



Northwest (HHS Region 10)

**ATTC**

Addiction Technology Transfer Center Network  
Funded by Substance Abuse and Mental Health Services Administration



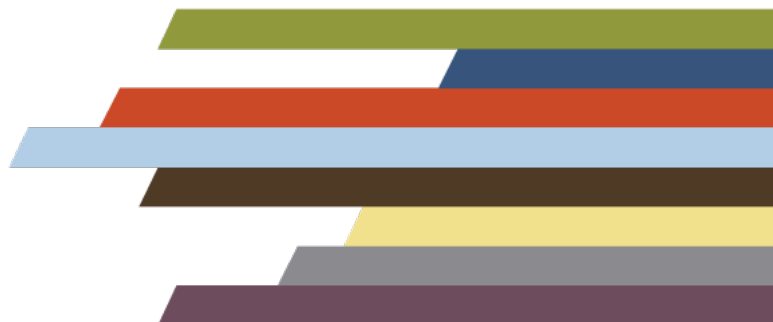
Northwest ATTC & CTN Western States Node present:

# Methamphetamine Use Disorder: Getting Up to Speed on Trends & Treatments

**SAMHSA**  
Substance Abuse and Mental Health  
Services Administration



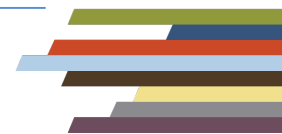
Northwest  
**ATTC**



# Methamphetamine Use Disorder

## Robrina Walker, PhD

- Associate Professor, Dept. of Psychiatry, U Texas Southwestern Medical Center
- Helped lead CTN Texas Node
  - Co-Lead Investigator of CTN-0068
  - Co-Investigator of CTN-0090
- Co-Investigator of the COMEBACK study



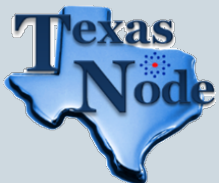
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# Methamphetamine Use Disorder: Getting Up to Speed on Trends and Treatments

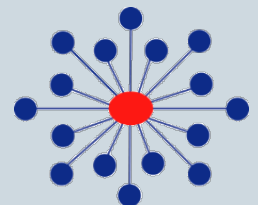
Robrina Walker, PhD

Associate Professor

University of Texas Southwestern Medical Center



February 25, 2020





# Disclosures

- Disclosures
  - Alkermes: Provided injectable extended-release naltrexone (Vivitrol®) for CTN-0054 ADAPT-MD
  - Alkermes: Provided injectable extended-release naltrexone (Vivitrol®) and matched injectable placebo for CTN-0068 ADAPT-2
- Funding
  - NIDA UG1 DA020024 (PI: Trivedi)
  - NIDA R34 DA045592 (PI: Nijhawan)

# Opioids are a Huge and Necessary Focus...

## Why fentanyl is deadlier than heroin, in a single photo

By ALLISON BOND / SEPTEMBER 29, 2016



On the left, a lethal dose of heroin; on the right, a lethal dose of fentanyl.  
NEW HAMPSHIRE STATE POLICE FORENSIC LAB





## Experts Warn of Emerging ‘Stimulant Epidemic’

By Brenda Goodman, MA



April 3, 2018 – With the nation still reeling from the [opioid crisis](#), drug forecasting experts say a new wave of [addiction](#) is coming and the United States isn't ready for it.

Abuse of stimulants like [methamphetamine](#), [cocaine](#), and even [prescription drugs](#) like Adderall and Ritalin is surging across the country, fed by cheap, potent, and plentiful supplies.

“No one is paying attention to this,” said John Eadie, coordinator for the National Emerging Threat Initiative, which provides research to the government’s High Intensity Drug Trafficking Areas program.



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“Everyone, correctly, is focused on opioids and should be because of the known problem there. But this other problem is catching up with us very rapidly.”

<https://www.webmd.com/mental-health/addiction/news/20180403/experts-warn-of-emerging-stimulant-epidemic>

<https://www.npr.org/sections/health-shots/2018/10/25/656192849/methamphetamine-roils-rural-towns-again-across-the-u-s>

# Methamphetamine Roils Rural Towns Again Across The U.S.

October 25, 2018 - 1:29 PM ET  
Heard on All Things Considered

FRANK MORRIS

FROM KCUR 89.3



A drug specialist in the Mexican army shows crystal methamphetamine paste seized at a clandestine laboratory in Mexico's Baja California in August. Much of the meth sold in the U.S. today comes from Mexico, according to DEA officials.  
GUILLERMO ARIAS/AFP/Getty Images





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HEALTH • PUBLIC HEALTH

## Opioids Are In the Spotlight. But Meth Hospitalizations Are Surging



By ANNA GOODMAN / WEBMD HEALTH NEWS November 21, 2018



The paste seized at a clandestine laboratory in Mexico's states from Mexico, according to DEA officials.

<https://www.webmd.com/mental-health/addiction/news/20180403/experts-warn-of-emerging-stimulant-epidemic>

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[http://time.com/5460632/meth-hospitalizations-](http://time.com/5460632/meth-hospitalizations-opioids/?utm_source=twitter.com&utm_medium=social&utm_campaign=time&xid=time_socialflow_twitter)

[opioids/?utm\\_source=twitter.com&utm\\_medium=social&utm\\_campaign=time&xid=time\\_socialflow\\_twitter](http://time.com/5460632/meth-hospitalizations-opioids/?utm_source=twitter.com&utm_medium=social&utm_campaign=time&xid=time_socialflow_twitter)



Opinion

# Gay Men Are Dying From a Crisis We're Not Talking About

No one's really grappling with the meth disaster.

By **Jim Mangia**

Mr. Mangia runs a network of community health centers in Los Angeles.

Jan. 22, 2020



Opinion

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Mr. Mangia runs a network of community health centers in Louisiana.

Jan. 22, 2020

HEALTH

## Arkansas leads U.S. in meth use, study finds



(Source: AP)



# Objectives

1. Describe trends in the use of methamphetamine
2. Describe evidence-based treatments for methamphetamine use disorder
3. Summarize current research investigating new treatments for methamphetamine use disorder



# Methamphetamine Trends



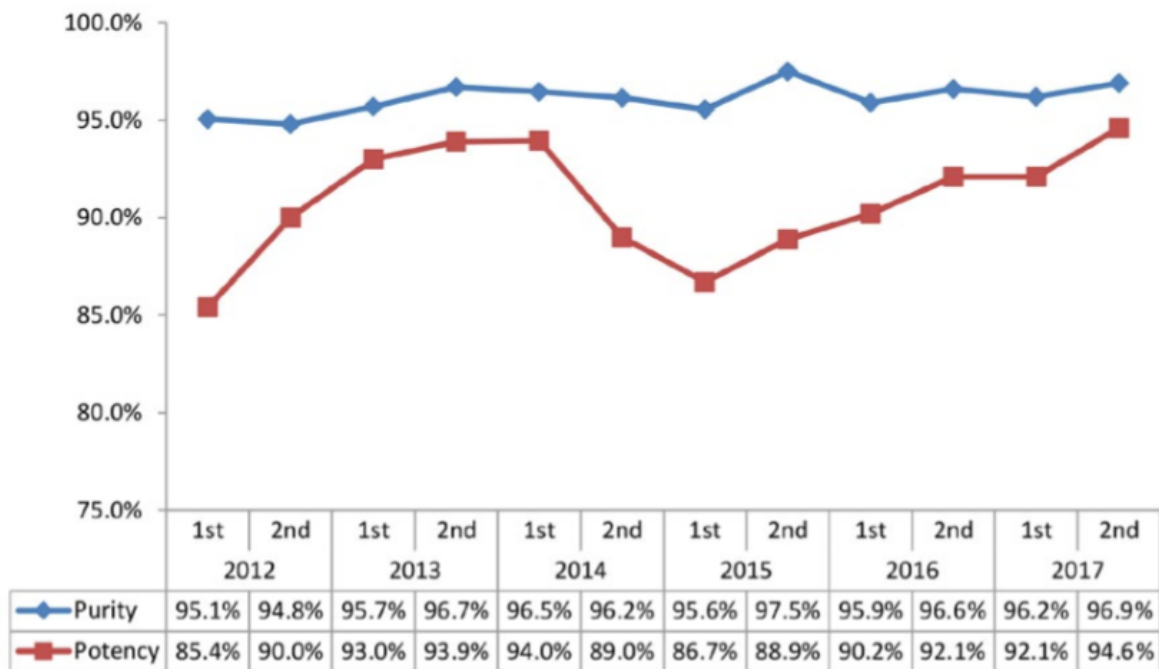
# What is Methamphetamine?



- Forms:
  - Powder – speed; low to medium potency
  - Crystallized – crystal, glass, ice; high potency
- Routes of administration:
  - Smoked (most common route), injected (near-immediate euphoria)
  - Ingested, snorted
  - Dissolved sublingually, taken rectally, solubilized and consumed as a liquid
- Long half-life (8-12 hours intranasal, oral)

# Methamphetamine Purity and Potency

Figure 70. Methamphetamine Purity and Potency.



Source: DEA Methamphetamine Profiling Program

<sup>38</sup> Purity is defined as a measure of the amount of an illicit substance present in a sample compared to other substances in the sample such as adulterants, diluents, or solvents.

<sup>39</sup> Potency is defined as the measure of drug activity in terms of the dosage required to exert an effect on the body and is measured by the amount of the highly potent d-isomer present in the drug substance.

# Why Methamphetamine?

- It's a stimulant!
- Reinforcing effects:
  - eliminates fatigue, decreases appetite, focuses attention,
  - euphoria, elevated mood,
  - loss of inhibition, heightens libido



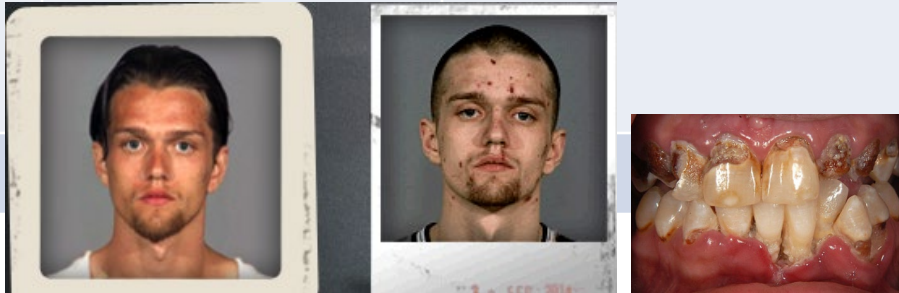
# Negative Consequences of MA Use

Psychiatric	Neurologic	Cardiac	Other Physiological
Paranoia	Headache	Chest pain	Skin ulcerations
Hallucinations	Seizures	Tachycardia	Dermatological infections
Depression	Stroke	Hypertension	Dental caries
Anxiety	Cerebral vasculitis	Arrhythmias	Anorexia
Insomnia	Hyperkinetic movements	Myocardial infarction	Pulmonary hypertension
Suicidality	Neurocognitive impairment	Coronary artery disease	Pulmonary edema
Aggression		Cardiomyopathy	Hyperthermia
Poor quality of life			Fetal growth restriction
			Hepatitis C and HIV



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# Who?

Populations disproportionately at risk:



■ Justice-involved individuals

- Impulsive behavior, violent crime (high homicide rates), psychosis



■ Women

- Often start using for weight loss/increased energy to get things done/self-treatment of mental health problems; target of violence



■ MSM

- Injection or non-injection, risky sexual behaviors and HIV

# Stimulants Fuel High-Risk Sexual Behavior

- Stimulants particularly associated with behaviors high-risk for HIV
  - Meth: heighten sexual impulses/desires/pleasure, increase energy, poor decision making, & disinhibition - increase probability of high-risk sexual behavior
- “Chemsex” – using specific drugs before/during sex to facilitate, prolong, sustain, or intensify experience and reduce inhibitions
  - Often: stimulant (meth or mephedrone) + GHB, poppers, erectile dysfunction meds (eg, sildenafil, tadalafil, vardenafil)



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- Among “non-heterosexual” individuals [(gay, lesbian, bisexual) and MSM], extensive literature on meth use associated with high-risk sexual behavior:
  - Frequency of unprotected anal sex
  - Inconsistent condom use
  - Frequency of sex with multiple partners
  - HIV infection

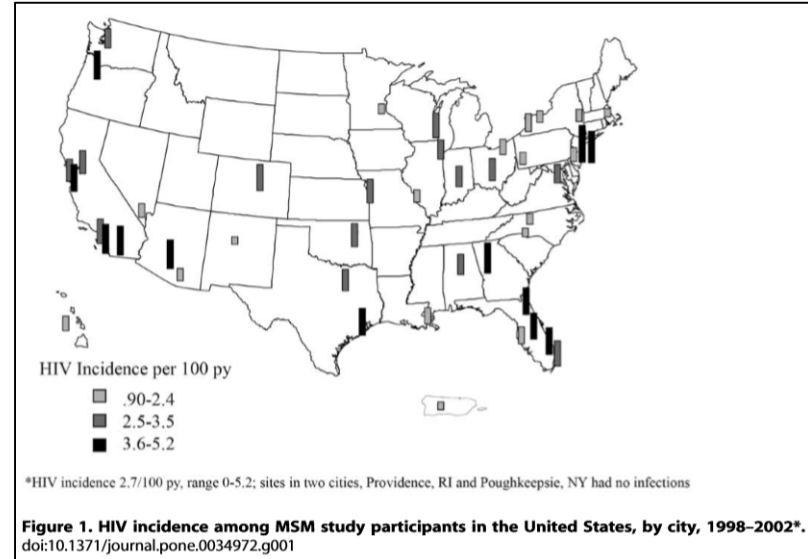




# MSM, Meth, and HIV

- MSM have **28X higher risk acquiring HIV than heterosexual men**...HIV risk factors for this group?
- N=4684 HIV-negative high-risk MSM, 18-60yo, 1998-2002, 47 U.S. cities, HIV vaccine efficacy RCT that included HIV risk reduction counseling, followed 36 months, **excluded MSM who reported injection drug use**:

- **Use of amphetamines (aHR=1.6) linked to significantly higher risk of acquiring HIV**
- Other significant risk factors:
  - Use of amyl nitrates (poppers) (aHR=1.7)
  - 18-30yo (aHR=2.4),
  - >10 sex partners in last 6 months (aHR=2.4),
  - $\geq 1$  HIV-pos partner (aHR=1.6),
  - Unprotected anal intercourse with HIV-pos/unknown partner (aHR=1.7)



Use of club drugs, *particularly methamphetamine*, is associated with high-risk sexual behaviors and increased HIV incidence among MSM.

