Developing Novel Therapies for Stimulant Use Disorder

Marriott Metro Center

December 16, 2019

Welcome and Overview

Save the Date!

Public Meeting on Patient-Focused Drug Development for Stimulant Use Disorder

March 10, 2020
Silver Spring, MD and Webcast

FDA is interested in hearing perspectives from individuals with stimulant use disorder and other stakeholders on the:

- Health effects and daily impacts of their condition
- Impact (if any) of opioid and polysubstance use on their condition
- Treatment goals
- Decision factors considered when seeking out or selecting a treatment

Registration will open online in January 2020!

For more information, please visit: https://www.fda.gov/drugs/news-events-human-drugs/public-meeting-patient-focused-drug-development-stimulant-use-disorder-03102020-03102020.

Questions? PatientFocused@fda.hhs.gov

Welcome and Overview

Opening Keynote

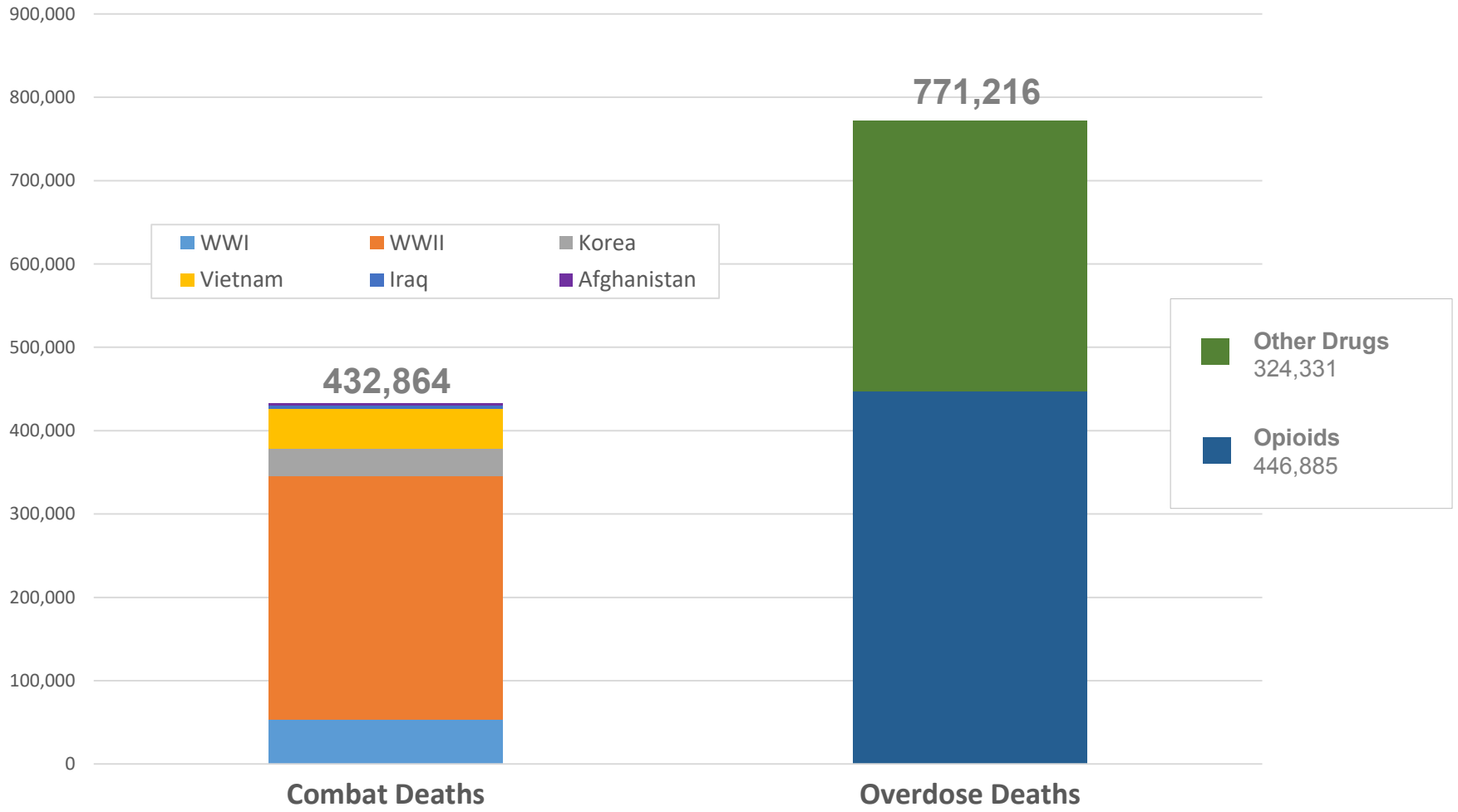
OFFICE OF THE ASSISTANT SECRETARY FOR HEALTH




ADDRESSING THE 4TH WAVE OF THE OVERDOSE CRISIS

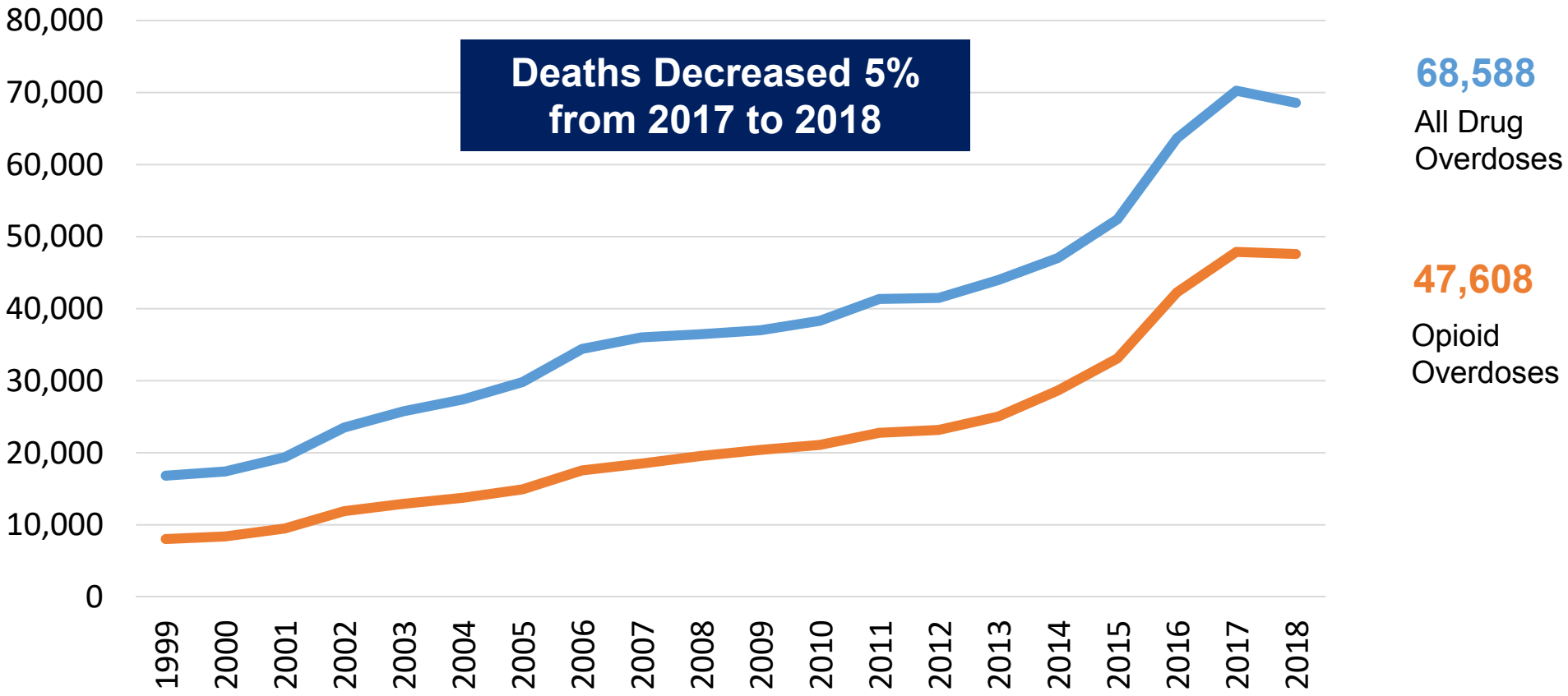
ADMIRAL BRETT P. GIROIR, M.D.
Assistant Secretary for Health
Commissioner of Food and Drugs (Acting)

U.S. OVERDOSE DEATHS (1999-2018)*
COMPARED TO COMBAT DEATHS



* 2018 Provisional Data, CDC NVSS

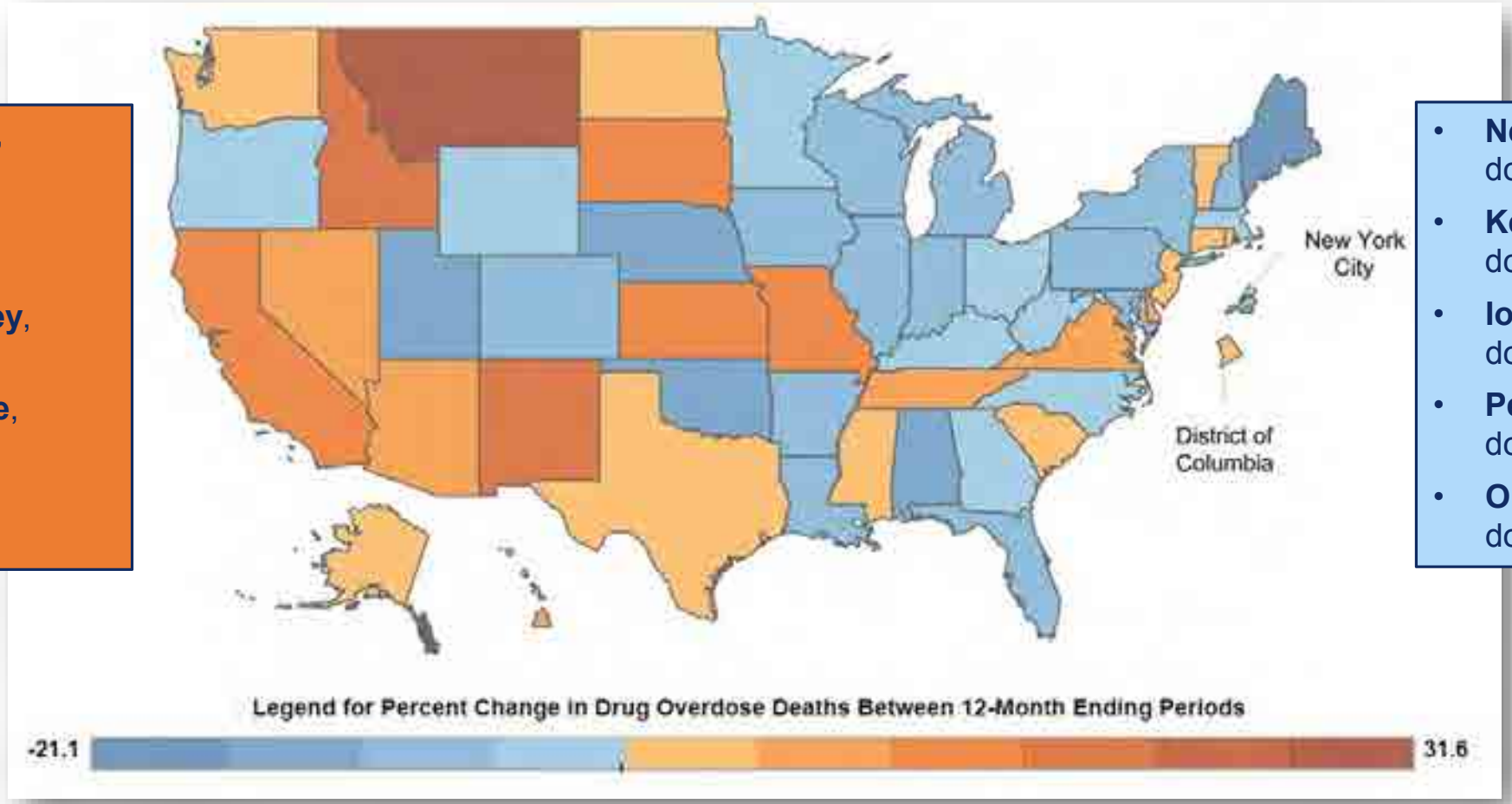
U.S. DRUG OVERDOSE DEATHS: TRENDS



SOURCE: NCHS, National Vital Statics System, Mortality

PERCENT CHANGE IN 12 MONTH OVERDOSE DEATHS
CDC, May 2019

- **California**, up 10.6%
- **Texas**, up 2.3%
- **New Jersey**, up 4.8%
- **Tennessee**, up 7.5%
- **Arizona**, up 9.9%



- **New Hampshire**, down 8.8%
- **Kentucky,** down 2.8%
- **Iowa,** down 8.3%
- **Pennsylvania**, down 10.4%
- **Ohio,** down 3.5%

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Source: CDC National Vital Statistics System, retrieved December 11, 2019

OVERDOSE MORTALITY BY CLASS OF DRUG

ADAPTED FROM CDC STATISTICS

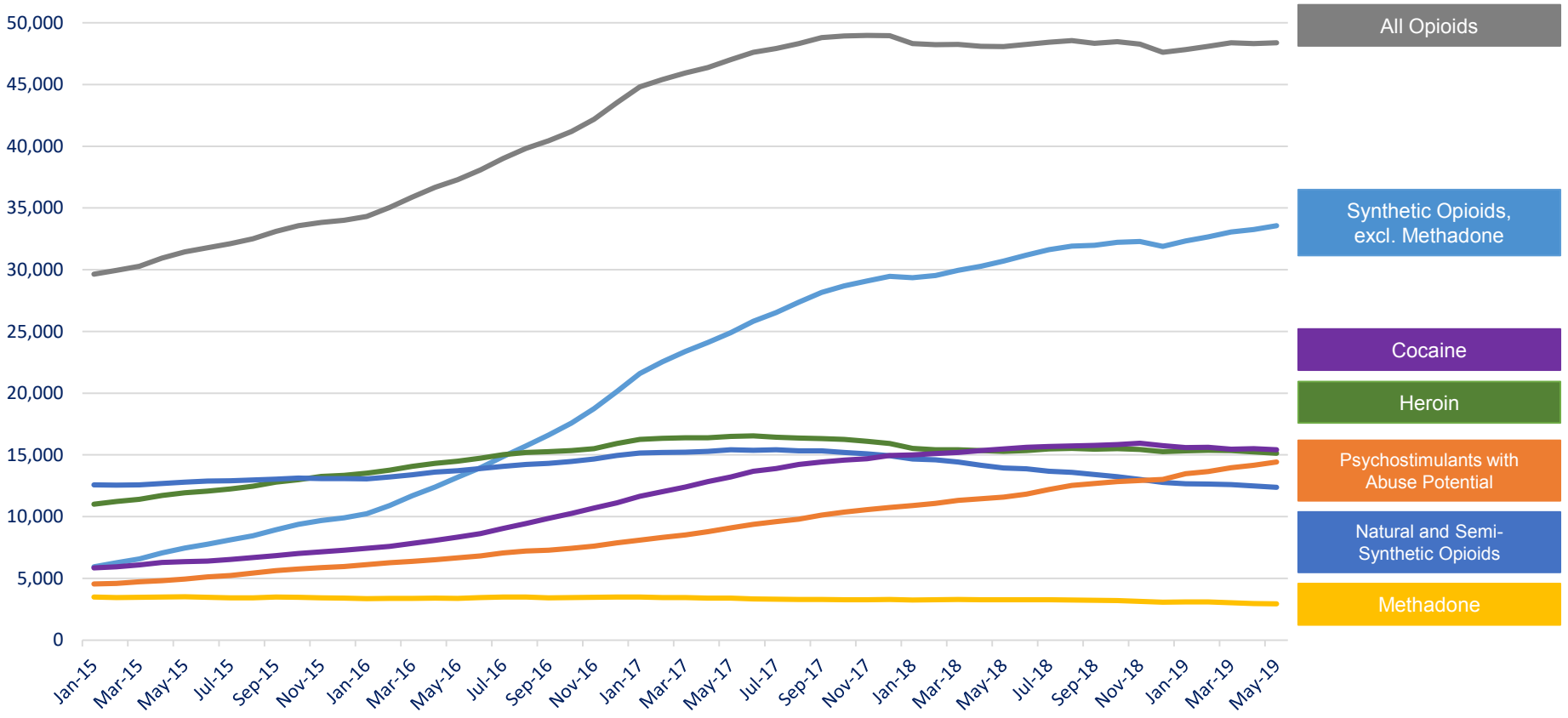
	HEROIN	NAT & SEMI – SYNTHETIC	METHADONE	SYNTHETIC OPIOIDS	COCAINE	PSYCHO-STIMULANTS
MAY 2018 *	15,476	13,927	3,265	30,692	15,476	11,572
MAY 2019 *	15,130	12,368	2,935	33,568	15,407	14,419
Change	**-2.24%**	**-11.19%**	**-10.11%**	**9.37%**	**-0.45%**	**24.60%**

- Number of predicted deaths for the 12 months ending in May of the indicated year

Source: CDC National Vital Statistics System, retrieved December 11, 2019

OVERDOSE DEATHS BY DRUG (CDC, MAY 2019)

12 MONTH-ENDING PROVISIONAL NUMBER OF DRUG OVERDOSE DEATHS BY DRUG OR DRUG CLASS, UNITED STATES

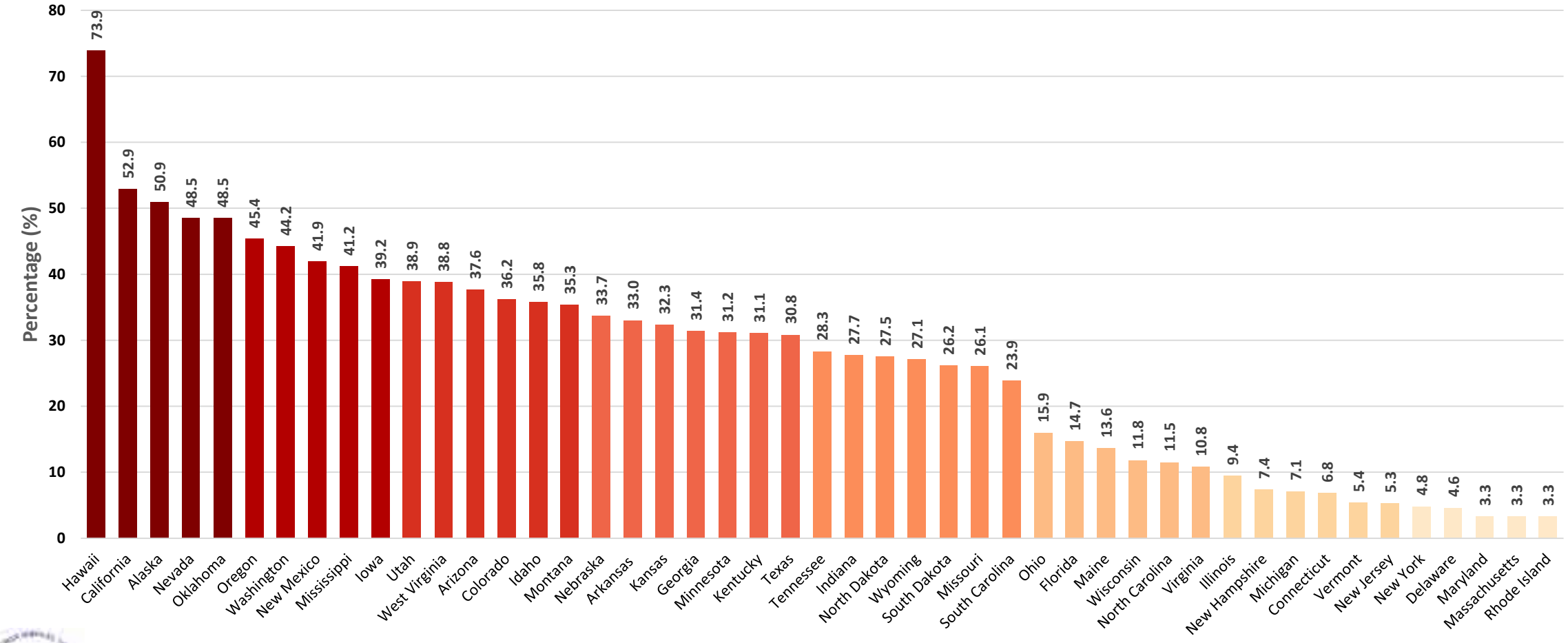


- Currently provisional counts by drug class are available for 35 states, New York City and the District of Columbia
- All 50 states reported end of year final data (through 2017)

Source: CDC National Vital Statistics System, retrieved December 11, 2019

METHAMPHETAMINE INVOLVEMENT IN OVERDOSE DEATHS

Percentage of Drug Overdose Deaths involving Psychostimulants, by Select Jurisdictions
United States, Provisional Mortality Data (March 2018 - February 2019)



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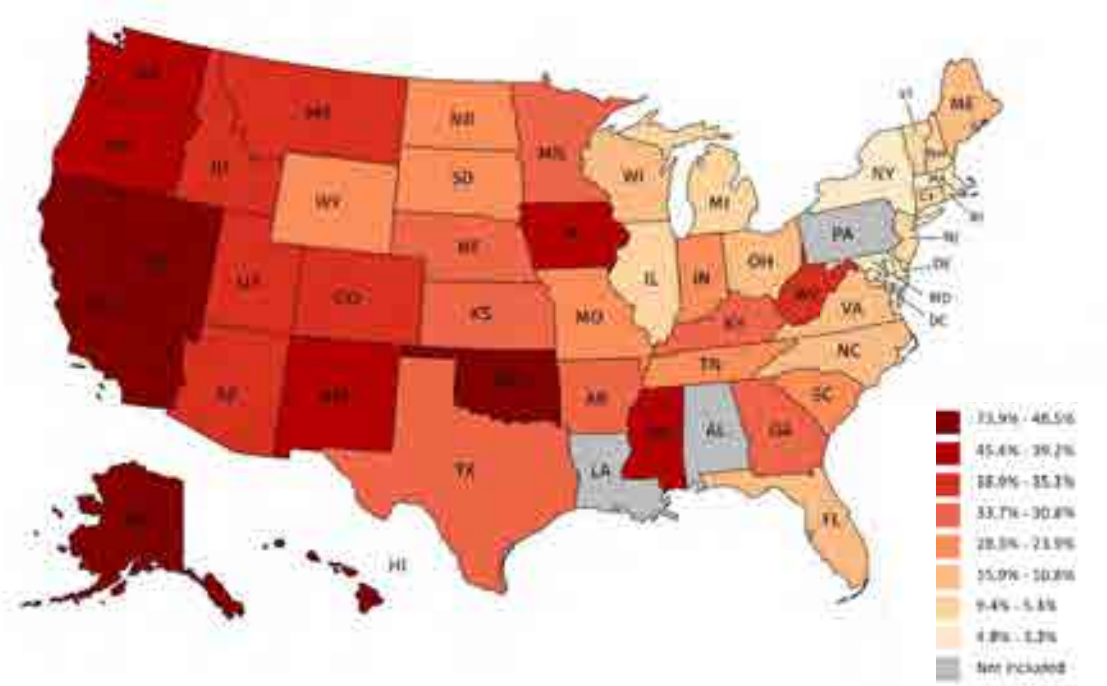
Source: CDC National Vital Statistics System, retrieved September 12, 2019

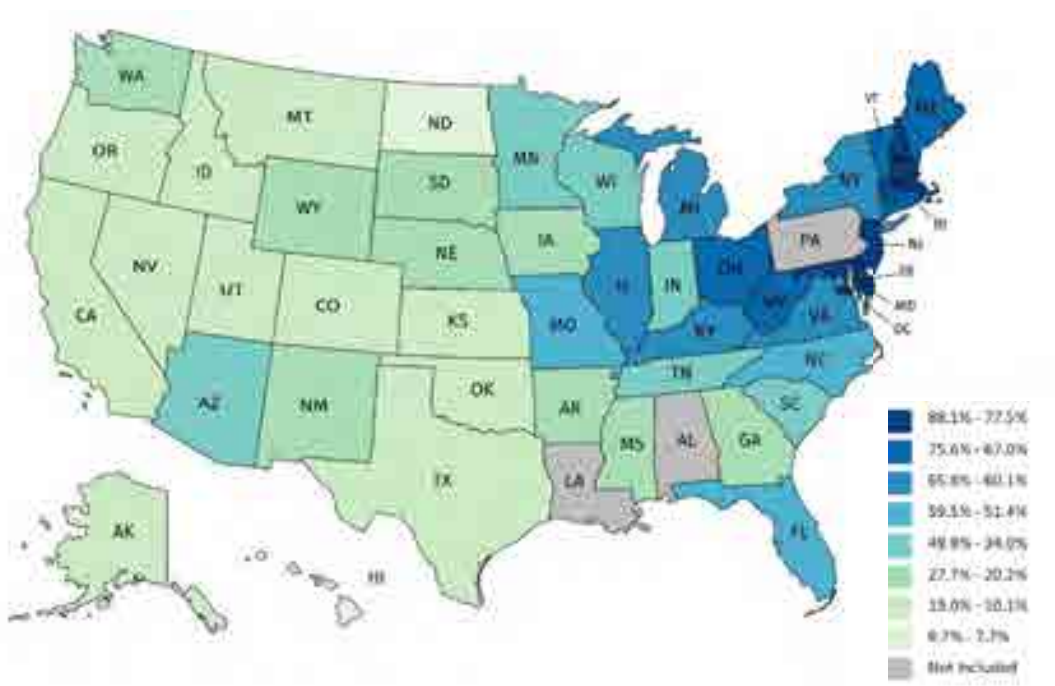
REGIONAL DIFFERENCES IN OVERDOSE DEATHS

Percentage of Drug Overdose Deaths by drug class by select jurisdictions:
United States, provisional mortality data from March 2018 - February 2019

PSYCHOSTIMULANTS



SYNTHETIC OPIOIDS



Source: CDC National Vital Statistics System, retrieved September 12, 2019

PATHWAYS TO METHAMPHETAMINE ABUSE

- The methamphetamine crisis is linked to the opioid crisis
  - Increasing prevalence of polysubstance use among those with OUD
  - Since 2008, >300% increase in methamphetamine use among heroin treatment admissions
  - 50% of psychostimulant-related overdose deaths involved opioids (2017)
- People using methamphetamine have
  - High rates of co-occurring mental illness (~50%)
  - Poly-substance abuse pre-dating methamphetamine use (cigarettes, alcohol, cannabis, cocaine)
- Adverse Childhood Experiences (ACEs, including physical and sexual abuse) are a key risk factor for SUD generally and methamphetamine specifically

The geography of methamphetamine abuse is highly correlated with methamphetamine supply:
transnational cartels are creating demand among vulnerable individuals

KRGV.com
Rio Grande Valley, Tx.

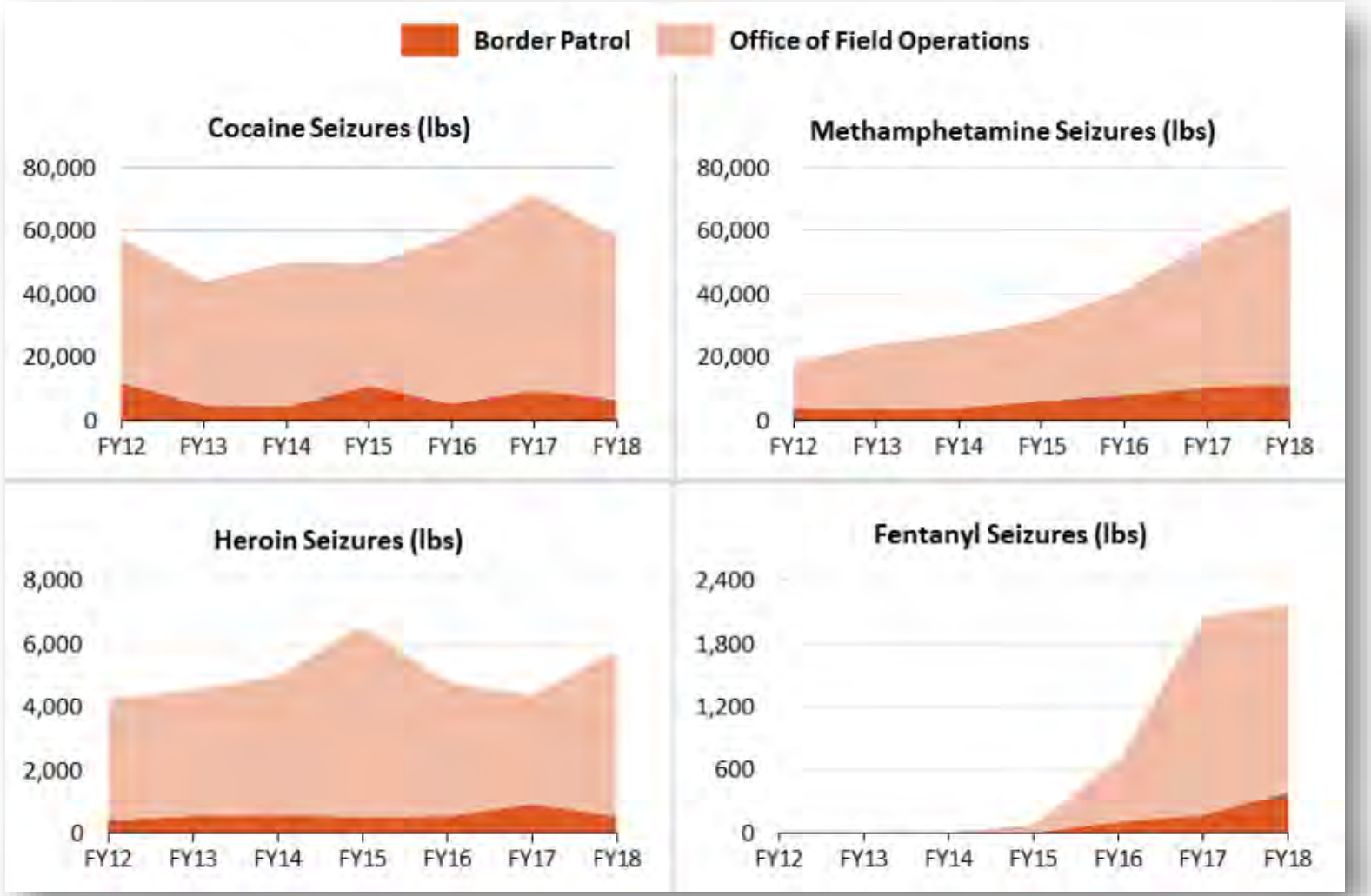
Friday, June 07 2019

CBP Officers Discover Nearly $14M in Meth Hidden Inside Coconuts

- Customs and Border Protection officers prevented nearly $14 million worth of liquid methamphetamine from making its way into the U.S.
- The seizure happened at the Pharr-Reynosa International Bridge.
- CBP officers made the discovery in a commercial shipment containing coconuts and limes.
- Officials seized 981 pounds of the alleged drug.
- CBP says a total of 1,017 bags of narcotics were extracted from the produce shipment and placed them in buckets.

https://khn.org/news/federal-grants-a-lifesaver-in-opioid-fight-but-states-still-struggle-to-curb-meth/

CBP DRUG SEIZURES



DEMOGRAPHICS OF METHAMPHETAMINE ABUSE AND DEATHS

- All age groups are impacted
- Death rates highest in AI/AN and non-Hispanic whites, but rapidly increasing in blacks
- Higher odds of past-year methamphetamine use among people living in non-metro and small metro areas compared to large metro areas
- Women are experiencing significant burden compared to men
  - Higher rates of methamphetamine treatment admissions, methamphetamine use among heroin treatment admissions, and psychostimulant-involvement in heroin or synthetic opioid-related overdose deaths

CHALLENGES & LIMITATIONS

- No FDA-approved medications for treatment (no MAT)
- No “rescue therapy” for toxicities (e.g., naloxone)
- Medication development for stimulant use disorder has been difficult, with few candidates in the pipeline
- Treatment relies on behavioral interventions which are:
  - time consuming
  - require special training and intense follow-up
  - often limited by attrition/retention issues

Federal Grants ‘A Lifesaver’ In Opioid Fight, But States Still Struggle To Curb Meth

JUNE 17, 2019

“I don’t need more opiate money. I need money that will not be used exclusively for opioids.”

