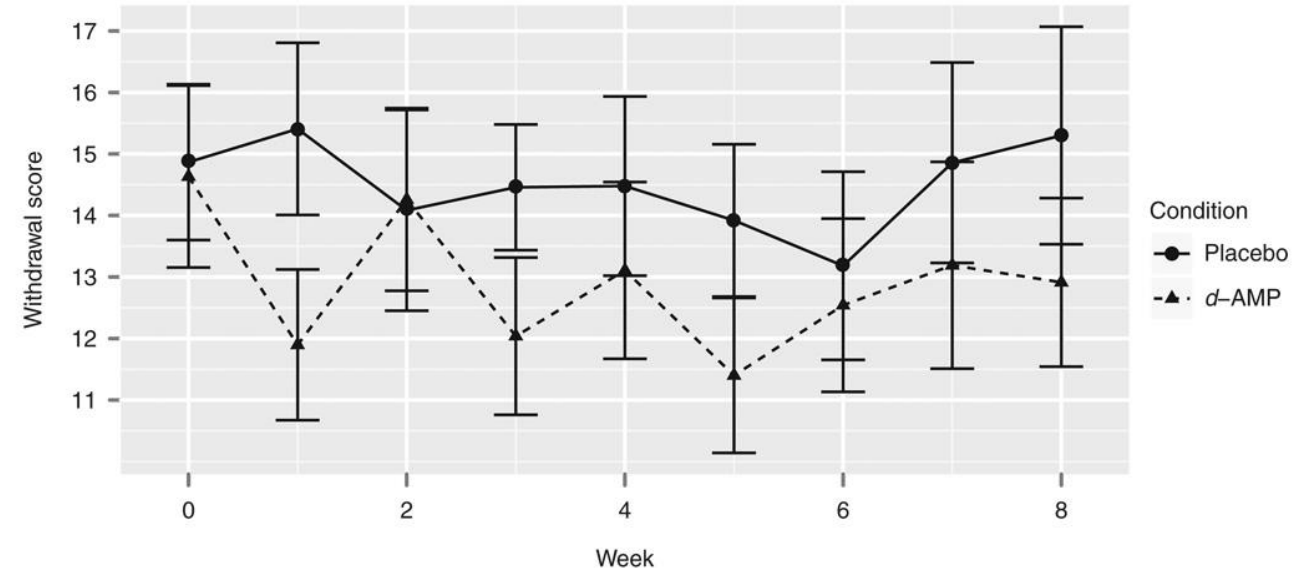
Methylphenidate—no effect on use. May improve retention in treatment.



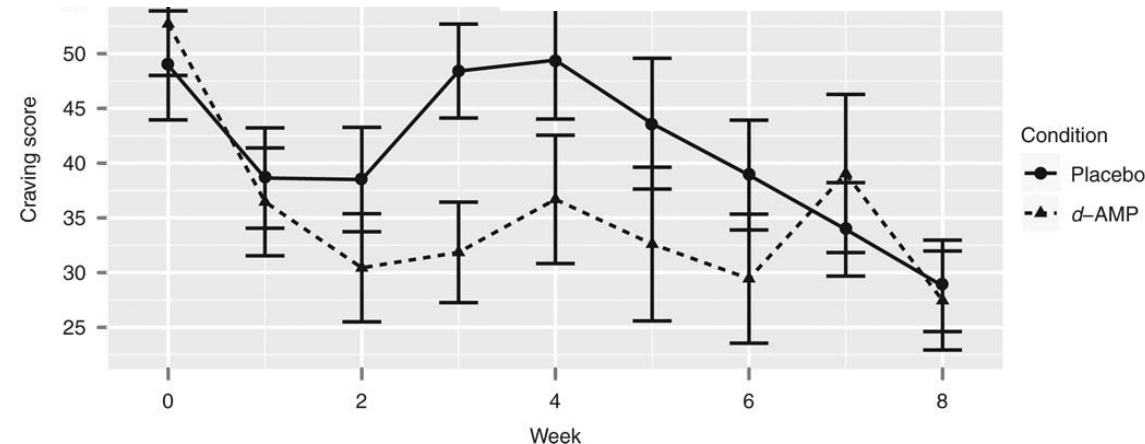
Dextroamphetamine SR in methamphetamine use disorder



Amphetamine Withdrawal Questionnaire scores by time and group



Methamphetamine craving visual analog scale scores by time and group



Interventions

- 60 mg dextroamphetamine SR daily x 8 weeks
- 50 minutes of psychotherapy/week both groups

Pharmacological treatment

Mirtazapine

Meta-analysis of two trials suggest slight efficacy in reducing positive urine at 12 weeks.