# High-Risk Sexual Behavior

- Among heterosexuals who **use** meth (compared to **non-users**):
  - 37% to 72% more likely to engage in high-risk sexual behaviors
    - Unprotected vaginal intercourse (1.37 OR)
    - Unprotected anal intercourse (1.52 OR)
    - Inconsistent condom use (1.72 OR)
  - Fast-Lane intervention – promising (reduced unprotected sex, increased protected sex) but high attrition (Mausbach et al 2007)

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  - Fast-Lane intervention – promising (reduced unprotected sex, increased protected sex) but high attrition (Mausbach et al 2007)
- Among heterosexuals who **use** meth (compared to times when **not using**):
  - Doubled odds of being sexually active when using meth (1.9 OR)
  - When sexually active, more likely to have:
    - Multiple partners (3.3 OR) and casual partners (3.9 OR),
    - Condomless sex with casual partners (2.6 OR)

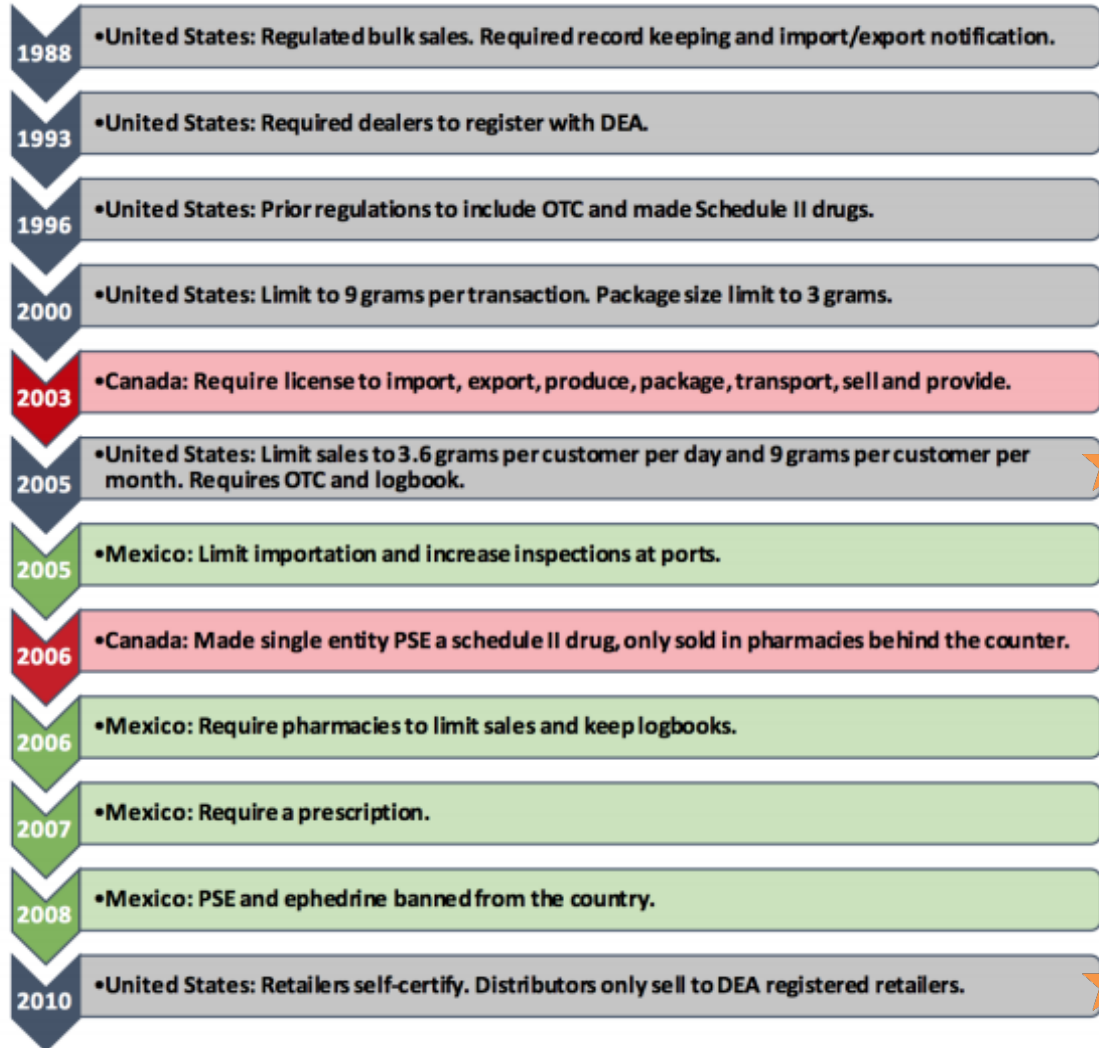


# Supply Side: Meth Availability

# Manufacturing and Control of Meth

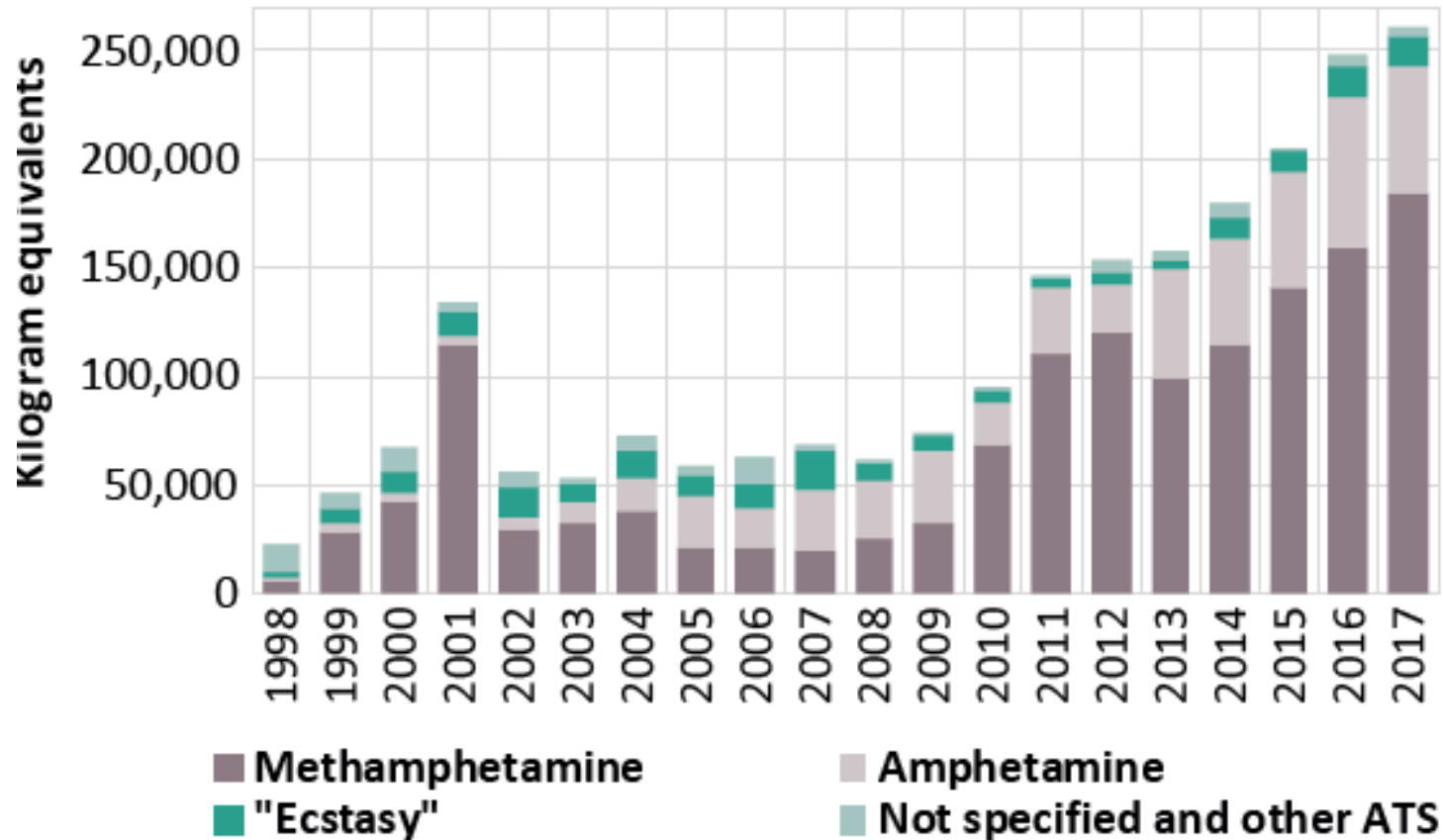


Figure 1: U.S, Canada and Mexico Federal PSE Regulations



# Methamphetamine Seizures Worldwide

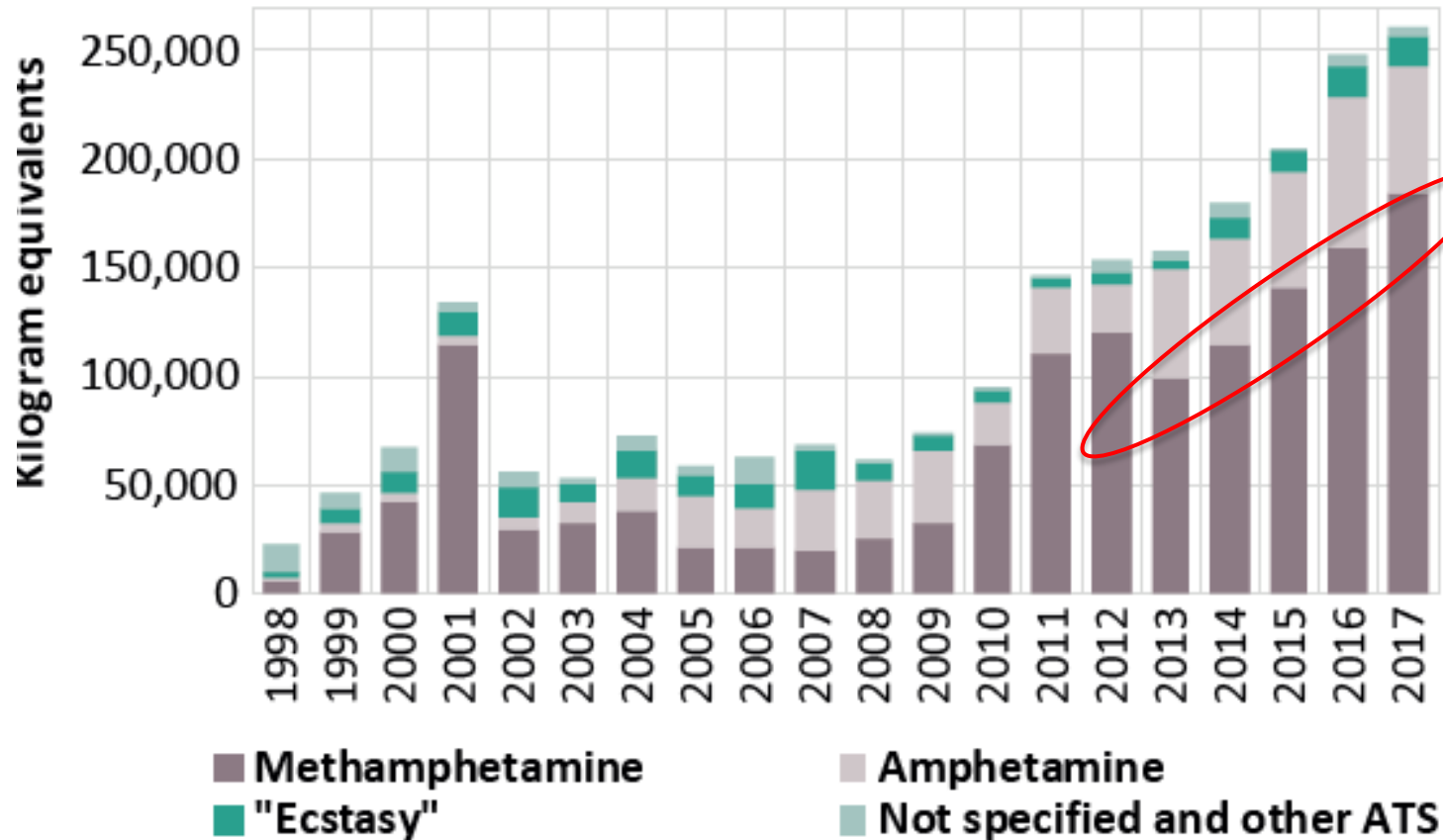
## Global quantity of amphetamine-type stimulants seized, 1998–2017





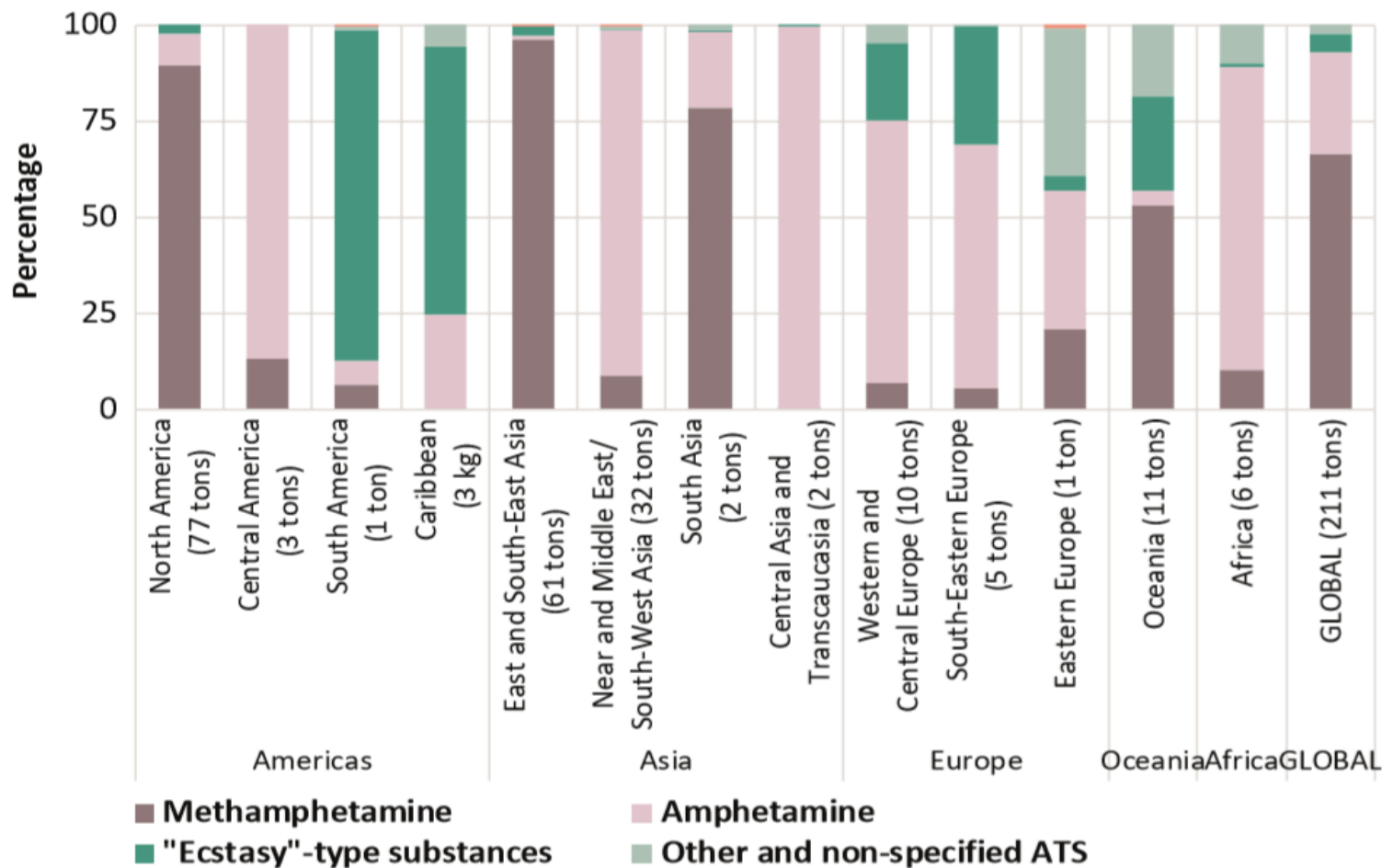
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# Seizures in N. America = Meth

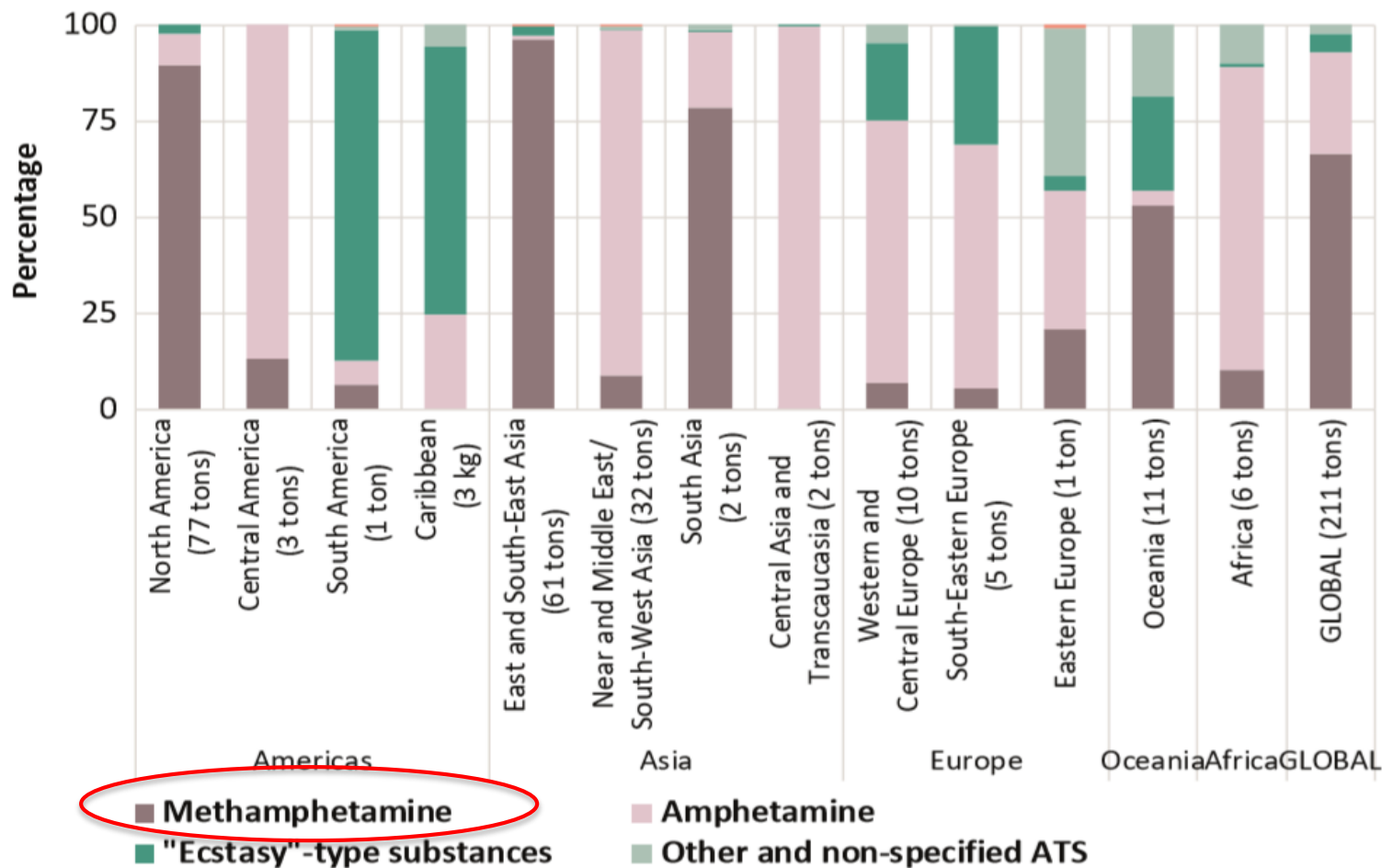
**FIG. 28** Distribution by substance of the average annual quantity of amphetamine-type stimulants seized, by subregion, 2013–2017



Source: UNODC, responses to the annual report questionnaire.