- David Crowe, executive director of Crawford County, PA, Drug and Alcohol Executive Commission

… while local officials are grateful for the funding, the {SOR} grants can be spent only on creating solutions to combat opioids, such as prescription OxyContin, heroin and fentanyl.

https://khn.org/news/federal-grants-a-lifesaver-in-opioid-fight-but-states-still-struggle-to-curb-meth/

HHS Interagency Methamphetamine Working Group

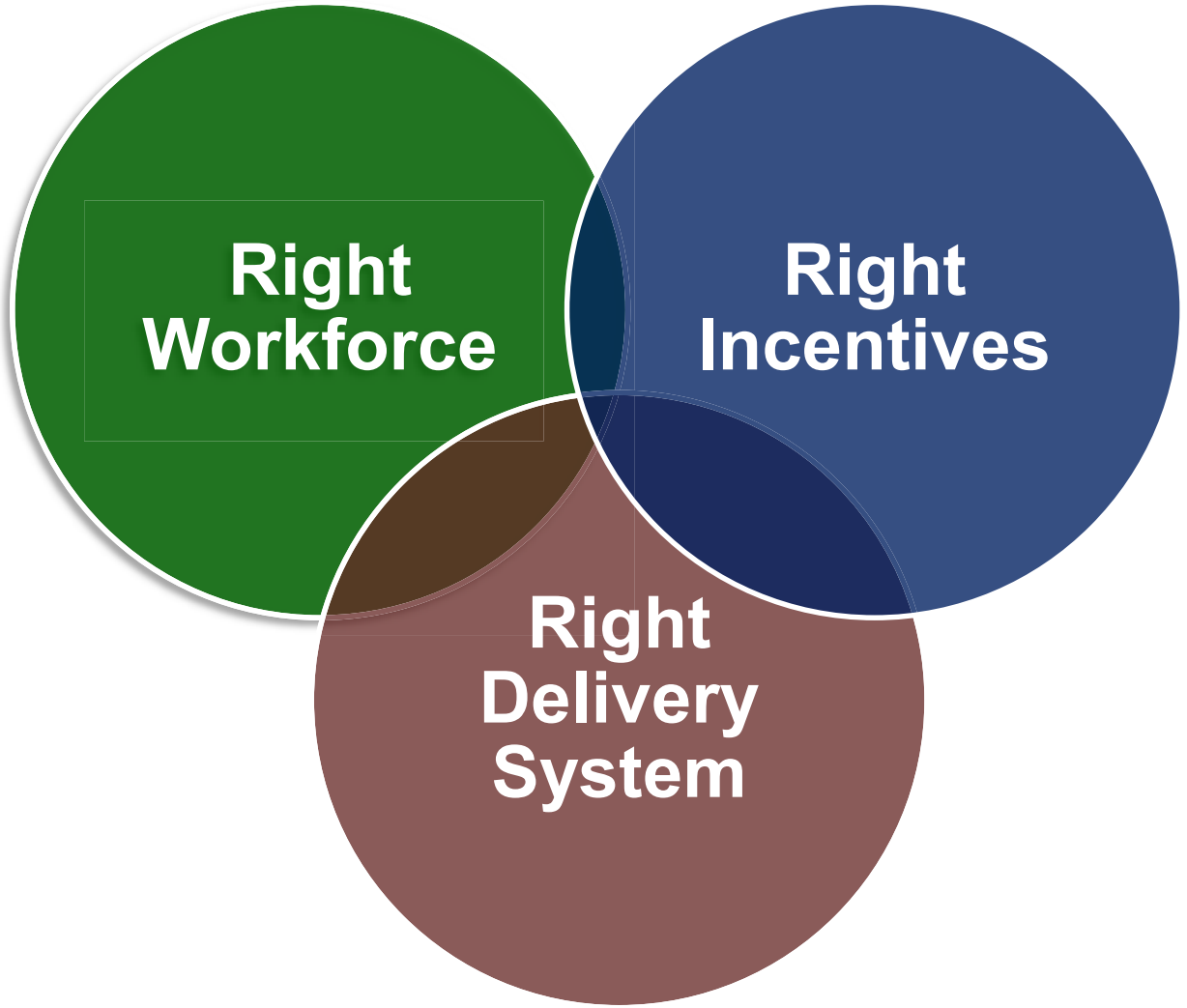
- Convened in March 2019; continues as action catalyst
- Improving data collection through CDC and SAMHSA
- Increased technical assistance for treatment (SAMHSA)
- FDA and NIH collaboration and industry outreach to support development of new therapeutics
- Provided TA to Congress on increasing flexibility of SOR funding
- Coordination with ONS, DoJ, CBP, ONDCP
- Multiple state and local fact finding and feedback tour planned for early 2020
- Developing “real time” situational awareness tools to track and intervene (methamphetamine, fentanyl analogs, etc.)
- Continuing overall SUD efforts (grants, payment reform, workforce, treatment, SDH)

DEVELOPING A SUSTAINABLE MODEL

Transition from a “crisis framework” into an integrated, sustainable, predictable, and resilient public health system for preventing and treating substance use and other behavioral health disorders.

CMS
CENTERS FOR MEDICARE & MEDICAID SERVICES
HRSA
Health Resources & Services Administration
SAMHSA
Substance Abuse and Mental Health Services Administration
CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION
FDA
AHRQ
Agency for Healthcare Research and Quality
NIH

DEVELOPING A SUSTAINABLE SYSTEM



RESEARCH ARTICLE SUMMARY

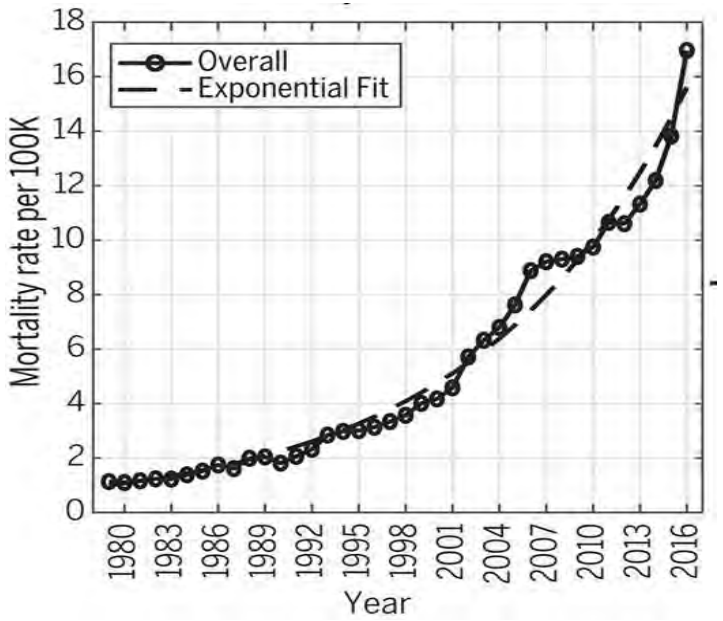
PUBLIC HEALTH

Sept 21, 2018

Science

Changing dynamics of the drug overdose epidemic in the United States from 1979 through 2016

Hawre Jalal, Jeanine M. Buchanich, Mark S. Roberts, Lauren C. Balmert, Kun Zhang, Donald S. Burke*



"The U.S. drug overdose epidemic has been inexorably tracking along an exponential growth curve since at least 1979. …a future overdose epidemic may be driven by a new or obscure drug that is not among the leading causes of drug overdose death today. "

We must understand, engage, and remedy the underlying root causes of addiction, suicides, and other behavioral health issues.

A PIVOTAL MOMENT

BRETT P. GIROIR, M.D.

ADM, U.S. Public Health Service

Assistant Secretary for Health

Commissioner of Food and Drugs (Acting)

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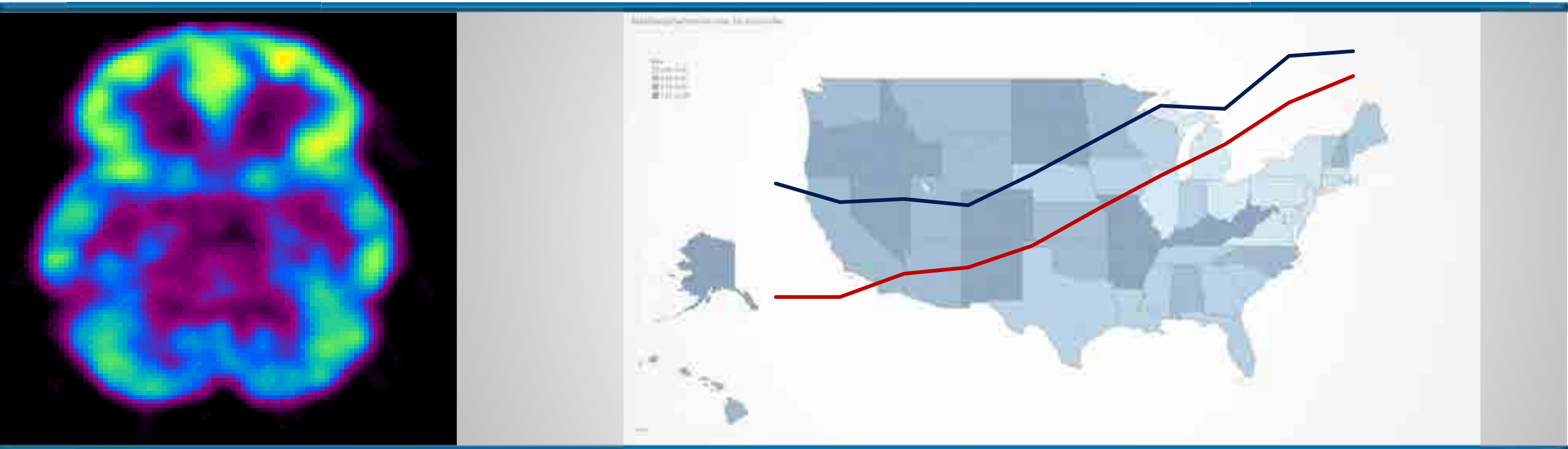
Session I: Overview of Stimulant Use Disorder and Emerging Trends

Stimulants: *Persistent and Emerging Public Health Concerns*



Wilson M. Compton, M.D., M.P.E.

Deputy Director

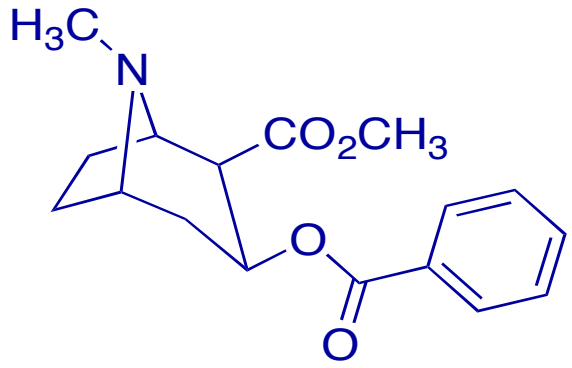
National Institute on Drug Abuse

NIH National Institute on Drug Abuse

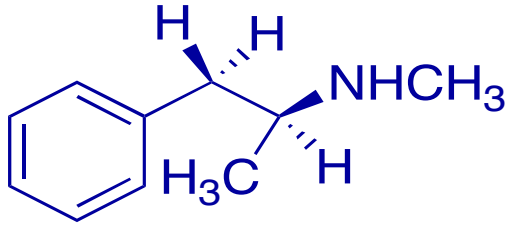
Advancing Addiction Science

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

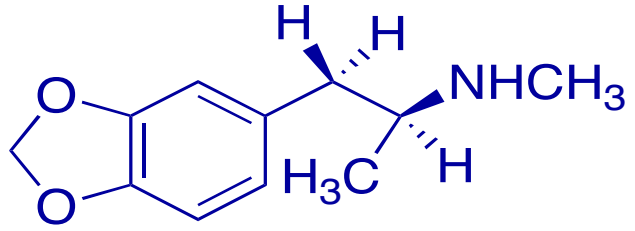
Psychostimulant Drugs



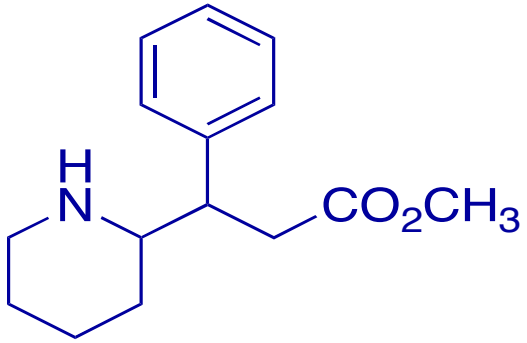
cocaine



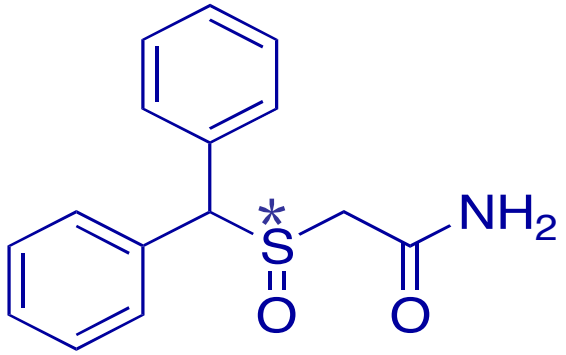
d-methamphetamine



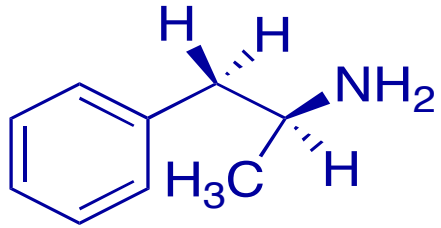
MDMA



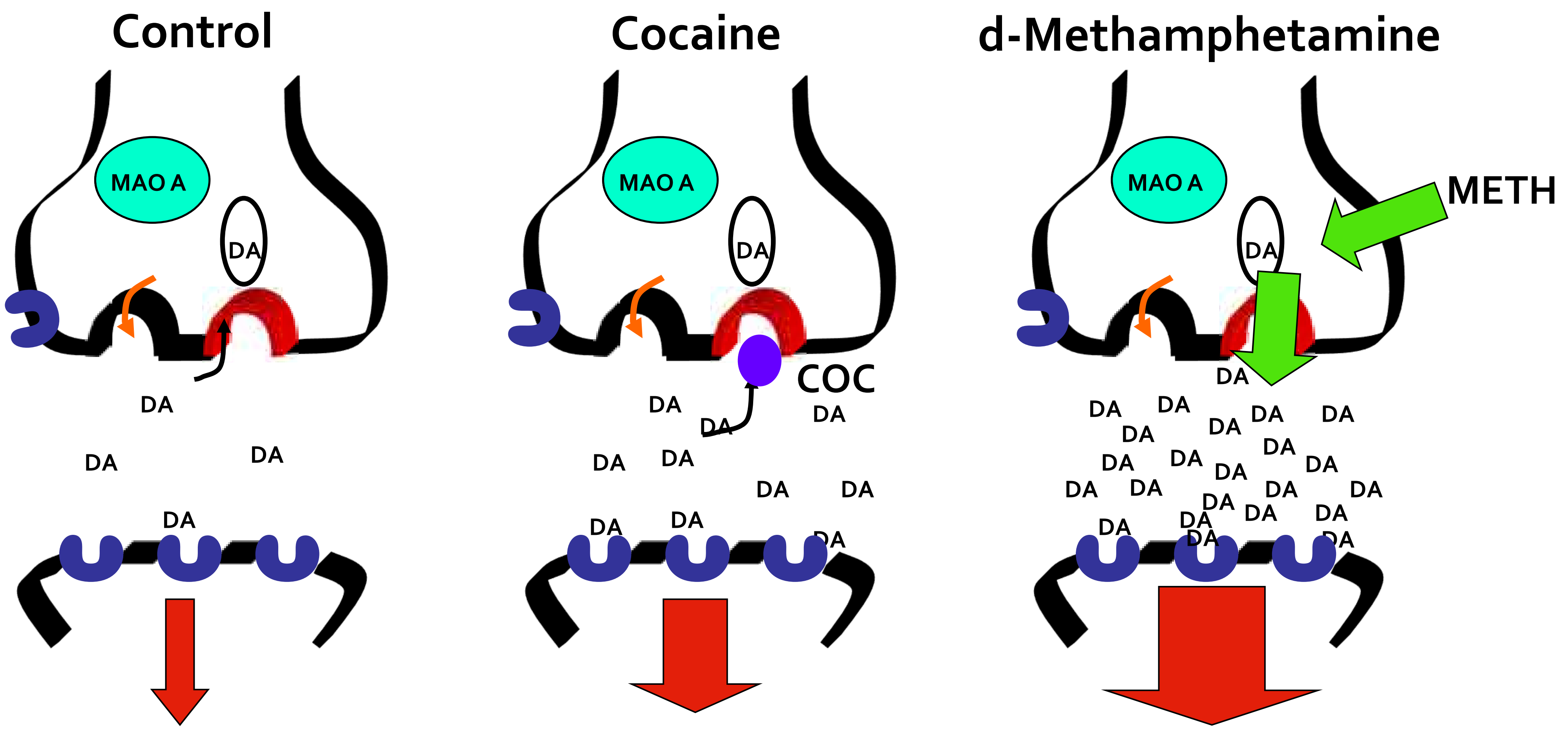
methylphenidate



modafinil

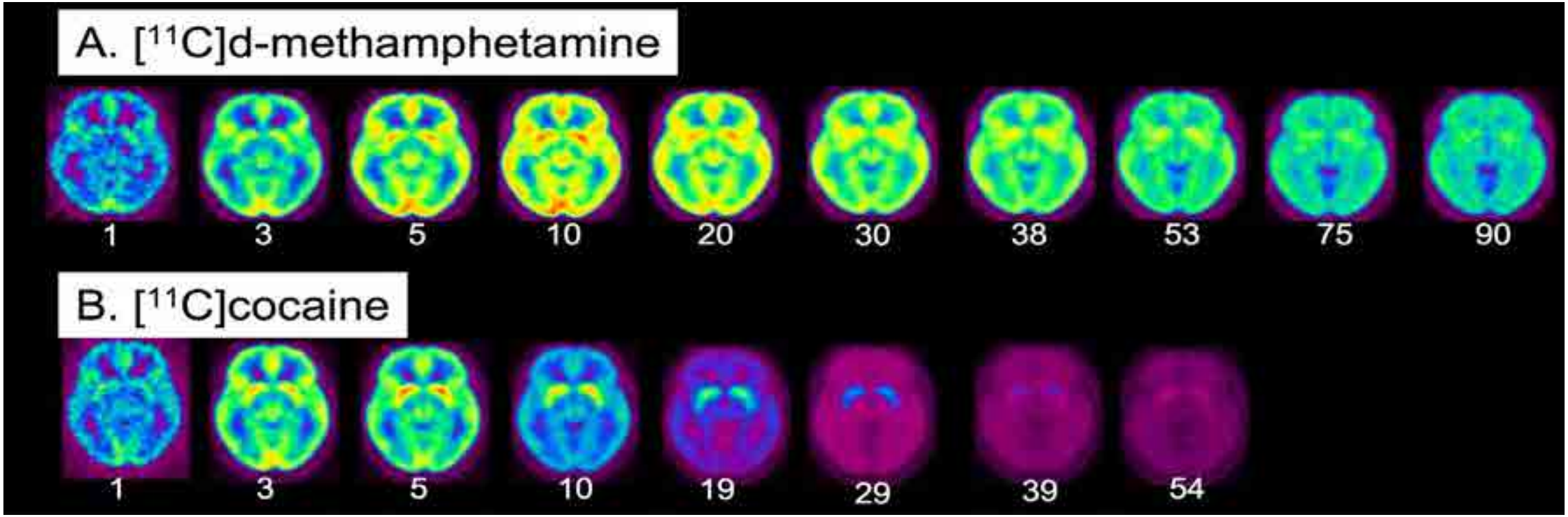


amphetamine



COC blocks DA reuptake;
METH blocks DA reuptake and releases DA from vesicles

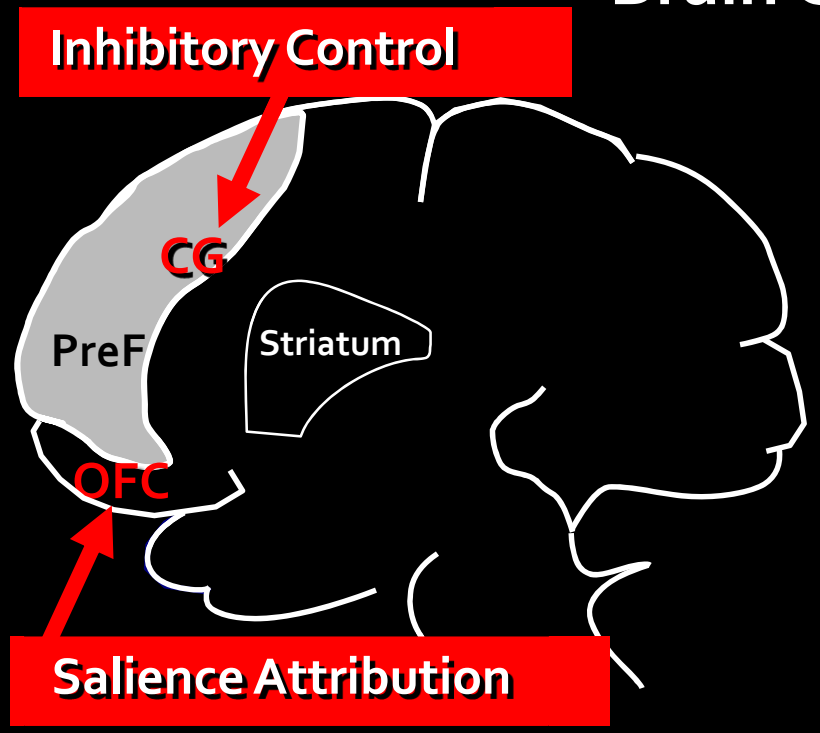
Comparison of Methamphetamine and Cocaine Pharmacokinetics in Striatum

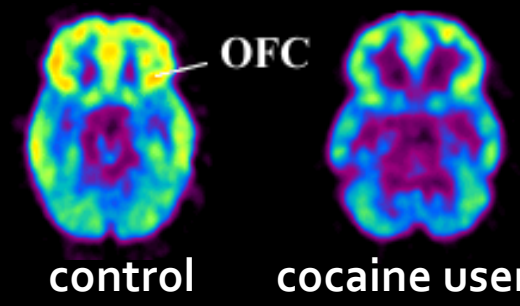


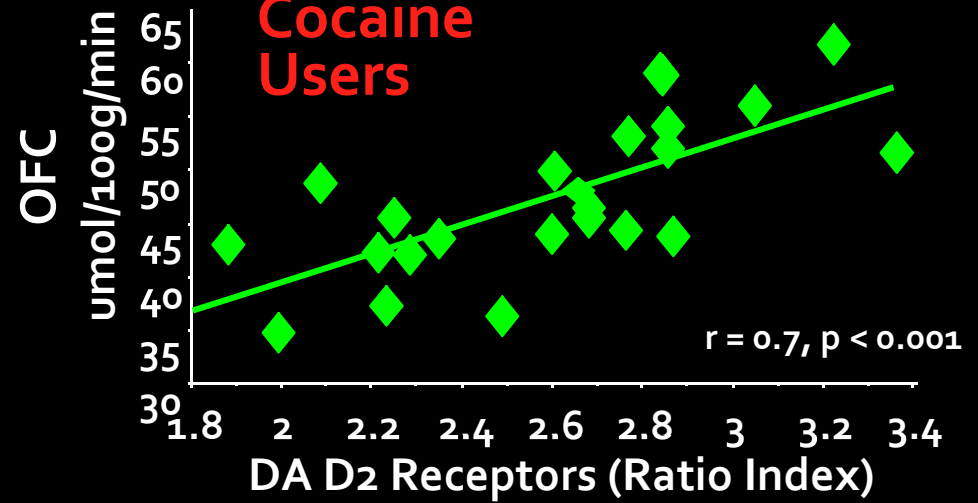
METH clears slowly from the striatum relative to cocaine which clears rapidly

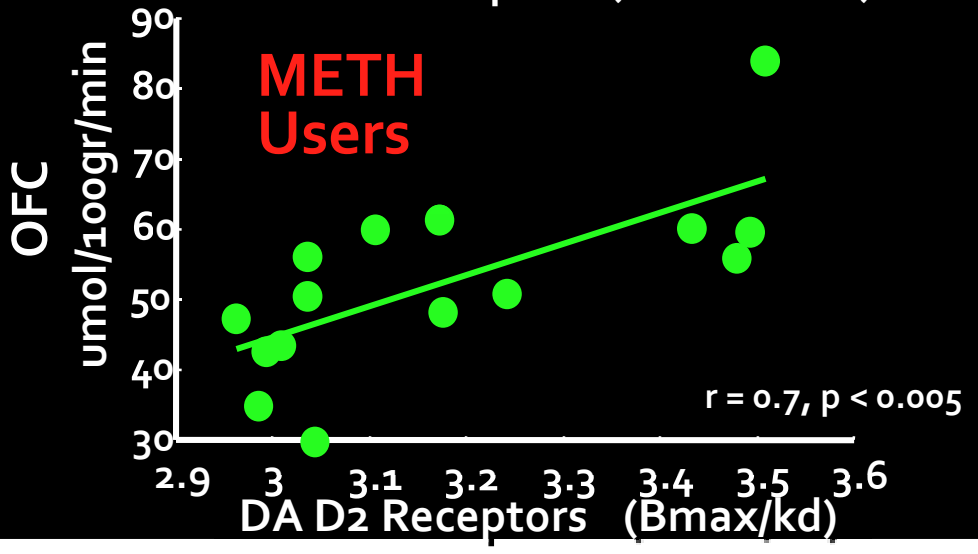
Chronic Drug Use Disrupts Inhibitory Control

Correlations Between D2 Receptors in Striatum and Brain Glucose Metabolism



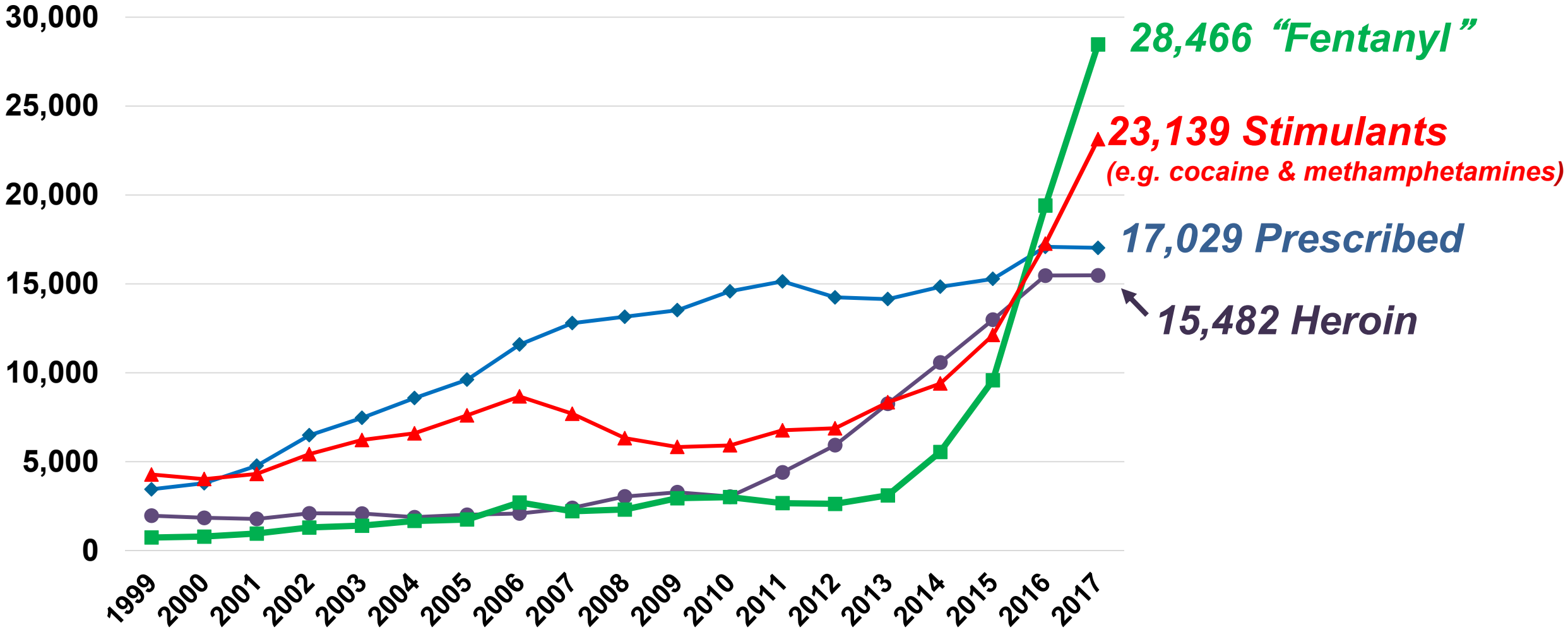






Evolution of Drivers of Overdose Deaths:

Analgesics ➡ Heroin ➡ Fentanyl ➡ Stimulants



See: Compton WM & Jones CM, *Ann NY Acad Sci, 2019;* Data from CDC WONDER Database

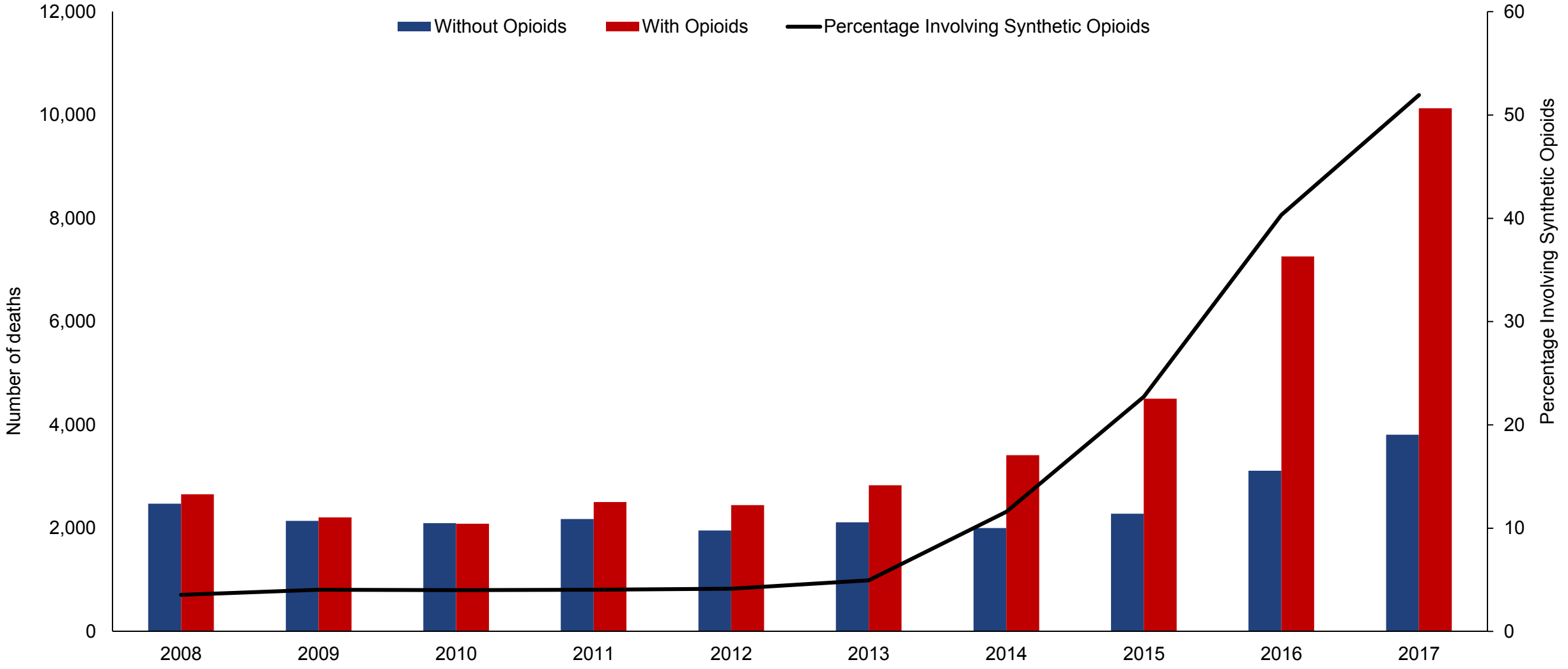
12 Month-Ending Predicted Provisional Overdose Mortality by Class of Drug**, 12-Month Ending, April 2018-April 2019

	Drug Overdose Deaths	Any Opioid	Prescription Opioids	Heroin	Synthetic Opioids	Psychostimulants	Cocaine
April 2018*	70,548	48,099	16,742	15,361	30,284	11,447	15,341
April 2019*	69,294	48,330	14,872	15,240	33,255	14,152	15,498
Abs Change	-1,254	231	-1,870	-121	2,971	2,705	157
Percent Change	-1.8%	0.5%	-11.2%	-0.8%	9.8%	23.6%	1.0%

* Number of predicted deaths for the 12 months ending in April of the indicated year
** Categories are not mutually exclusive

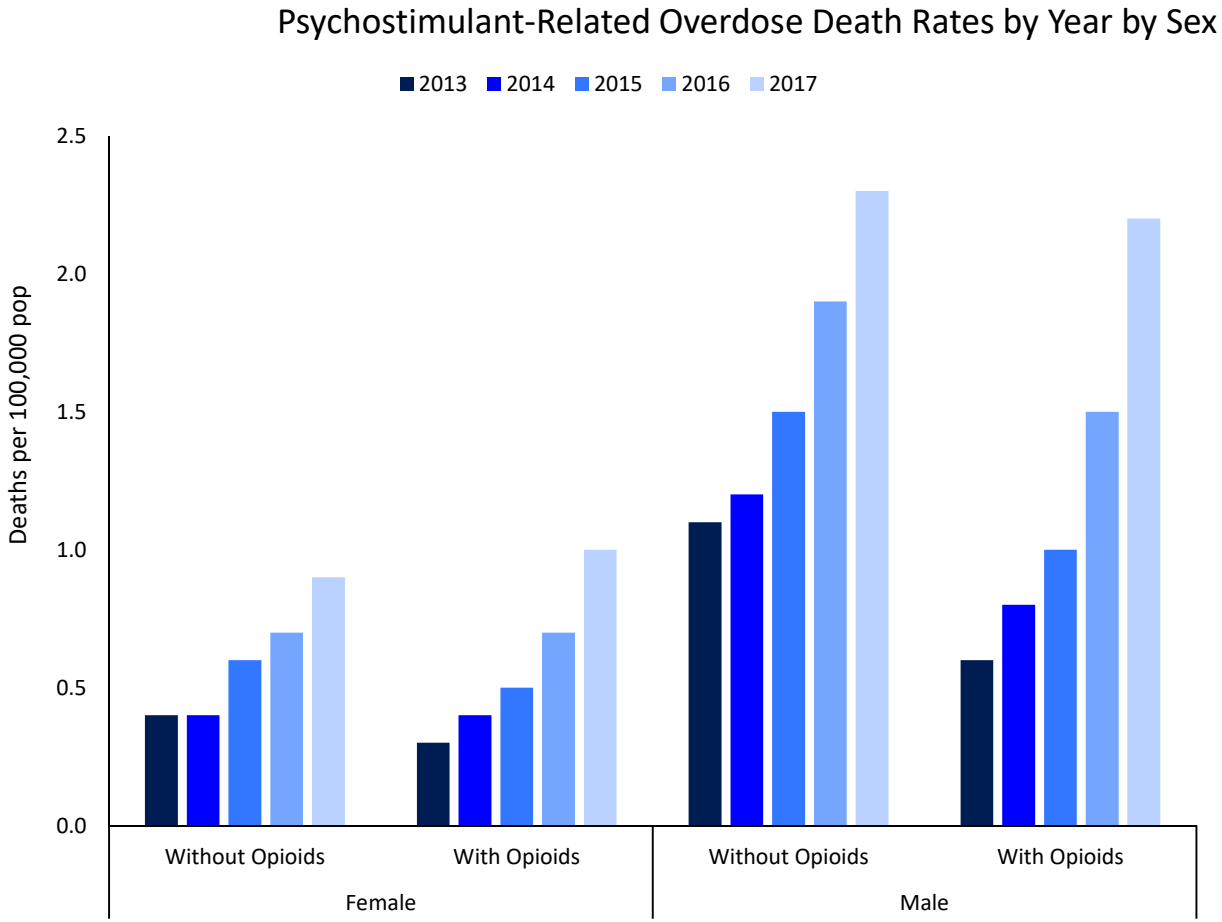
Source: CDC NHCS: https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm