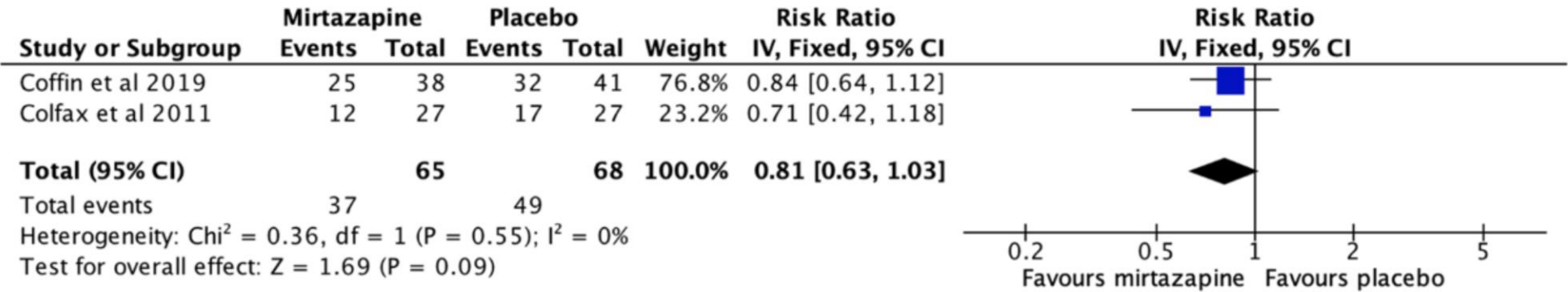


Fig. 2. : Forest plot and meta-analysis of reduction in methamphetamine positive urine toxicology screens at 12 weeks.

No effects on retention in treatment or depression.

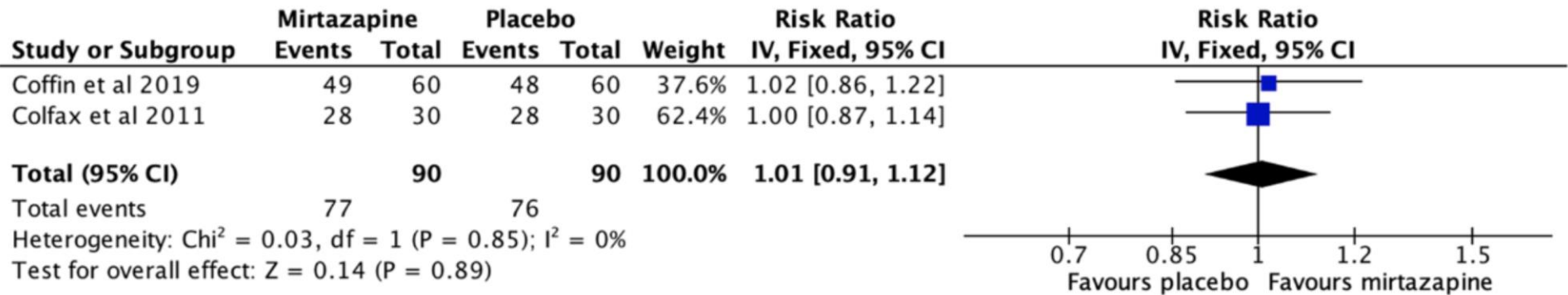
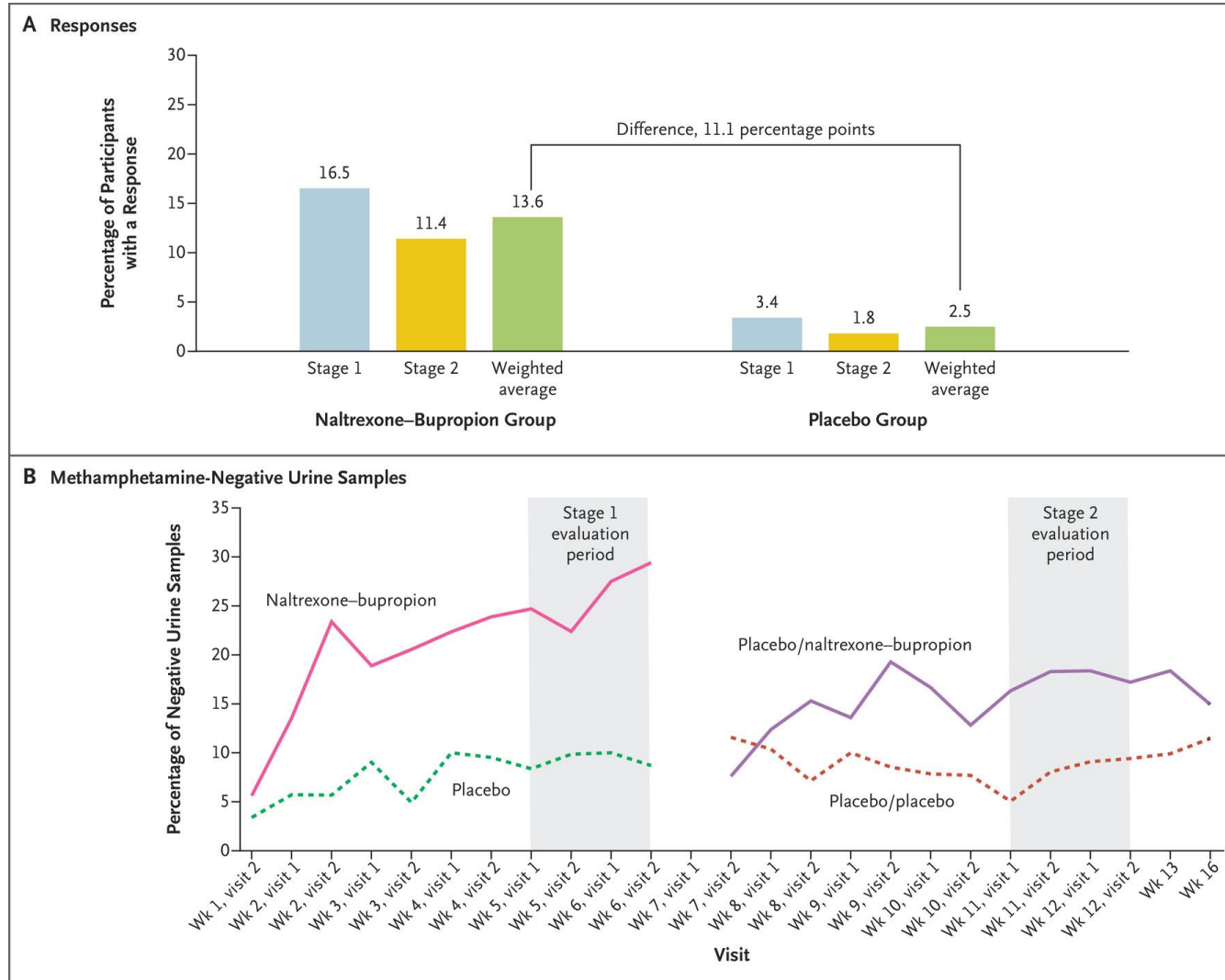