# Seizures in N. America = Meth

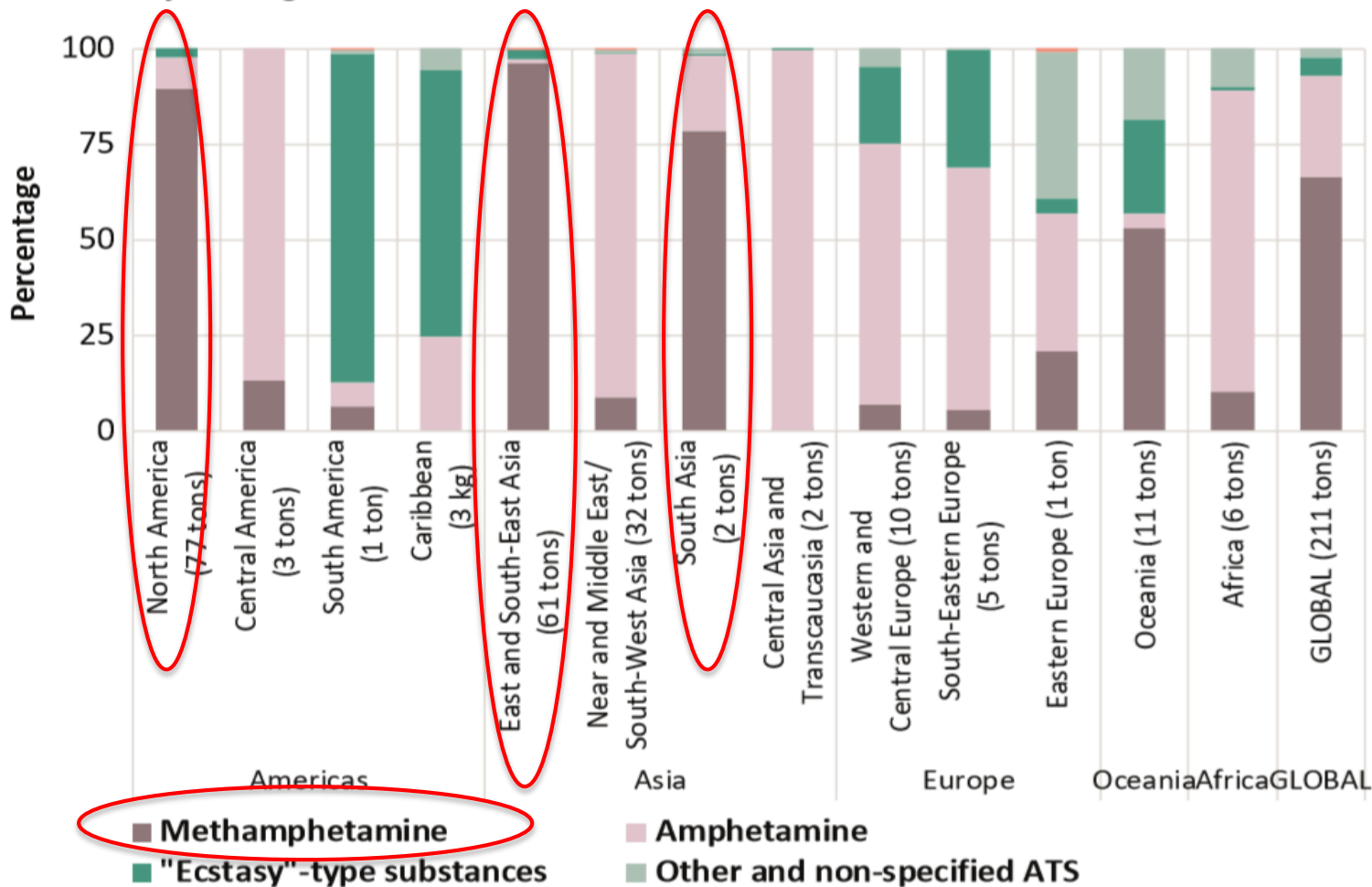
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# Customs Intercepts \$12M in Meth at Border

The methamphetamine was smuggled inside a truck carrying frozen strawberries from Mexico, CBP says.

By Megan Trimble, Digital News Editor Feb. 20, 2019



Packages containing 906 pounds of methamphetamine seized by Customs and Border Patrol officers at the Pharr-Reynosa International Bridge cargo facility in Texas. (COURTESY OF CBP HIDALGO)

CRIME & COURTS

## U.S. seizes record 3,800 pounds of meth intended for Australia

Authorities said the seizure would have a noticeable impact on the worldwide meth market.



Methamphetamine seized last month at the Los Angeles/Long Beach seaport in Southern California. Australian Federal Police

Feb. 8, 2019, 12:34 AM CST / Updated Feb. 8, 2019, 3:04 AM CST

By Alex Johnson

SPONSORED STORIES by Taboola

<https://www.usnews.com/news/national-news/articles/2019-02-20/customs-agents-intercept-more-than-12m-in-meth-at-border-crossing>

<https://www.nbcnews.com/news/crime-courts/u-s-seizes-record-3-800-pounds-meth-intended-australia-n969196>

February 20, 2020

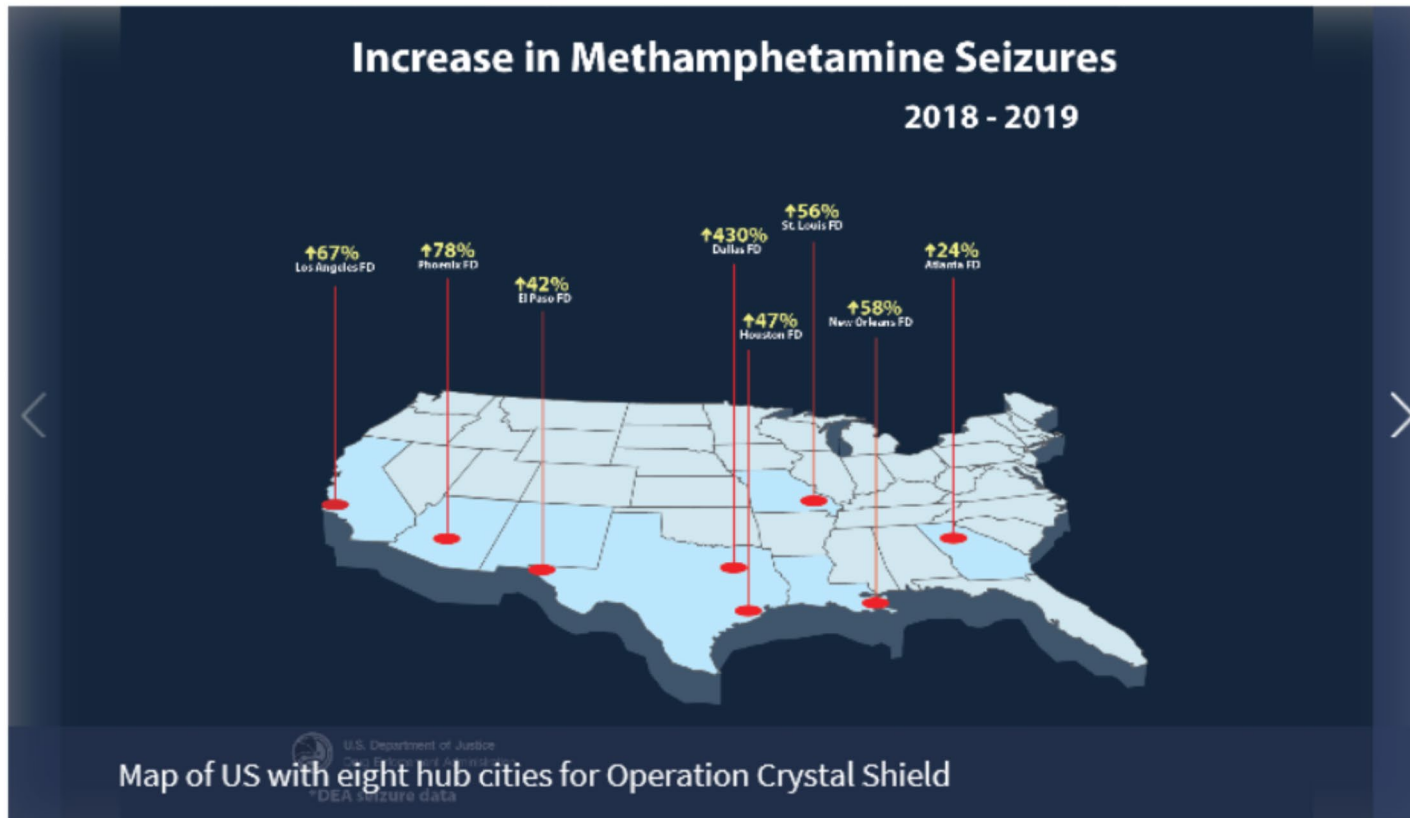
FOR IMMEDIATE RELEASE

Contact: National Media Affairs Office

Phone Number: [\(202\) 307-7977](tel:(202)307-7977)

## DEA announces launch of Operation Crystal Shield

Efforts will focus on main U.S. methamphetamine trafficking transportation hubs





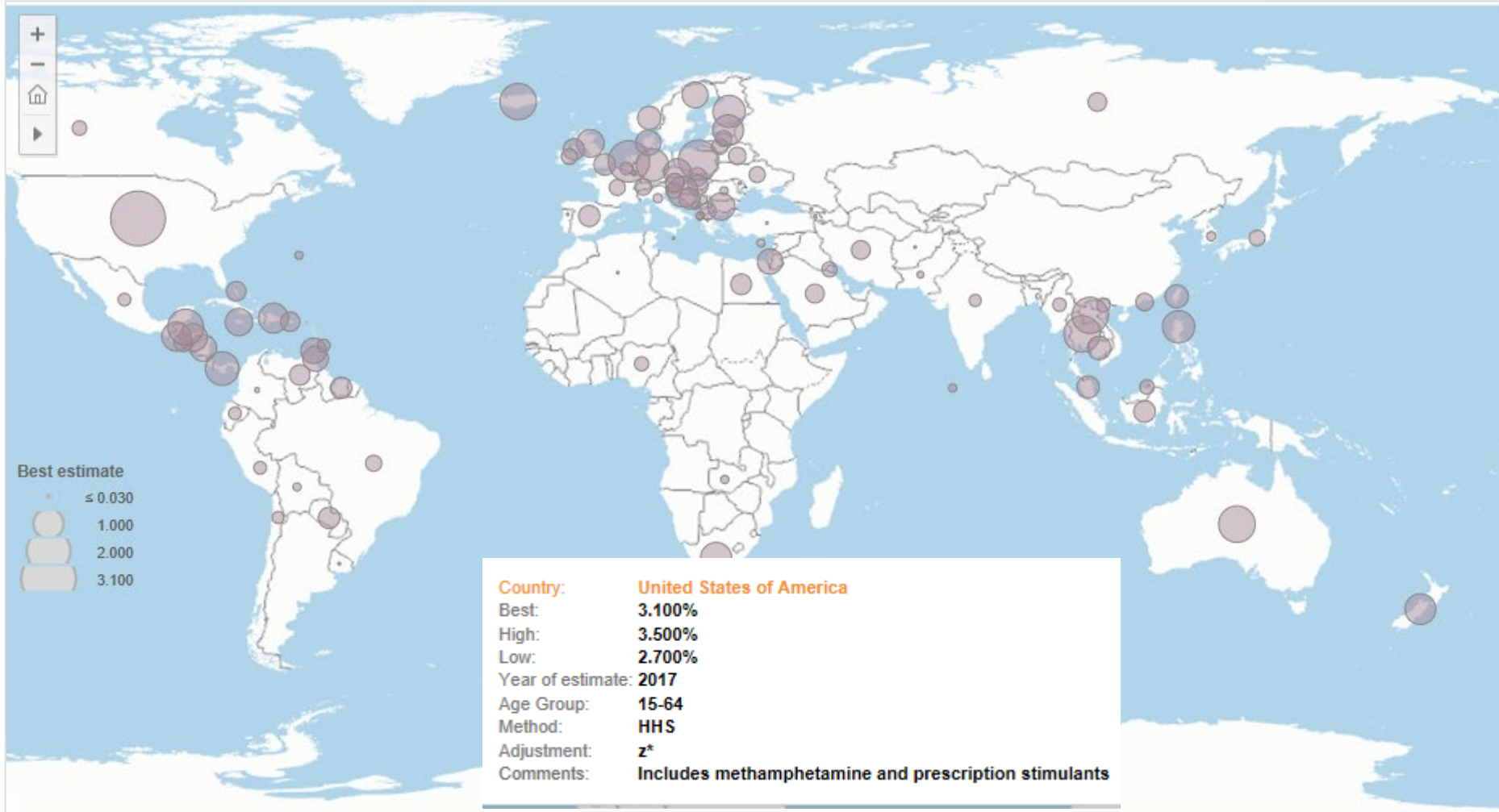


# Demand Side: Drug Use Data

# “We’re #1” – U.S. and Amphetamine Use

Annual prevalence of use of drugs in 2017 (or latest year available)

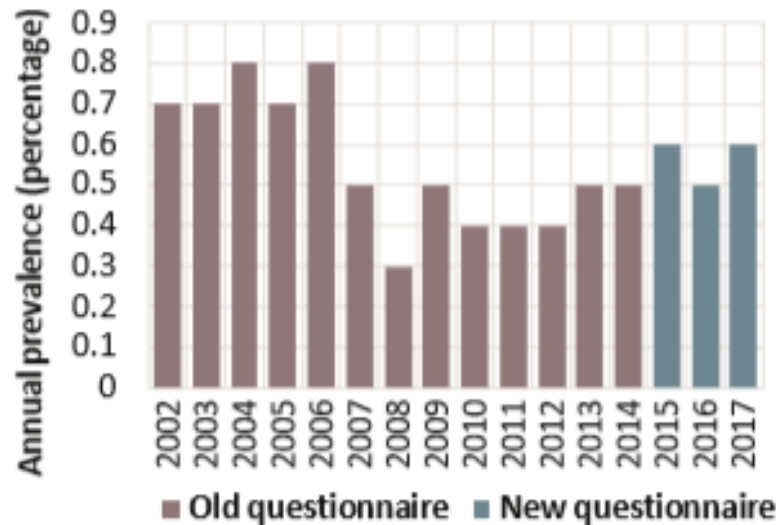
Amphetamines



[https://wdr.unodc.org/wdr2019/en/prevalence\\_map.html](https://wdr.unodc.org/wdr2019/en/prevalence_map.html)