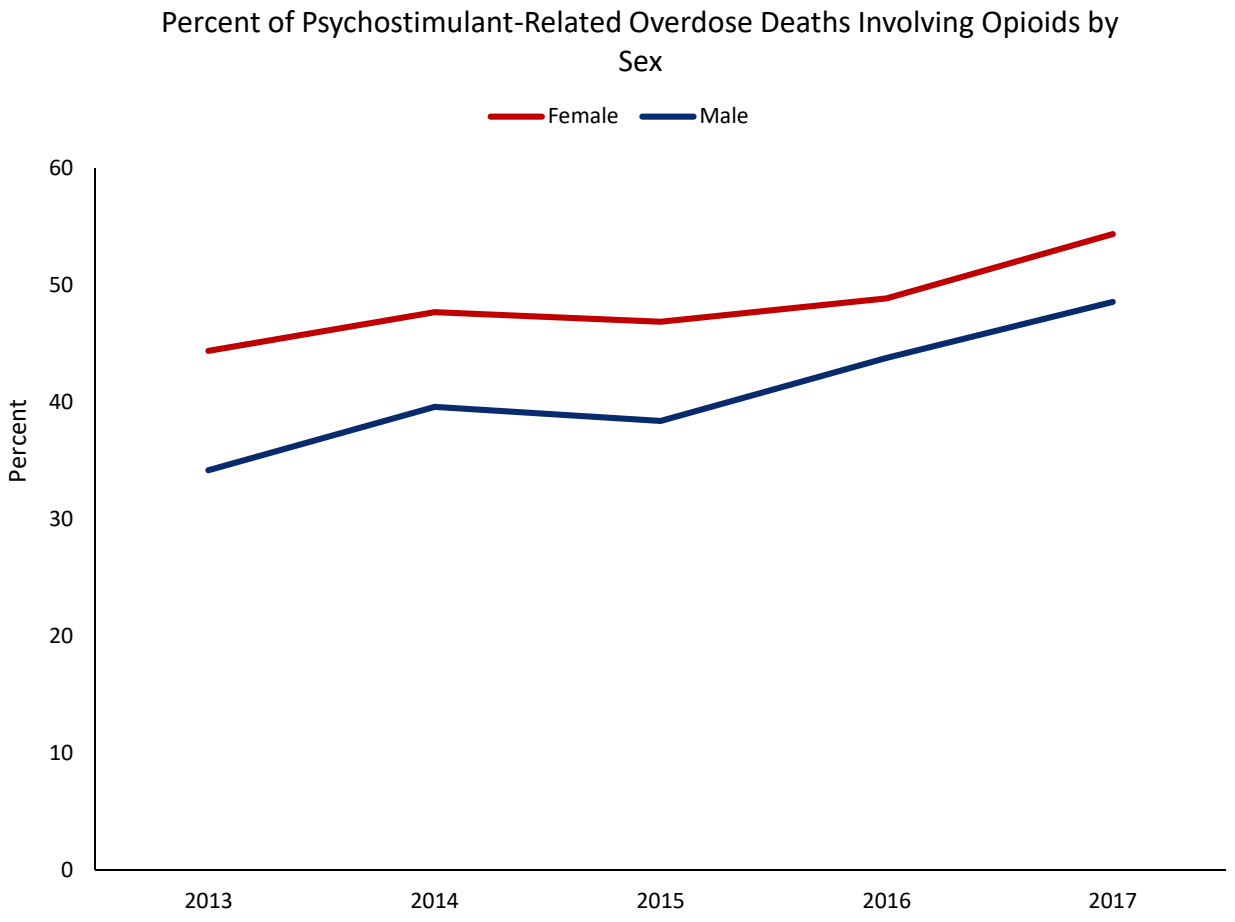
Cocaine-Related Overdose Deaths With and Without Opioids



Source: CDC NVSS 2008-2017

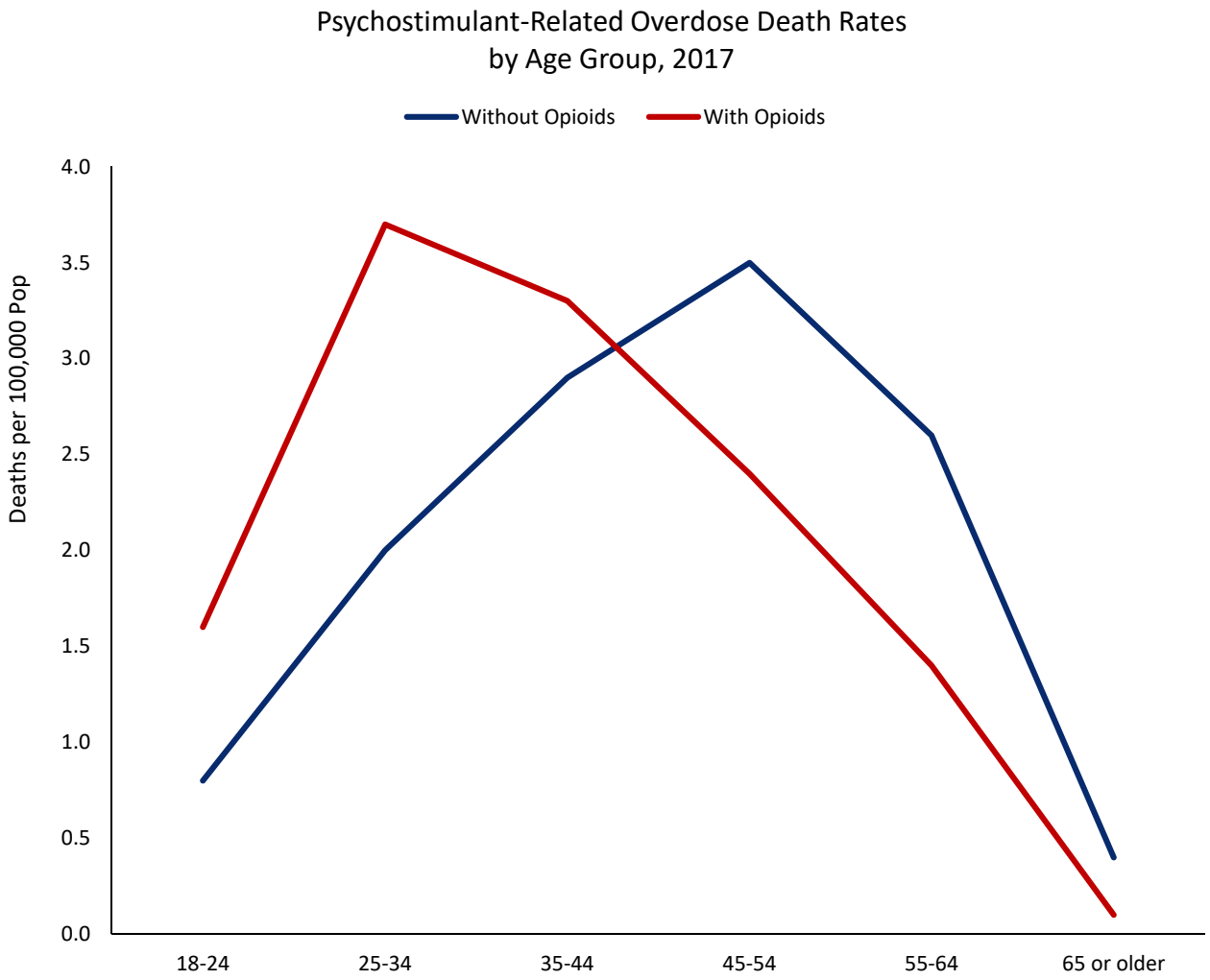
Psychostimulant-Related Overdose Deaths With and Without Opioids by Sex, 2013-2017

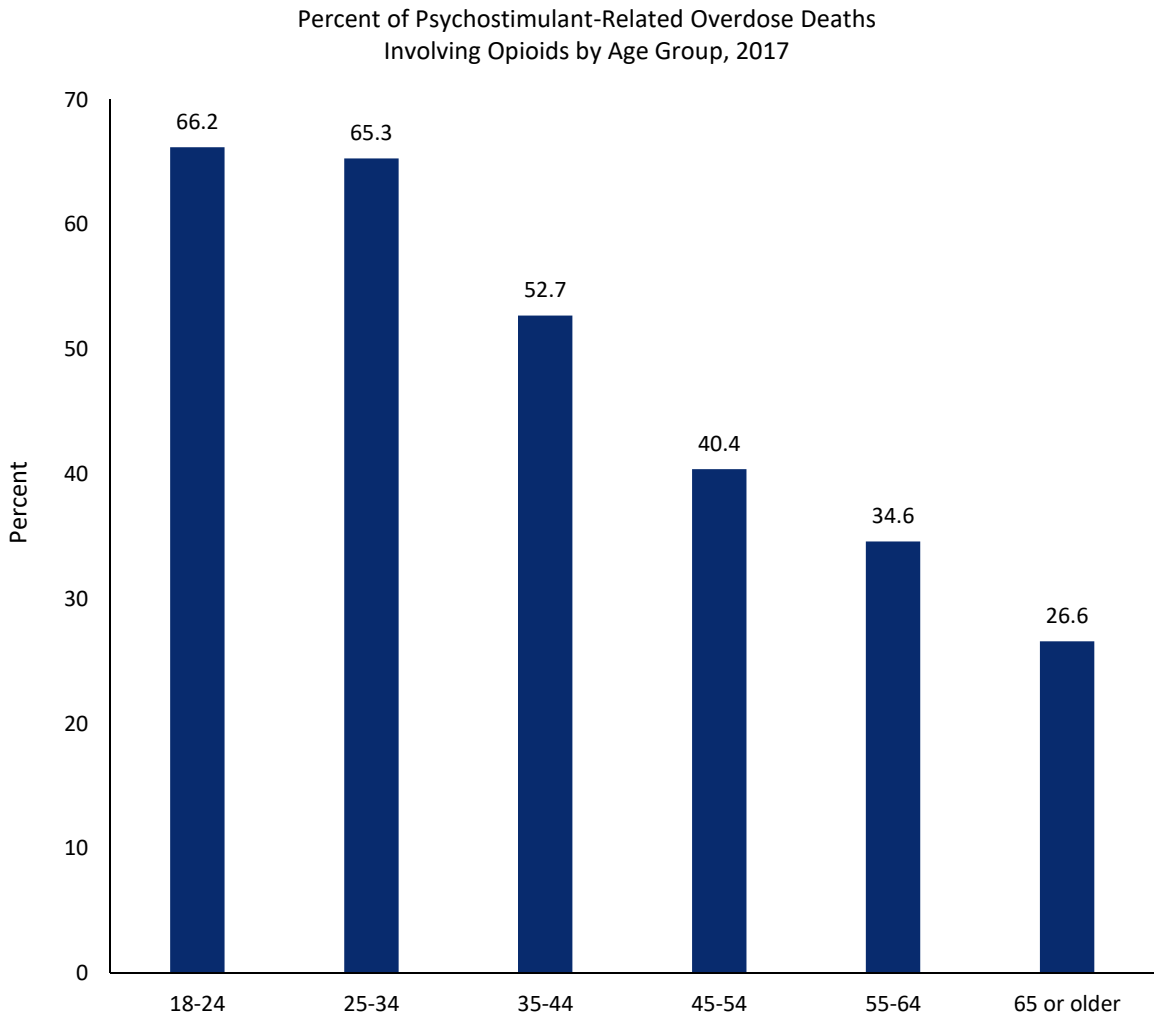




Source: Jones CM Analysis of CDC NVSS, 2013-2017

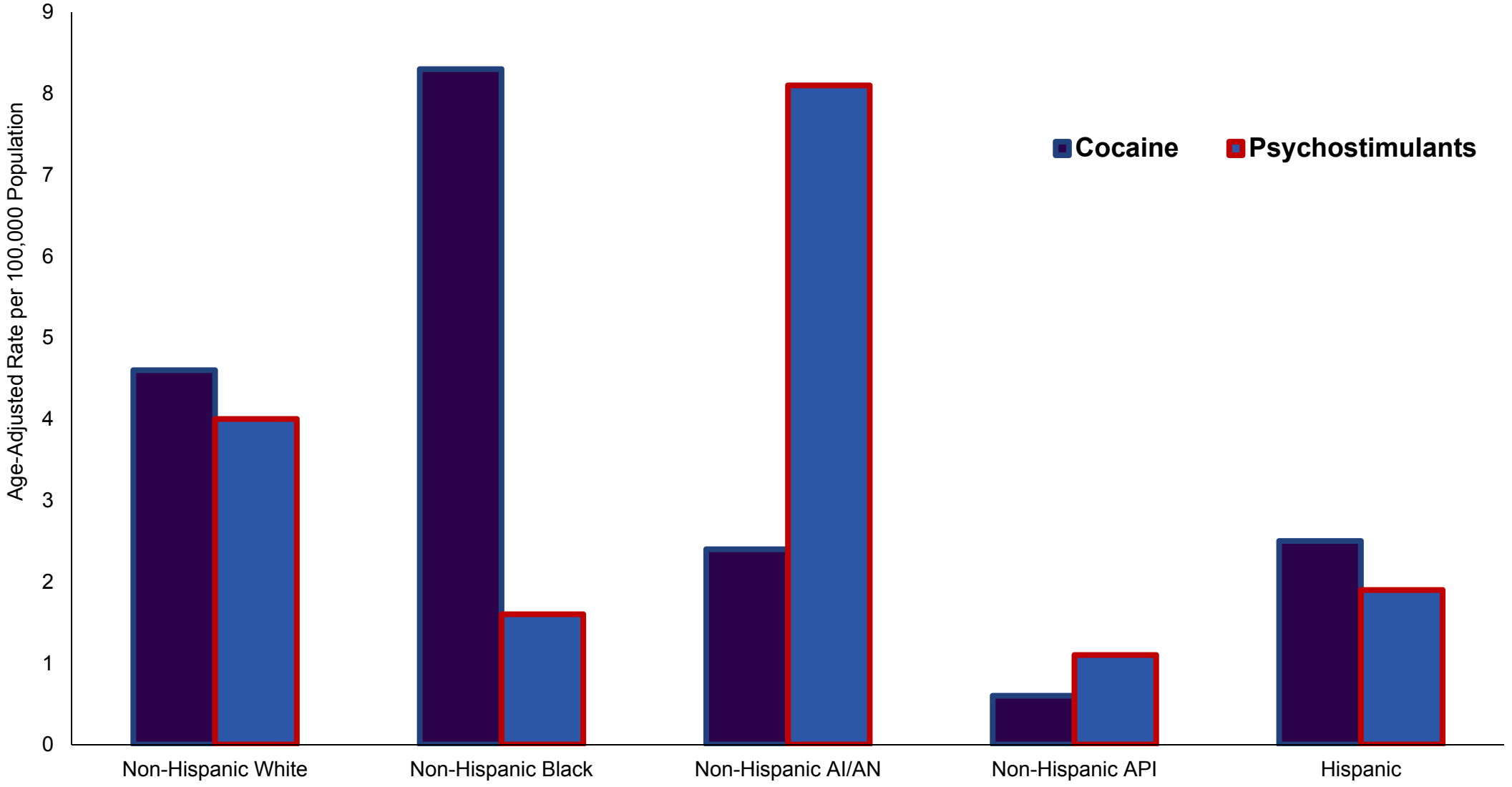
Psychostimulant-Related Overdose Deaths With and Without Opioids by Age, 2017





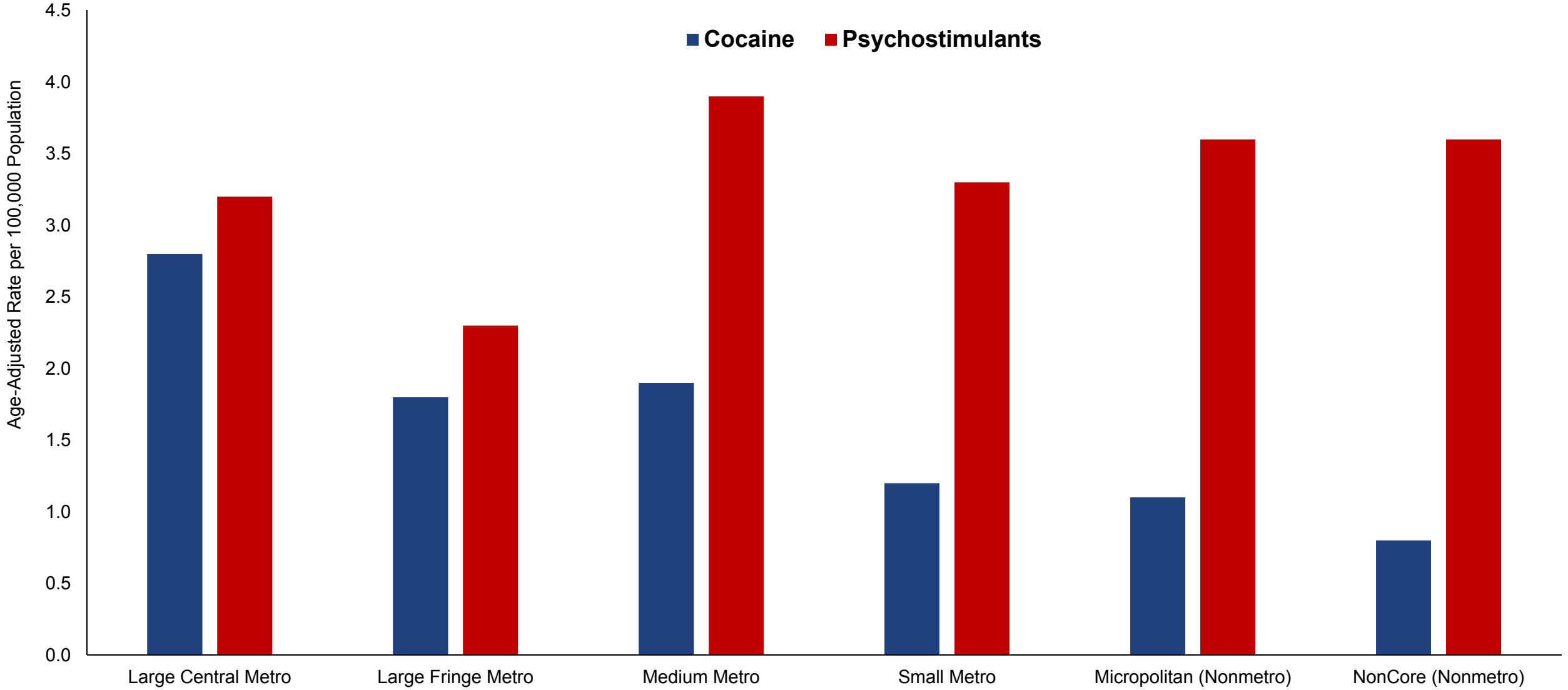
Source: Jones CM Analysis of CDC NVSS, 2017

Cocaine and Psychostimulant Overdose Deaths by Race/Ethnicity, 2017



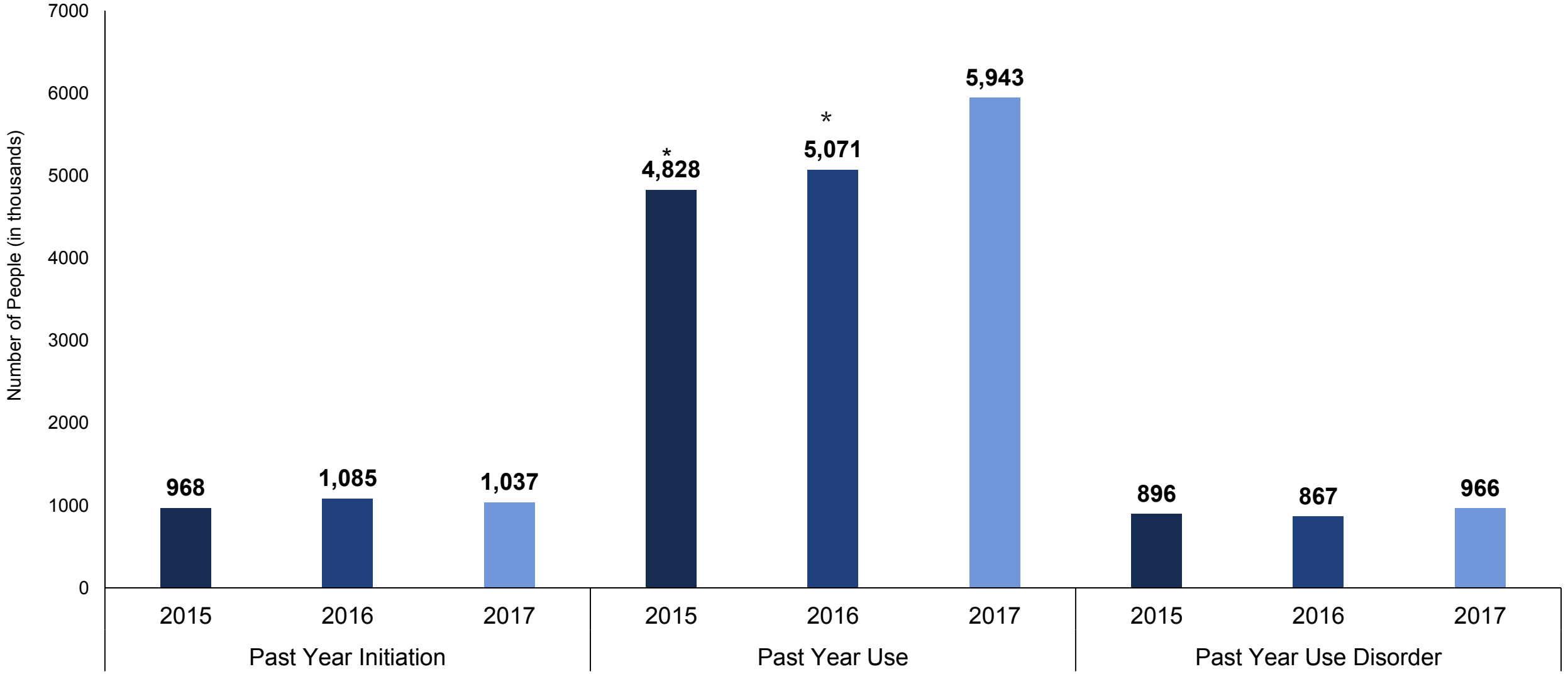
Source: CDC NVSS, 2019

Cocaine and Psychostimulant Overdose Deaths, by Urbanicity, 2017



Source: CDC NVSS, 2019

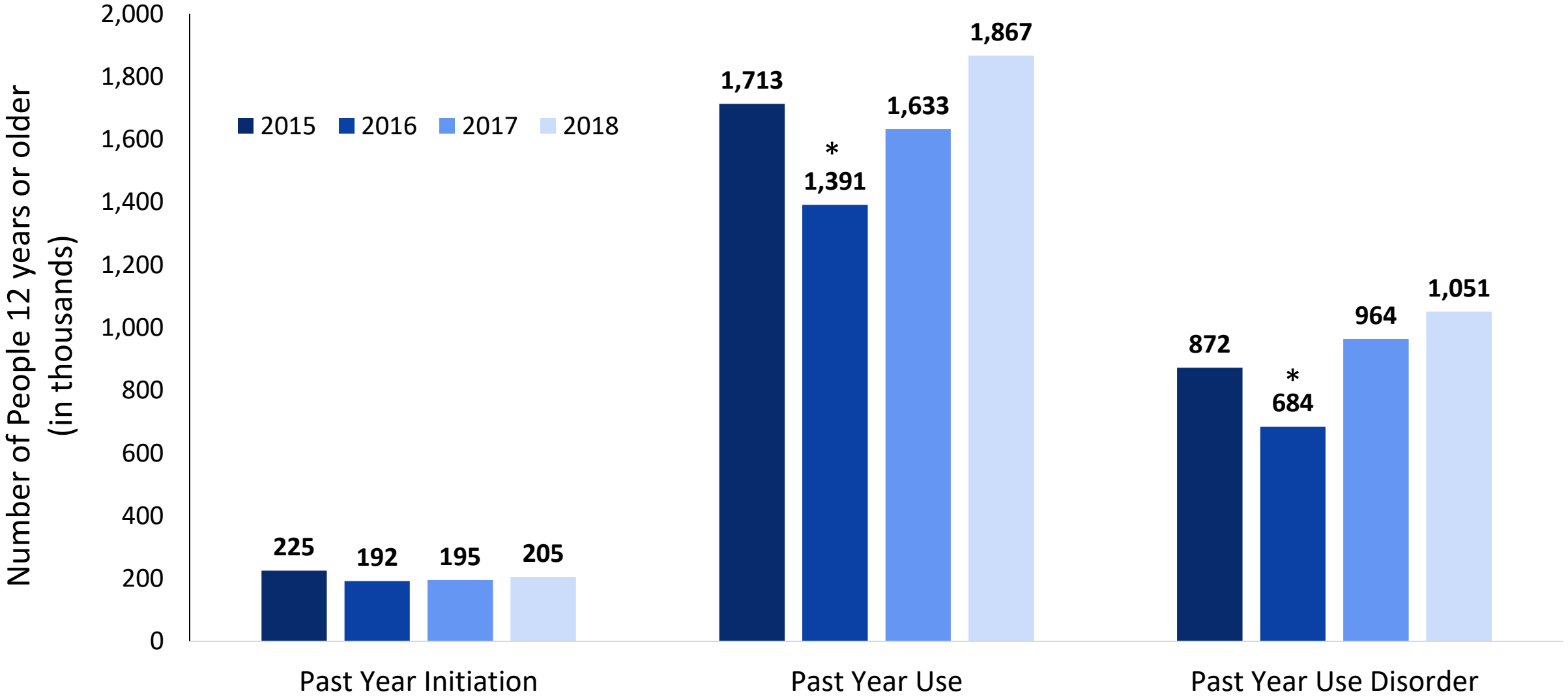
Trends in Cocaine Use, among People 12 Years or Older, U.S., 2015-2017



Source: SAMHSA NSDUH, 2015-2017

* Estimate is statistically significantly different than 2017 estimate

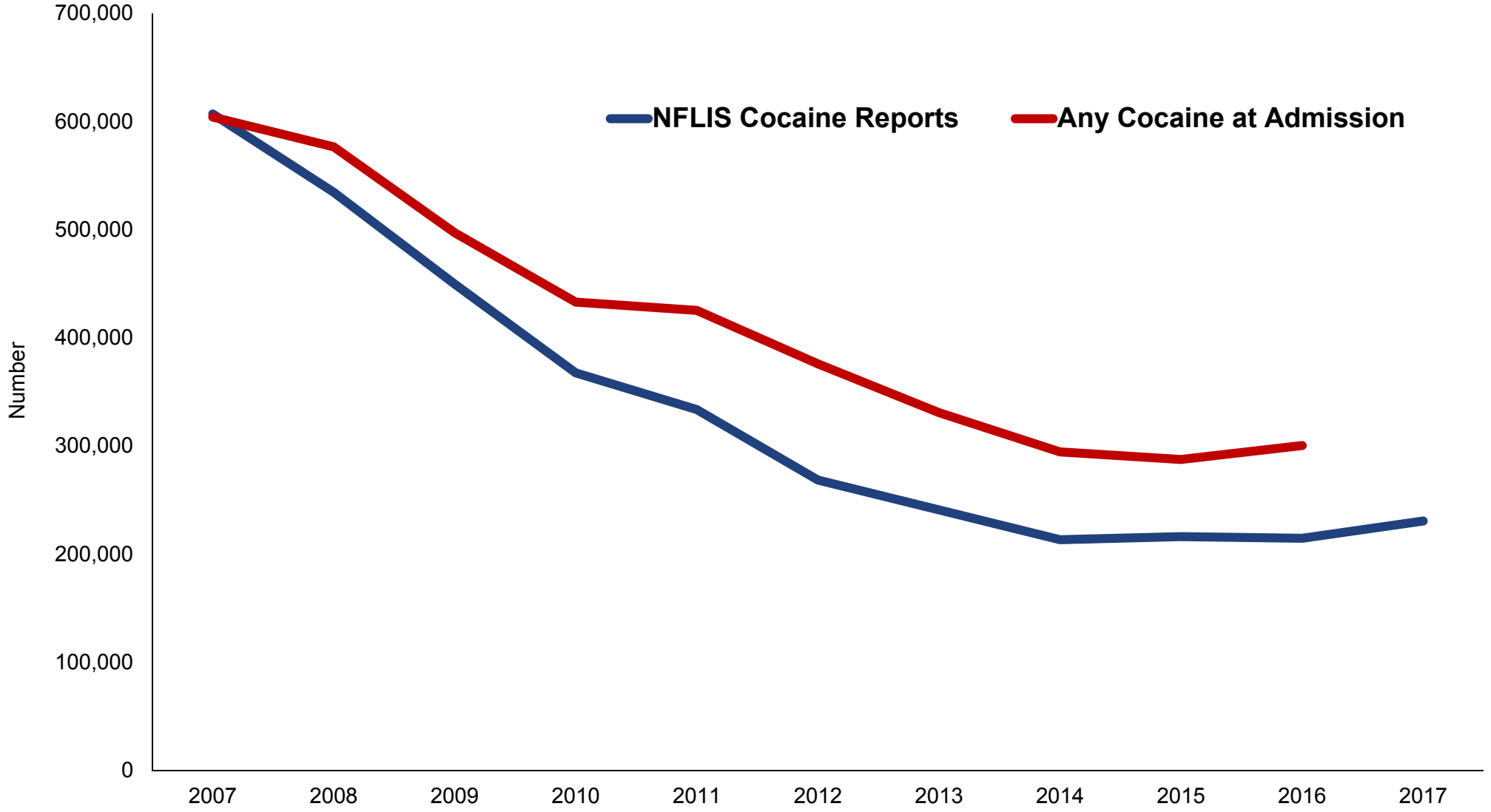
Trends in Methamphetamine Use, among People 12 Years or Older, U.S., 2015-2018



Source: SAMHSA NSDUH 2019

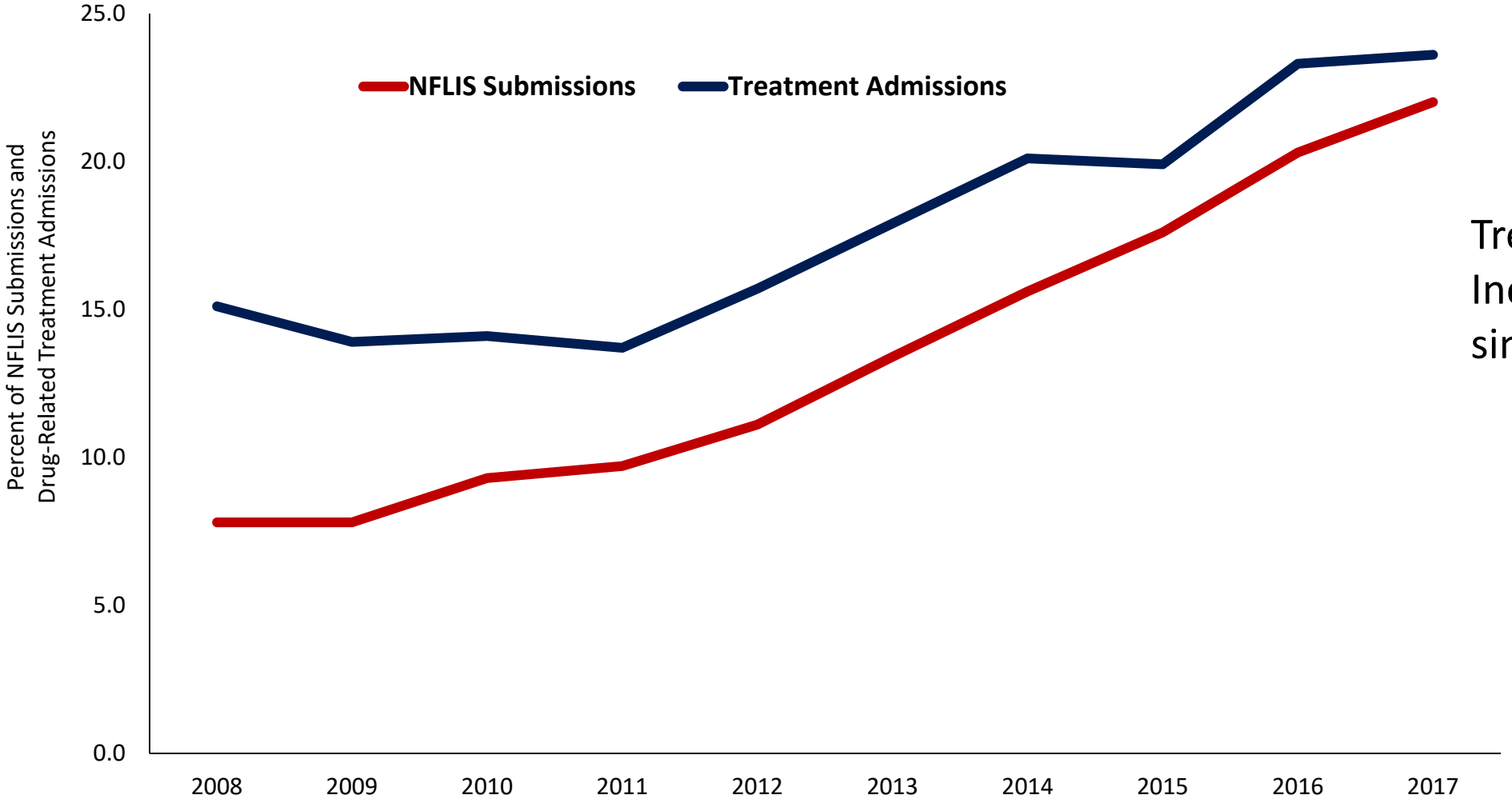
* Statistically significant difference compared to 2018, p<0.05