Fig. 3. : Forest plot and meta-analysis of retention in treatment at 12 weeks.

Pharmacological treatment

Bupropion
plus
naltrexone
shows
promise



Regimen

- extended-release injectable naltrexone (380 mg every 3 weeks)
- plus
- oral extended-release bupropion (450 mg per day)

Psychological and behavioral treatments

Contingency management (CM) has the greatest effect

- decreased methamphetamine use, improved treatment retention, decreased psychiatric symptoms, less risky sexual behavior. Unclear duration of effect.

Cognitive behavioral therapy (CBT)

- likely less effective than CM. Decreases use, craving, and relapse.

Psychological and behavioral treatments

Matrix model

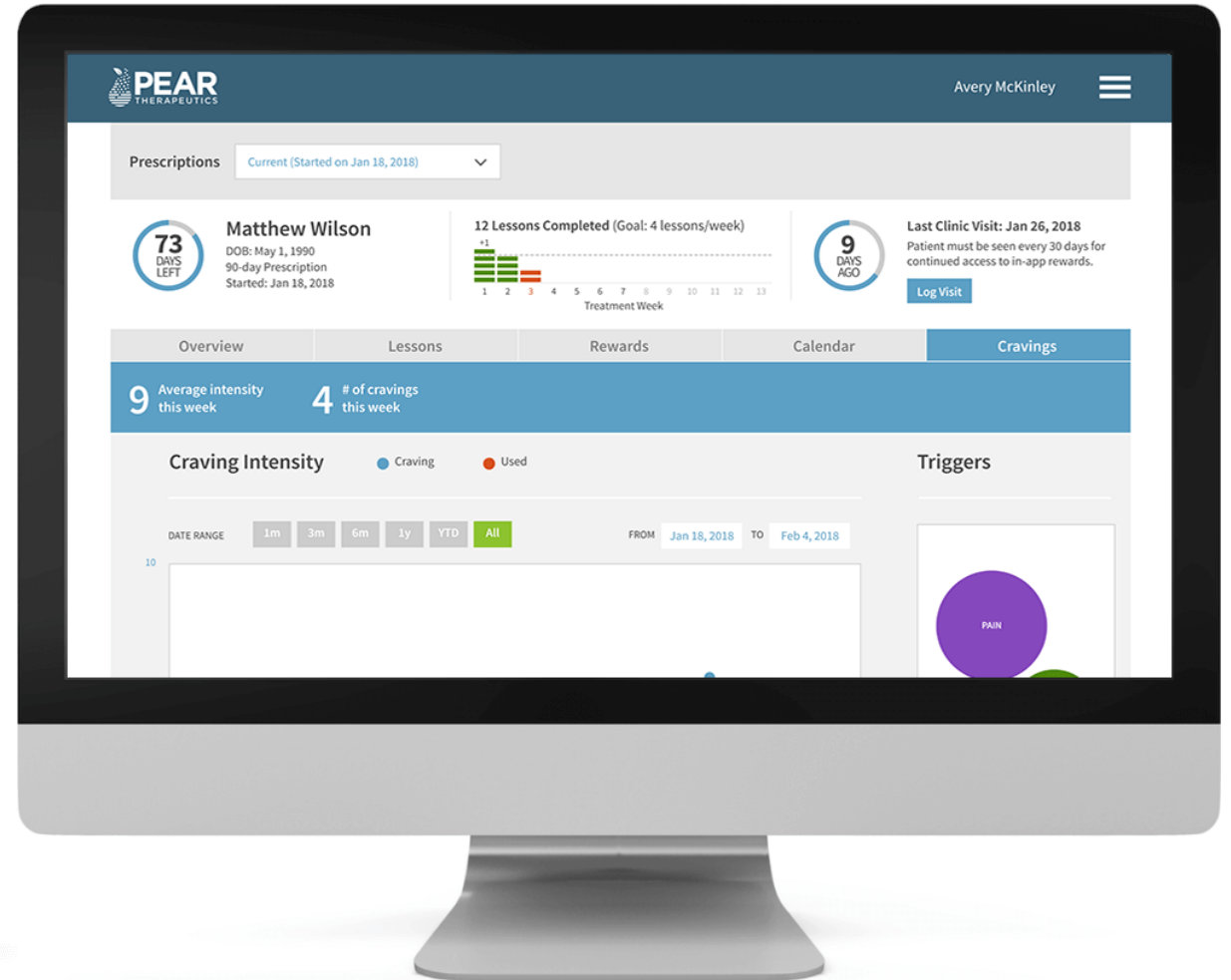
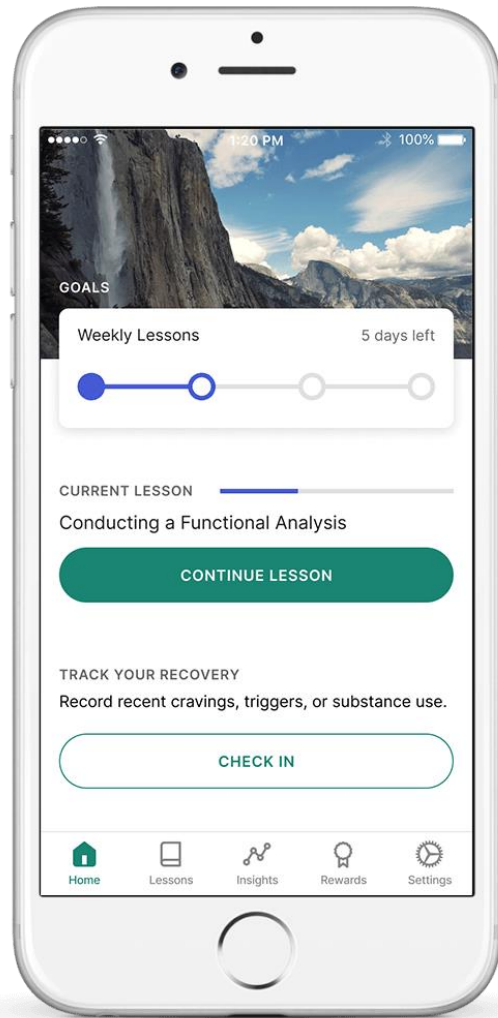
- incorporates CM, CBT, 12-step programs, motivational interviewing
- leads to reduced methamphetamine use, higher abstinence, reduced craving

reSET mobile app (Prescription Digital Therapeutic)

- FDA approved for 90-day app-based CBT delivery in conjunction with contingency management
- reduces methamphetamine use and craving

Psychological and behavioral treatments

reSET[®]



Current US clinical trials for methamphetamine use disorder

- TMS—targeting craving
- Ibudilast—targeting brain inflammation and impact on decision making
- Monthly injectable buprenorphine
- Progesterone in post-partum women to prevent return to use
- Laser acupuncture
- Contingency management
- Acceptance and Commitment Therapy (ACT)
- IXT-m200—anti meth monoclonal antibody

Summary

Methamphetamine

- Used widely
- Is neurotoxic, especially to monoamine neurons
- Has cardiac and vascular toxicity
- Second highest cause of drug overdose deaths
- Is associated with structural brain change
- Is associated with psychiatric illness and cognitive impairments
- No established pharmacological treatments
- Contingency management and CBT show the best treatment effects



Thanks!