# Annual Prevalence Rate Fairly Stable

**FIG. 52** Methamphetamine use among the population 12 and older in the United States, 2002–2017



## *Reminder*

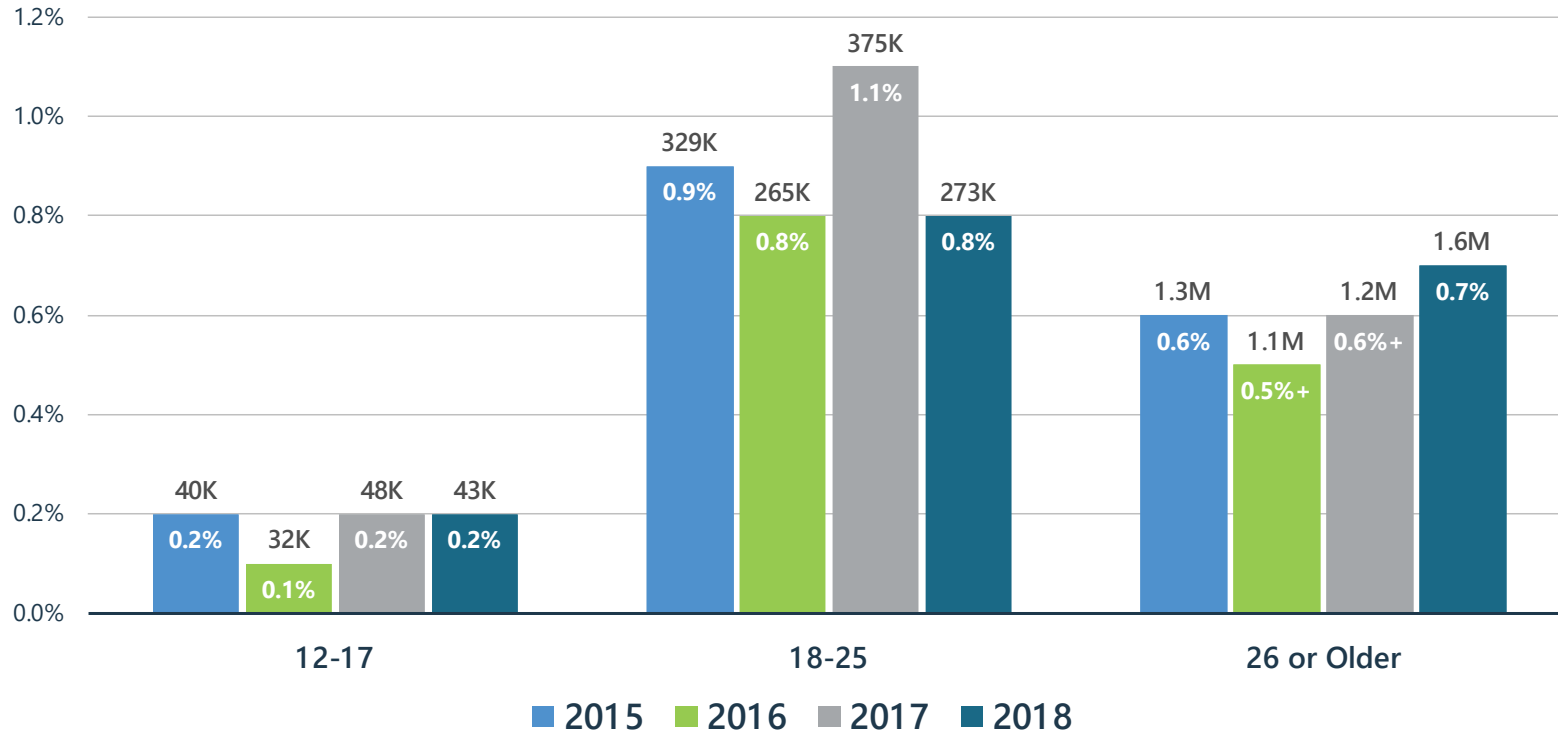
Prevalence = number of cases in a population at a given time

Source: SAMHSA, National Survey on Drug Use and Health (different years).

*Note: Owing to changes in the questionnaire in 2015, the trends between 2002 and 2014 and 2015 and 2017 are not comparable.*

# Methamphetamine Use: Significant Increase in Adults >26yo

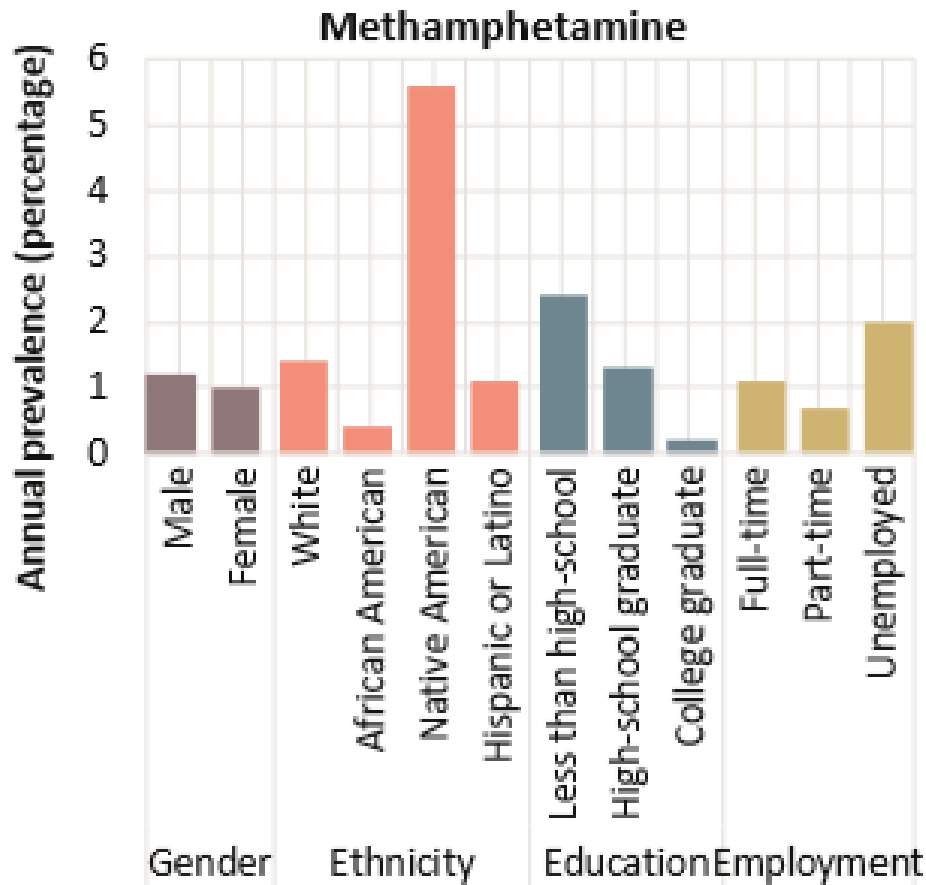
PAST YEAR, 2015-2018 NSDUH, 12+



+ Difference between this estimate and the 2018 estimate is statistically significant at the .05 level.

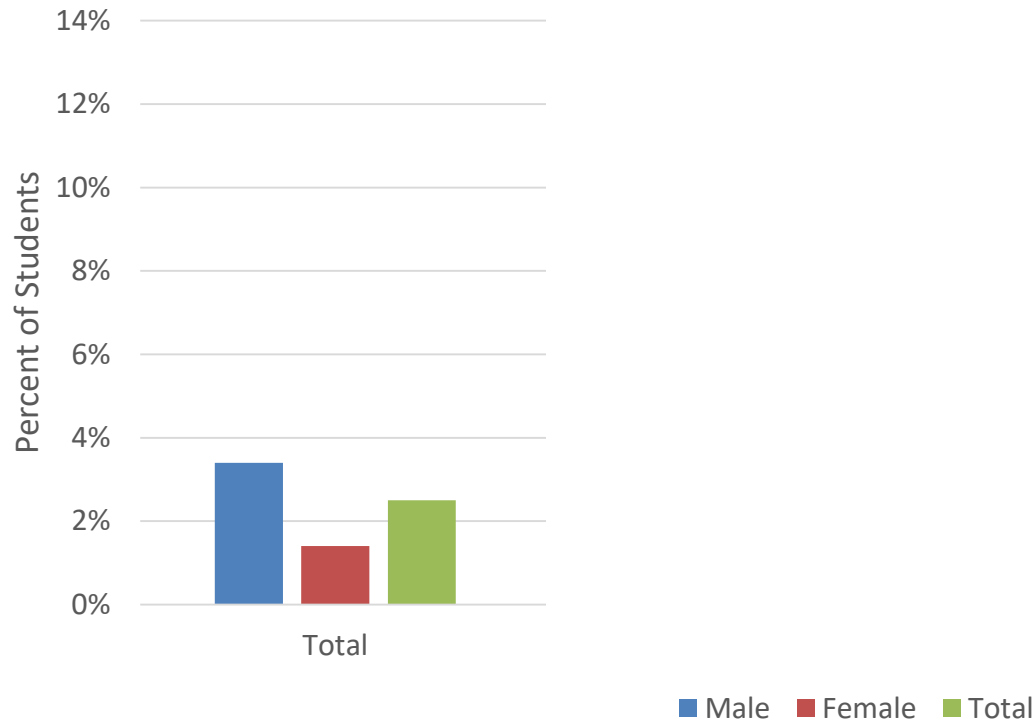
# Understanding 18-25yo People Who Use Meth

**FIG. 53** Methamphetamine use and non-medical use of prescription stimulants among young people aged 18–25 in the United States by sociodemographic characteristics, 2017



# Ever used Methamphetamines, 2017

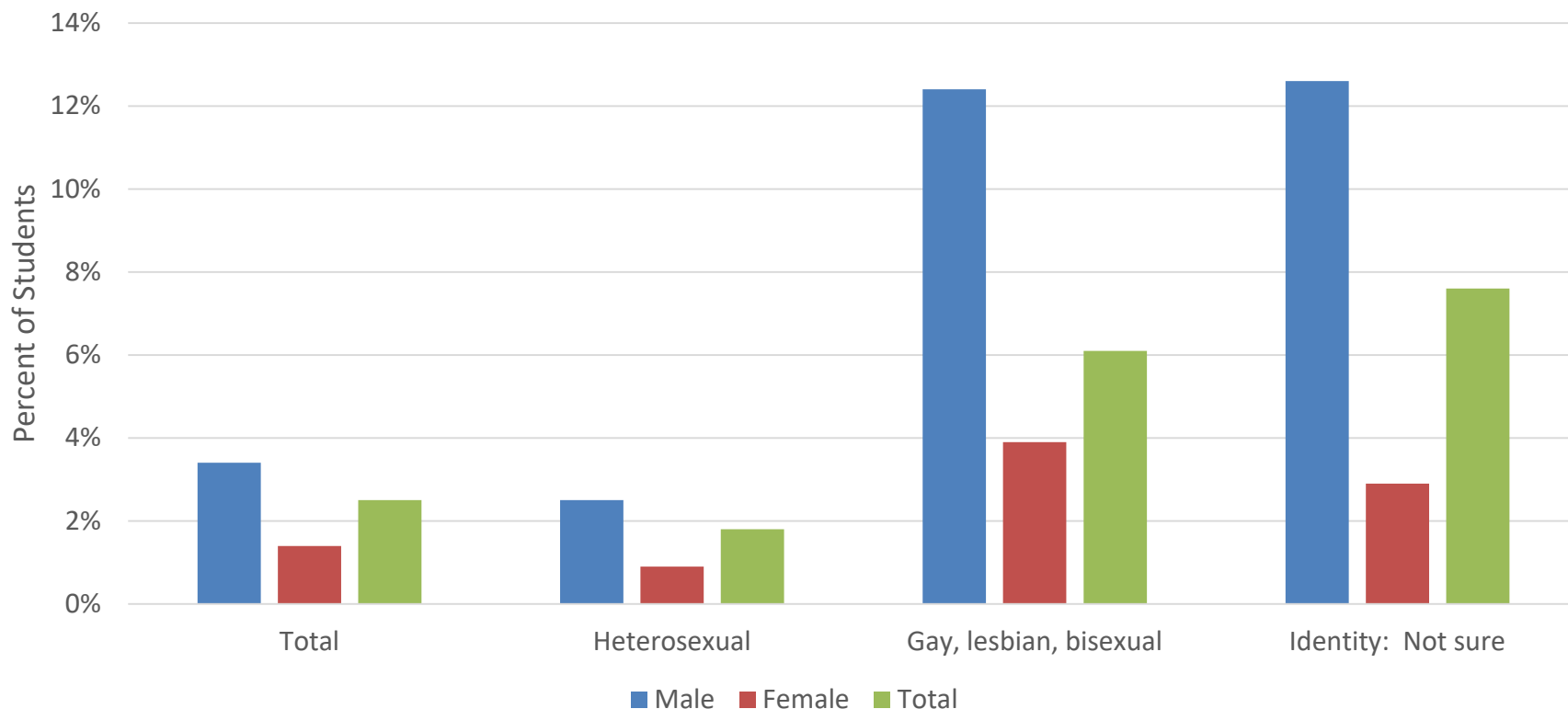
## METH USE IN U.S. HIGH SCHOOL STUDENTS, BY SEX