Cocaine:
Treatment Admissions and DEA NFLIS Reports



Source: Jones CM Analysis of TEDS PUF, 2007-2016; DEA NFLIS, 2007-2017

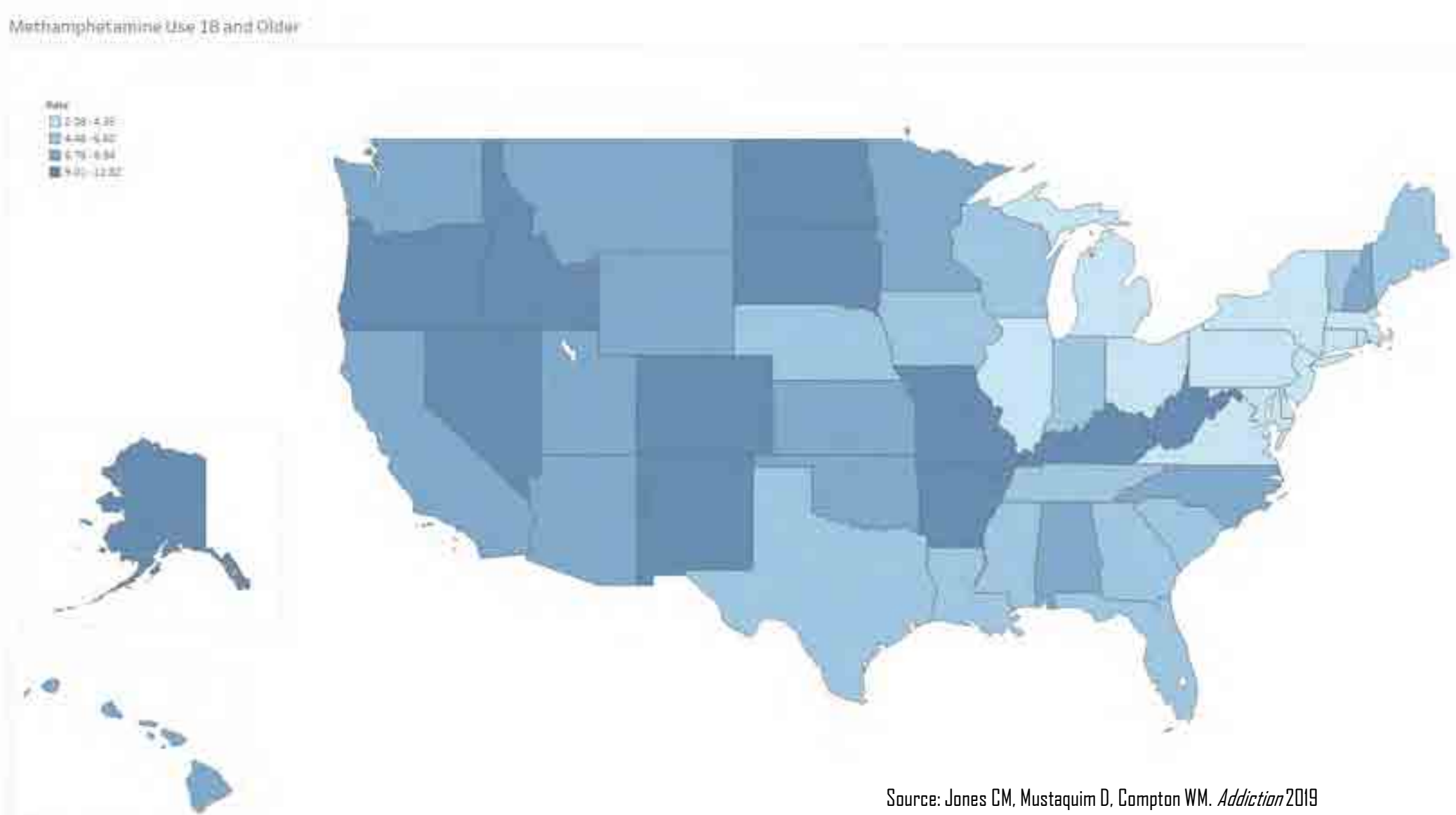
Methamphetamine: Treatment Admissions and DEA NFLIS Reports



Treatment Admissions Increasing 9% per year since 2010

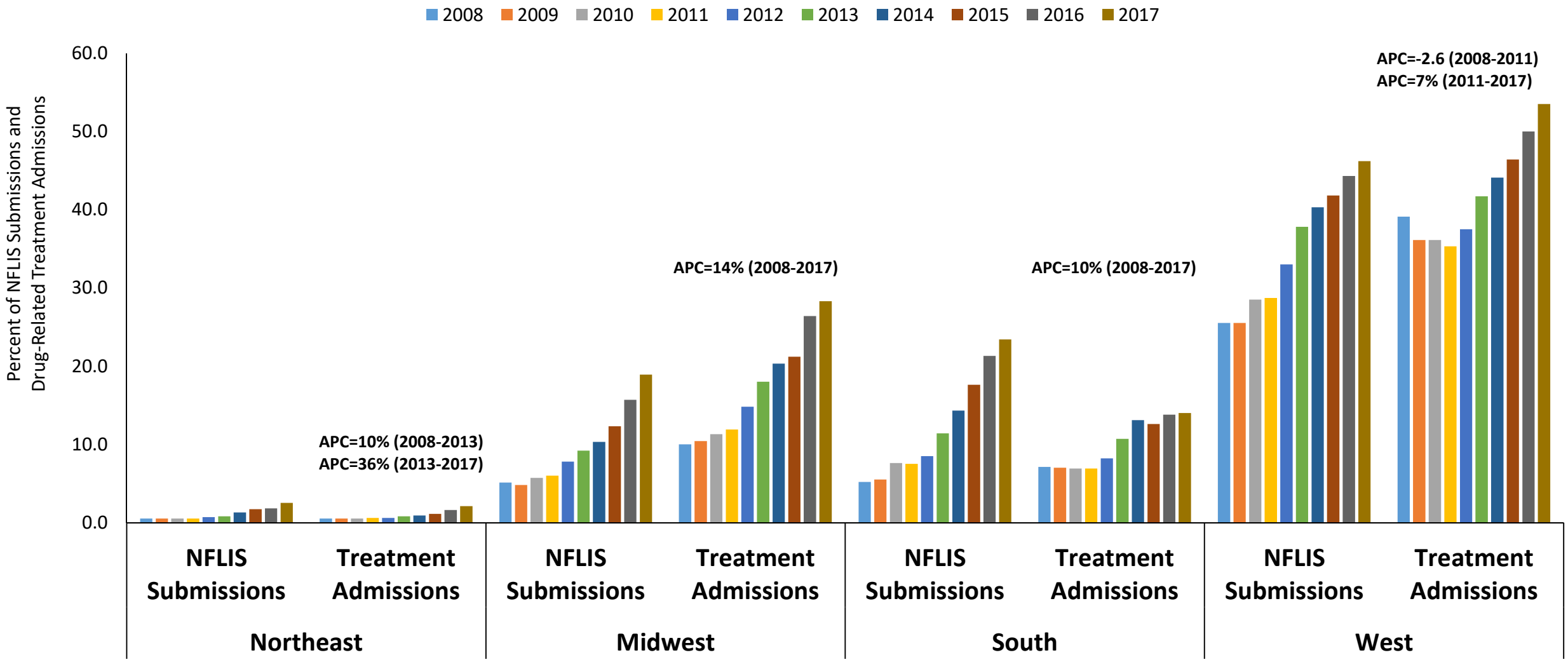
Source: SAMHSA TEDS, 2008-2017, DEA NFLIS, 2008-2017

Methamphetamine: Rates (per 1000 adults) of Past Year Use, By State, 2016-2017 (NSDUH)



Source: Jones CM, Mustaquim D, Compton WM. *Addiction* 2019

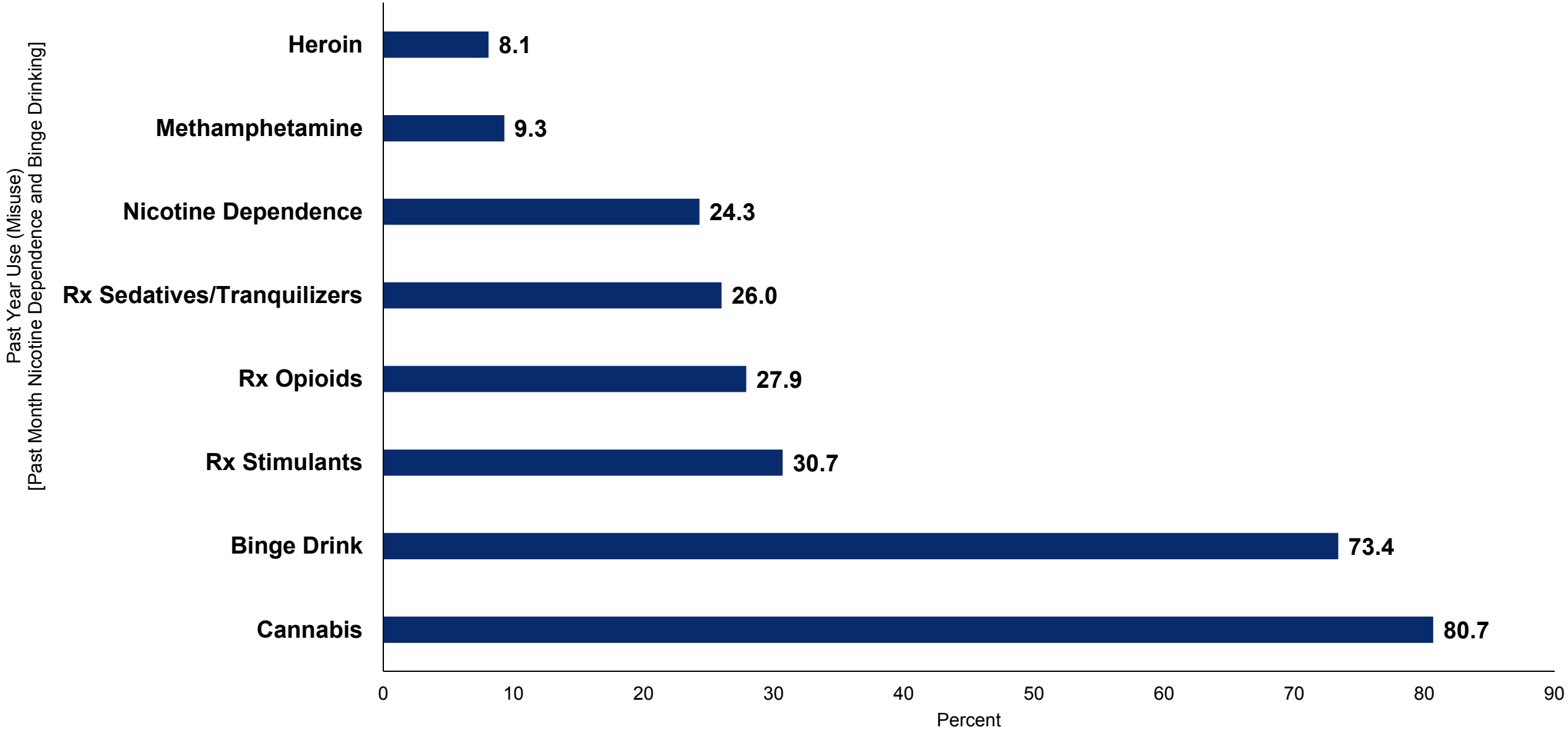
Methamphetamine: Treatment Admissions and DEA NFLIS Reports, Across U.S. Census Regions



Source: SAMHSA TEDS, 2008-2017, DEA NFLIS, 2008-2019, Jones CM, Olsen EO, O'Donnell J, Mustaquim D.. Manuscript under review 2019

APC= Annual Percent Change

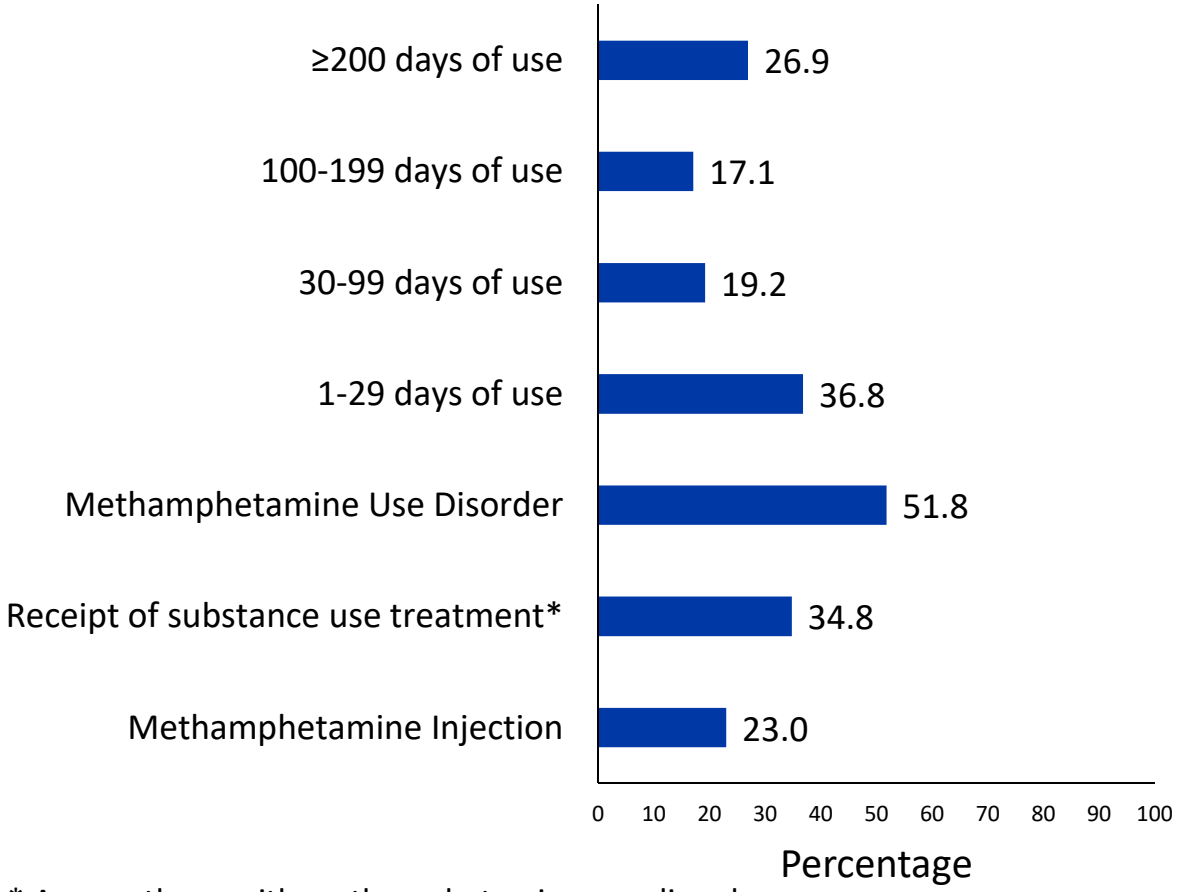
Substance Use Among Those Using Cocaine in Past Year



Source: Jones CM Analysis of NSDUH PUF 2017

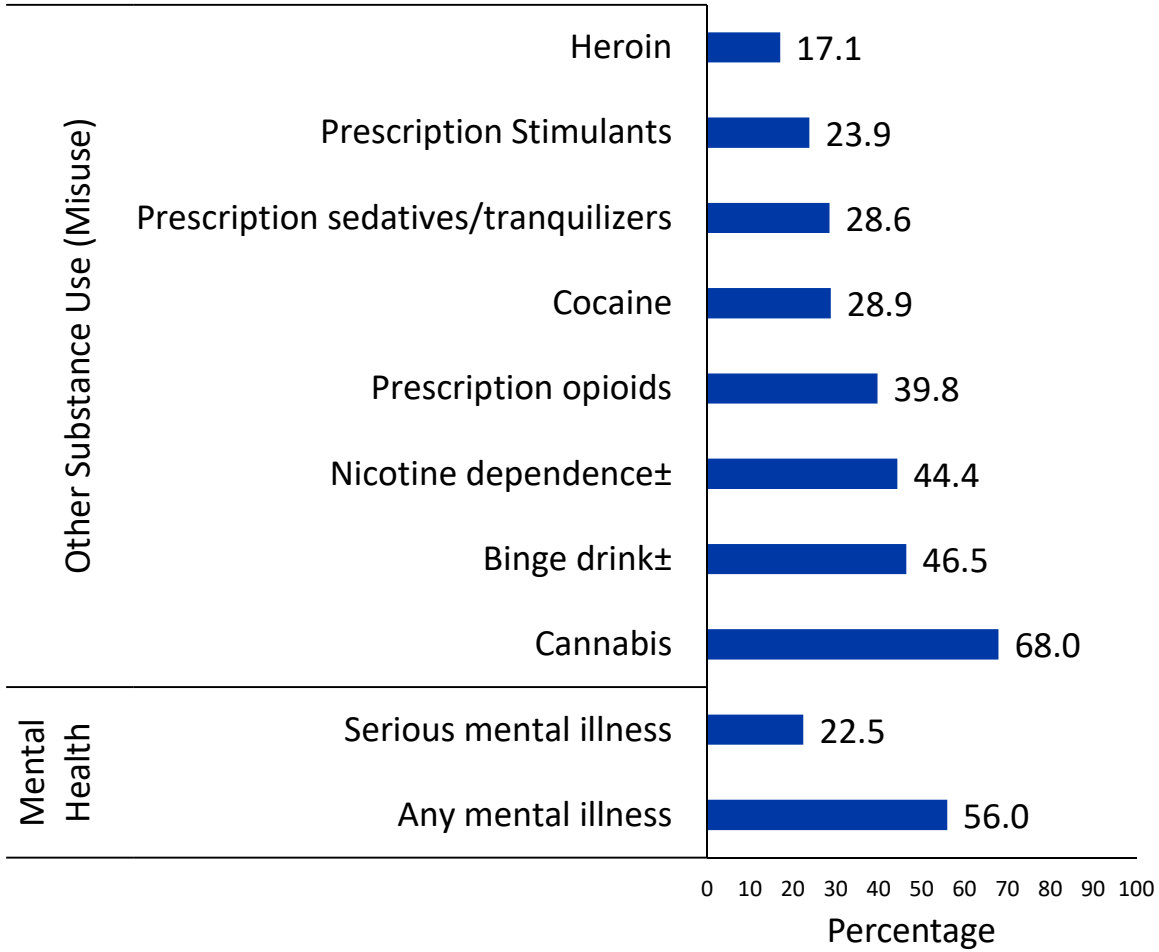
Methamphetamine: Use Behaviors, Other Substance use and Mental Illness among Past-Year Users, 2015-2017

Methamphetamine Use Behaviors



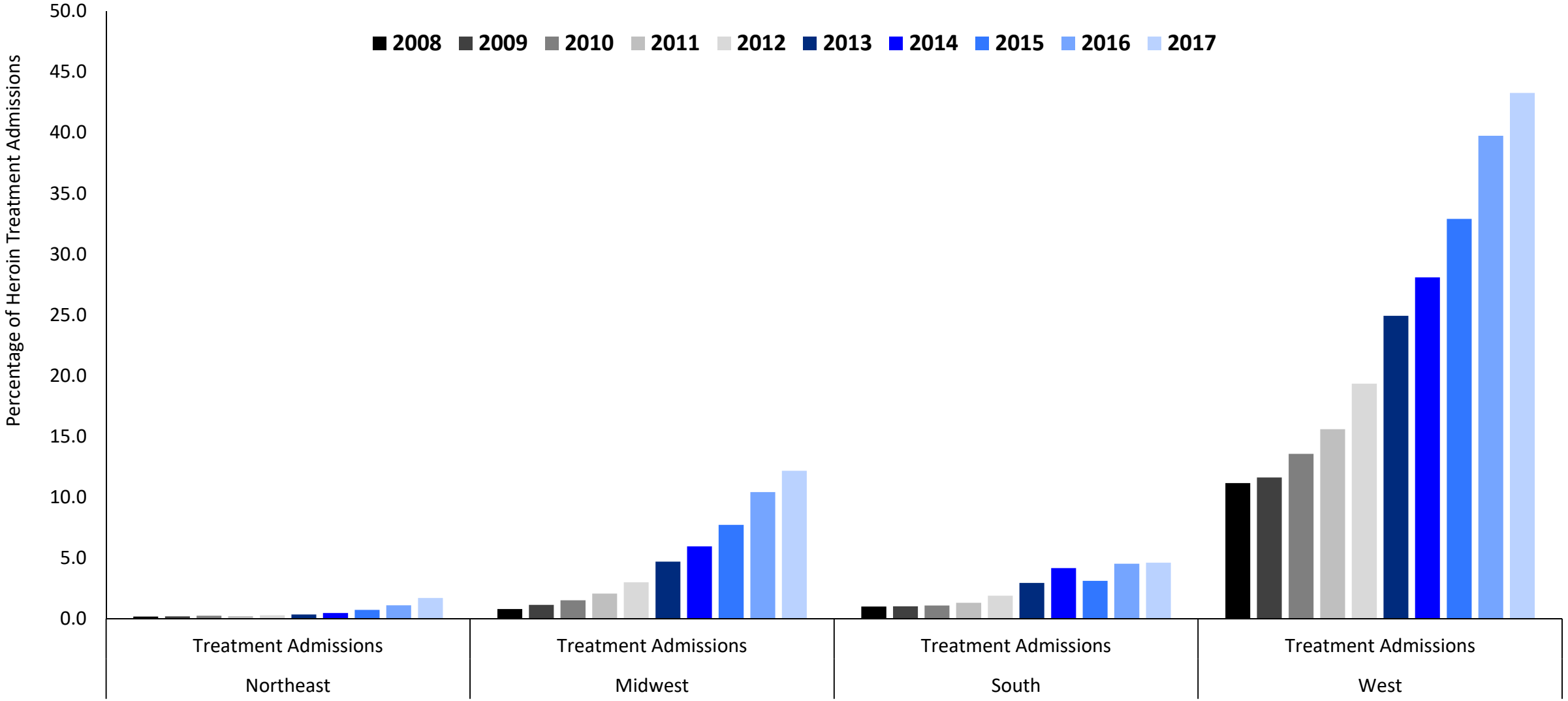
* Among those with methamphetamine use disorder

Other Substance Use and Mental Illness



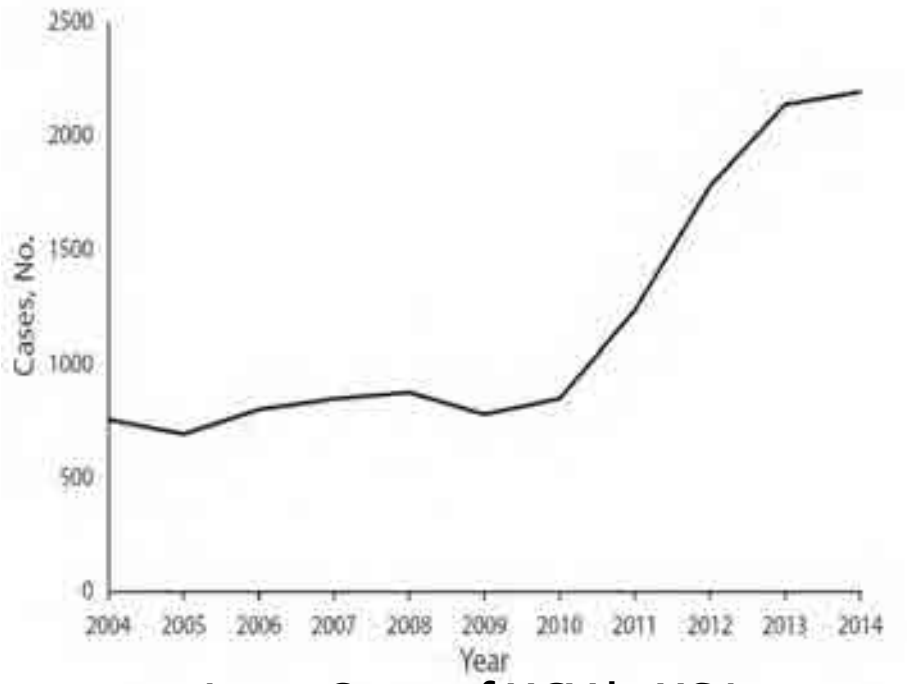
Source: Jones CM, Mustaquim D, Compton WM. 2019

Methamphetamine Use among Primary Heroin Treatment Admissions, By U.S. Census Region



Source: Jones CM, Underwood N, Compton WM, Addiction, 2019

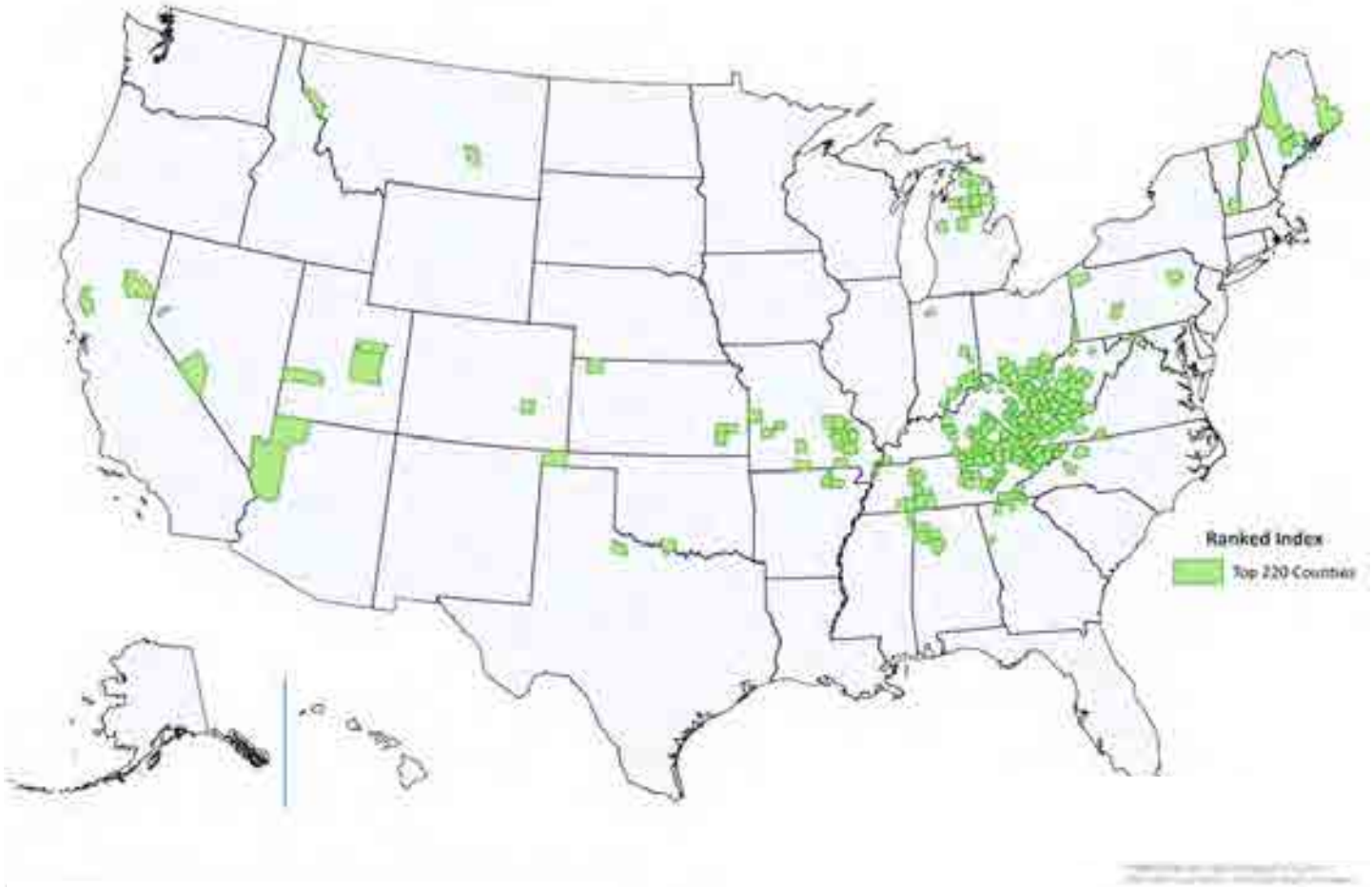
Rising rates of HCV



Acute Cases of HCV in USA

Zibbell et al. ***Am J Public Heath*** 2018;108:175-181

Counties Deemed Highly Vulnerable to Rapid Dissemination of HCV or HIV



Source: Van Handel et al, JAIDS 2016

Rising Methamphetamine Use Reported Among Syringe Service Programs

- 16 of 23 programs interviewed (70%), reported meth injection in the past 2-3 years.
- Increases seen as connected to opioid crisis. In some cases, SSPs reported an increase in individuals injecting opioids and methamphetamine together.
  - *"We are seeing way more meth[amphetamine] injections than we were seeing even two or three years ago…about 80% of people who reported being primarily opiate users reported having injected methamphetamines in the last three months. That's 50% more than it was; 30% had reported that [two years prior]."*
- Other SSPs (especially in Eastern U.S.) said some participants were switching to meth from opioids due to concerns about the unpredictability of fentanyl and other synthetic opioids.
  - *"Yes, methamphetamine use is changing. It used to be where they didn't use opioids and methamphetamine together. They're mixing them and even some of them are transitioning over to methamphetamine because of the danger of heroin overdose. Of course, now we're finding out that they're putting fentanyl in methamphetamine."*
- SSPs expressed significant concern about impacts of increasing meth use, both from policy and intervention perspectives.
  - *"Overall I would say that the increase in methamphetamine use has created a lot more 'not in my backyard' than we've seen historically. We've had a lot more problems with people being upset about discarded syringes and things like that…Here we're seeing a huge shift away from just opiates to opiates and methamphetamines. There are good interventions around opiate addiction; we've got great medication-assisted treatment options. We've got nothing for meth[amphetamine]."*

Source: Jones CM, International Journal of Drug Policy, 2019

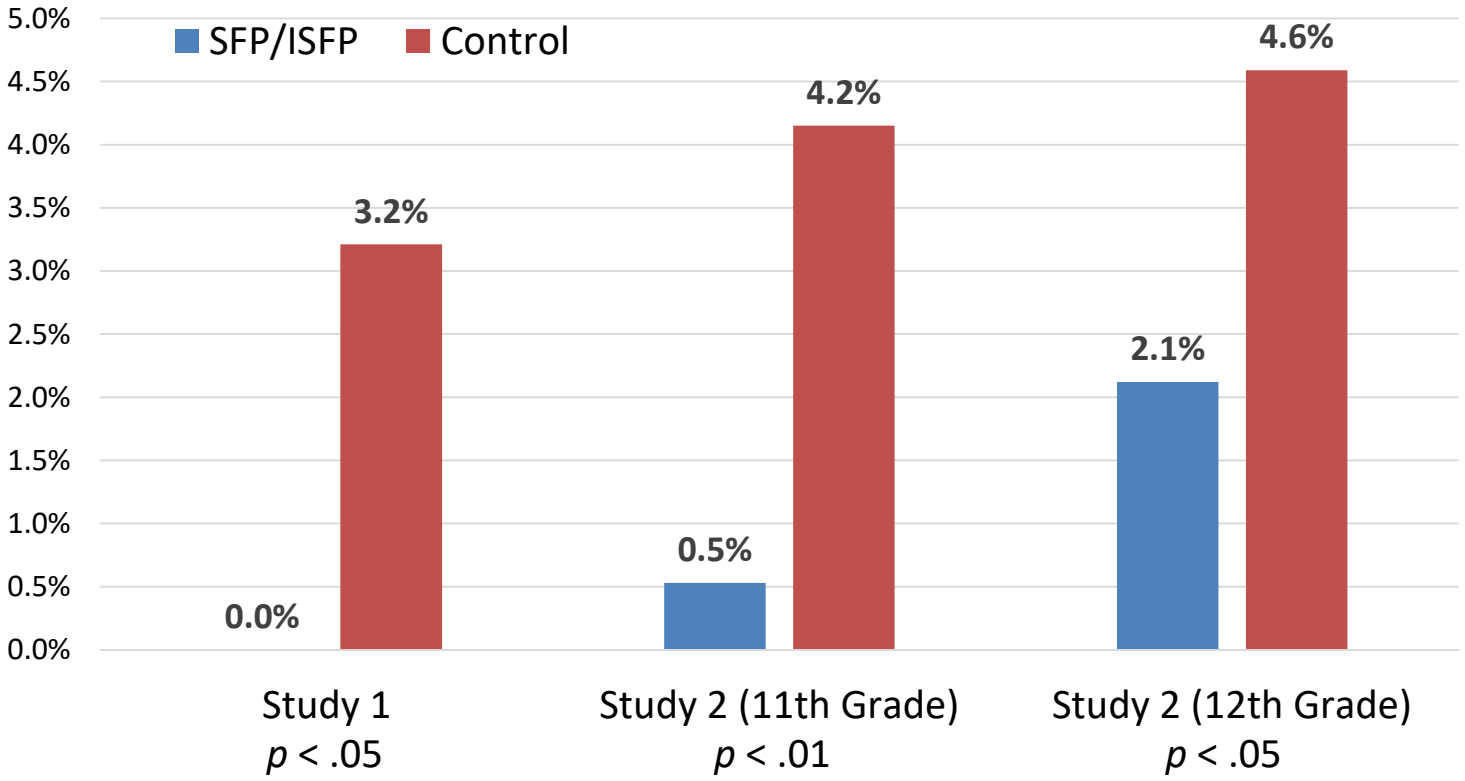
Challenges and Limitations

- **No FDA-approved medications for treatment (no MAT)**
- **No "rescue therapy" for toxicities (e.g., naloxone)**
- **Treatment relies on behavioral interventions which are:**
  - ***time consuming***
  - ***require special training and intense follow-up***
  - ***often limited by attrition/retention issues***

Universal Drug Abuse Prevention:

Studies suggest impact on opioids and methamphetamine

Past Year Methamphetamine Use 4½ to 6½ Years Past Baseline



Note: Study 2 included both ISFP and LST interventions

Source: R Spoth et al. *Arch Pediatr Adolesc Med* 2006;160:876-882

Targeting Youth to Prevent Later Substance Use Disorder: An Underutilized Response to the US Opioid Crisis

Compton WM, Jones CM, Baldwin GT, Harding FM, Blanco C, Wargo EM

American Journal of Public Health

2019;109:2185-S189.

Summary:

- **Cocaine and methamphetamine consequences are increasing in the context of mixed evidence for overall population prevalence increases**
- **Links to the evolving opioid overdose crisis**
  - Increasing prevalence of stimulant use among those with OUD
  - Since 2008, >300% increase in methamphetamine among heroin treatment admissions
  - 50% of psychostimulant-related overdose deaths involved opioids (2017)
- **People using stimulants have**
  - High rates of co-occurring mental illness
  - Poly-substance use is common (*including nearly universal prior use of cigarettes, alcohol, cannabis*)
- **The geography of methamphetamine abuse is highly correlated with methamphetamine supply data suggesting that cartels are creating demand among vulnerable individuals**

Session I: Overview of Stimulant Use Disorder and Emerging Trends

Of Speedballs and Goofballs: Stimulants and the 4th Wave of The Opioid Crisis

Dan Ciccarone, MD, MPH

Professor, Family and Community Medicine, University of California, San Francisco

Sarah Mars, PhD

Family and Community Medicine, University of California, San Francisco

Dan Rosenblum, PhD

Dalhousie University

Jay Unick, PhD

University of Maryland

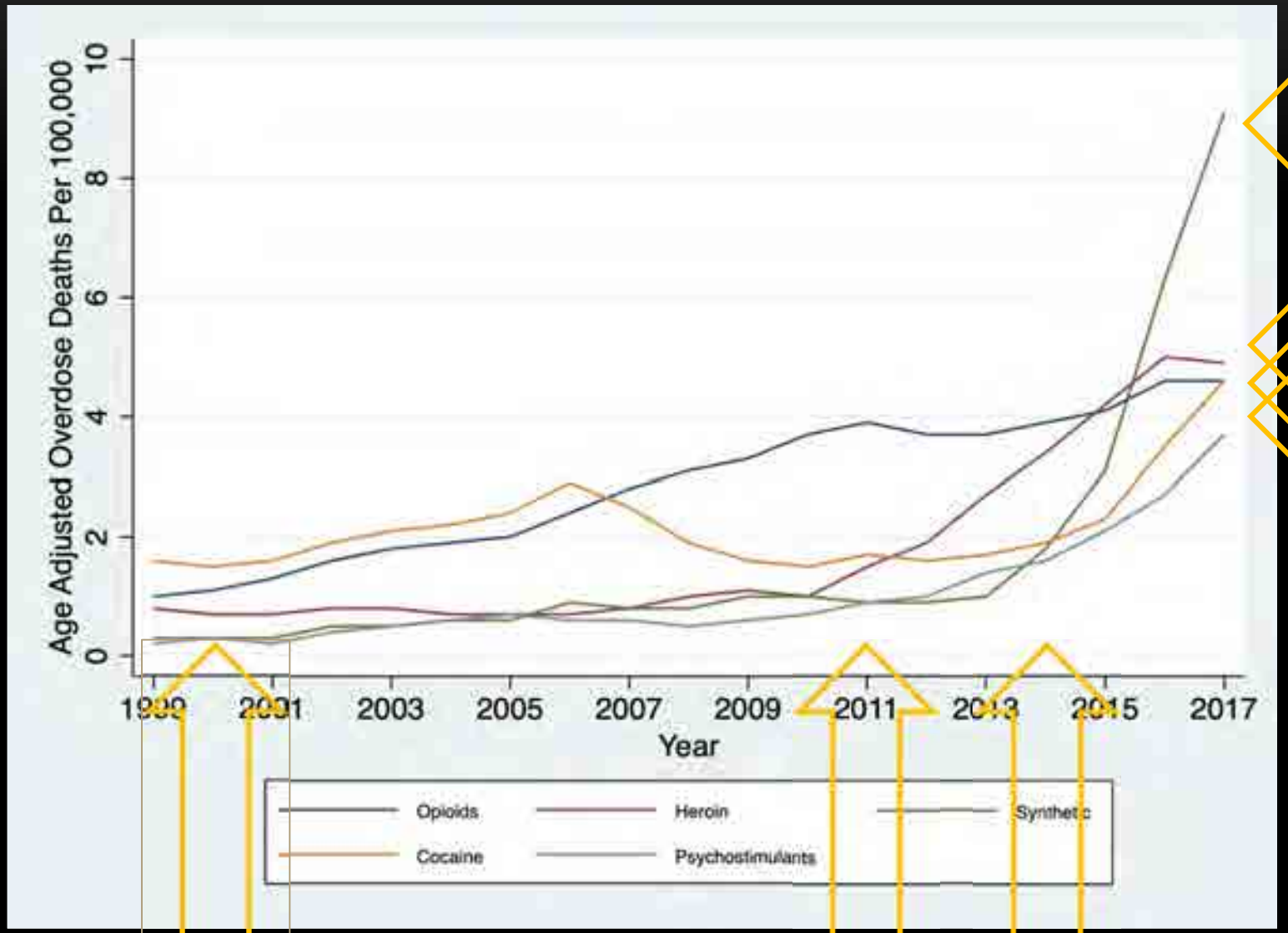
HEROIN IN TRANSITION ("HIT") STUDY

- NIH: National Institute of Drug Abuse (DA037820)
- Multi-methodological study: quantitative and qualitative aims
  - Supply changes >> medical consequences including OD
    - Ohio Crime Lab drug seizure data
  - Ethnographic: New drug forms and user perceptions, adaptation, etc.

PUBLICALLY AVAILABLE DATA:

- Centers for Disease Control and Prevention, National Center for Health Statistics
- US Drug Enforcement Administration
- Other academic literature

THE FOURTH WAVE Epidemiologists



WHAT IS DRIVING THE INCREASE?

- Increase in supply?
  - Changes in production
  - Purity/Potency
  - Contamination eg with synthetic opioids
- Increase in use?
  - Increase in numbers of users
  - Increases in co-use of stimulants and opioids

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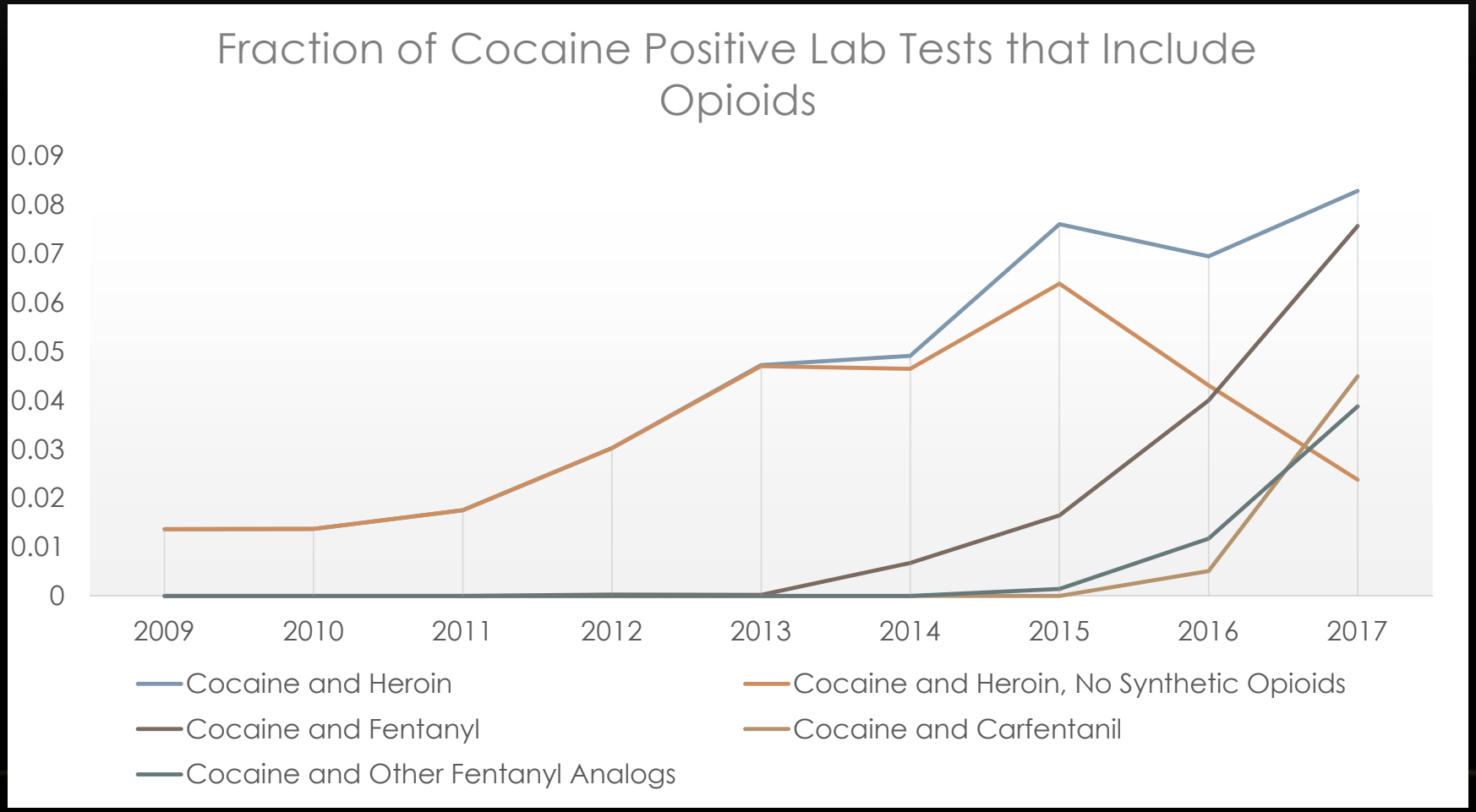
Ohio Crime Lab Study

DRUG SEIZURE DATA

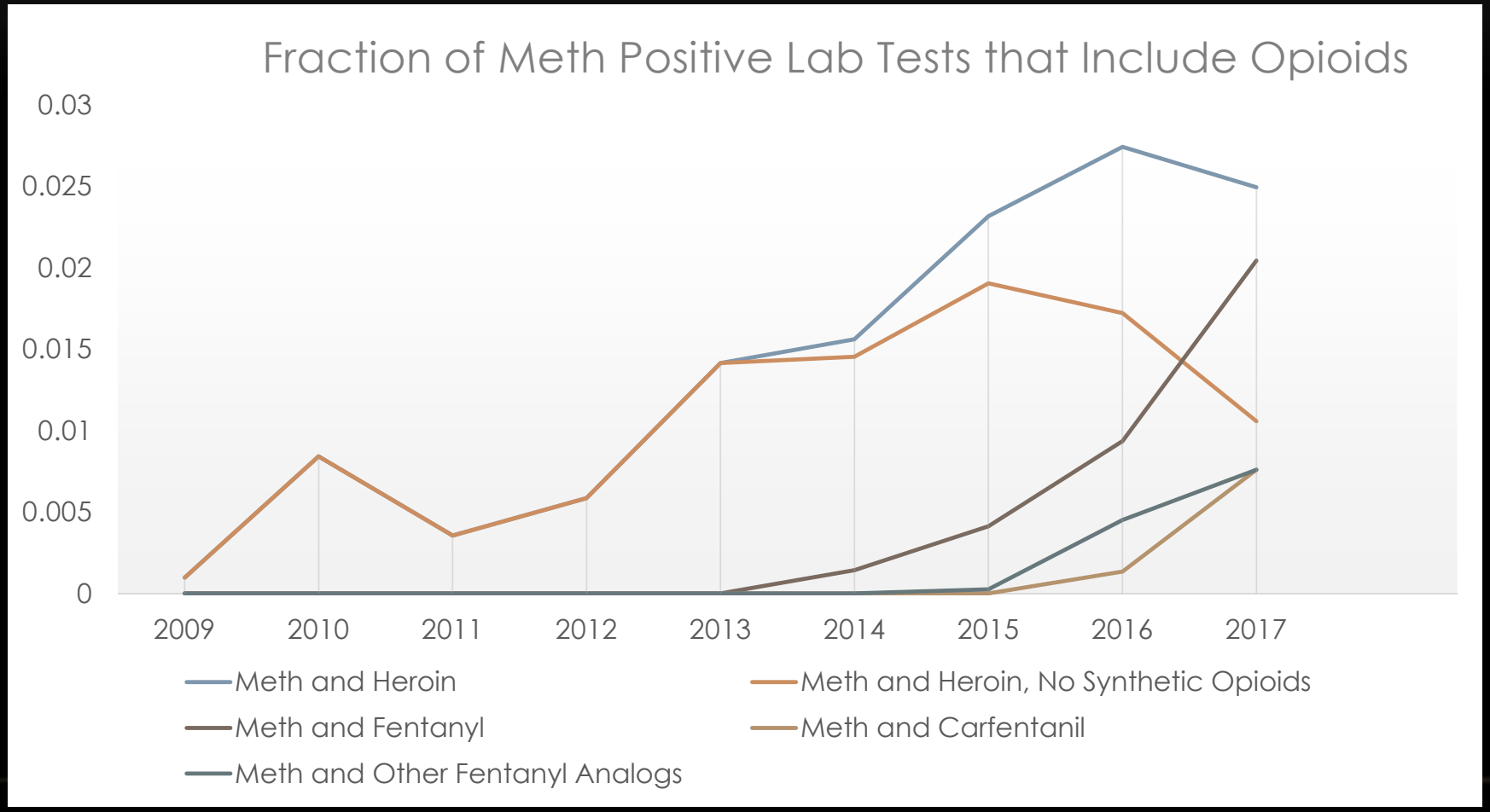
- Three Ohio Bureau of Criminal Investigation labs:
  - Data obtained through multiple FOIA requests
  - Lab tests completed between 1.1.2009 and 12.31.2017
    - Final sample: 204,951samples across 87 counties
    - 8,352 county-month observations
  - Categories: fentanyl, fentanyl analogs, heroin, prescription opioids, cocaine, meth/amphetamines, benzodiazepines, synthetic cannabinoids, MDMA and other designer drugs
- Caveats: private crime labs; no Hamilton County

Acknowledge: Dennis Cauchon, Harm Reduction Ohio, for obtaining the BCI data

CRIME LAB STUDY RESULTS



CRIME LAB STUDY RESULTS



STIMULANT-FENTANYL CONTAMINATION

- Meaningful levels?
  - 8% cross contamination for cocaine
  - 3% for methamphetamine
  - Caveat: no purity measurements
- Contamination: accidental or purposeful?
  - Pre-dates fentanyl era (ie heroin in cocaine)
  - Co-use is high; so perhaps is co-dealing

INCREASE IN USE?

- Increase in supply?
  - Changes in production
  - Purity/Potency
  - Contamination eg with synthetic opioids
- Increase in use?
  - Increase in numbers of users
  - Increases in co-use of stimulants and opioids

SPEEDBALLS AND GOOFBALLS

- "Speedball": co-use of he
  - Traditional
  - Makes sense
  - Well-liked
- "Goofball": Co-use of heroin and methamphetamine
  - Unusual historically
  - Physiologically challenging
  - Requires exploration

Photo: D Ciccarone

Ethnographic Study

ETHNOGRAPHIC METHODS

- "Hotspot study" where our team of researchers goes to visit areas in the country where significant changes in the drug supply or overdoses have been reported
  - West Virginia: Charleston, Nitro, Ripley, Huntington
  - Sept 2017 and Sept 2019
  - 48 participants
- Our aims are to understand the experiences and beliefs of the users themselves, to observe first hand the drugs currently being used
  - Helps build explanatory models but not conclusive
- Methods: TED-X talk: https://www.youtube.com/watch?v=R7z6qPvL1iY

West Virginia

Photos: D. Ciccarone and J. Ondocsin

METHAMPHETAMINE IS BACK

- Supply has changed since about 2015:
  - Less: 'Shake and Bake' – locally made
  - More: Mexican-sourced 'Ice'
    - Less expensive by weigh
    - Possibly of higher quality
  - Polysubstance dealing

Photo: D Ciccarone

ICE OVER HEROIN

- 'Ice' has become a popular alternative or addition to heroin. For those who used it, including Julie, suffering from scoliosis-induced chronic pain—there was both a pain-management and market-based rationale:

"If I can get heroin, that's all I want just for the pain. Now, if I don't have the money or can't get [heroin], I'll get Ice. Because it's so much easier, it's cheaper. […] And even if I'm feeling the pain, it gives me the energy that I can at least get something accomplished."

Photo: D Ciccarone

THE ~~GOOFBALL~~ Speedball IS BACK

- The combination of meth and heroin/fentanyl is resurgently popular.
  - Rediscovered since about 2015.
  - Called ‘speedball’; ‘goofball’ term is unheard of here
- Those who like it say it is a “fantastic feel”
  - Fentanyl is strong enough to meet meth
- Those who don‘t say it‘s a bit of a ‘fight’ between the ‘up’ and ‘down’ physiological feelings

THE VARIETIES OF Speedball

- The combined use of 'heroin' and meth is part of a spectrum of meth use:
  - From none to occasional (don't like but if free)
  - to casual (like but r
  - to regular use (in co separately from her
  - to reducing heroin use.

Photo: D Ciccarone

- Rebecca, 30s, preferred methamphetamine to heroin but also liked to inject both together:

A: I like heroin and stuff like that but it's not my choice preference. And actually mixing it with meth is the better buzz, believe it or not.

Q: How do you decide on a given day?

A: Just what we feel like. …if the dope sickness is not bad we'll choose meth because then you can fend off the dope sickness …by being high on meth you won't feel it.

Photo: D Ciccarone

RESPONSES TO FENTANYL

- Meth and speedball injection can be seen as *organic responses* to the fentanyl overdose epidemic
  - Some like fentanyl but most accept it and adjust to it
  - Meth use is popularly construed as:
    - Helping to decrease heroin/fentanyl use/need
    - Helping with heroin withdrawal symptoms
    - Protecting for OD when in combination with heroin/fentanyl
    - Useful to reverse OD in a pinch

ON SPEEDBALLS AND GOOFBALLS: SUMMARY

- Co-use:
  - Methamphetamine and the speedball are back
  - Supply may be driving this
    - But may be the result of fentanyl prohibition
  - Adaptive responses are also important:
    - Meth be substituting for heroin and reducing fentanyl exposure
  - ***Fentanyl is still the problem*** (folks should not be dying from meth)

Photo: D Ciccarone

CRISIS RESPONSE

- Firstly, don't panic
  - Stigma remains our biggest enemy
- The rise in stimulants requires a broadening of our public policy
- Three pillars of demand reduction:
    - Overdose prevention
    - Harm reduction
    - Treatment

ACKNOWLEDGEMENTS

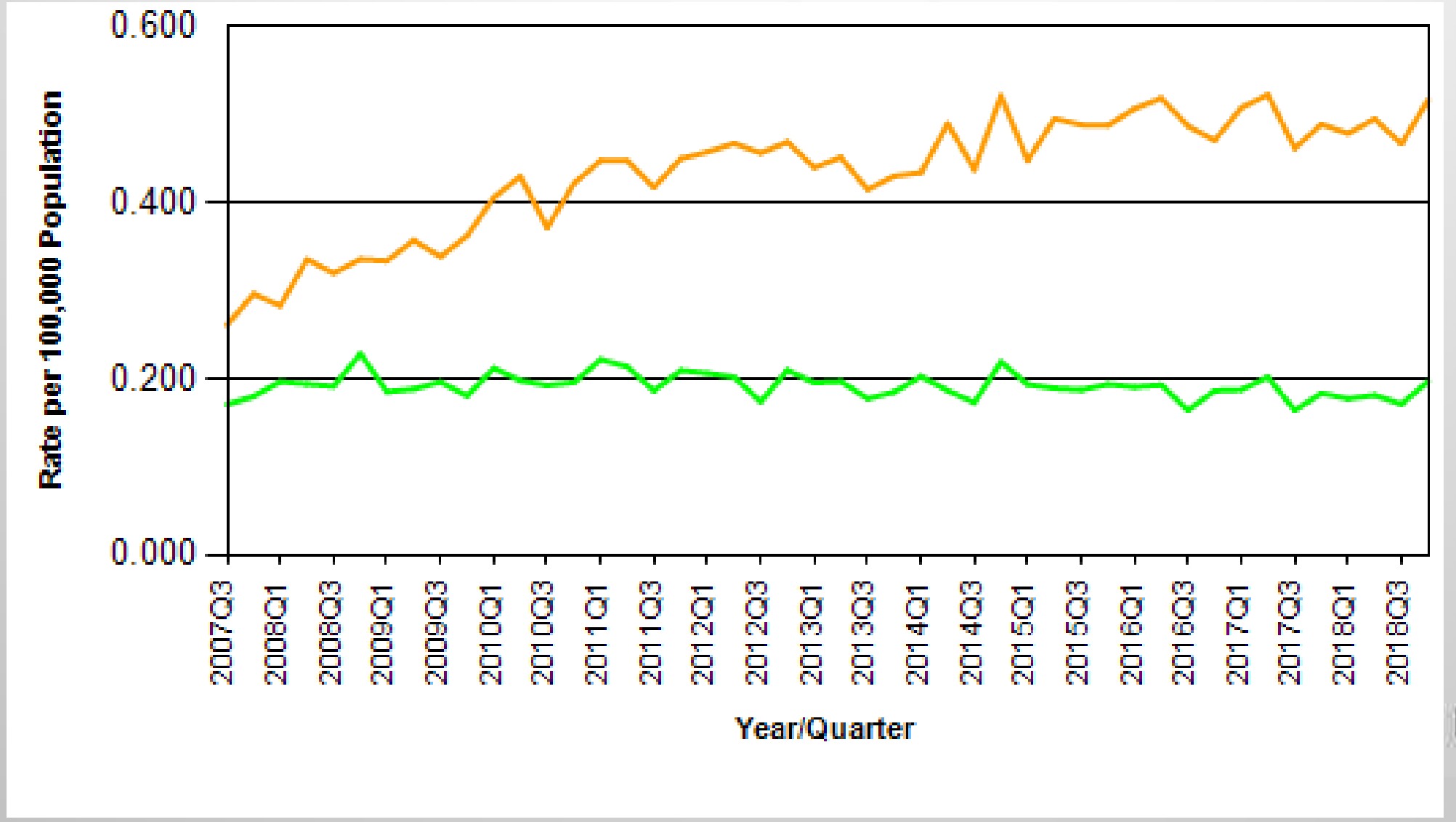
- **Heroin in Transition study**:
  - **HIT team: Sarah Mars, Jay Unick, Jeff Ondocsin, Eliza Wheeler, Mary Howe, Fernando Castillo, Philippe Bourgois, Dan Rosenblum**
  - NIH/NIDA funding: R01DA037820
- Photo credits: Dan Ciccarone, Jeff Ondocsin

Photo: D Ciccarone

Session I: Overview of Stimulant Use Disorder and Emerging Trends

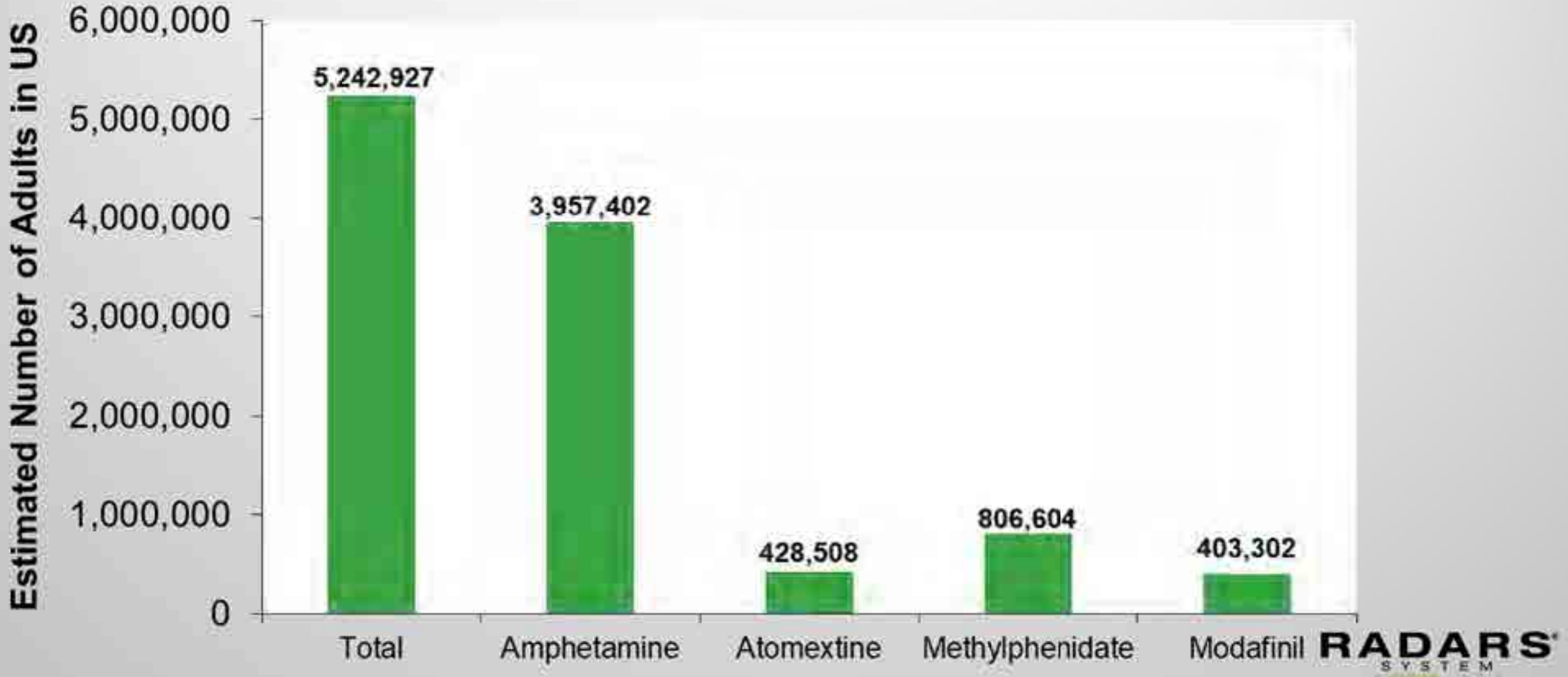
RADARS Poison Center Program

Prescription Stimulant Intentional Exposures per Population



RADARS SYSTEM

RADARS Survey of Nonmedical Use of Prescription Drugs
2018 Prescription Stimulant Nonmedical Use



Session I: Overview of Stimulant Use Disorder and Emerging Trends

16 December 2019

Developing Novel Therapies for Stimulant Use Disorder - Epidemiological Data

Jody L. Green, PhD, FAACT
Chief Scientific Officer
jgreen@Inflexxion.com

Epidemiological Data from National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO)

- **NAVIPPRO**
  - Real-time monitoring of patterns and trends of illicit drug use as well as medication use, abuse potential, and related behaviors and outcomes using diverse data sources

- **NAVIPPRO** data sources
  - ASI-MV /BHI-MV (Adult Substance Abuse Treatment Centers)
  - CHAT (Comprehensive Health Assessment for Teens; Adolescent Substance Abuse Treatment Centers)
  - Online Surveys (General Population, Targeted Populations of Interest)
  - National Poison Data System (Poison Center Data from AAPCC)
  - Web Information Services (Targeted Web Chatter, Forum Surveys, Online Surveys)
  - PainCAS (Pain Patient Data)

ASI-MV/BHI-MV and CHAT Key Findings
*clinical assessment tools used during standard work flow

POPULATION	Patients Seeking Substance Abuse Treatment 01 January 2010 through 30 September 2017	
DATA SOURCE	**ASI-MV (adults) N=512,972**	**CHAT (adolescents) N=20,305**
Past 30-day Rx Stimulant NMU	1.7%	4.3%
PLUS Past 30-day Rx Opioid NMU *PLUS Past 30-day Methamphetamine Use*	72% 34%	43% 29%
% who reported alternate route of administration of Rx stimulant	56% Snort 39%, Smoke 4%, Inject 12%	51% Snort 42%, Smoke 5%, Inject 3%
Source – Family/Friend **Source - Dealer**	55% 27%	55% 27%

Study funded by Arbor Pharmaceuticals, LLC; NMU=nonmedical use; Rx=prescription

General Population & College Students

POPULATION		Online Survey Panels	
DATA SOURCE		**General Population N=12,000**	**College Students w/Past 5 Year Rx Stimulant NMU (N=583)**
Lifetime Rx Stimulant NMU		6.4% (n=762)	100% (n=583; inclusion criteria)
Lifetime Rx Stimulant AND Rx Opioid NMU		4.2%	*57% of respondents
Comorbidities	ADHD	39%	43%
	Anxiety	64%	70%
	Depression	62%	70%
Concurrent Use	Alcohol	48%	44%
	Marijuana	39%	39%
	Cocaine	14%	12%
	Methamphetamine	10%	8%
Pathway/First Drug	Marijuana	77%	75%

Studies funded by Arbor Pharmaceuticals, LLC; NMU=nonmedical use; Rx=prescription

inflexxion | IBH

Key Findings

- Stimulant abuse is often part of a broader substance use pattern
  - Most often starts with illicit drug (primarily marijuana), then expands to prescription NMU
  - Concurrent use of alcohol, opioids, cocaine, methamphetamine
  - Motivations are key

- Underlying behavioral/mental health issues in those who report prescription stimulant NMU are 2 to 10 times more common than in those who do not
  - Depression
  - Anxiety
  - ADHD
  - Bipolar
  - Alcohol/Substance Use Disorder
  - Conduct/Oppositional Defiant Disorder
  - Learning Disability

Session I: Overview of Stimulant Use Disorder and Emerging Trends

Break

Session II: Medication Development – Challenges, Lessons Learned, and the Current Development Pipeline

Developing Novel Therapies for Stimulant Use Disorder

Washington Marriott at Metro Center
775 12th St NW • Washington, DC 20005
December 16, 2019

Session II: Medication Development – Challenges, Lessons Learned, and the Current Development Pipeline

David J. McCann, Ph.D.
Associate Director, NIDA Division of Therapeutics and Medical Consequences

The NIDA Medications Development Program

Congressional Mandate to NIDA

March, 1990

Establish a national program on biological and pharmacological approaches to heroin and cocaine addiction treatment.

Develop a close working relationship with the pharmaceutical industry.

Conduct studies to gain approval of new medications for addiction treatment.

Work with the FDA to assure that efficacy of compounds is expeditiously evaluated and approved.

NDA Approvals

Levo-alpha acetyl methadol (Orlamm® - *withdrawn)*

Buprenorphine (Subutex®) & buprenorphine/naloxone (Suboxone®) SL tablets

Once-monthly naltrexone injection (Vivitrol®)

Buprenorphine 6-month implant (Probuphine®)

Nasal naloxone (Narcan® nasal spray)

Lofexidine (Lucemyra ®)

Why the Lack of Success for Cocaine & Methamphetamine Use Disorder?

Lack of knowledge regarding the neurobiology of stimulant addiction? (lack of targets?)

Lack of appropriate animal models?

Lack of appropriate human laboratory models?

Failure to recruit appropriate subjects for efficacy trials?

Failure to design appropriate “proof of concept” efficacy trials?

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Failure to design appropriate “proof of concept” efficacy trials?

Medication Nonadherence & Professional Subjects

J Clin Psychopharm 35: 556, 2015

REVIEW ARTICLE

Medication Nonadherence, "Professional Subjects," and Apparent Placebo Responders

Overlapping Challenges for Medications Development

David J. McCann, PhD, Nancy M. Petry, PhD,† Anders Bresell, PhD,‡ Eva Isacsson, MSc,‡ Ellis Wilson, MS, MBA,‡ and Robert C. Alexander, MD‡*

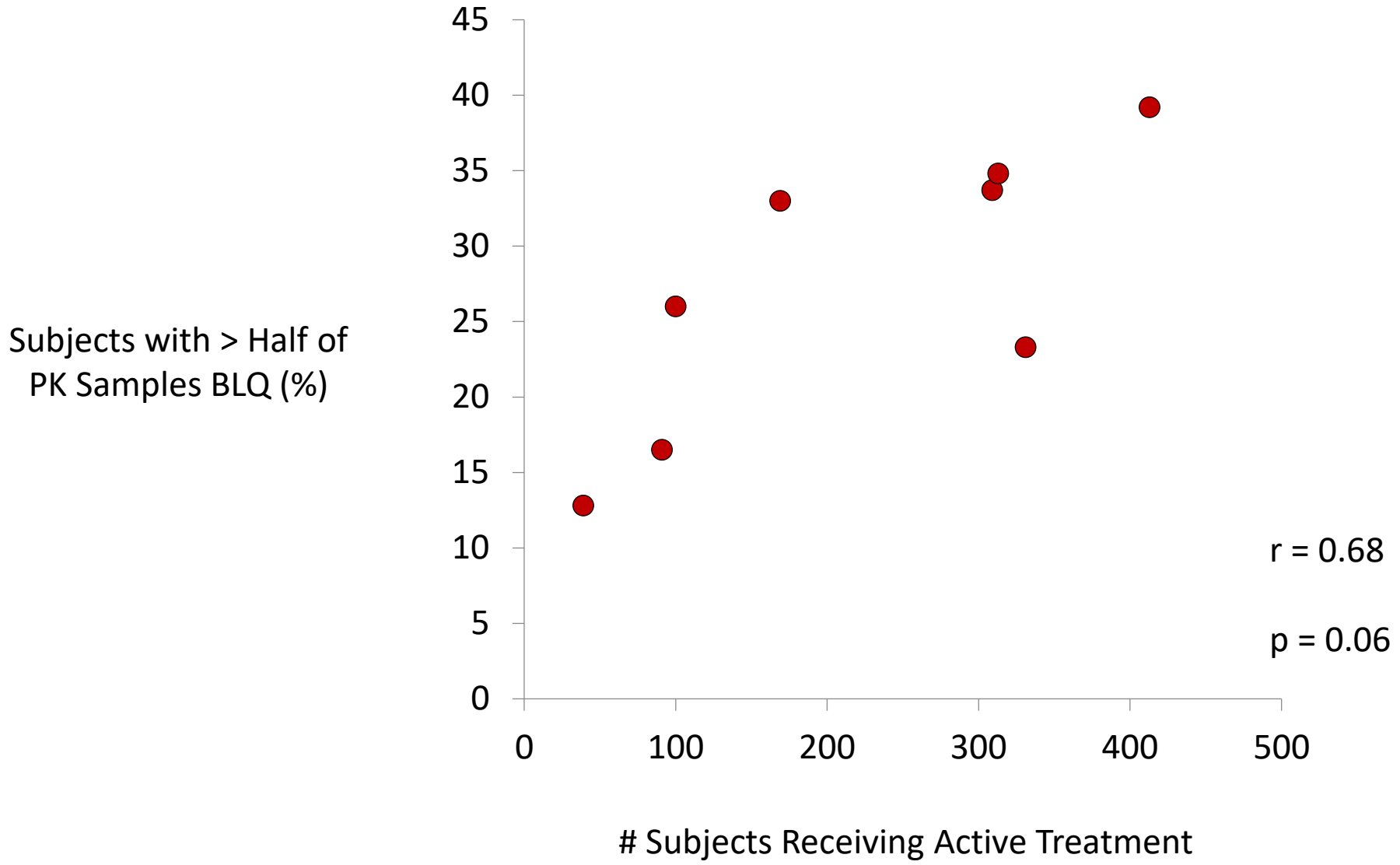
Abstract: Nonadherence is a major problem in clinical trials of new medications. To evaluate the extent of nonadherence, this study evaluated pharmacokinetic sampling from 1765 subjects receiving active therapy across 8 psychiatric trials conducted between 2001 and 2011. With nonadherence defined as greater than 50% of plasma samples below the limit of quantification for study drug, the percentage of nonadherent subjects ranged from 12.8% to 39.2%. There was a trend toward increased nonadherence in studies with greater numbers of subjects, but an association with nonadherence was not apparent for other study design parameters or subject characteristics. For 2 trials with multiple recruitment sites in geographical proximity,

medical practice[8] and can preclude the detection of an efficacy signal in clinical trials.[9,10] Beyond concerns about nonadherence in "real world patients," clinical trials have to contend with purposeful nonadherence. Thus, some individuals participate in clinical trials only for financial gain and may have no intention of taking study medication. Referred to henceforth as "professional subjects," these individuals present a challenging problem. Among a surveyed[11] group of repeat clinical trial participants, 25% admitted to exaggerating health problems, and 14% to pretending to have the disorder under study. A subject who feigns illness to gain enrollment and then answers questions truthfully

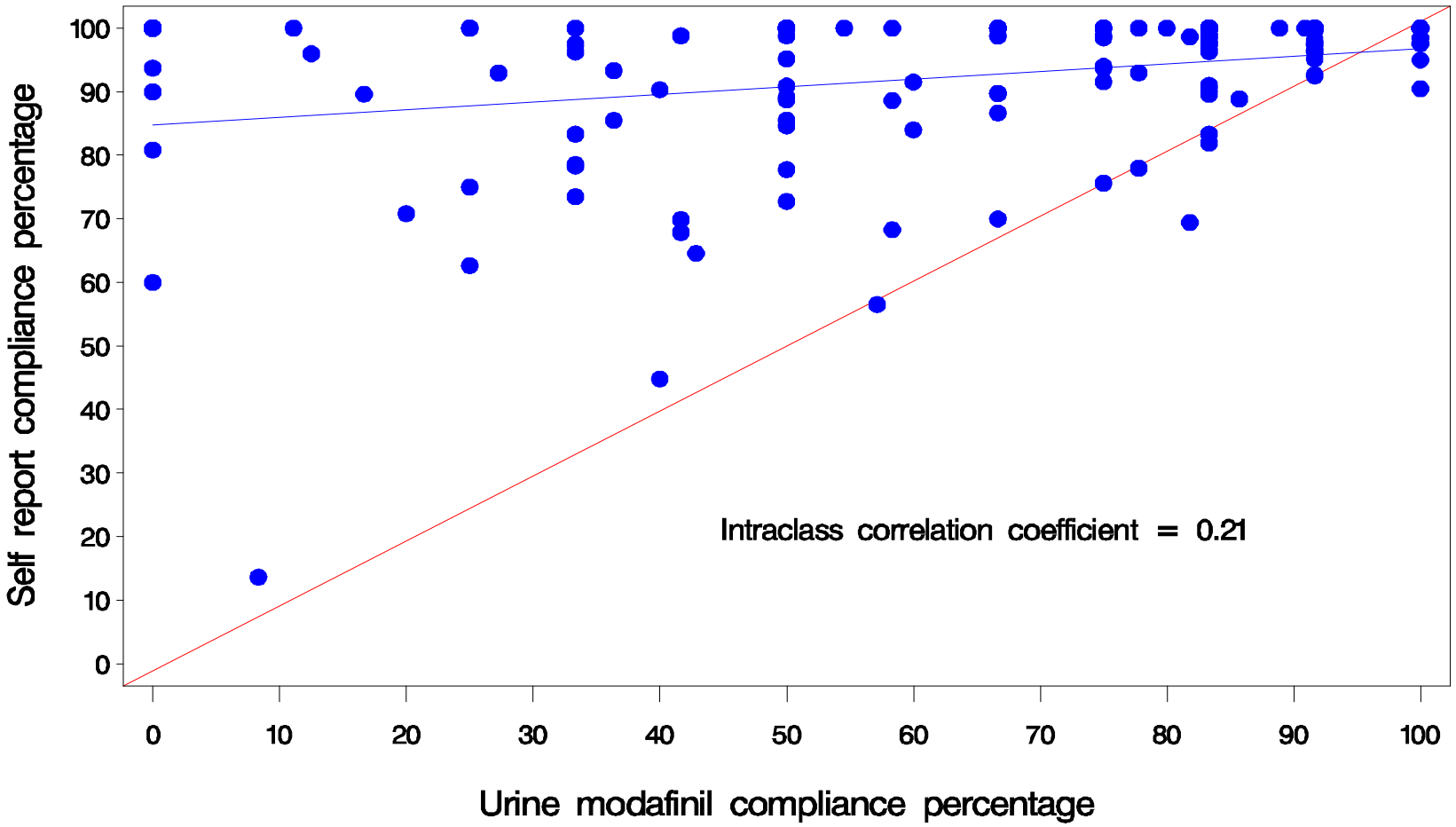
Medication Nonadherence in AstraZeneca Psychiatry Trials, 2001-2011

Indication	Number of Subjects Receiving Active Treatment	Name of Drug Under Study	Subjects with > Half of PK Samples BLQ (%)	Nonadherence Calculated from Pill Counts (%)
MDD	39	AZD2066*	12.8	NC
MDD	91	AZD7268†	16.5	2.9
MDD	100	AZD5077†	26.0 ¶	2.2
GAD	169	AZD7325‡	22.5	2.8
GAD	309	AZD7325‡	21.7	5.1
CIAS	313	AZD3480§	20.1	4.6
MDD	331	AZD5077†	23.3 ¶	0.0
GAD	413	AZD5077†	39.2 ¶	NC

BLQ, Below the Limit of Quantification
MDD, Major Depressive Disorder
GAD, Generalized Anxiety Disorder
CIAS, Cognitive Impairment Associated with Schizophrenia
NC, Not Calculated.
*Limit of Quantification (LQ) = 1.00 nmol/L. †LQ = 0.5 ng/mL. ‡LQ = 0.05 ng/mL. §LQ = 0.04 nmol/L.
¶Only one PK sample was obtained in the study.