# Ever used Methamphetamines, 2017

## METH USE IN U.S. HIGH SCHOOL STUDENTS, BY SEX AND SEXUAL IDENTITY



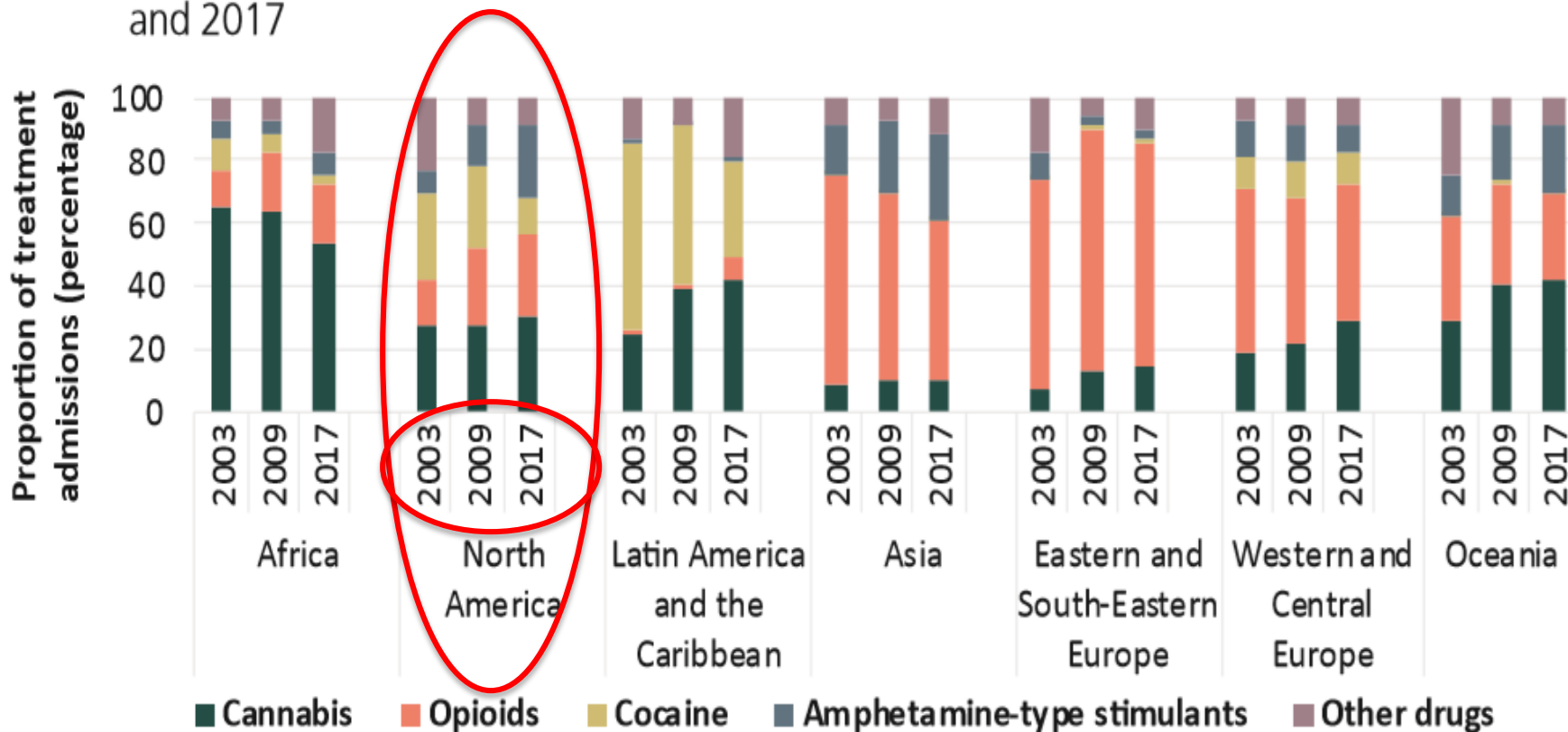


# Treatment Data



# Seeking Treatment for What Drugs?

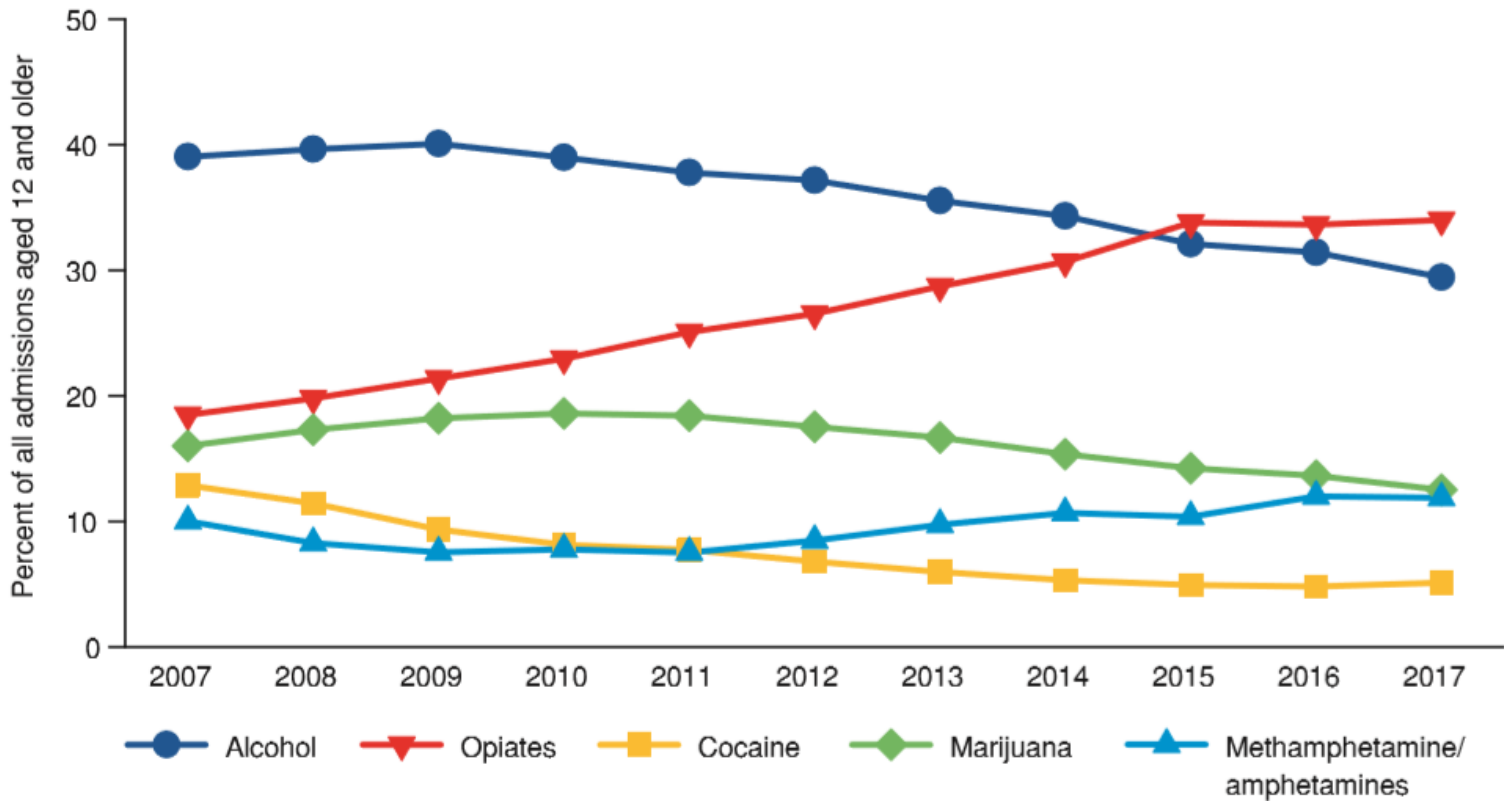
**FIG. 4** Trends in the primary drug of concern in drug treatment admissions, by region, 2003, 2009 and 2017



Source: UNODC, responses to the annual report questionnaire.

# Meth Surpasses Cocaine Treatment Admissions in U.S.

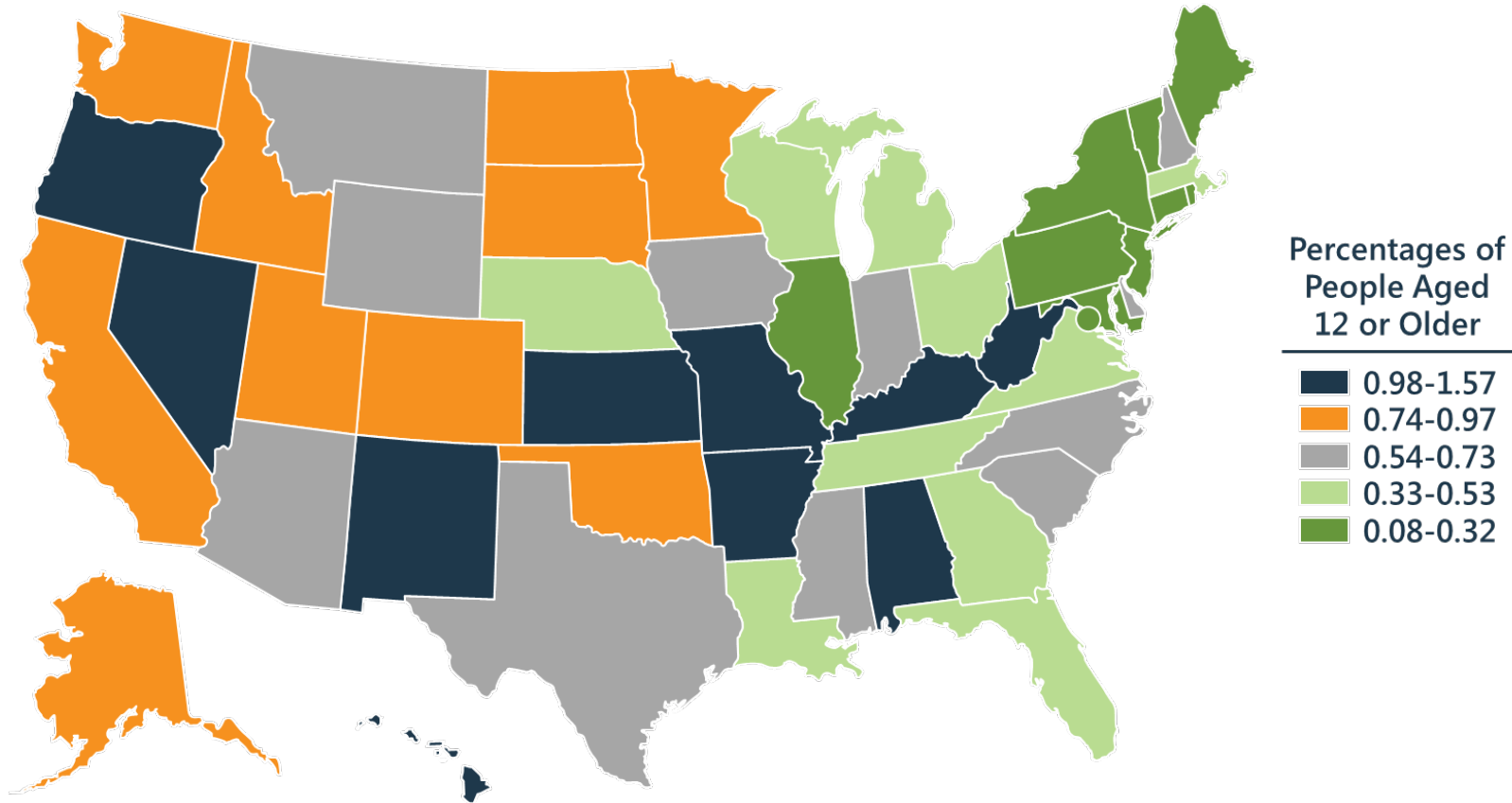
Figure 1. Primary substance use at admission: 2007–2017



SOURCE: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration, Treatment Episode Data Set (TEDS). Data received through 11.21.18.

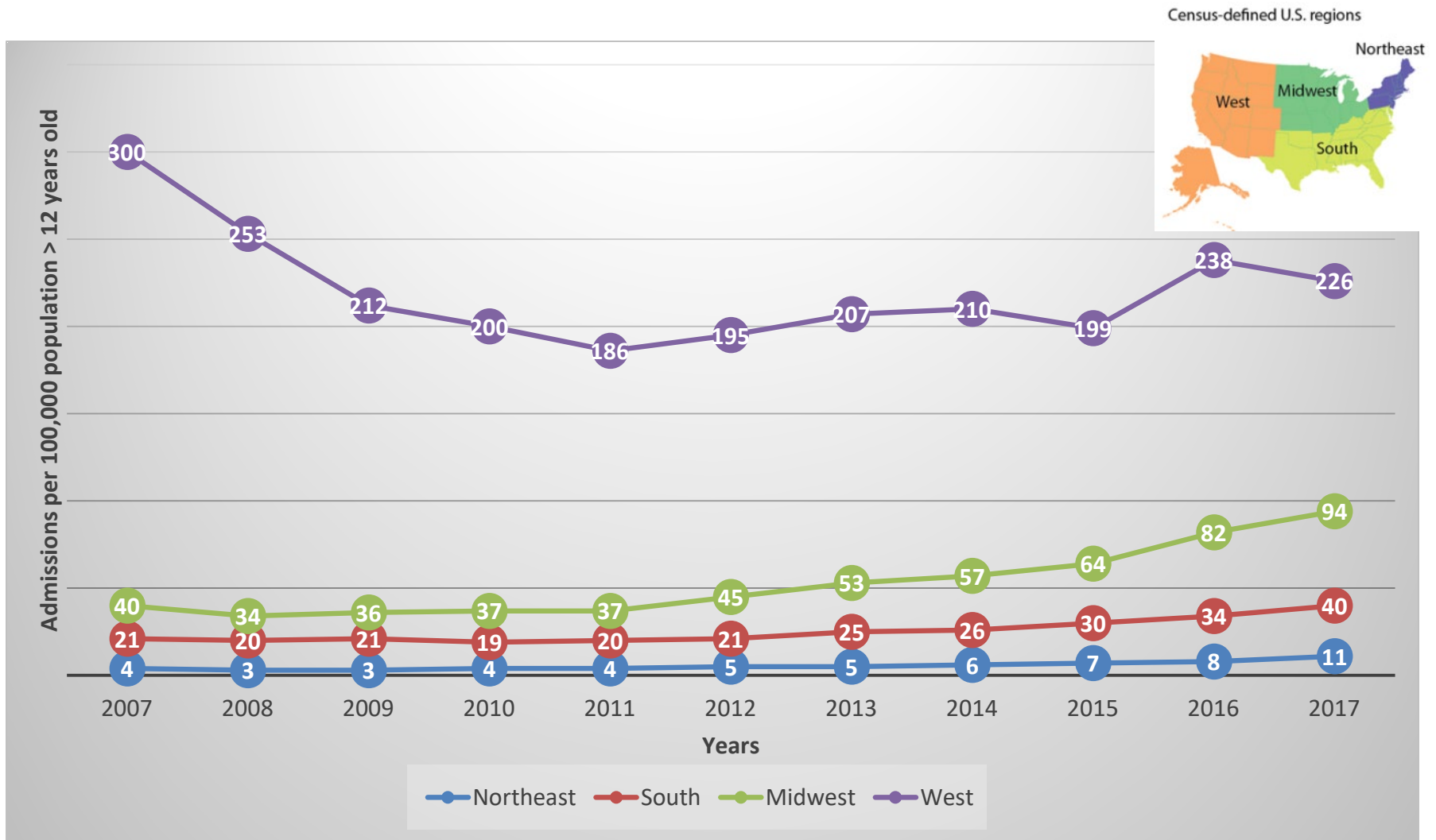
# Methamphetamine Use by State

PAST YEAR, POOLED 2016-2017 NSDUH, 12+



Differences in colors across states do not indicate significant differences in estimates.

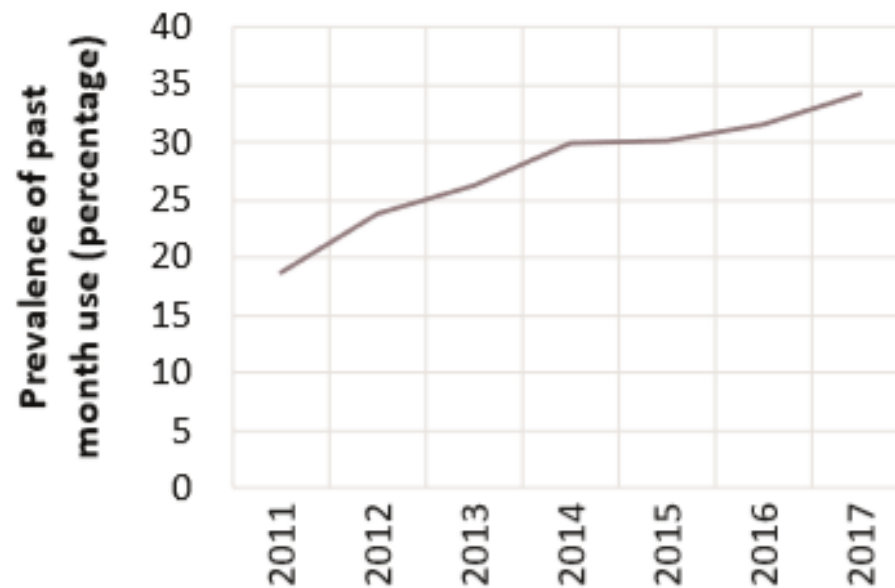
# Primary Methamphetamine Admissions by Census Region





# OUD Treatment Admissions with Meth Use

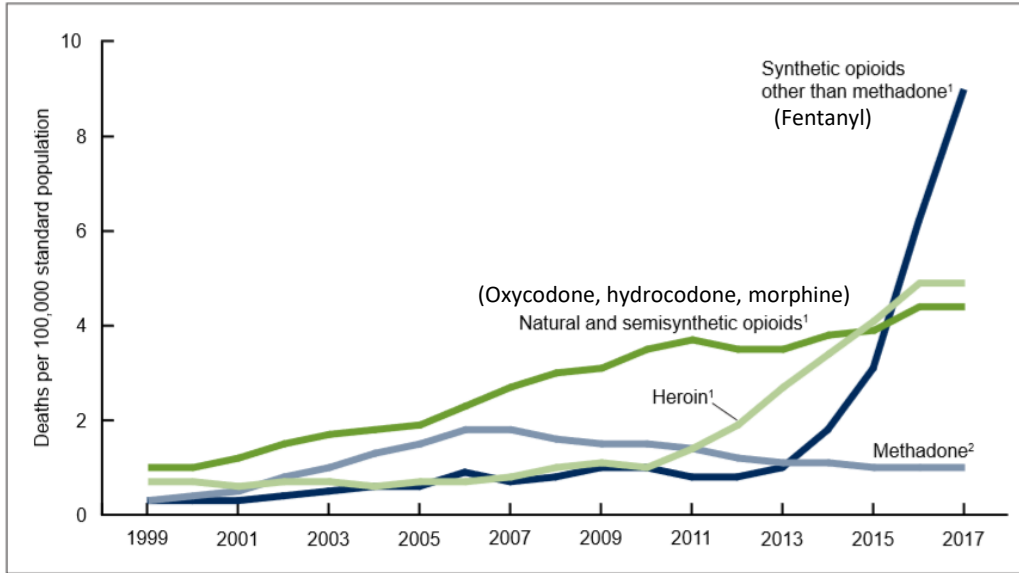
**FIG. 54** Methamphetamine use among people in the United States with opioid use disorders who were entering treatment, 2011–2017



Source: Matthew S. Ellis, Zachary A. Kasper and Theodore J. Cicero, "Twin epidemics: the surging rise of methamphetamine use in chronic opioid users", *Drug and Alcohol Dependence*, vol. 193 (December 2018).