Subjects with > Half of PK Samples BLQ (%)
45
40
35
30
25
20
15
10
5
0
0
100
200
300
400
500
r = 0.68
p = 0.06
# Subjects Receiving Active Treatment

VA/NIDA Study #1026: Modafinil for Methamphetamine Dependence



Anderson *et al.*, 2012

Analysis 2: Agreement Analysis of self report compliance with urine modafinil compliance

Doc Path: H:\p1026\reports\docs\Agreement.doc; Prgm Path: H:\p1026\reports\MEDCOMP−v2.sas; Date run: 09/03/2010; Data last updated: 03/10/2010

Compliance Based on Urine Modafinil
(% compliance = % urines containing any detectable modafinil)

≥ 90% Compliance:	34/142 (24%)
≥ 80% Compliance:	61/142 (43%)
≥ 70% Compliance:	73/142 (51%)
0% Compliance:	14/142 (10%)

Compliance Based on Urine Modafinil
(% compliance = % urines containing any detectable modafinil)

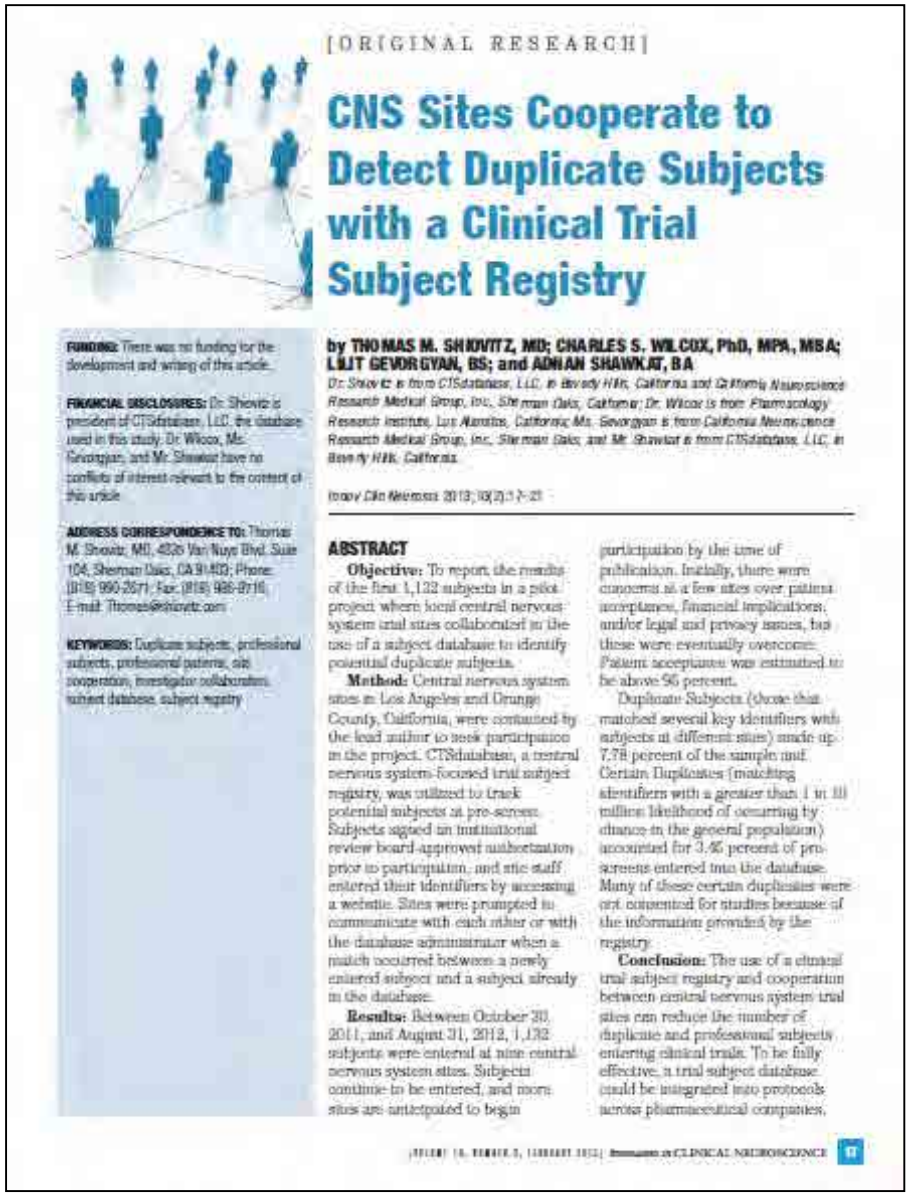
≥ 90% Compliance:	34/142 (24%)
≥ 80% Compliance:	61/142 (43%)
≥ 70% Compliance:	73/142 (51%)
0% Compliance:	14/142 (10%)

Why do some subjects enroll with no apparent intention of taking study medication?

(Professional Subjects)

“Professional Subjects”

We know they exist because they have been caught and/or confessed.



[ORIGINAL RESEARCH]

CNS Sites Cooperate to Detect Duplicate Subjects with a Clinical Trial Subject Registry

FUNDING: There was no funding for the development and writing of this article.

FINANCIAL DISCLOSURES: Dr. Shovitz is president of CTSdatabase, LLC, the database used in this study. Dr. Wilcox, Ms. Gevorgyan, and Mr. Shawkat have no conflicts of interest relevant to the content of this article.

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KEYWORDS: Duplicate subjects, professional subjects, professional patients, site cooperation, investigator collaboration, subject database, subject registry

by THOMAS M. SHOVITZ, MD; CHARLES S. WILCOX, PhD, MPA, MBA; LILIT GEVORGYAN, BS; and ADNAN SHAWKAT, BA

Dr. Shovitz is from CTSdatabase, LLC, in Beverly Hills, California and California Neuroscience Research Medical Group, Inc., Sherman Oaks, California; Dr. Wilcox is from Pharmacology Research Institute, Los Alamitos, California; Ms. Gevorgyan is from California Neuroscience Research Medical Group, Inc., Sherman Oaks; and Mr. Shawkat is from CTSdatabase, LLC, in Beverly Hills, California.

Innov Clin Neurosci 2013; 10(2):1-7

ABSTRACT

Objective: To report the results of the first 1,132 subjects in a pilot project where local central nervous system trial sites collaborated in the use of a subject database to identify potential duplicate subjects.

Method: Central nervous system sites in Los Angeles and Orange County, California, were contacted by the lead author to seek participation in the project. CTSdatabase, a central nervous system-focused trial subject registry, was utilized to track potential subjects at pre-screen. Subjects signed an institutional review board-approved authorization prior to participation, and site staff entered their identifiers by accessing a website. Sites were prompted to communicate with each other or with the database administrator when a match occurred between a newly entered subject and a subject already in the database.

Results: Between October 20, 2011, and August 31, 2012, 1,132 subjects were entered at nine central nervous system sites. Subjects continue to be entered, and more sites are anticipated to begin participation by the time of publication. Initially, there were concerns at a few sites over patient acceptance, financial implications, and/or legal and privacy issues, but these were eventually overcome. Patient acceptance was estimated to be above 95 percent.

Duplicate Subjects (those that matched several key identifiers with subjects at different sites) made up 7.78 percent of the sample unit. Certain Duplicates (matching identifiers with a greater than 1 in 10 million likelihood of occurring by chance in the general population) accounted for 3.45 percent of pre-screens entered into the database. Many of these certain duplicates were not consented for studies because of the information provided by the registry.

Conclusion: The use of a clinical trial subject registry and cooperation between central nervous system trial sites can reduce the number of duplicate and professional subjects entering clinical trials. To be fully effective, a trial subject database could be integrated into protocols across pharmaceutical companies.

CLINICAL TRIALS *ETHICS*

Clinical Trials 2013; 10: 935–948

Concealment and fabrication by experienced research subjects

Eric G Devine[a], Megan E Waters[a], Megan Putnam[b], Caitlin Surprise[a], Katie O'Malley[a], Courtney Richambault[a], Rachel L Fishman[a], Clifford M Knapp[a], Elissa H Patterson[a], Ofra Sand-Segal[a], Chris Streeter[a], Laurie Colanan[a] and Domenic A Ciraulo[a]

Background Subjects who enroll in multiple studies have been found to use deception at times to overcome restrictive screening criteria. Deception undermines subject safety as well as study integrity. Little is known about the extent to which experienced research subjects use deception and what type of information is concealed, withheld, or distorted.

Purpose This study examined the prevalence of deception and types of deception used by subjects enrolling in multiple studies.

Method Self-report of deceptive behavior used to gain entry into clinical trials was measured among a sample of 100 subjects who had participated in at least two studies in the past year.

Results Three quarters of subjects reported concealing some health information from researchers in their lifetime to avoid exclusion from enrollment in a study. Health problems were concealed by 32% of the sample, use of prescribed medications by 28%, and recreational drug use by 20% of the sample. One quarter of subjects reported exaggerating symptoms in order to qualify for a study and 14% reported pretending to have a health condition in order to qualify.

Limitations Although this study finds high rates of lifetime deceptive behavior, the frequency and context of this behavior is unknown. Understanding the context and frequency of deception will inform the extent to which it jeopardizes study integrity and safety.

Conclusion The use of deception threatens both participant safety and the integrity of research findings. Deception may be fueled in part by undue inducements, overly restrictive criteria for entry, and increased demand for healthy controls. Screening measures designed to detect deception among study subjects would aid in both protecting subjects and ensuring the quality of research findings. *Clinical Trials* 2013; 10: 935–948. http://ctj.sagepub.com

Introduction

The use of human subjects in clinical trials is a necessary component of drug and device development. These areas of research expose subjects to potential risks. The ethical issues related to balancing the risk and benefit to human subjects in research have been the subject of intense media coverage following high-profile studies in which healthy volunteers died during phase 1 medication

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Email: edevine@bu.edu

10.1177/1740774513492917

A high percentage of "destined to fail" professional subjects could greatly reduce response rates in the placebo & active arms

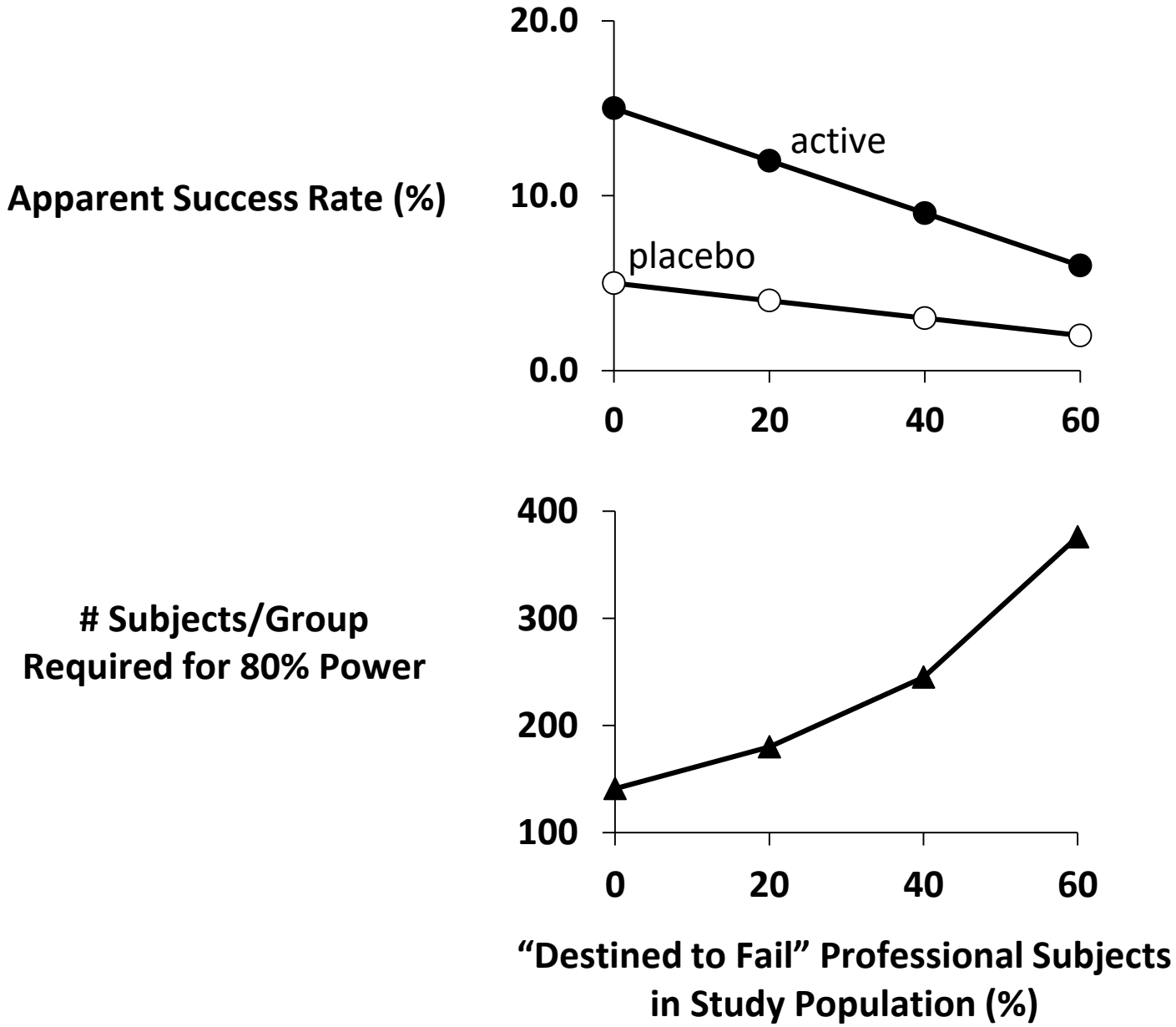
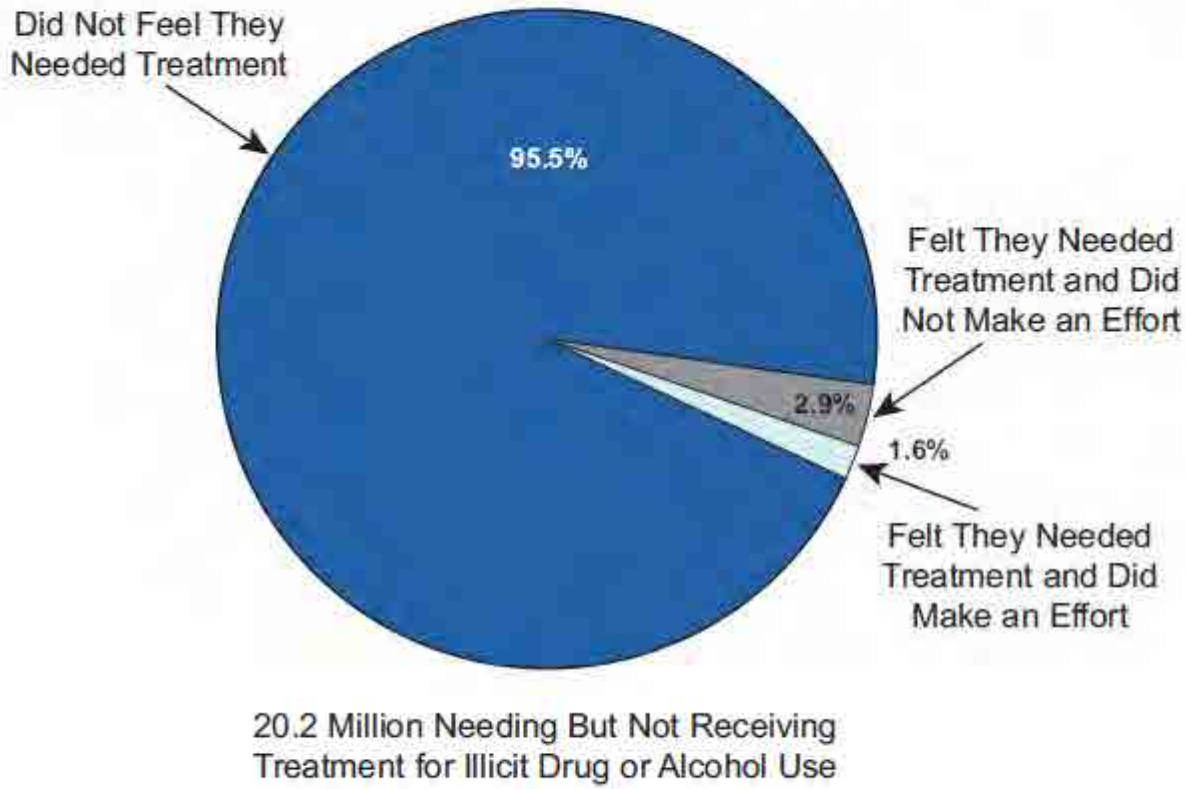


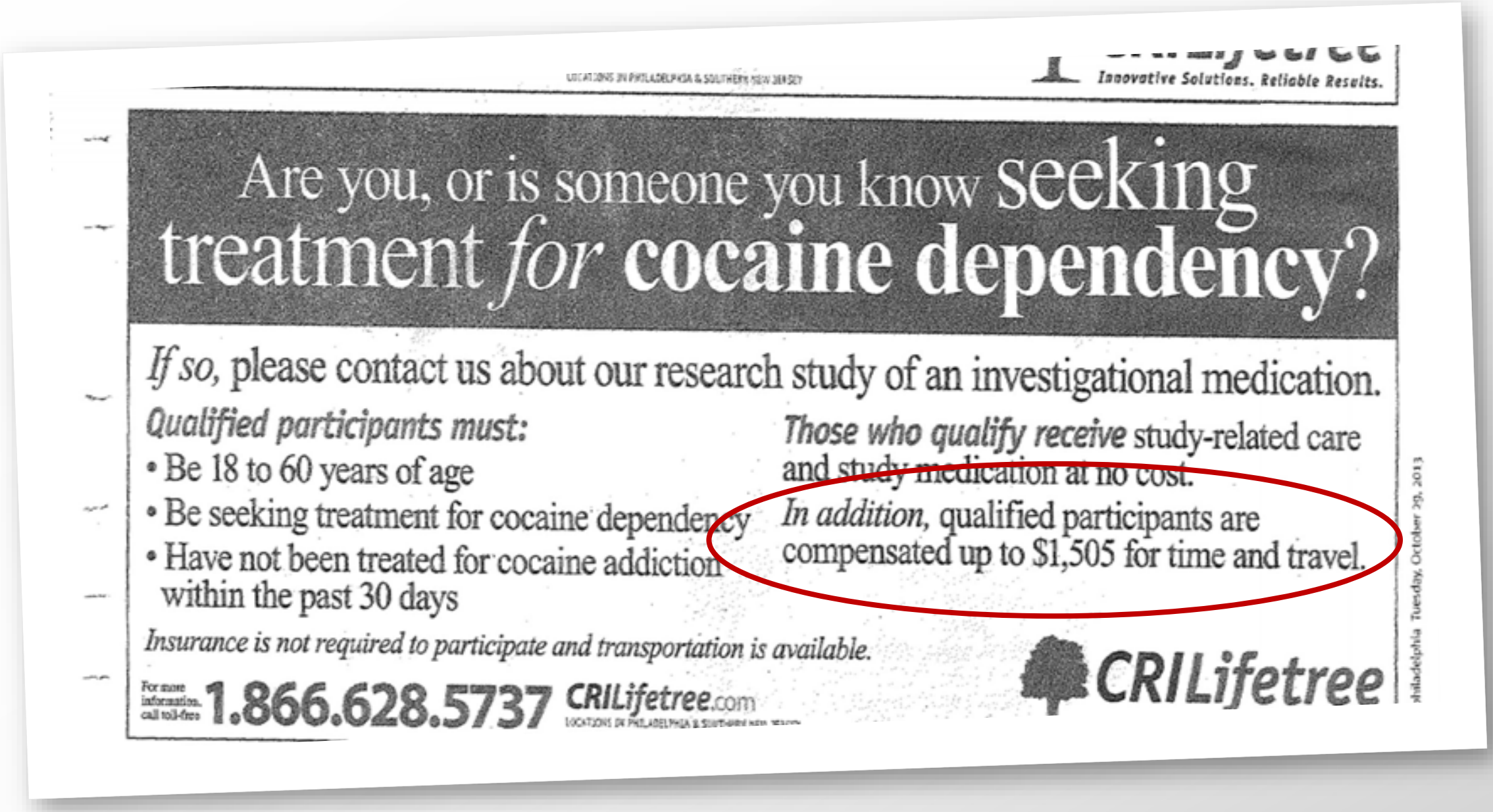
Figure 7.10 Past Year Perceived Need for and Effort Made to Receive Specialty Treatment among Persons Aged 12 or Older Needing But Not Receiving Treatment for Illicit Drug or Alcohol Use: 2013



Approximately 50% were less than fulltime employed

2013 NSDUH (SAMHSA)

We have to be smarter than this!!



LOCATIONS IN PHILADELPHIA & SOUTHERN NEW JERSEY

Innovative Solutions. Reliable Results.

Are you, or is someone you know seeking treatment *for* cocaine dependency?

If so, please contact us about our research study of an investigational medication.

Qualified participants must:

- Be 18 to 60 years of age
- Be seeking treatment for cocaine dependency
- Have not been treated for cocaine addiction within the past 30 days

Those who qualify receive study-related care and study medication at no cost.

In addition, qualified participants are compensated up to $1,505 for time and travel.

Insurance is not required to participate and transportation is available.

For more information, call toll-free **1.866.628.5737** CRILifetree.com

LOCATIONS IN PHILADELPHIA & SOUTHERN NEW JERSEY

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Philadelphia Tuesday, October 29, 2013

How can we Adapt to the Reality of Medication Nonadherence & Professional Subjects?

- **Always use a subject registry to prevent dual enrollment within a trial (same subject at multiple sites) and to reduce enrollment of “professional subjects.”**

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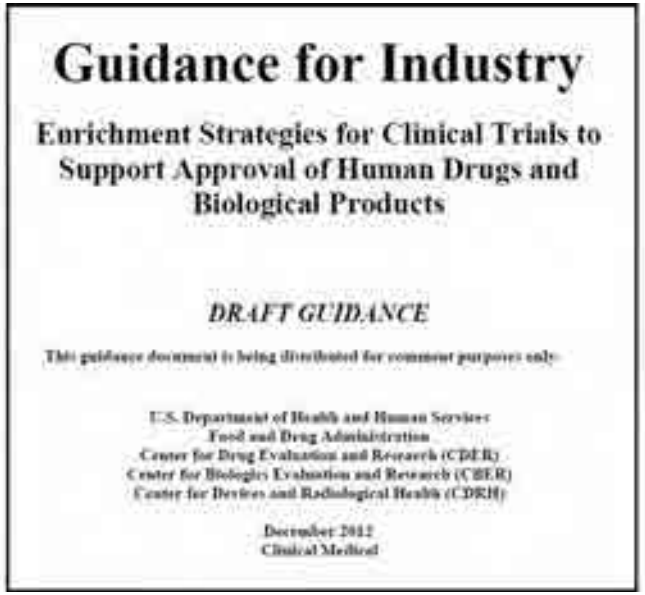

Guidance for Industry

Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

December 2012
Clinical/Medical

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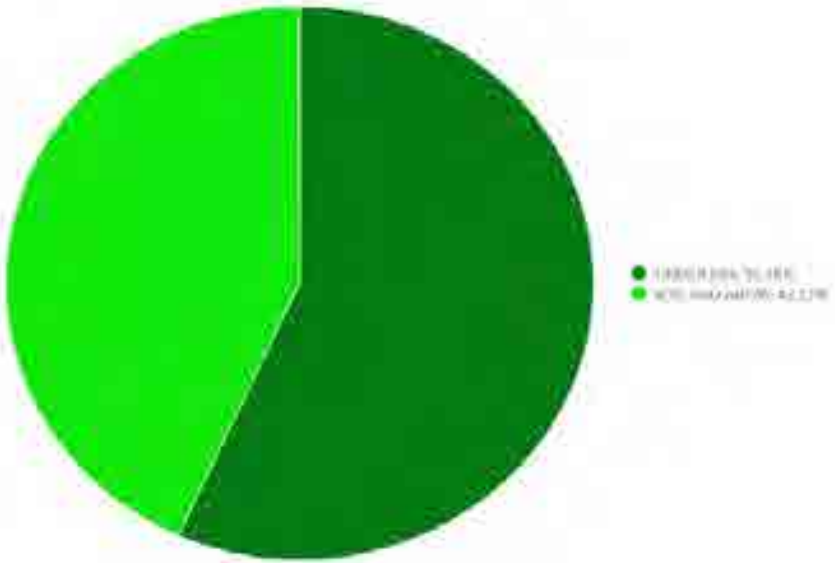
- **Prior to randomization, try to detect subjects who are likely to be medication nonadherent and exclude them from randomization…or exclude their data from analysis for the primary efficacy endpoint.**
- **After randomization, consider active promotion of medication adherence through:**
  - **counseling**
  - **dosing reminders**
  - **observed, in-clinic dosing**
  - **observed, at-home dosing**

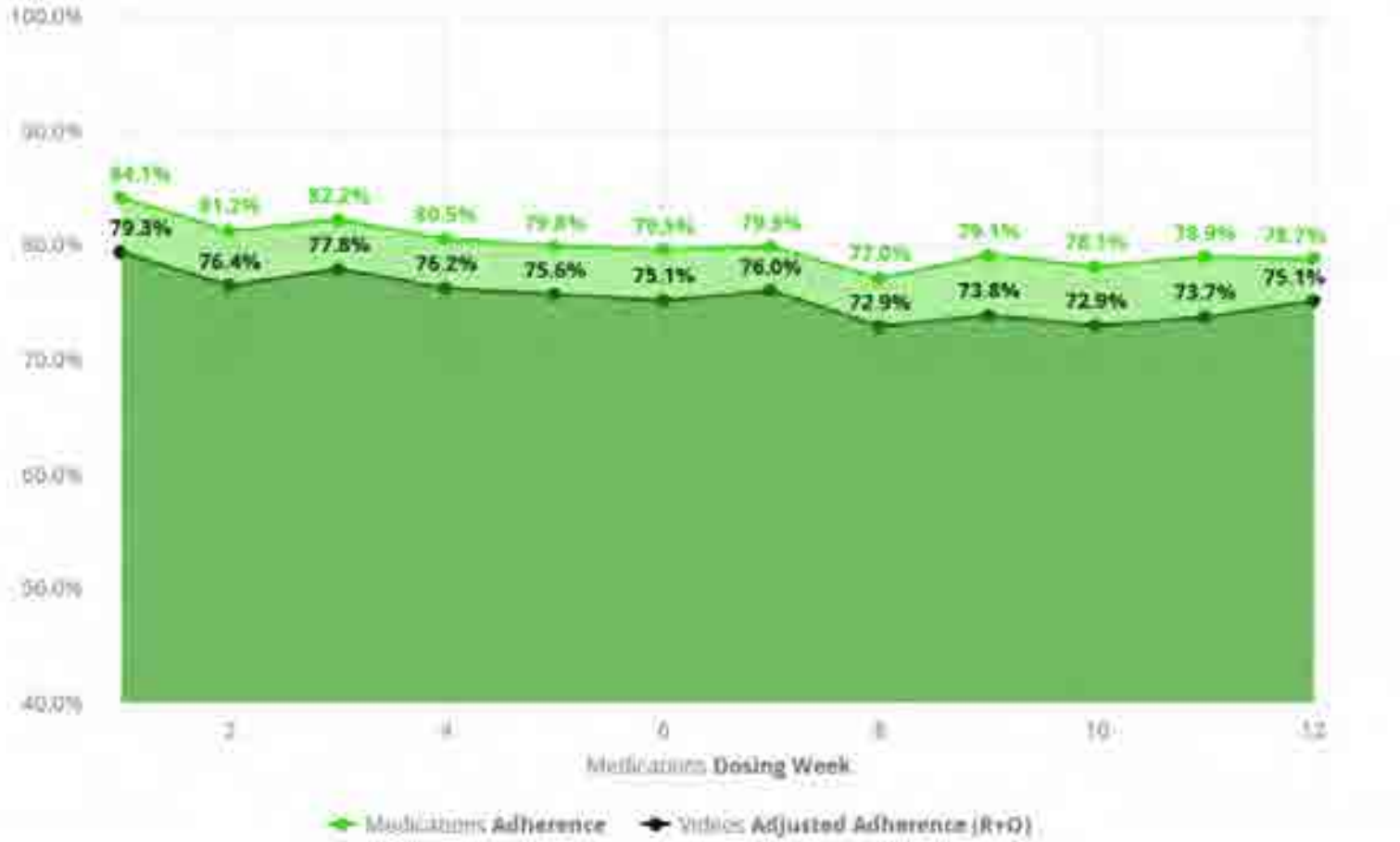
AiView software

3 Key Steps:

Collection of self-report too: Daily cocaine & alcohol use

43% of subjects > 80% adherent
Adherence remained relatively stable throughout the trial





How can we Adapt to the Reality of Medication Nonadherence & Professional Subjects?

Consider developing implants and SR injection formulations.

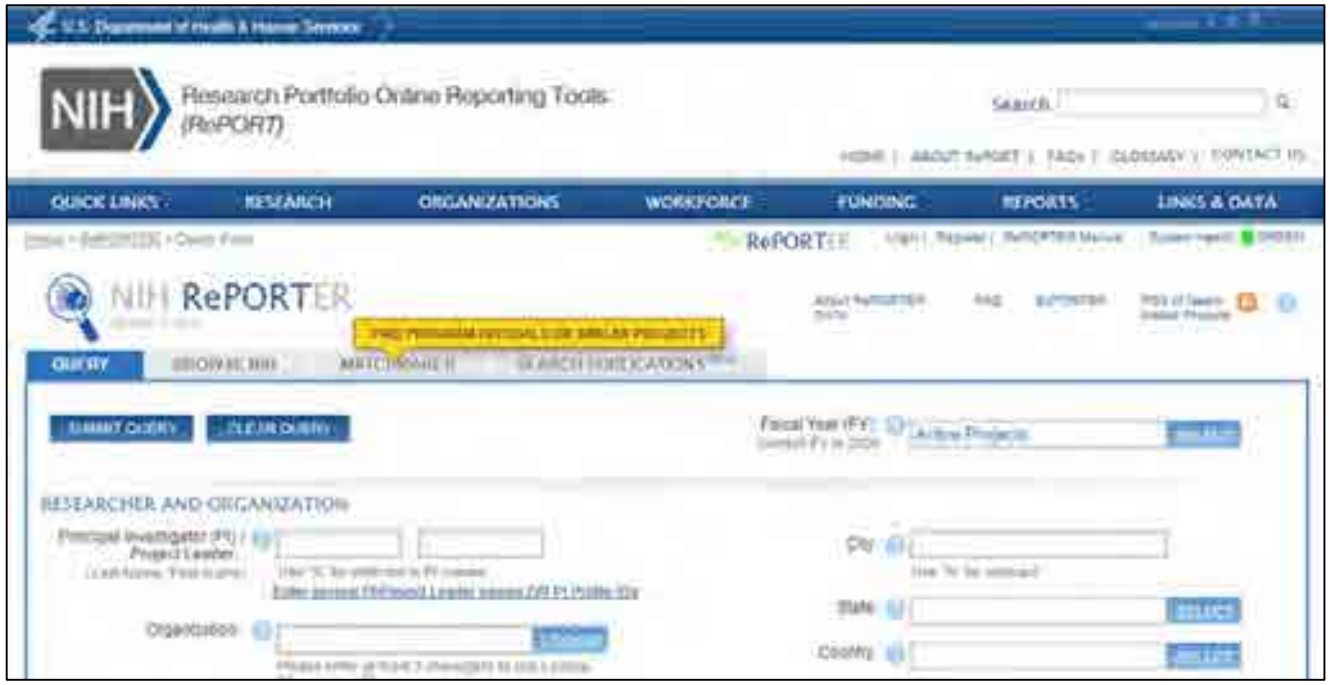
Understandably, many pharma companies will want to see evidence of efficacy first.

What's in the Development Pipeline?

(clinical highlights)

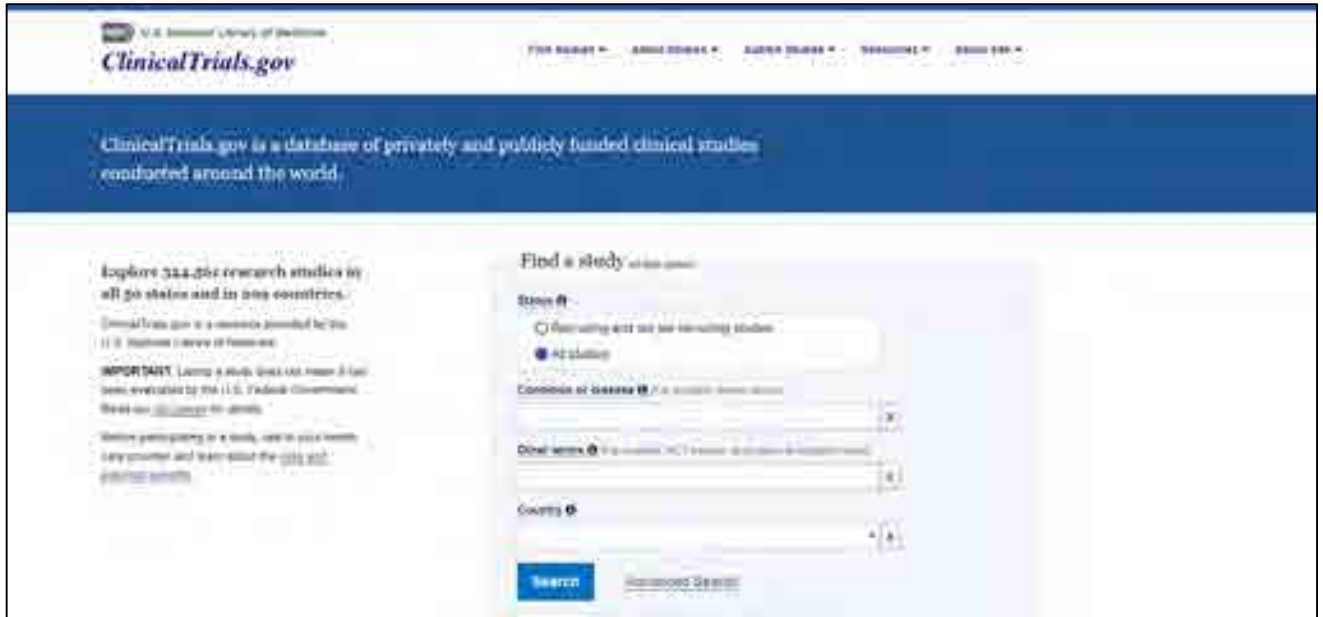
Public information on all NIH-funded grants can be found at:

projectreporter.nih.gov



Public information on clinical trails can be found at:

clinicaltrials.gov



Multi-Site Efficacy Trials

Lorcaserin vs. cocaine use disorder
(5-HT2C agonist)
NIDA/VACSP; 12 sites; N=272; draft clinal study report under review

Mavoglurant vs. cocaine use disorder
(mGluR5 antagonist)
Novartis; 12 sites; N=68; Estimated completion date January 2020

Ketamine vs. cocaine use disorder
(subanesthetic doses)
E. Dakwar/Columbia; NIDA grant U01-DA040646; 2 sites, N=150; Estimated completion date April 2021

EMB-001 vs. cocaine use disorder
(metyrapone/oxazepam)
B. McCarthy/Embera; NIDA grant U01-DA038879; Not yet listed in clinicaltrails.gov

Single Site Efficacy Trials

NS2359 vs. cocaine use disorder
(DAT/NET/SERT inhibitor)
K. Kampman; U Penn/Dana Foundation; N=80; Estimated completion date June 2021

Adderall vs. cocaine use disorder
(mixed amphetamine salts)
K. Carpenter/F. Levin; Columbia; NIDA grant R01-DA034087; N=155; Estimated completion date April 2020

Bupropion vs. cocaine use disorder
(DAT/NET inhibitor)
K. Dunn; Johns Hopkins; NIDA grant R01-DA034047; N=200; Estimated completion January 2020

Guanfacine vs. cocaine use disorder with comorbid substance use disorders – women only
(alpha2A agonist)
R. Sinha; Yale; NIDA grant R01-DA047094; N=100; Estimated completion date June 2021

Phase Ib or IIa Studies

IXT-m200 – Methamphetamine users
(Anti-meth mAb) M. Stevens; Intervexion; NIDA grant U01-DA045366

Pomaglumetad methionil – Methamphetamine users
(mGluR2/3 agonist prodrug) K. Heinzerling; UCLA; NIDA grant R01-DA043238

Duloxetine & Methylphenidate – Methamphetamine users
(DAT/NET/SERT inhibition) C. Rush; U Kentucky; NIDA grant R01-DA047391

tDCS – Cocaine users
(device) A. Datta; Soterix; NIDA SBIR contract HHSN271201800035C

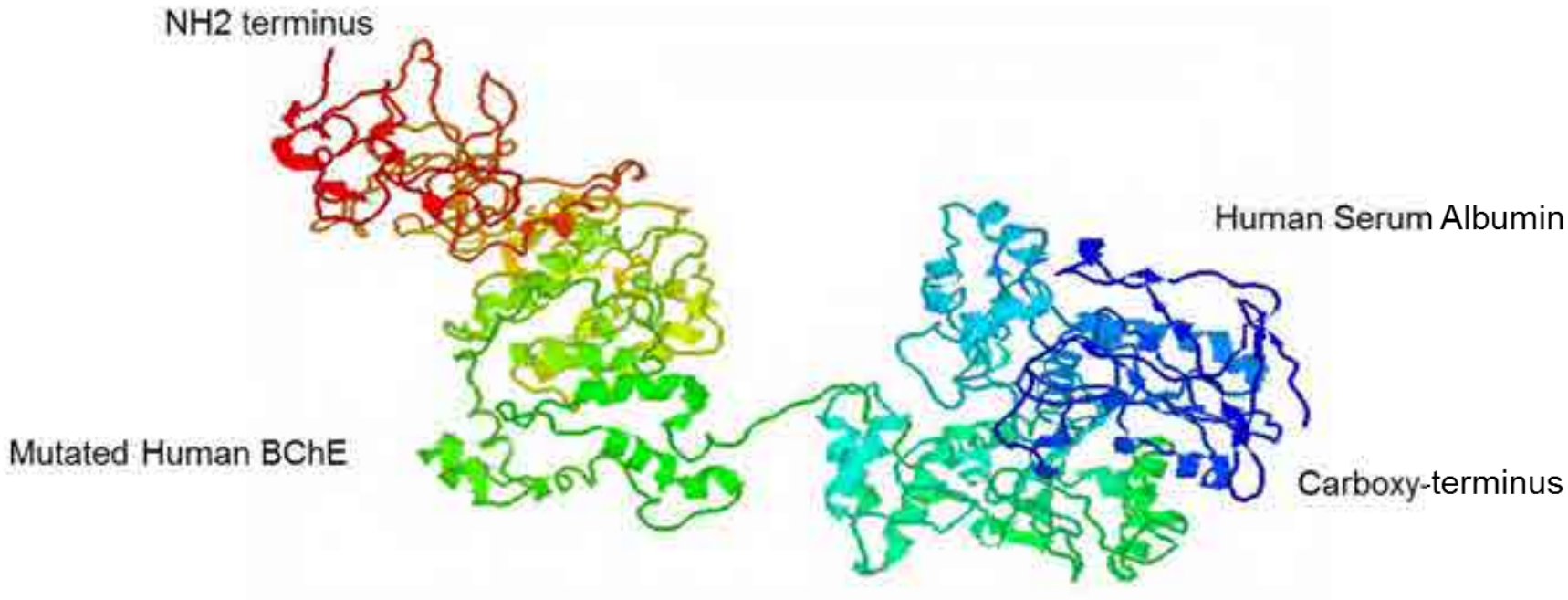
Cariprazine – Cocaine users
(D3/D2/5HT1A partial agonist) A.R. Childress; U Penn; NIDA grant R01-DA039215

Phase I

dAd5GNE (anti-cocaine vaccine)
R. Crystal; Cornell; NIDA grant U01-DA048524 - Recruiting

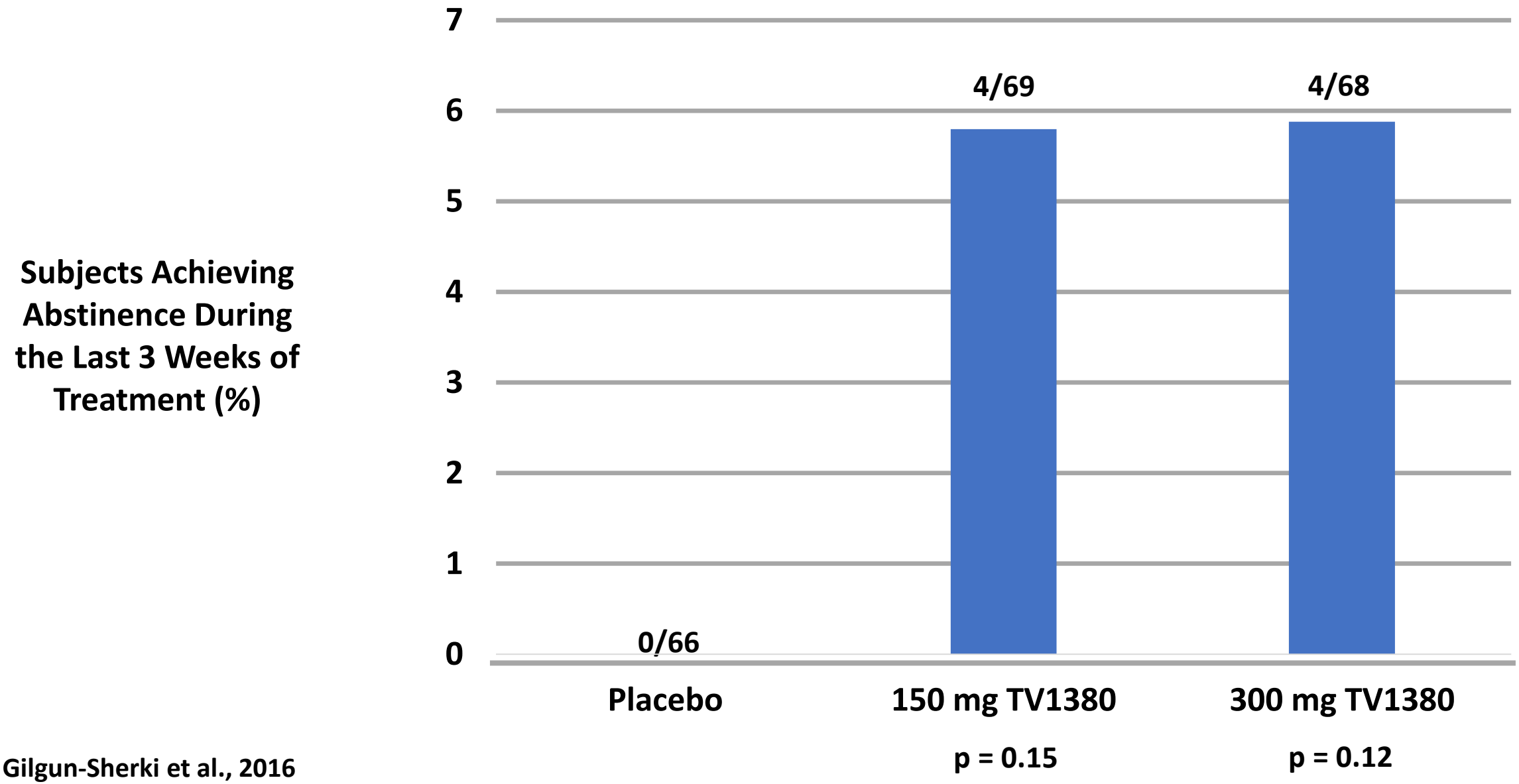
h2E2 (anti-cocaine mAb)
A. Norman; U Cincinnati; NIDA grant U01-DA048525 – IND approved

Cocaine hydrolase gene therapy
W.S. Brimijoin; Mayo; NIDA grant UH3-DA042492 – IND approved



Predicted molecular model of TV-1380

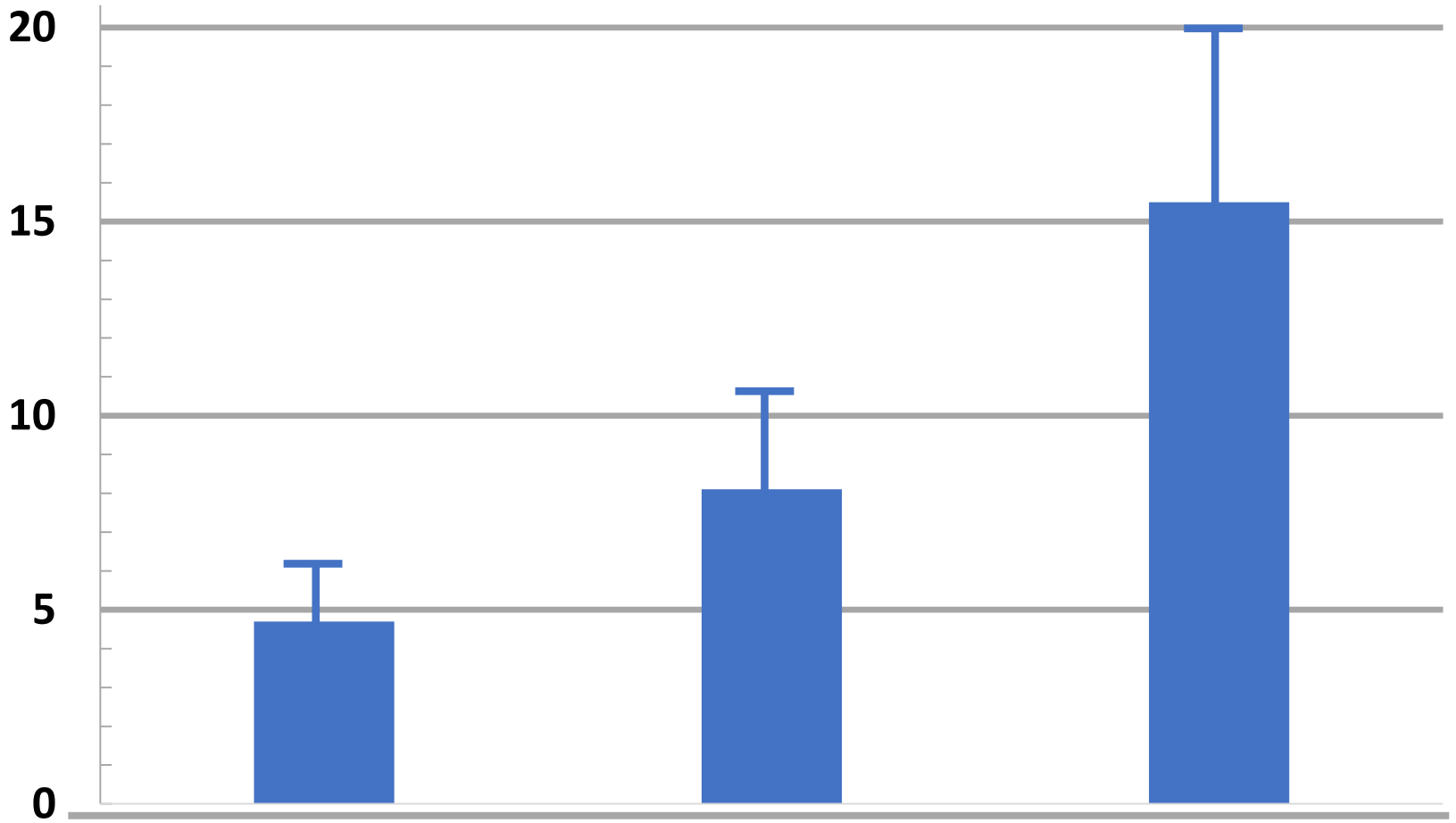
Primary Endpoint



Gilgun-Sherki et al., 2016

Secondary Endpoint

Percentage of BE- and EME-Negative Urines During the Last 8 Weeks of Treatment



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DMCCANN@NIH.GOV

Session II: Medication Development – Challenges, Lessons Learned, and the Current Development Pipeline

Lunch

Session III: Assessing Clinical Endpoints and Methods for Data Collection

The Search for Meaningful outcome indicators:
Findings from a pooled dataset of 7 randomized clinical trials for cocaine use disorder.

Kathleen M Carroll, Brian D Kiluk,
Charla Nich & Corey Roos

Yale University School of Medicine

Supported by NIDA R21/33 DA 041661, R01 DA15969 (supplement), P50 DA09241, U10 DA015831, R01 DA019078, & R01 DA 10679

Kathleen.carroll@yale.edu

Disclosure: Kathleen Carroll is a member of CBT4CBT LLC

Overview:

Series of analyses based on large (N=720) pooled data set to:

- Compare different commonly-used indicators of outcome in terms of prediction of cocaine use and general functioning during 1-year follow-up.
- Relate within-treatment reduction in cocaine use frequency to general functioning during follow up
- Identify participants with ‘good posttreatment functioning’, relate to cocaine use during treatment
- Relate change in DSM symptom counts and severity to outcome

Common approach across multiple cocaine treatment RCTs, N=720

Study 1: Carroll, K.M., Nich, C., Ball, S.A., et al. 1998. Treatment of cocaine and alcohol dependence with psychotherapy and disulfiram. *Addiction* 93, 713-728.

Study 2 : Carroll, K.M., Fenton, L.R., Ball, S.A., et al. 2004. Efficacy of disulfiram and cognitive-behavioral therapy in cocaine-dependent outpatients: A randomized placebo controlled trial. *Archives of General Psychiatry* 64, 264-272.

Study 3: Carroll, K.M., Eagan, D., Nich, C., et al. 2012,. Efficacy of Twelve Step Facilitation and disulfiram for cocaine-using methadone-maintained individuals. *Drug and Alcohol Dependence* 126, 224-231

Study 4: Carroll, K.M., Ball, S.A., Martino, S., et al. 2008. Computer-assisted cognitive - behavioral therapy for addiction. A randomized clinical trial of 'CBT4CBT'. A*merican Journal of Psychiatry* 165, 881-888.

Study 5: Carroll, K.M, Kiluk, B.D., Nich, C., et al. 2014. Computer-Assisted Delivery of Cognitive-Behavioral Therapy: Efficacy and durability of CBT4CBT among cocaine - dependent individuals maintained on methadone. *The American Journal of Psychiatry, 171*, 436-444

Study 6: Carroll, K.M., Nich, C., Petry, N.M., et al. 2016. A randomized factorial trial of disulfiram and contingency management to enhance cognitive behavioral therapy for cocaine dependence. *Drug and Alcohol Dependence*, 160:135-42.

Study 7: Carroll, K.M., Nich, C., DeVito, E.E., Shi, Julia M., & Sofuoglu, M. 2018. Galantamine and computerized cognitive behavioral therapy for cocaine dependence: A randomized clinical trial. *Journal of Clinical Psychiatry;* 79:17m11669

Overview of 720 participants*

Baseline characteristics

- 36% female, mean age 37
- 36% Black, 11% Latino
- 76% HS grads
- 62% unemployed
- 72% lifetime AUD
- 20% lifetime MDD
- 40% methadone-maintained OUD
- Mean 14 days of cocaine use past 28

Treatment outcomes

- Mean 39% cocaine-neg utox
- 34% 3 or more weeks continuous abstinent
- 25% complete treatment and abstinent last 2 weeks
- 13% complete abstinence
- 9% ‘problem free functioning’ at EOT

Common design features

- 12 weeks outpatient treatment;
  - Behavioral therapies were manual guided with independent fidelity assessment OR standardized, computer delivered
  - Medications placebo controlled with riboflavin checks (non-OUD samples) or provided with daily methadone
  - 1-3/x weekly urine toxicology screens
- Follow-ups with urine collection at 1, 3, 6 (12) months,
- >80% of intention-to-treat sample for all studies

COMMON ASSESSMENT BATTERY

- Substance Use Calendar/Timeline FollowBack
  - Day by day frequency of cocaine use during entirety of study
  - Average 13% discrepancy from urine results (urine positive, self-report negative
- Addiction Severity Index at each assessment, source for psychosocial functioning

Follow-up outcome indicators

- Mean days of cocaine use 1, 3, 6, & 12 month follow ups via TLFB
- Abstinent throughout full follow-up
- Mean days of problems in each of the non-cocaine ASI areas during follow-up
- Composite measure of self-reported 'problem free functioning" from ASI:
  - Days of employment problems = 0, Days of legal problems = 0, Days of psych problems=0, Days of cocaine use = 0

Desirable features of indicators

- Easy to calculate, interpret
- Psychometrically sound
- Low susceptibility to missing data
- Verifiable (biologic indicator, other)
- Sensitive to treatment effects
- Predicts long-term cocaine outcomes
- Related to indicators of good longer term functioning

Drug and Alcohol Dependence 137 (2014) 3–19

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Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Review

Toward empirical identification of a clinically meaningful indicator of treatment outcome: Features of candidate indicators and evaluation of sensitivity to treatment effects and relationship to one year follow up cocaine use outcomes

Kathleen M. Carroll[a,*], Brian D. Kiluk[a], Charla Nich[a], Elise E. DeVito[a], Suzanne Decker[a,b], Donna LaPaglia[a], Dianne Duffey[a], Theresa A. Babuscio[a], Samuel A. Ball[a,c]

[a] Department of Psychiatry, Yale University School of Medicine, 950 Campbell Avenue, 151D, West Haven, CT 06516, United States
[b] New England Mental Illness, Research Education and Clinical Center, VA Connecticut Healthcare System, United States
[c] The APT Foundation, New Haven Connecticut, 1 Long Wharf, New Haven, CT 06511, United States

	Indicator		Ease of computation	Verifiability	Vulnerability to missing data	Relative cost	Operationalization for these analyses
1	Days retained in treatment protocol	C	Easy	Yes-	Low	Low	Days from randomization to endpt
2	Percentage of urine specimens testing positive	C	Easy for complete data	Yes, by definition	Assumes independence of urine specimens (denominator), assumes numerator is unbiased by collection schedule or missing data.	High	Number of cocaine-negative urine specimens collected / all specimens collected
3	Maximum consecutive days abstinent	C	Easy for complete data	Yes, provided appropriate schedule of data/urine collection	Likely to result in casewise missingness or reduced sample size	Moderate, due to biological verification and derivation from TLFB	Longest continuous cluster of self-reported abstinence within treatment
4	Percent days of abstinence from cocaine	C	Depends on treatment duration, level of missing data, and intermittent missingness	Yes, provided appropriate schedule of data/urine collection	Likely to result in casewise missingness or reduced sample size	Moderate, due to biological verification and derivation from TLFB	Number of self-reported days of abstinence from cocaine / days in treatment (retention)
5	Maximum days of continuous abstinence during last two weeks of treatment	C	Complex for intermittent and monotone, dropouts	Yes, provided appropriate schedule of data/urine collection	Low	Moderate, due to biological verification and derivation from TLFB	For those retained 14+ days, longest cluster of abstinence in final 2 weeks; otherwise 0
6	Completely abstinent last two weeks of treatment	D	Easy	Yes, provided appropriate schedule of data/urine collection	Low	Moderate, due to biological verification and derivation from TLFB	For those retained 14+ days, 0 days of use in last 14 days, otherwise 0
7	3 or more weeks of continuous abstinence	D	Easy	Yes, provided appropriate schedule of data/urine collection	Low	Moderate, due to biological verification and derivation from TLFB	“Yes” if participant retained 21+ days, max days abstinent > 20. Otherwise No
8	2 or more weeks of continuous abstinence	D	Easy	Yes, provided appropriate schedule of data/urine collection	Low	Moderate, due to biological verification and derivation from TLFB	“Yes” if participant retained 14+ days, max days abstinent > 13. Otherwise No

Note. C=continuous, D=Dichotomous, TLFB=Timeline Followback method

Candidate indicators, 1: Continuous measures, verifiable

- Retention (days in treatment/protocol)
  - Easy to calculate, little missing data
  - Clinical data suggests linked to better outcomes
- Percent cocaine-negative urine toxicology
  - Timing is critical (overlap, missing data)
  - Complex for missing data, esp. differential attrition
  - Need for clarity regarding denominator (collected/expected)
  - Cocaine versus all drugs?

Candidate indicators, 2: Continuous-self report measures

- Longest abstinence during treatment
  - Linked to longer term outcome
- Maximum days abstinent at end of treatment
- Percent days abstinent

  Verifiable via utox, complexity depends on missing data

Candidate indicators, 3: *Dichotomous measures*

- Complete abstinence
- Abstinence at end of treatment
- Abstinence of fixed duration (3 or more weeks, within or end of treatment
- Treatment completion with end of treatment abstinence
- Achieved XX% reduction in use from baseline*
  - Days of use?
  - Quantitative measures
  - Requires valid baseline information

TABLE 5: relationship to follow-up indicators

	Outcome indicator		Days of cocaine Use Month 1	Days of cocaine Use Month 3	Days of cocaine Use Month 6	Days of cocaine Use Month 12	Totally abstinent throughout follow-up		Good functioning at Month 1	Good functioning at Month 3	Good functioning at Month 6	Good functioning at Month 12
1	Days retained in treatment protocol	r	-.12						.10			
		p	.01						.04			
2	Percent cocaine negative urine specimens	r	-.31	-.28	-.30	-.16	.33		.33	.29	.25	.22
		p	.00	.00	.00	.01	.00		.00	.00	.00	.00
3	Maximum consecutive days of abstinence	r	-.30	-.24	-.26	-.12	.30		.34	.26	.24	.17
		p	.00	.00	.00	.02	.00		.00	.00	.00	.00
4	Percent days of abstinence	r	-.39	-.37	-.35	-.24	.19		.23	.21	.18	.14
		p	.00	.00	.00	.00	.00		.00	.00	.00	.01
5	Maximum days of consecutive abstinence during participants last two weeks of treatment	r	-.46	-.35	-.30	-.21	.32		.31	.33	.19	.24
		p	.00	.00	.00	.00	.00		.00	.00	.00	.00
6	Number and percent completely abstinent last two weeks of treatment	r	-.30	-.25	-.19		.28		.29	.31	.21	.19
		p	.00	.00	.00		.00		.00	.00	.00	.00
7	Percent attaining 3+ weeks of abstinence	r	-.33	-.30	-.28	-.16	.25		.26	.26	.24	.24
		p	.00	.00	.00	.00	.00		.00	.00	.00	.00
8	Percent attaining 2+ weeks of abstinence	r	-.26	-.26	-.28	-.14	.24		.24	.26	.22	.20
		p	.00	.00	.00	.01	.00		.00	.00	.00	.00
9	Percent attaining 1+ week of abstinence	r	-.27	-.22	-.24	-.10	.11		.21	.17	.15	.17
		p	.00	.00	.00	.05	.02		.00	.00	.00	.00
10	Percent completely abstinent during treatment	r					.23		.28	.17	.14	.19
		p					.00		.00	.00	.00	.00
11	Completed treatment and abstinent in the last week	r	-.30	-.24	-.22		.23		.22	.23	.19	.12
		p	.00	.00	.00		.00		.00	.00	.00	.03
12	Percent reduction in frequency of cocaine use	r	-.32	-.26	-.22		.18		.24	.22	.17	.14
		p	.00	.00	.00		.00		.00	.00	.00	.01
13	Percent attaining 50% reduction	r					-.16					
		p					.00					
14	Percent attaining 75% reduction	r					-.11					
		p					.02					
5	**'Good outcome'-no cocaine use or problems past 28**	r	-.20	-.20	-.15		.29		.37	.28	.24	.21
		p	.00	.00	.00		.00		.00	.00	.00	.00

	Indicator	Sensitivity to disulfiram effects	Sensitivity to behavioral therapies	Relationship with post tx cocaine use	Relationship to measures of general functioning/
1	Days retained in treatment protocol	X			
2	Percent negative cocaine urine specimens		x	x	X
3	Maximum consecutive days abstinent	X		x	X
4	Percent days of abstinence from cocaine	X	x	x	
5	Maximum days of continuous abstinence during last two weeks of treatment*	X		x	x
6	Completely abstinent last two weeks of treatment	X	x	x	x
7	3 or more weeks of continuous abstinence	x	x	x	x
8	2 or more weeks of continuous abstinence		x	x	x
9	1 or more weeks of continuous abstinence				
10	Completely abstinent from cocaine during treatment				
11	Completed treatment and abstinent in last week	x		x	
12	% reduction (28 days prior/days last 4 weeks)			x	
13	50% reduction in cocaine use				
14	75% reduction in cocaine use				
15	“Good outcome” (few/no problems in non-drug ASI areas		x	x	x

Summary, so far

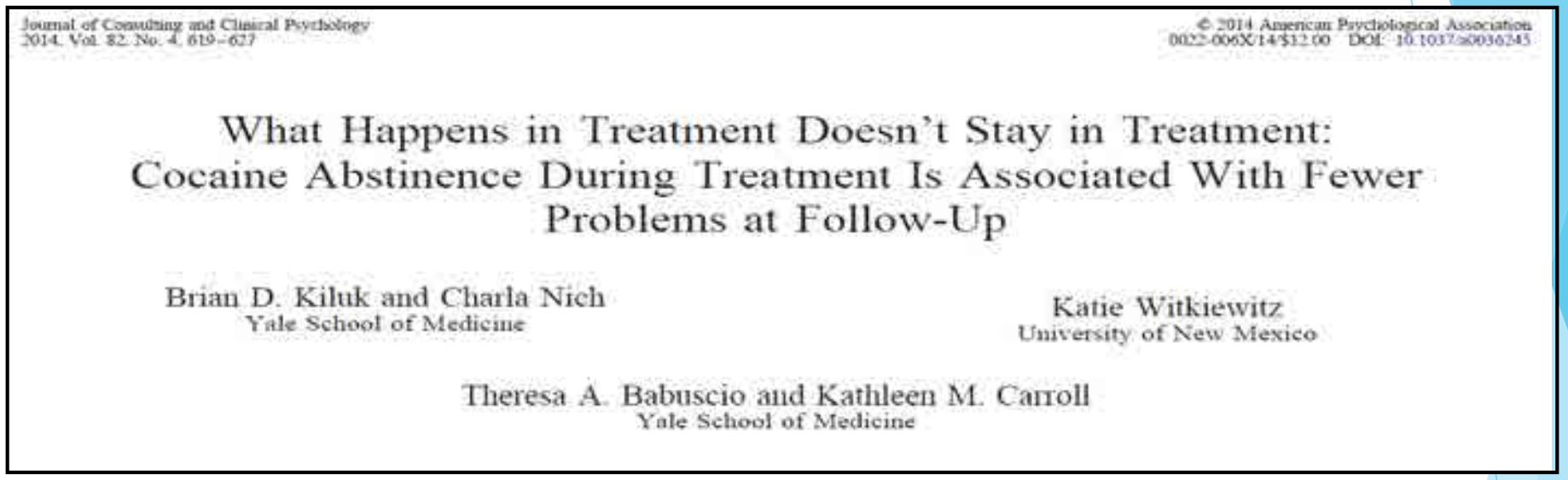
- Existing widely-used continuous measures are consistent predictors of cocaine use and good general functioning in follow up:

  Percent days abstinent, maximum days of consecutive abstinence, percent cocaine-free urine specimens, max days abstinence in last 2 weeks

- Poorer performance for retention, ‘reduction’ measures, as well as ‘complete abstinence during treatment’

- End of treatment abstinence, 3+ weeks abstinence relative good performance, still room for improvement in predicting long term outcome.