# Drugs Most Frequently Involved in Overdose Deaths

Figure 4. Age-adjusted drug overdose death rates, by opioid category: United States, 1999–2017



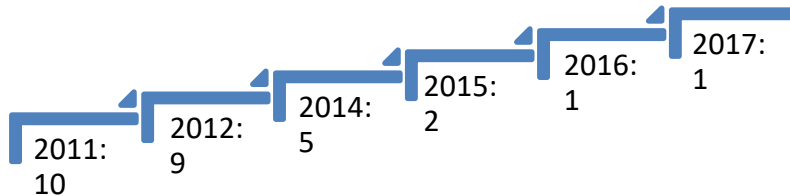
<sup>1</sup>Significant increasing trend from 1999 through 2017 with different rates of change over time,  $p < 0.05$ .

<sup>2</sup>Significant increasing trend from 1999 through 2006, then decreasing trend from 2006 through 2017,  $p < 0.05$ .

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: heroin, T40.1; natural and semisynthetic opioids, T40.2; methadone, T40.3; and synthetic opioids other than methadone, T40.4. Deaths involving more than one opioid category (e.g., a death involving both methadone and a natural and semisynthetic opioid) are counted in both categories. 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%–88% from 2014 through 2017. Access data table for Figure 4 at: [https://www.cdc.gov/nchs/data/databriefs/db329\\_tables-508.pdf#4](https://www.cdc.gov/nchs/data/databriefs/db329_tables-508.pdf#4).

SOURCE: NCHS, National Vital Statistics System, Mortality.

## Yearly Rank of **Fentanyl** Involved Deaths:

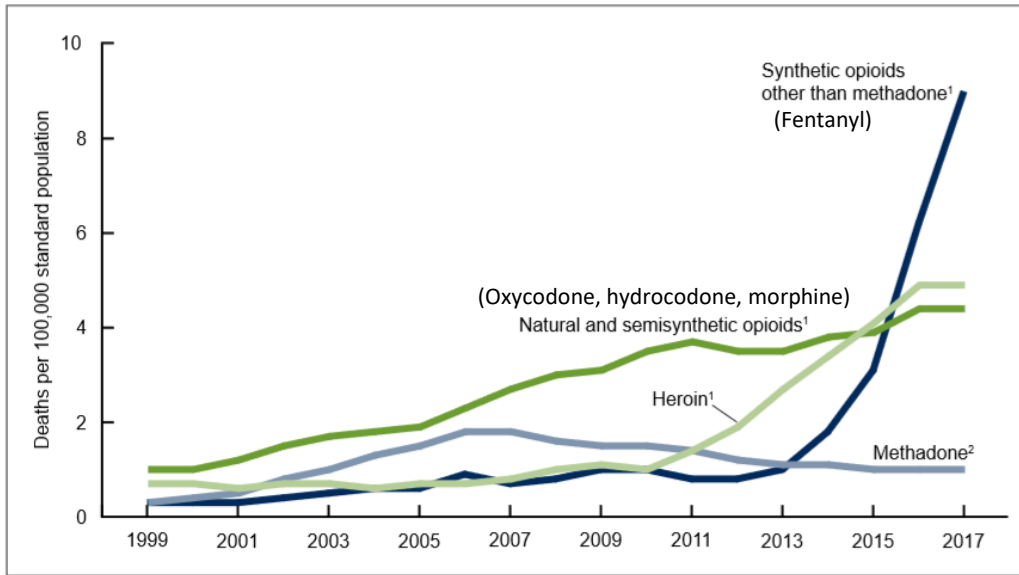


Hedegaard et al. National Vital Statistics Reports. 2018. 67(9).

Hedegaard et al. National Vital Statistics Reports. 2019. 68(12).

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 SOURCE: NCHS, National Vital Statistics System, Mortality.

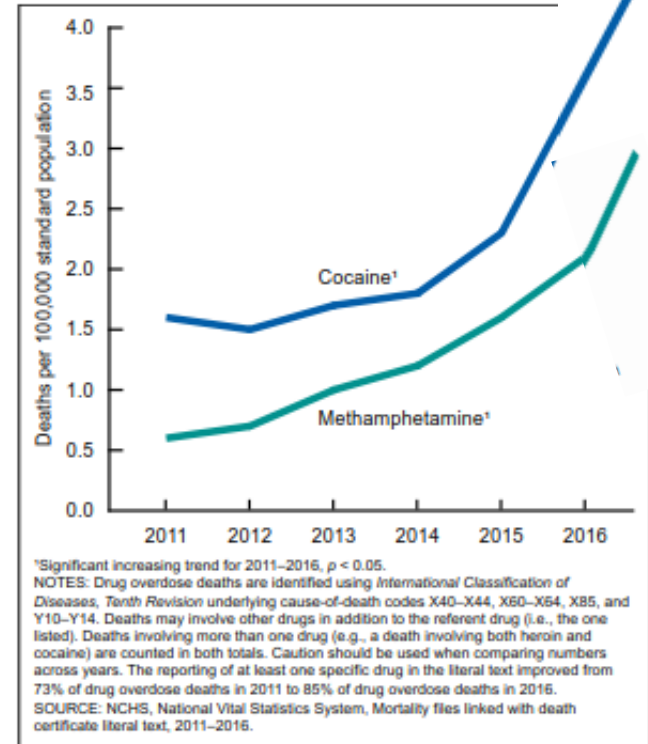
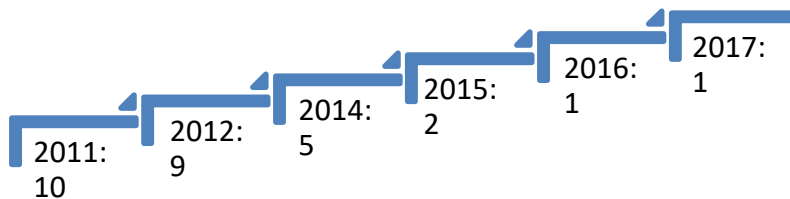


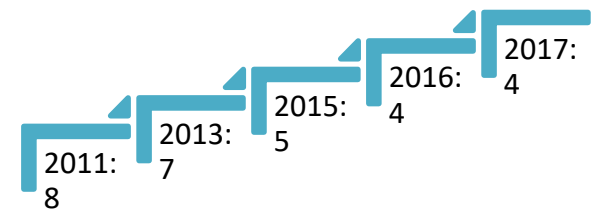
Figure 3. Age-adjusted rates for drug overdose deaths involving selected stimulants, 2011–2016

<sup>1</sup>Significant increasing trend for 2011–2016,  $p < 0.05$ .  
 NOTES: Drug overdose deaths are identified using *International Classification of Diseases, Tenth Revision* underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Deaths may involve other drugs in addition to the referent drug (i.e., the one listed). Deaths involving more than one drug (e.g., a death involving both heroin and cocaine) are counted in both totals. Caution should be used when comparing numbers across years. The reporting of at least one specific drug in the literal text improved from 73% of drug overdose deaths in 2011 to 85% of drug overdose deaths in 2016.  
 SOURCE: NCHS, National Vital Statistics System, Mortality files linked with death certificate literal text, 2011–2016.

## Yearly Rank of Fentanyl Involved Deaths:

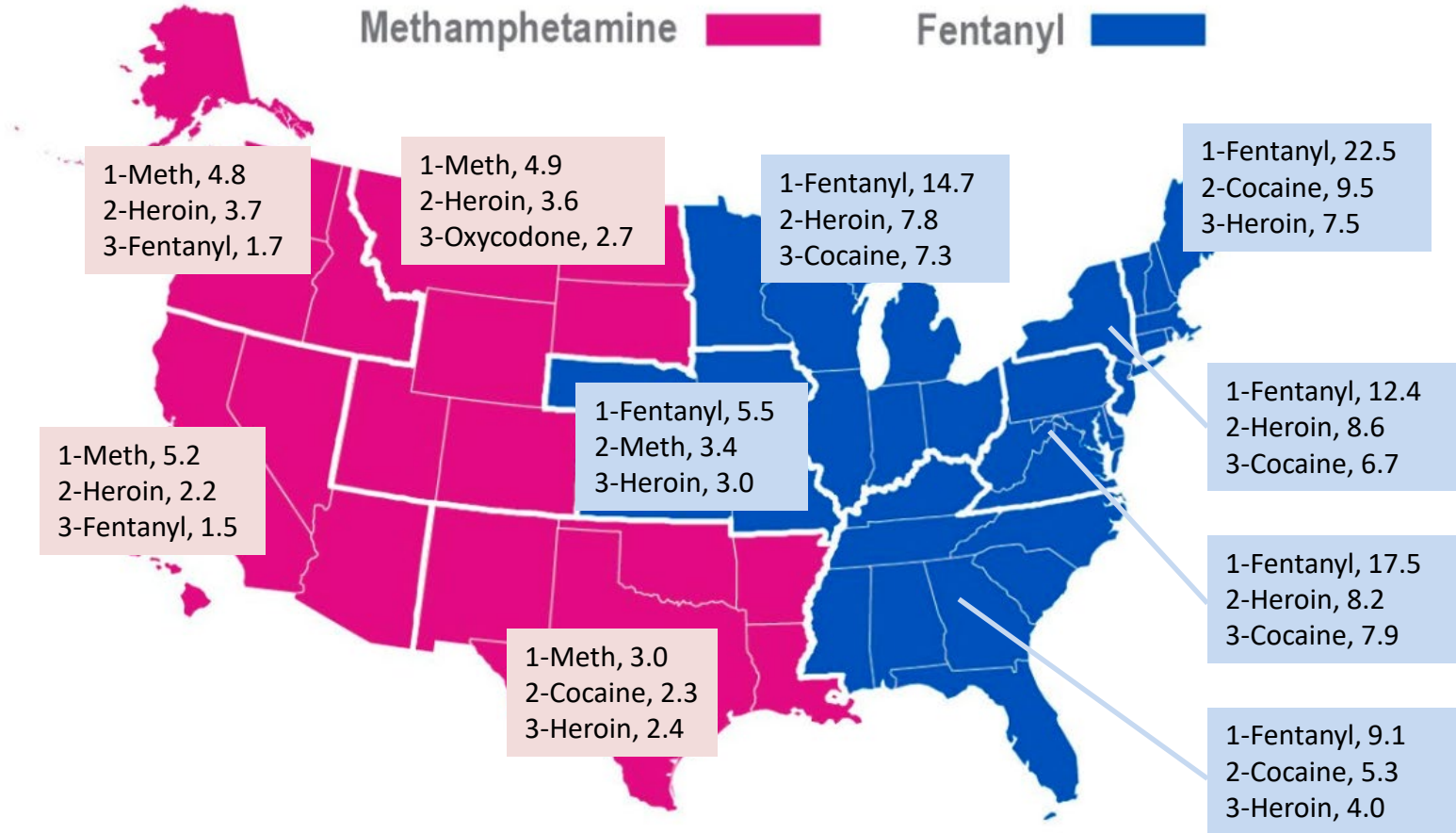


## Yearly Rank of Meth Involved Deaths:



# Drug overdose deaths by region

Methamphetamine was the top drug involved in overdose deaths in most of the western half of the U.S. while fentanyl pervaded the eastern half.



NOTE: Data from 2017. Deaths may include additional drugs.

SOURCE: NCHS National Vital Statistics System



# Summary of Trends

- ✓ Meth availability seems to be increasing, with high purity & decreased price
- ✓ Reports of recent use appear stable, but some groups affected more than others
- ✓ Treatment admissions rising
  - ✓ Increases in meth use among people in tx for OUD, especially in western US, urban/suburban settings, and women
- ✓ Meth is becoming involved in more overdose deaths
  - ✓ Heroin and fentanyl are involved in some overdose deaths attributed to meth

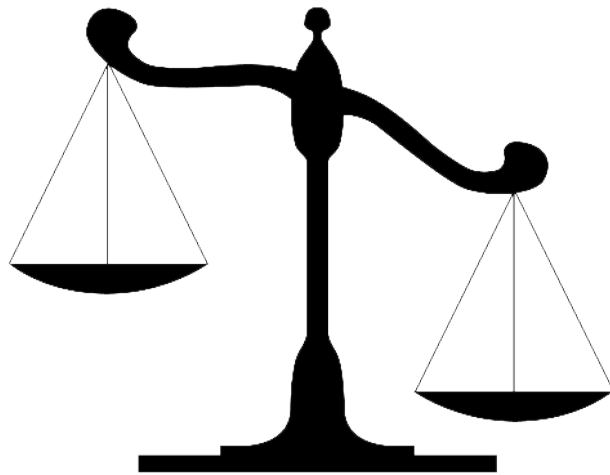


# Evidence-Based Treatments

# Factors Related to Treatment Outcomes

## ASSOCIATED WITH SUCCESSFUL OUTCOMES

- Lower levels of meth use at admission (<15 days out of previous 30)
- Shorter history of meth use ( $\leq 2$  years)
- Retained in treatment for  $\geq 90$  days
- $\geq 3$  consecutive weeks of abstinence during treatment



## ASSOCIATED WITH POOR OUTCOMES

- Continued meth use during treatment
- Injection use
- < High school education
- Young age at admission
- Having a disability
- Polydrug use
- Childhood trauma and abuse
- Having an underlying psychiatric disorder



# Keeping Patients who use Meth in Tx is Difficult

- 2019 meta-analysis of dropout rates of in-person psychosocial SUD tx
  - **Dropout from treatment is a robust predictor of relapse**
  - Meta-analysis aimed to estimate average dropout rates and potential predictors of dropout from in-person psychosocial SUD tx
    - **If know what can predict dropout, perhaps can intervene**
  - Analyzed 151 studies of in-person psychosocial SUD tx
  - Average dropout rate from all studies and all study arms was 30.4% but varied widely with population, drug of abuse, and treatment characteristics.
    - **Dropout rates were highest for studies targeting cocaine, methamphetamine, all stimulants; lowest for alcohol, tobacco, heroin. But there were few studies on meth, all stimulants, and heroin.**
    - **Programs with more treatment sessions and greater average session length associated with higher dropout rates.**

# Which Psychosocial Treatment?

- Clinical guidelines recommend psychosocial interventions as first-line treatment
- But *which* psychosocial treatment?
- 50 RCTs evaluating 12 psychosocial interventions (vs. TAU or active control) in 6,942 pts
  - Outcomes: abstinence based on negative UDS, acceptability based on retention, longest duration of abstinence
  - Time points: end of treatment, 12 weeks, long-term outcome

# A: CM + Community Reinforcement

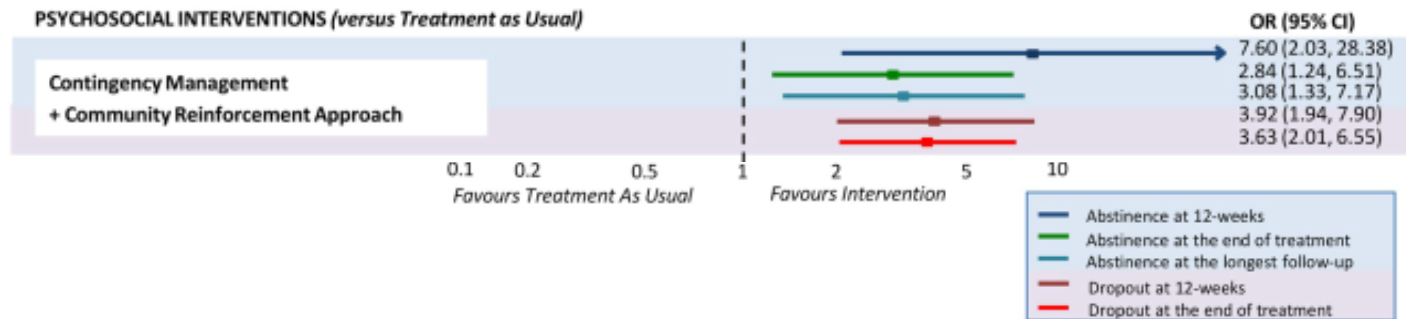


Fig 4. Abstinence and dropout at different time-points for each psychosocial intervention versus treatment as usual. Estimates are reported by ORs, where an OR above 1 favours the psychosocial intervention indicated on the left side over treatment as usual. For each intervention, efficacy outcomes are reported in the blue-shaded area, while acceptability outcomes are reported in the pink-shaded area. OR, odds ratio.

- **Contingency Management**
  - Behavioral approach
  - Contingently rewards drug-free urine samples
- **Community Reinforcement Approach**
  - Multi-layered and comprehensive behavioral intervention package
  - Functional analysis, coping-skills training, and social, familial, recreational, vocational reinforcements

# Pharmacological Treatments

## Goals / Needs:

1. Medications that counteract specific acute intoxication effects
2. Medications that help initiate abstinence
3. Medications that prolong abstinence



# Pharmacotherapy

- Existing FDA approved medications for all SUDs is extremely limited
  - YES: Alcohol, nicotine, opioid use disorders
  - NONE: Cannabis, cocaine, **methamphetamine**, etc.

**TABLE 1. Drugs approved by the FDA for treatment of substance use disorders<sup>a</sup>**

Substance and Medication	FDA Approval	Mechanism of Action
<b>Opioids</b>		
Methadone	Treatment of opioid dependence	$\mu$ -Opioid receptor agonist
Buprenorphine	Treatment of opioid dependence	$\mu$ -Opioid receptor partial agonist
Extended-release naltrexone	Treatment of opioid dependence	$\mu$ -Opioid receptor antagonist
Lofexidine	Treatment of opioid withdrawal	$\alpha_{2A}$ -Adrenergic receptor agonist
Naloxone	Reversal of opioid overdose	$\mu$ -Opioid receptor antagonist
<b>Alcohol</b>		
Acamprosate	Treatment of alcohol dependence	NMDA antagonist, GABA-A allosteric modulator
Naltrexone	Treatment of alcohol dependence	$\mu$ -Opioid receptor antagonist
Disulfiram	Treatment of alcohol dependence	Acetaldehyde dehydrogenase inhibitor
Gabapentin	Used off-label to treat alcohol dependence	Unknown; increases GABA concentration
Topiramate	Used off-label to treat alcohol dependence	Voltage-gated sodium channel blocker, GABA-A allosteric modulator, AMPA/kainate receptor antagonist, carbonic anhydrase inhibitor
<b>Nicotine</b>		
Nicotine replacement therapy	Nicotine cessation	Nicotinic acetylcholine receptor agonist
Varenicline	Nicotine cessation	$\alpha 4\beta 2$ Nicotinic acetylcholine receptor antagonist
Bupropion	Nicotine cessation	Dopamine and norepinephrine transporter blocker

<sup>a</sup> AMPA= $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; FDA=U.S. Food and Drug Administration; GABA= $\gamma$ -aminobutyric acid; NMDA=*N*-methyl-D-aspartate.

# Medications Previously Evaluated

Risperidone

Fluoxetine

Sertraline

Quetiapine

Gabapentin

Aripiprazole

Haloperidol

Baclofen

Topiramate

Ondansetron

Citicoline

Mirtazapine

Dexamphetamine

Ibudilast

Methylphenidate

Modafinil

Bupropion

Imipramine

Naltrexone

Brensilver, Heinzerling, & Shoptaw. (2013). Pharmacotherapy of amphetamine-type stimulant dependence: An update. *Drug and Alcohol Review*, 32:449-460.

Courtney & Ray. (2014). Methamphetamine: An update on epidemiology, pharmacology, clinical phenomenology, and treatment literature. *Drug and Alcohol Dependence*, 143:11-21.

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Ballester, et al. (2017). "Pharmacological treatments for methamphetamine addiction: Current status and future directions." Expert Review of Clinical Pharmacology.

Chan, et al. (2019). "Pharmacotherapy for methamphetamine/amphetamine use disorder-a systematic review and meta-analysis." Addiction.



# Medications Previously Evaluated

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Chan, et al. (2019). "Pharmacotherapy for methamphetamine/amphetamine use disorder-a systematic review and meta-analysis." Addiction.

# Recent Atomoxetine Data

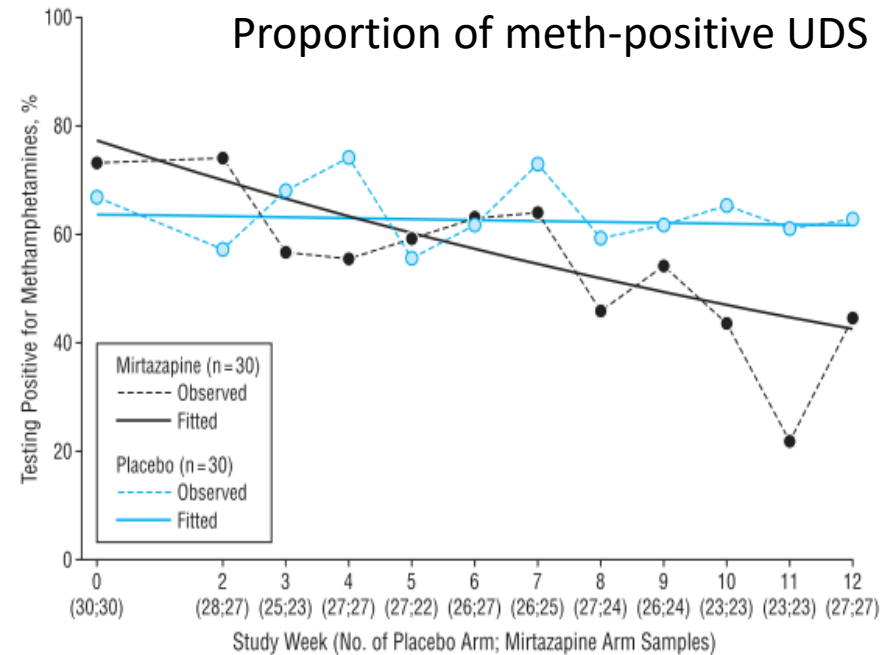
- Atomoxetine – selective norepinephrine reuptake inhibitor, for ADHD
- RCT for patients with OUD + methamphetamine use disorder
  - N=69 males (n=33 atomoxetine, 33 placebo), all received buprenorphine
  - Proportion of stimulant-negative UDS: significantly higher in atomoxetine group
  - Proportion of days abstinent: both groups significantly increased
- Tolerated, safe, some potential efficacy in population of OUD treated with buprenorphine

# Recent Mirtazapine Data

Mirtazapine – antidepressant

M1.0 Study, Phase 2a trial

- N=60 MSM (30 to mirtazapine, 30 to placebo), 12 weeks, included 30 minute SUD counseling
- Reduced relative risk of meth use by more than 40% (RR=0.57), significantly reduced many sexual risk behaviors
- Adherence 48.5% by MEMS



# Recent Mirtazapine Data

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- Reduced relative risk of meth use by more than 40% (RR=0.57), significantly reduced many sexual risk behaviors
- Adherence 48.5% by MEMS

### M2.0 Study

- N=120 MSM (born as or identify as men) (60 to mirtazapine, 60 to placebo), 24 weeks, included 30 minute SUD counseling
- Reduced relative risk of meth use by more than 30% (RR=0.67), significantly reduced many sexual risk behaviors
- Adherence 38.5% by WisePill

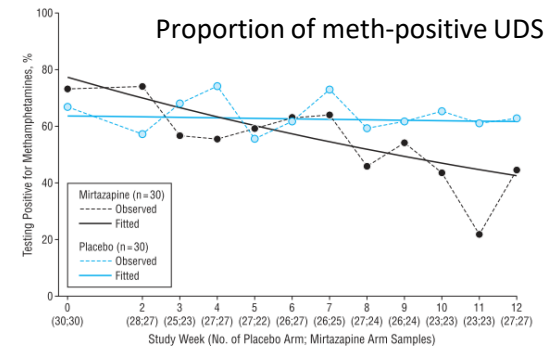
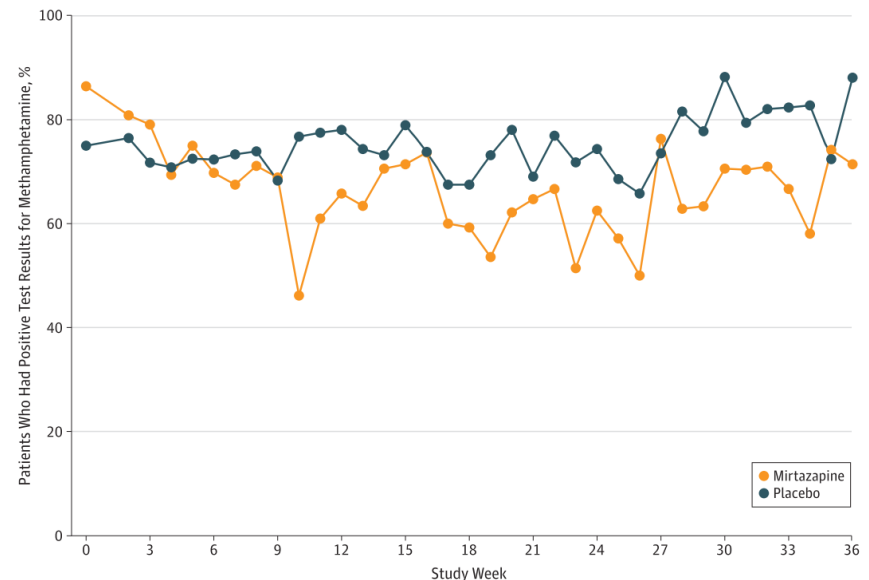


Figure 2. Proportion of Participants With Positive Urine Test Results for Methamphetamine During Follow-up, by Arm





# Current Research

# Background

- Independent clinical utility of each medication for treatment of meth use disorder
- **Naltrexone** appears to:
  - Reduce reinforcing effects of amphetamine (Jayaram-Lindstrom et al., 2008)
  - Decrease craving (Ray et al., 2015)
- **Bupropion** (typically 300mg/day) appears to:
  - Reduce cue-craving (Newton et al., 2006)
  - Decrease MA use (Elkashef et al., 2008)
- Combination medication
  - One allows other to exert an effect
  - One enhances effect of another
  - Synergy between the two





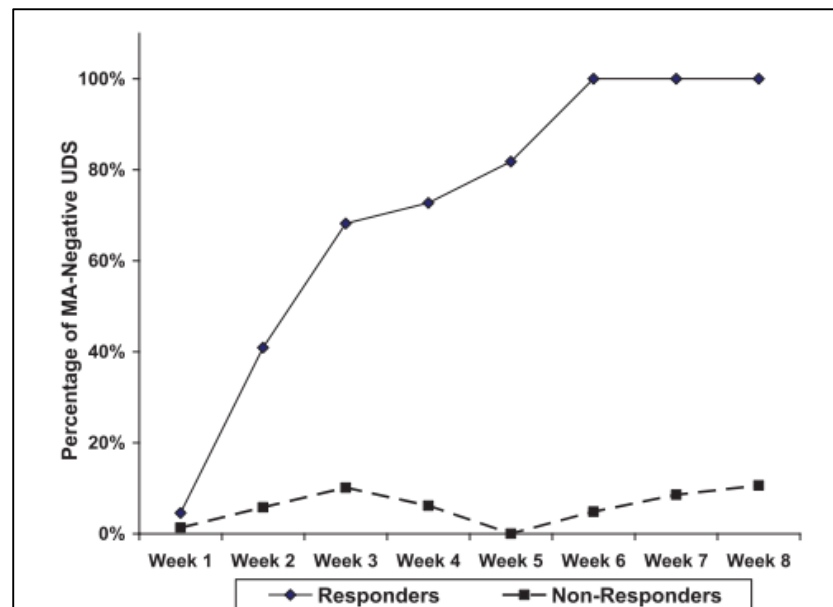
# CTN-0054 ADAPT-MD

## Utilizing a Two-stage Design to Investigate the Safety and Potential Efficacy of Monthly Naltrexone Plus Once-daily Bupropion as a Treatment for Methamphetamine Use Disorder

Larissa J. Mooney, MD, Maureen P. Hillhouse, PhD, Christie Thomas, MPH, Alfonso Ang, PhD, Gaurav Sharma, PhD, Garth Terry, MD, PhD, Linda Chang, MD, Robrina Walker, PhD, Madhukar Trivedi, MD, David Croteau, MD, Steven Sparenborg, PhD, and Walter Ling, MD

Baseline Characteristics (N=49)	% or M (SD)
Male	53.1%
Age	39.9 (10.76)
White	49.0%
Hispanic	30.6%
High school or some college	63.3%
Never married	61.2%
Unemployed	49.0%
METH use days prior to consent	27.0 (3.44)

## Accelerated Development of Additive Pharmacotherapy Treatment for Methamphetamine Use Disorder



**FIGURE 2.** Percentage methamphetamine-negative urine drug screen by responder status by study week. The proportion of MA-negative urines was significantly higher at each week for the responder group as compared with the nonresponder group ( $P = <0.05$ ). MA indicates methamphetamine.





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Never married	61.2%
Unemployed	49.0%
METH use days prior to consent	27.0 (3.44)

11 of 49 (22%) met “responder” definition → development of CTN-0068 ADAPT-2 trial

## Accelerated Development of Additive Pharmacotherapy Treatment for Methamphetamine Use Disorder

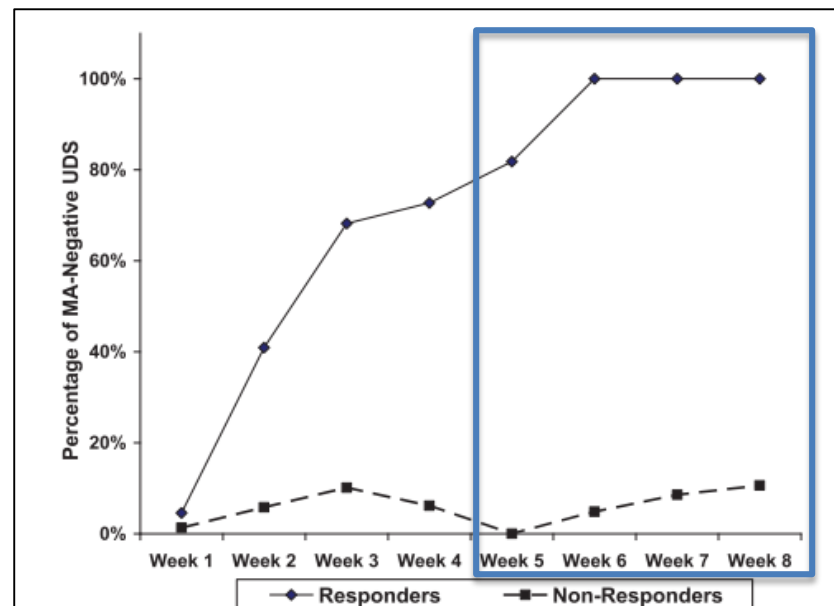


FIGURE 2. Percentage methamphetamine-negative urine drug screen by responder status by study week. The proportion of MA-negative urines was significantly higher at each week for the responder group as compared with the nonresponder group ( $P = <0.05$ ). MA indicates methamphetamine.

# Oral Medication Adherence via Video Observed Therapy

## Medication Adherence Monitoring Using Smartphone Video Dosing in an Open-label Pilot Study of Monthly Naltrexone Plus Once-daily Bupropion for Methamphetamine Use Disorder: Feasibility and Acceptability

*Robrina Walker, PhD, Maureen Hillhouse, PhD, Brian Perrochet, BA, Steven Sparenborg, PhD, Larissa Mooney, MD, and Walter Ling, MD*

### Likely Benefits of Providing Smartphones

Objective numerical indicator of lowest possible adherence rate

Means to incentive valid dosing videos

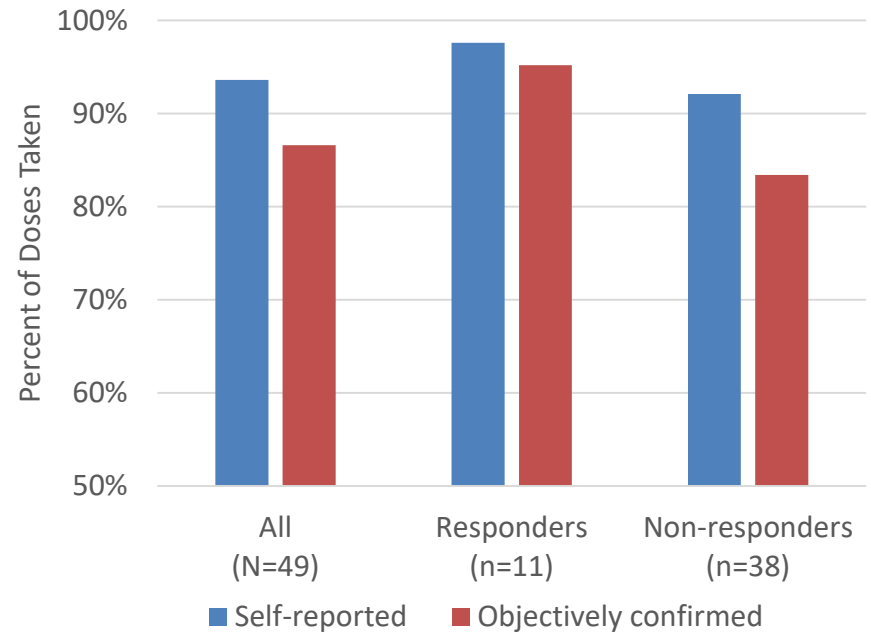
Reliable method of ppt contact

Tangible reminder of study participation

Smartphone calendar used for visit reminders

Fostered retention because ppts could keep smartphones

Adherence to Dispensed Oral Medication, by Method of Adherence Documentation

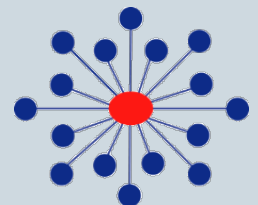
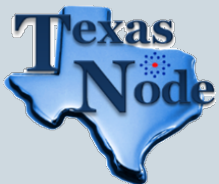


- Data provide low to high range of adherence rates

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# CTN-0068 ADAPT-2: Accelerated Development of Additive Pharmacotherapy Treatment for Methamphetamine Use Disorder

Funded by NIDA UG1DA020024



# ADAPT-2 Study Objectives

## Primary Aim:

- Assess efficacy of extended-release injectable naltrexone (380 mg) + extended release oral bupropion (450 mg) as combination pharmacotherapy for methamphetamine use disorder

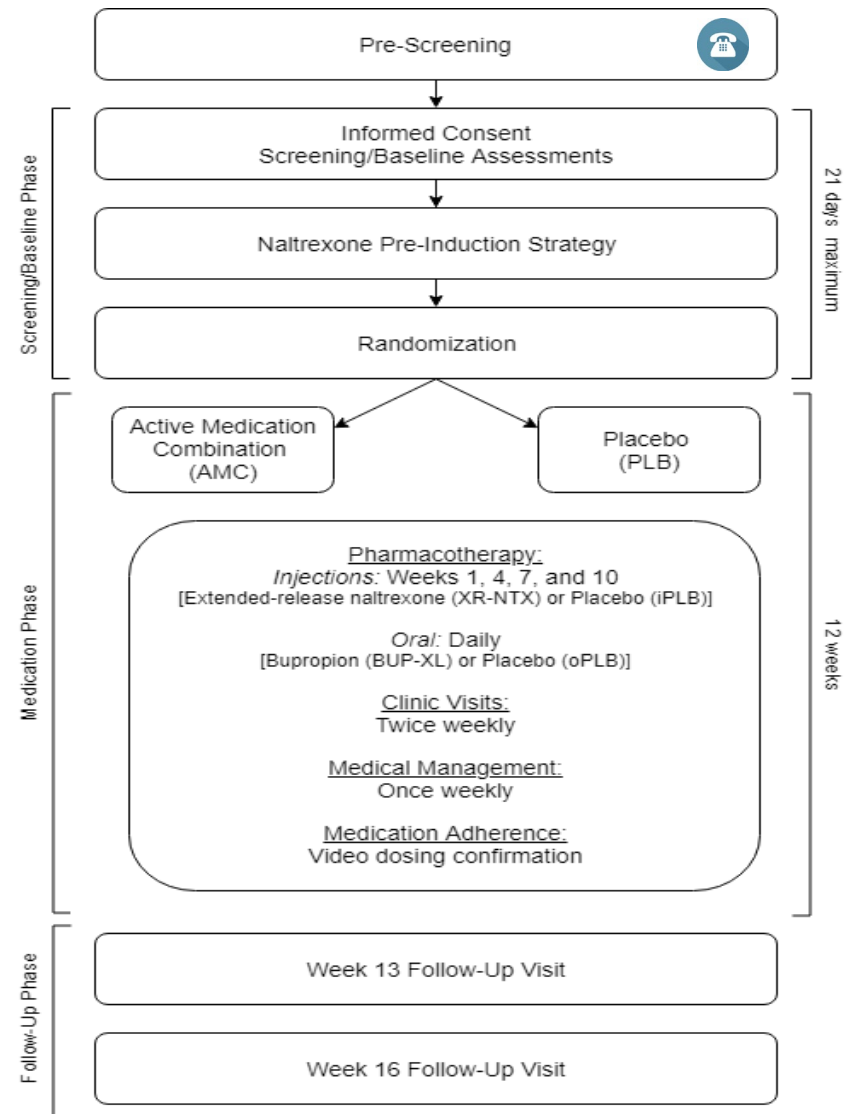


## Secondary Aims:

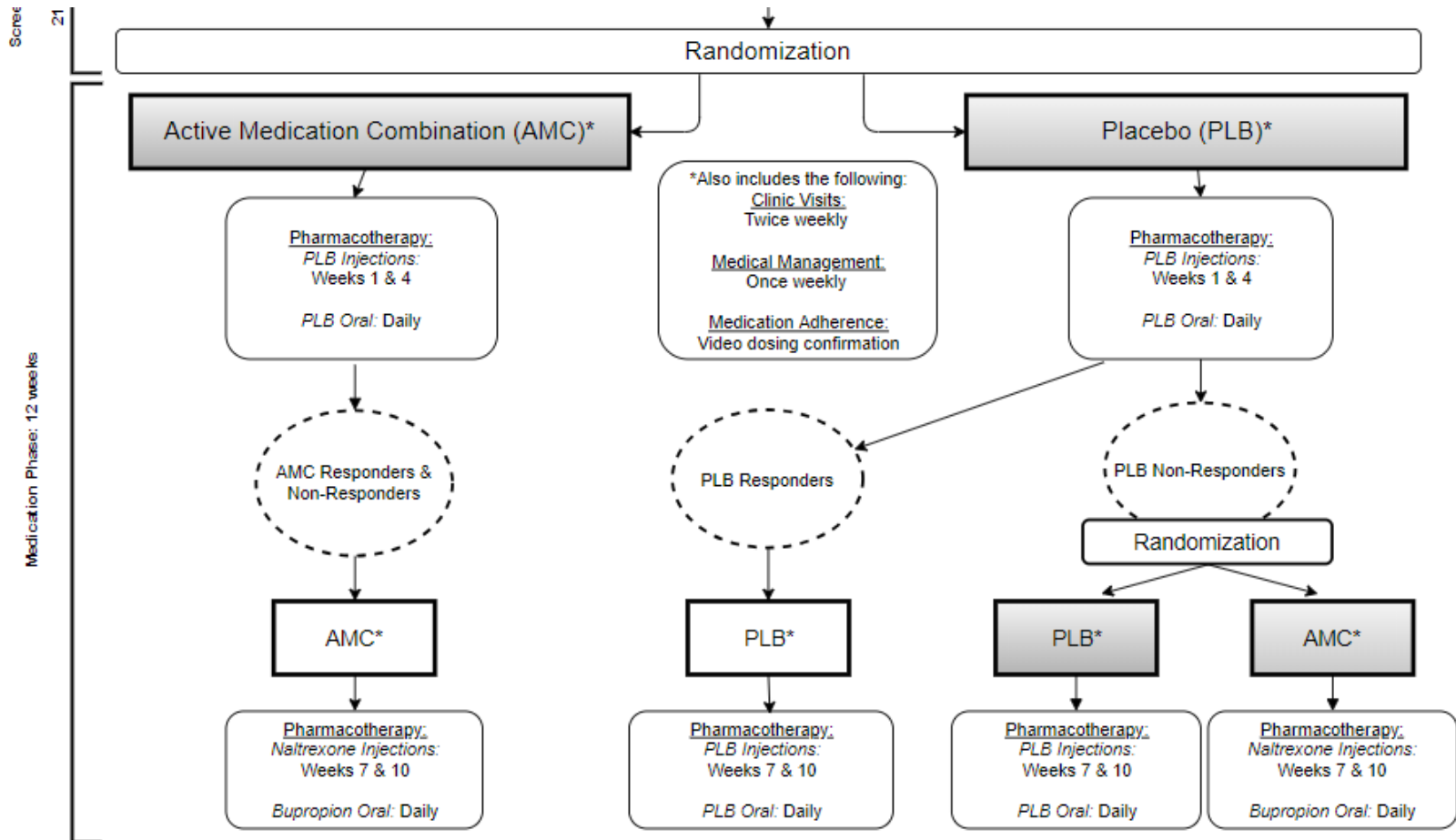
- Assess safety
- Assess efficacy on other SUD outcomes, depression symptom scores, quality of life ratings

# ADAPT-2 Study Design & Schema - Masked

- Double-blind, randomized, placebo-controlled, sequential parallel comparison design
- N = 403 in 8 sites
- Key Inclusion Criteria:
  - DSM-5 moderate or severe stimulant use disorder, methamphetamine type
  - Self-report using meth on most days in month prior to consent ( $\geq 18/30$ )
  - Fairly healthy
  - No concurrent addiction treatment
- Medication Phase
  - AMC: 450 mg bupropion (dispensed weekly) and XR-NTX every 3 weeks
  - PLB: matched oral and injectable
  - **Re-randomization may occur**



# Study Schema - Unmasked





# ADAPT-2 Primary Outcomes

- **Primary efficacy outcome measure**
  - Methamphetamine negative UDS results in Medication Phase (AMC vs PLB), in the ITT population
  - **“Responder”**: At least 3 Meth negative UDS (of possible 4), per Stage
    - Stage 1 evaluation period: Weeks 5 and 6
    - Stage 2 evaluation period: Weeks 11 and 12
- **Primary safety outcomes**: Adverse Events and Serious Adverse Events



# Safety Measures

# Efficacy Measures

- **Adverse Events**
- Physical examination
- Electrocardiogram
- Injection Site Examination
- Clinical Laboratory Tests
- Concise Health Risk Tracking
- Urine Pregnancy Test
- Vital Signs
- Prior & Concomitant Medications



- **Urine Drug Screen**
- Timeline Followback
- Visual Analog Craving Scale
- Patient Health Questionnaire-9
- Quality of Life
- Treatment Effectiveness Assessment
- Tobacco Use History




# Adherence Measures



- Study Medication Dosing Logs (self-report + staff observation)
- Injection Administration Form (staff observation)
- Oral Study Medication Blood Levels (prior to each injection)
- Video observed therapy via AiCure app (daily)

Patient daily use view

Reminder & dosing instructions ▶ Dosing administration steps




Support: CALL AICURE SUPPORT: 555-555-5555

Guidance:  

Performance: WEEKLY ADHERENCE: 75%

AI CURE

AI software algorithms automatically confirm ingestion through the front-facing webcam of a smartphone



Deep learning facial recognition

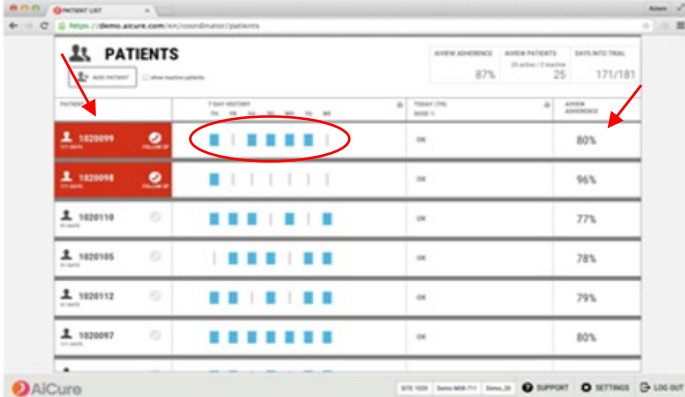
Pill and packaging computer vision recognition  
- shape  
- colors  
- markings

Ingestion confirmation  
- gesture  
- object detection  
- motion tracking

No manual video review is needed as the software does the confirmation.

AI CURE

## Study coordinator dashboard



PATIENTS	ADHERED	ADHERENCE	ADHERED PATIENTS	DAYS INTO TRIAL
1820019	OK	80%	25	171/181
1820018	OK	95%		
1820110	OK	77%		
1820105	OK	78%		
1820112	OK	79%		
1820097	OK	80%		

# Performance Sites

- **Western States Node:**
  - **Portland, OR** - CODA, Inc.
  - **San Francisco, CA** - SF Dept. of Public Health
- **Texas Node:**
  - **Los Angeles, CA** - UCLA Vine Street Clinic
  - **Dallas, TX** - UT Southwestern
  - **Houston, TX** - UTHealth Center for Neurobehavioral Research on Addiction
- **Northstar Node:**
  - **Minneapolis, MN** - Hennepin Healthcare/Berman Center for Research Outcomes
- **Southern Consortium:**
  - **Pickens, SC** - Behavioral Health Services
- **Greater New York Node:**
  - **New York, NY** - Columbia/NY State Psychiatric Institute





# Acknowledgements

## Texas Node

### **UT Southwestern Medical Center**

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Kathy Shores-Wilson, PhD

## **UCLA**

Walter Ling, MD

## Clinical Coordinating Center (CCC)

Bob Lindblad, MD

Eve Jelstrom

Matthew Wright

Prashanth Parmar

## Data & Statistics Center (DSC)

Gaurav Sharma, PhD

Paul Van Veldhuisen, PhD

Lauren Yesko

Anne Hoehn

Cathryn Mudrick

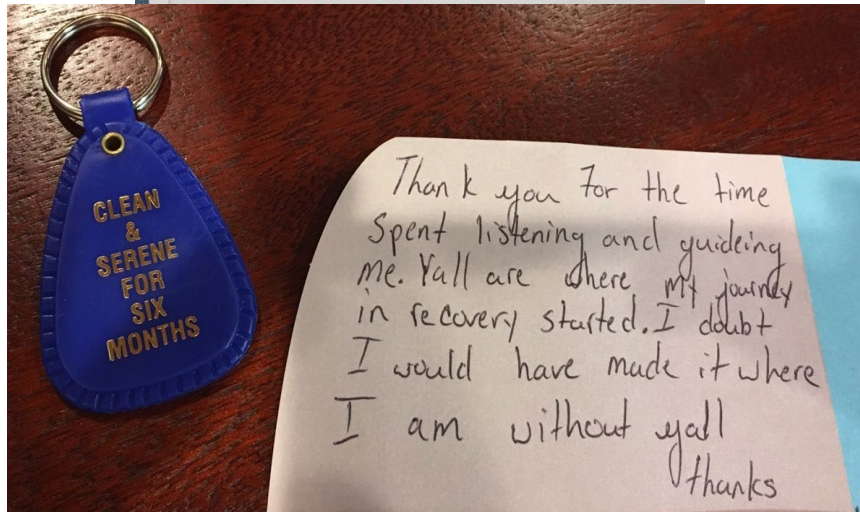
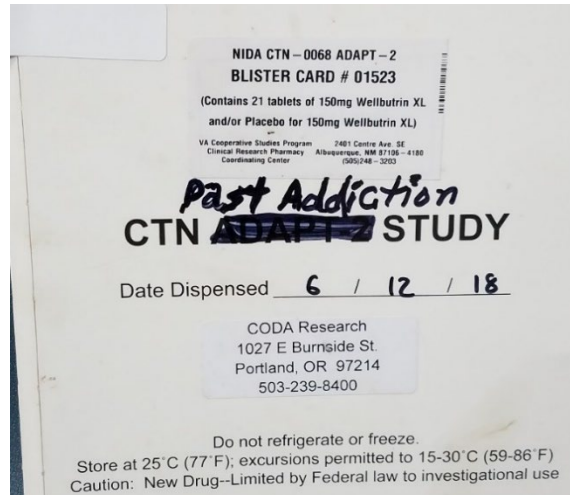
Ashley Case

## NIDA CCTN

Udi Ghitza, PhD




# Anecdotally...



## HOUSTON★CHRONICLE

Meth addiction has roared back in Texas. Can new experimental treatment stop it?

 Todd Ackerman | June 16, 2018 | Updated: June 18, 2018 11:14 a.m.

With less than a month to go in the study's 12-week drug regimen, Kim reports significant progress. She says she still uses some, but she's down to once a week or once every other week, usually just when friends with meth show up. She recently told her old dealer not to come around any more.

"I used to really chase it, but now I don't have those cravings," says Kim, who's been in rehab four times and to prison because of meth twice.

"I'm not all the way there yet," she said, "but I don't need to stay in bed for days at a time."

<https://www.houstonchronicle.com/news/houston-texas/houston/article/Meth-addiction-has-roared-back-in-Texas-Can-new-12998982.php#photo-15740582>

**UTSouthwestern**  
Medical Center



gracias cảm ơn bạn धन्यवाद 고맙습니다  
شكرا جزيلًا salamat благодарю вас 谢谢  
Dziękuję Ci **Thank** ευχαριστώ  
quyana tack **you!** አመሰግናለሁ  
धन्यवाद danke asante grazie  
hík'wu? merci הודת obrigado ขอบคุณ  
ありがとうございました спасиби mahalo



Northwest (HHS Region 10)

**ATTC** Addiction Technology Transfer Center Network  
Funded by Substance Abuse and Mental Health Services Administration