Continued Efforts to Identify Clinically Meaningful Outcomes



Journal of Consulting and Clinical Psychology
2014, Vol. 82, No. 4, 619–627

0022-006X/14/$12.00 DOI: 10.1037/a0036743

What Happens in Treatment Doesn't Stay in Treatment: Cocaine Abstinence During Treatment Is Associated With Fewer Problems at Follow-Up

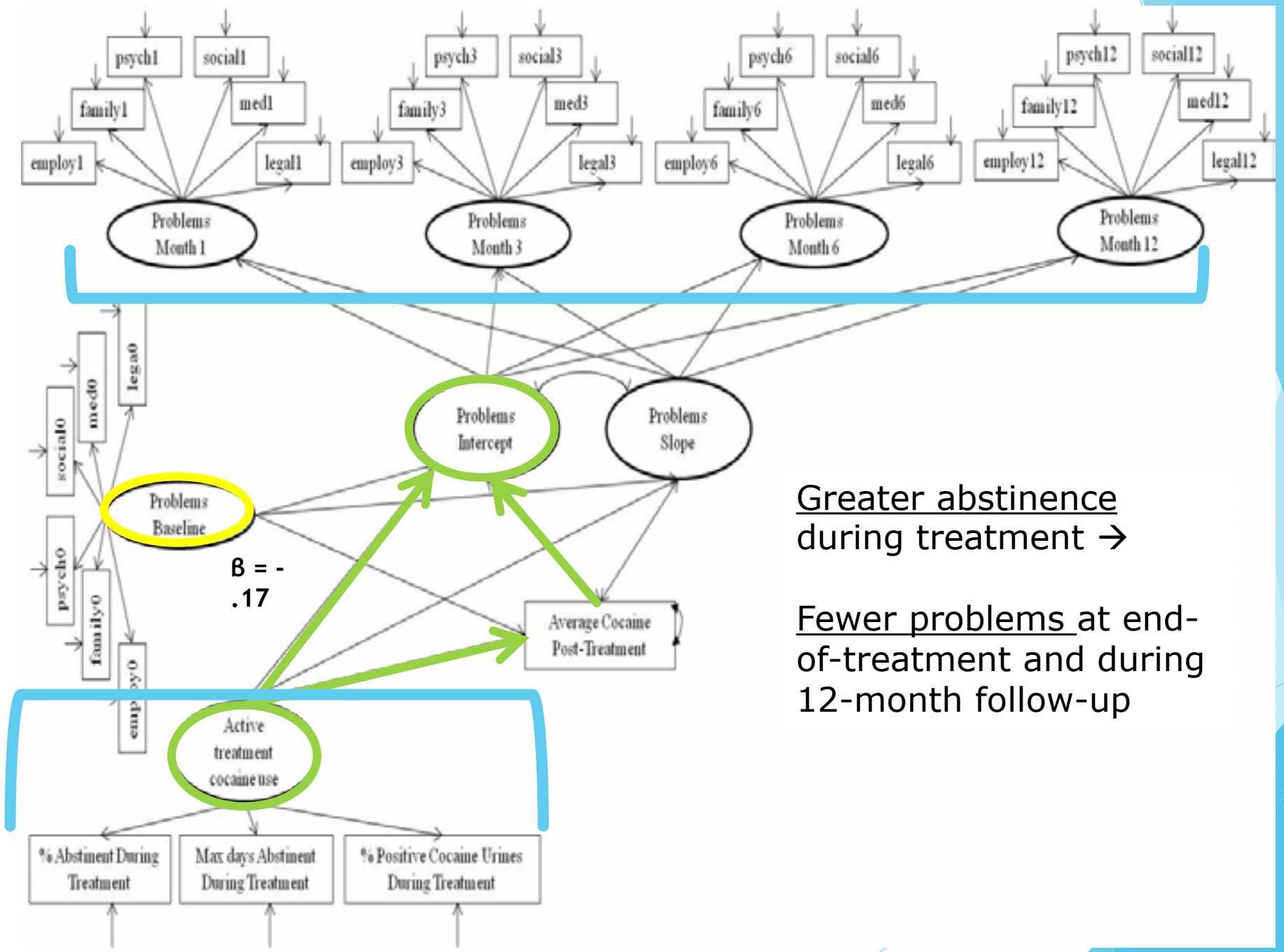
Brian D. Kiluk and Charla Nich
Yale School of Medicine

Katie Witkiewitz
University of New Mexico

Theresa A. Babuscio and Kathleen M. Carroll
Yale School of Medicine

- Pooled data across 5 RCTs (N=434)
- Establish relationship between frequency of cocaine use and long-term 'global problems' (days of problems from ASI)
- Latent growth curve modeling

Kiluk et al., 2014, *JCCP*



Greater abstinence during treatment →

Fewer problems at end-of-treatment and during 12-month follow-up

That’s great, but . . .

- Latent variables difficult to interpret regarding clinical relevance
- When using continuous outcome measure, statistically significant difference in group means could be driven by any number of phenomena
  - Treatment A = 60% days abstinent
  - Treatment B = 40% days abstinent
- What’s clinically meaningful?
- Responder analysis may better illustrate clinically important effect

Start with ‘good outcome’ then evaluate within-treatment cocaine use

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

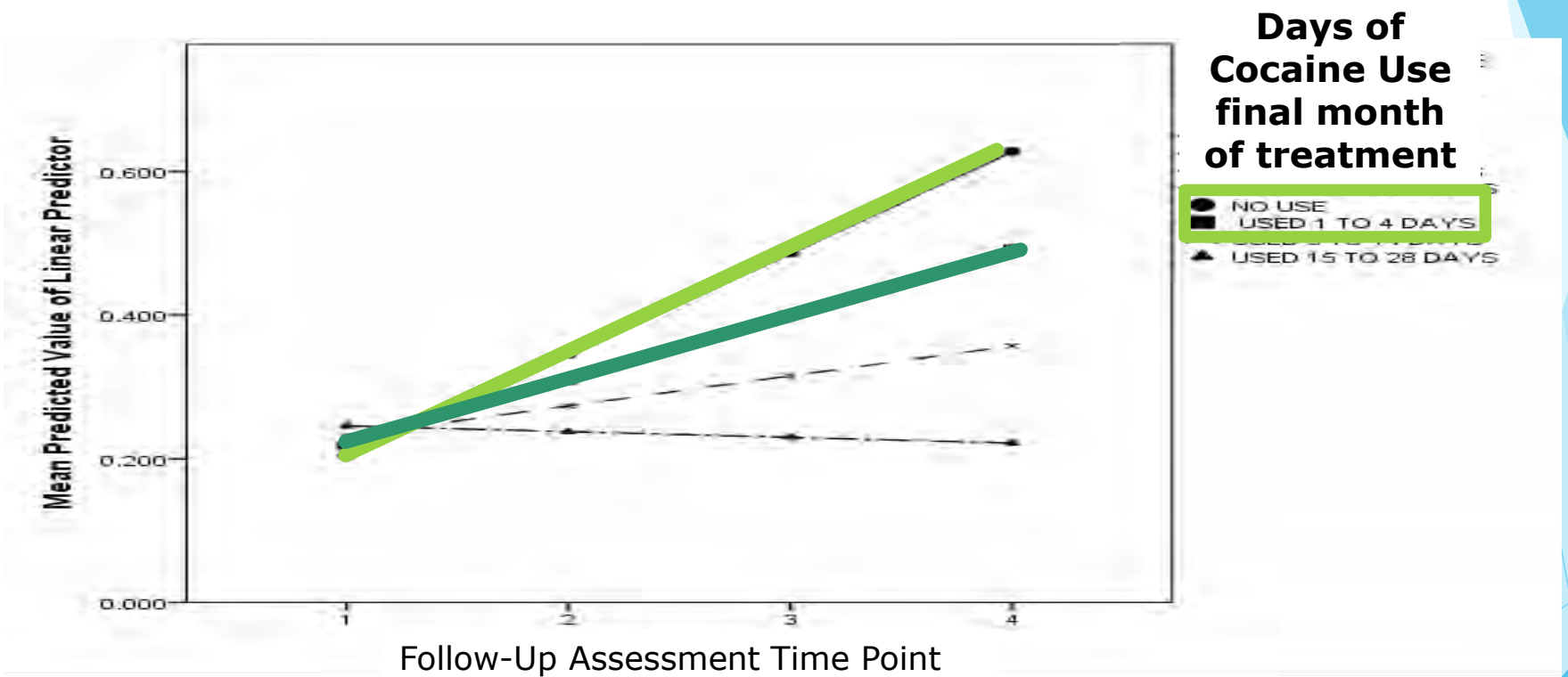
Initial validation of a proxy indicator of functioning as a potential tool for establishing a clinically meaningful cocaine use outcome

Brian D. Kiluk*, Theresa A. Babuscio, Charla Nich, Kathleen M. Carroll

Yale University School of Medicine, New Haven, CT, 06510, USA

- Data pooled across 7 RCTs (N = 718)
- ‘Problem Free Functioning’ (PFF)—absence of physical, psychological, other psychosocial problems
  - Operationalized as 0 days of problems reported across medical, legal, employment, family/social, psychological areas of ASI

Probability of Achieving Problem-Free Functioning During Follow-up Based on Days of Cocaine Use at End of Treatment



Drug and Alcohol Dependence 205 (2019) 107648

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Clinical validation of reduction in cocaine frequency level as an endpoint in clinical trials for cocaine use disorder

Corey R. Roos[a,*], Charla Nich[a], Chung Jung Mun[b], Theresa A. Babuscio[a], Justin Mendonca[a], André Q.C. Miguel[c,d], Elise E. DeVito[a], Sarah W. Yip[a], Katie Witkiewitz[e], Kathleen M. Carroll[a], Brian D. Kiluk[a]

- 3 frequency levels at baseline and end of treatment
  - Abstinence
  - Low frequency (1-4 days/month)
  - High frequency (>5 days month)
- 40% have at least one level reduction at end of treatment
- 1-level reduction (compared with no change) associated with reduced cocaine use during follow-up plus improvements in psychological, legal, employment functioning

Journal of Substance Abuse Treatment 106 (2019) 89–96

Contents lists available at ScienceDirect

Journal of Substance Abuse Treatment

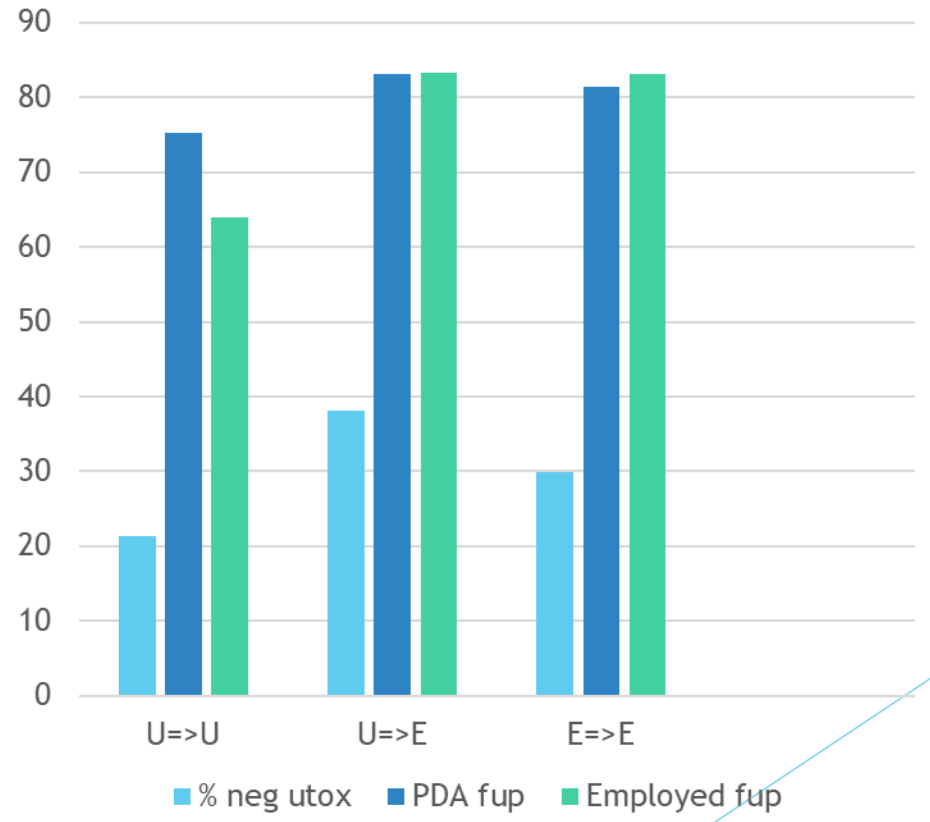
journal homepage: www.elsevier.com/locate/jsat

Change in employment status and cocaine use treatment outcomes: A secondary analysis across six clinical trials

André Q.C. Miguel[a,b,c,*], Brian D. Kiluk[b], Corey R. Roos[b], Theresa A. Babuscio[b], Charla Nich[b], Jair J. Mari[c], Kathleen M. Carroll[b]

Practical indicator-employment status

- Baseline employment status does not predict cocaine use outcomes, BUT
- *Moving from unemployed to employed* by end of treatment strongly associated with better cocaine use and general functioning outcomes



Work in progress: Is there a cut-off level of utox screens that is associated with good functioning posttreatment?

Rationale:

- 75% a conservative estimate based on reliable change index and consistent with indices used in previous health system evaluation studies (Marsden et al., 2009)
- Clinicians indicate 50% reduction as clinically meaningful (Miller & Manual, 2008)
- Allows for a potential “slip” or small number of cocaine positive urines during treatment
- Indicates some extended periods of abstinence

>75% cocaine-negative urine definition:

- Dichotomous (YES / NO)
- Must have submitted at least 3 samples (if <3 then “NO”)
- Sample submitted within first 3 days of treatment excluded (i.e., potential carryover from baseline cocaine use)

Cocaine Use Treatment Outcome Differences

YALE (N = 718)

	NO N = 604		YES N = 114			
	mean	sd	mean	sd	F	p
Days retained in treatment protocol	**50**	32.6	**64.6**	24.2	**20.58**	**<.01**
Percentage of cocaine positive urine specimens	**81**	26.3	**6.2**	8	**904.8**	**<.01**
Maximum consecutive days abstinent	**12.7**	14.5	**51.4**	25	**497.8**	**<.01**
Percent days of abstinence from cocaine	**66.5**	26.2	**96.6**	6.7	**144.5**	**<.01**
Maximum days of continuous abstinence during last two weeks of treatment	**5.1**	4.7	**12.6**	3.1	**192.4**	**<.01**
% reduction (28 days prior/days last 4 weeks)	**44**	0.36	**85**	0.3	**102.4**	**<.01**

UCONN (N = 416)

	NO N = 162		YES N = 254			
	mean	sd	mean	sd	F	p
Days retained in treatment protocol	X					
Percentage of cocaine positive urine specimens	**58.1**	32.9	**5.0**	7.6	**614.4**	**<.01**
Maximum consecutive days abstinent	**65.2**	20.3	**79**	11.6	**76.9**	**<.01**
Percent days of abstinence from cocaine	**79.8**	22.5	**96.1**	8.7	**79.1**	**<.01**
Maximum days of continuous abstinence during last two weeks of treatment	X					
% reduction (28 days prior/days last 4 weeks)	X					

Differences at Follow-up

YALE (N = 643)

	No		Yes			
	n	%	n	%	X2	p
Totally abstinent in FU time period	49	**9**	34	**33.7**	**45.9**	**<.01**
Problem-Free at 1 month	50	**9.3**	35	**35.4**	**48.96**	**<.01**
Problem-Free at 3 months	64	**12**	34	**34.3**	**32.02**	**<.01**
Problem-Free at 6 months	74	**14**	30	**31.6**	**18.02**	**<.01**
Problem-Free at 12 months	50	**17.6**	25	**34.7**	**10.12**	**<.01**

Chan indic

Alcoholism: Clinical and Experimental Research
Vol. 42, No. 8
August 2018

Change in DSM-5 Alcohol Use Disorder Criteria Count and Severity Level as a Treatment Outcome Indicator: Results from a Randomized Trial

Brian D. Kiluk, Tami L. Frankforter, Michelle Cusumano, Charla Nich, and Kathleen M. Carroll

- N=68 individuals with AUD
- DSM-5 SCID at pre-treatment, end of treatment, 6 month follow-up (past 30 days)
- Symptom count (1-11) and severity level (2-3-mild; 4-5 moderate, >6 severe.
- Baseline count associated with AUDIT, chronicity, SIP but NOT frequency of alcohol use
- Mean count goes from 6.1 to 2.6 (EOT), to 2.0 (follow-up)
- Reduction in count/severity strongly related to follow-up outcomes

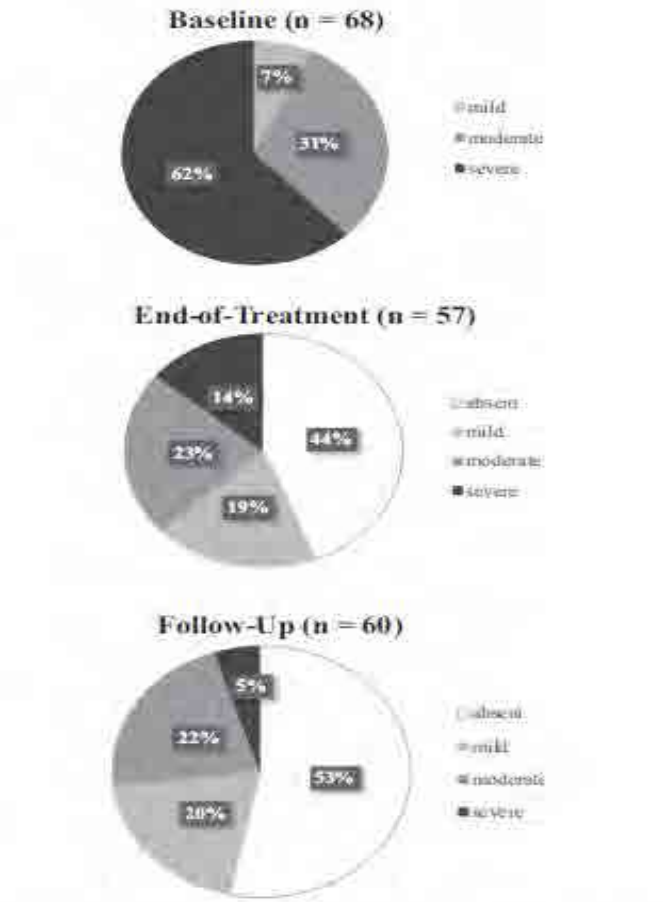
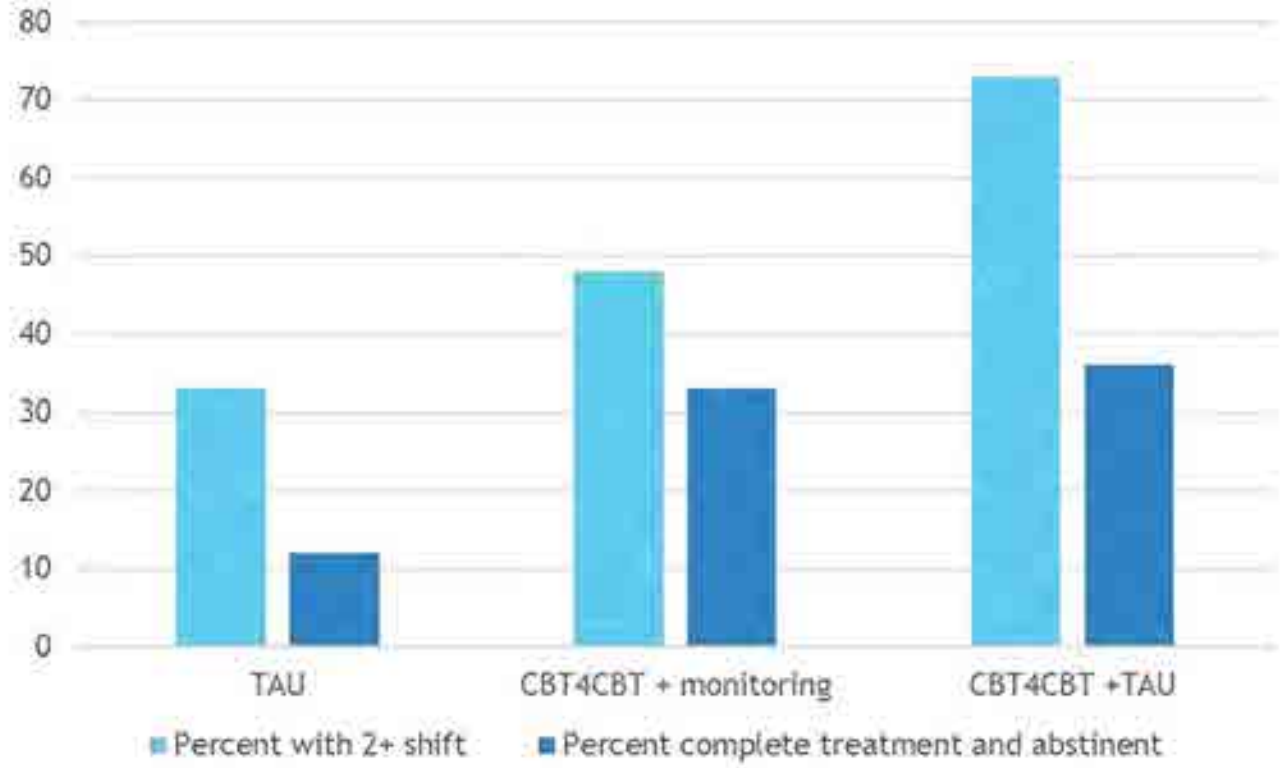


Fig. 1. Percentage of participants in each AUD severity category at each time point.

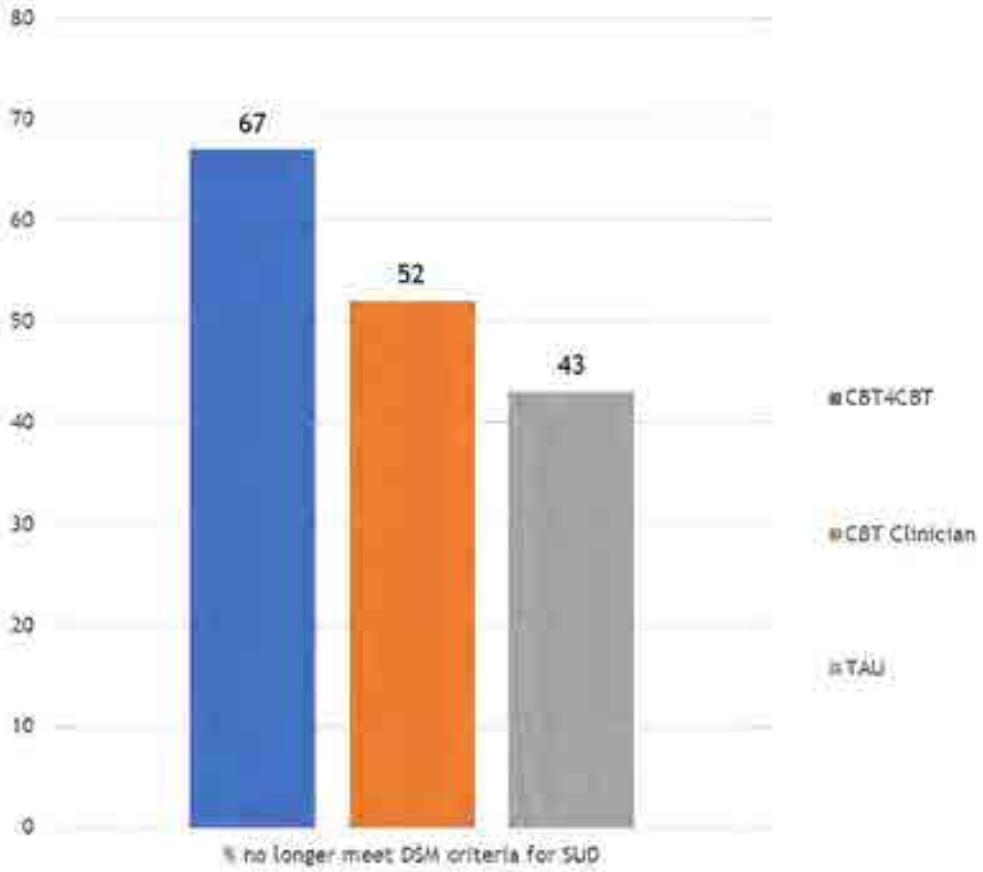
DSM criteria as outcome indicator, treatment effects

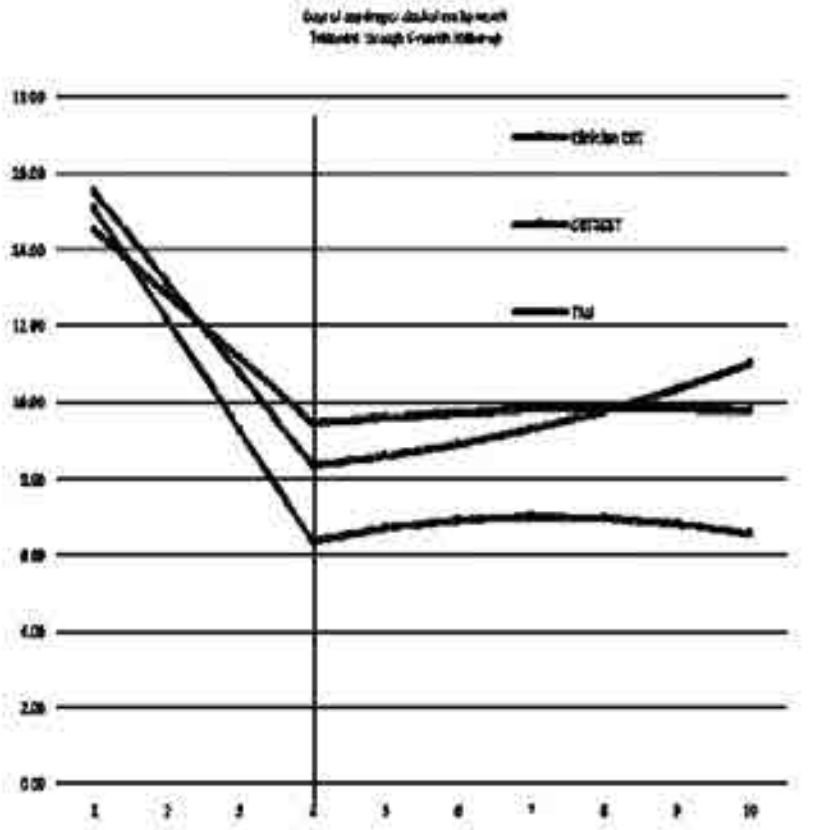


Kiluk et al., ACER, 2018

137 individuals with any current DSM-IV* substance use disorder at baseline, RCT of TAU versus clinician CBT versus computer CBT, Kiluk et al. 2018, Am J Psychiatry

% who no longer met criteria for dependence at end of treatment





Ongoing CUD study
N=99, follow-up phase

- Maintain blind, so no treatment effects presented
- DSM 5 symptom counts go from 8.0 (SD=2.3) to 3.2 (SD=2.9)
- End of *treatment* criteria CUD counts highly correlated with days of cocaine use in final month (r=.79)
- Of those who have completed treatment, 75% have one-level reduction, 51% have 2-level reduction.
- Those with 2 level reduction have significantly less cocaine use, improved general functioning during follow-up

Conclusions

- Utility of large pooled datasets for evaluating outcome indicators
- Continuous measures, end of treatment abstinence, are associated with long-term cocaine use and functioning
- Promising candidates linking cocaine use to functioning
  - Shifting to infrequent use
  - ≥ 75% cocaine negative urine samples
  - DSM criteria (reduction in symptom count, shift in severity)
- Ongoing work / Future directions
  - Sensitivity to treatment effects
  - Pending proposal to develop new measure based on DSM criteria (Kiluk/Hasin)

THANK YOU, and…

- NIDA R21/33 DA041661
- NIDA R01DA030369-04S1
- *P50 DA09241*
- Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION)

- Collaborators & Co-authors
  - Brian Kiluk, Ph.D.
  - Charla Nich, M.S.
  - Theresa Babuscio, M.A.
  - Corey Roos, Ph.D.
  - Katie Witkiewitz, Ph.D. (UNM)
  - Nancy Petry, Ph.D. (UCONN)
  - Carla Rash, Ph.D. (UCONN)

Session III: Assessing Clinical Endpoints and Methods for Data Collection

Break

Session IV: Current Treatment Paradigms

CURRENT TREATMENT PARADIGMS FOR STIMULANT USE DISORDER

Kelly J. Clark, MD, MBA, DFASAM, DFAPA
FDA/ Duke Margolis Center
December 16, 2019

ASAM American Society of Addiction Medicine

Disclosures: Kelly J. Clark, MD, MBA

- President, Addiction Crisis Solutions
- Director, DisposeRx
- Clinical Advisor, Path CCM

Definitions of Terms

- Use: taking a substance for a desired purpose
- Misuse: the use of a medication for a purpose or in a way other than as prescribed

Physical Dependence Not Addiction

- Substance Use Disorder (SUD): severe stage is "Addiction". Mild stage is NOT addiction

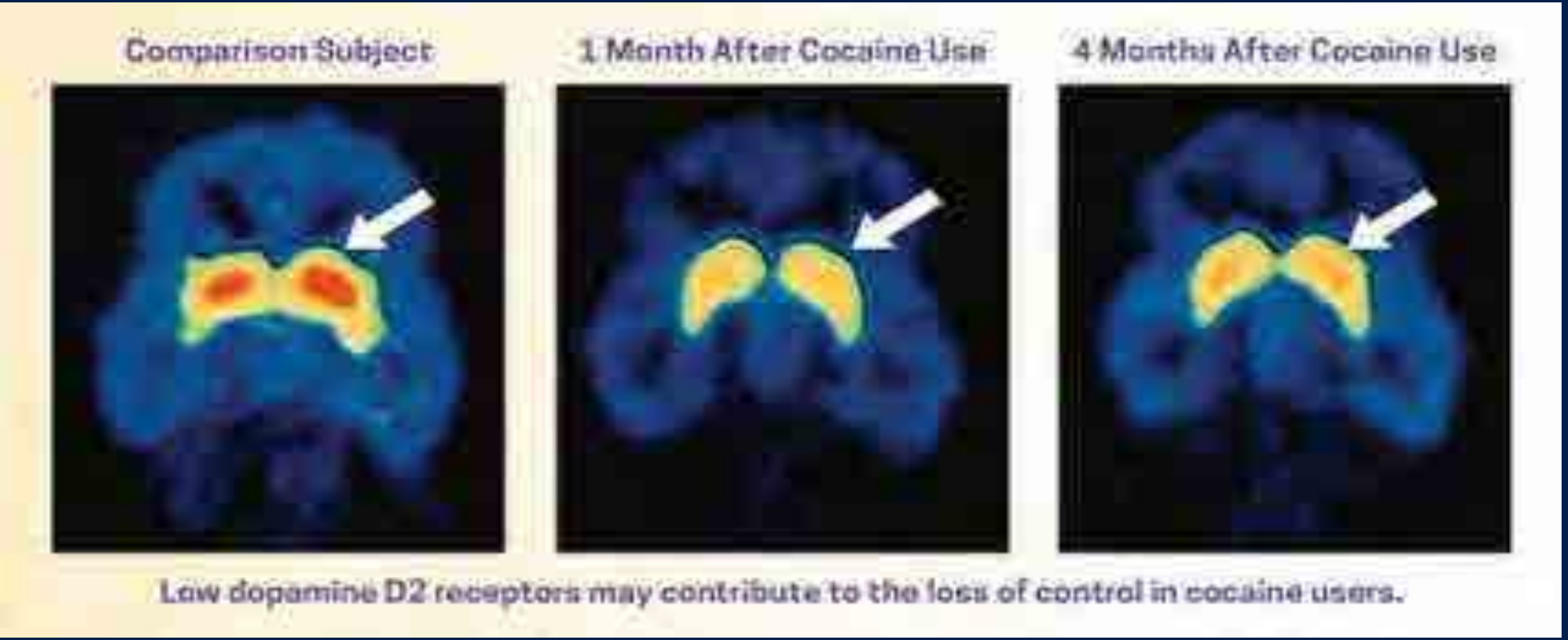
- Drug Addiction: a chronic brain disease which looks like a person who is:
  - loosing control of their drug use
  - loosing control of their lives because of that drug use

Remission vs. Recovery

- Remission is a lack of active signs or symptoms of a chronic disease
- Recovery is the process by which a person lives their best life and manages their chronic conditions

Remission is the medical goal
Recovery is the whole-person goal

Addiction: A Chronic Brain Disease



- N. Volkow

Addiction: A Chronic Brain Disease

"CHRONIC"

Requires a holistic approach to helping people manage their illness

"BRAIN"

People must fight stigma and moral blaming

"DISEASE"

Medical approach can be effectively used for treatment

Addiction: A Chronic Brain Disease

"CHRONIC"

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People must fight stigma and moral blaming

"DISEASE"

Medical approach can be effectively used for treatment

Desired Outcomes of treating any chronic disease:

- Decreased disease related morbidity and mortality; decreased total cost of care,and increase functioning

- Stay Alive! Become and stay healthy, stay out of hospital, and get back to work

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Implications of Addiction as a CBD

- Physicians are involved in care
- Medical care is not based in spirituality or philosophy
- The medical and scientific evidence base is the core of best practices
- Longitudinal, individualized, bio-psycho-social treatment plan
- Quality standards are needed
- Payment using health care dollars is needed, and needed at parity

How to Treat Chronic Disease:

- **Individualized treatment plan based upon structured best practices**

- Right **Provider** (physician, nurse, therapists, pharmacist)
- Right **Treatment Modality** (biological, psychological, social)
- Right **Place** (inpatient, outpatient)
- Right '**Dose**' – frequency and intensity of care (levels of inpatient and outpatient care)

- As needed at a specific point in time during the course of their disease
- For as long as necessary

Treating a Disease

- Evaluation by appropriate clinician
- Establish a Working Diagnosis
- Establish with Patient an Evidence Based Treatment Plan
- Deploy the Resources Needed and Work the Treatment Plan

- Repeat

THE US LACKS ADEQUATE INFRASTRUCTURE CAPACITY TO TREAT THE POPULATION WITH ADDICTION AT ALL STAGES

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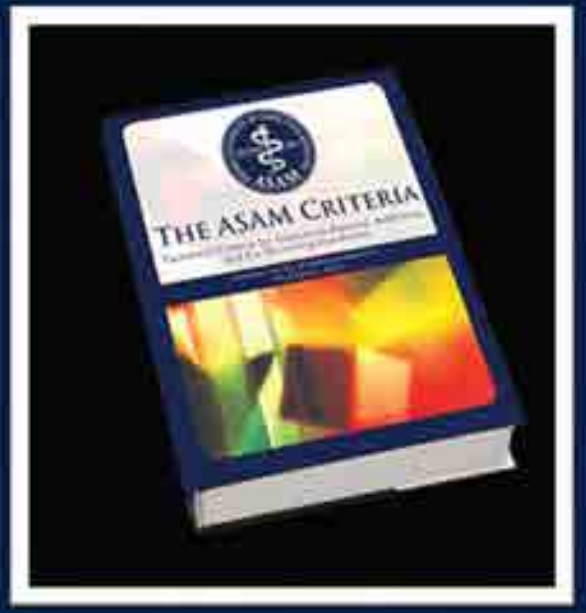
The ASAM Criteria

- Multidimensional patient assessment tool
- Used to match patients to the appropriate level of care (LOC) based on disease severity
- Establishes Universal standards



ASAM CO-Triage®: Provisional Assessment

For *provisional* SUD referral, in conjunction with clinical judgement

- ~20 Questions, based on CONTINUUM
- Quickly direct patients to ASAM Level(s)
- In-person OR by phone – 6 min.

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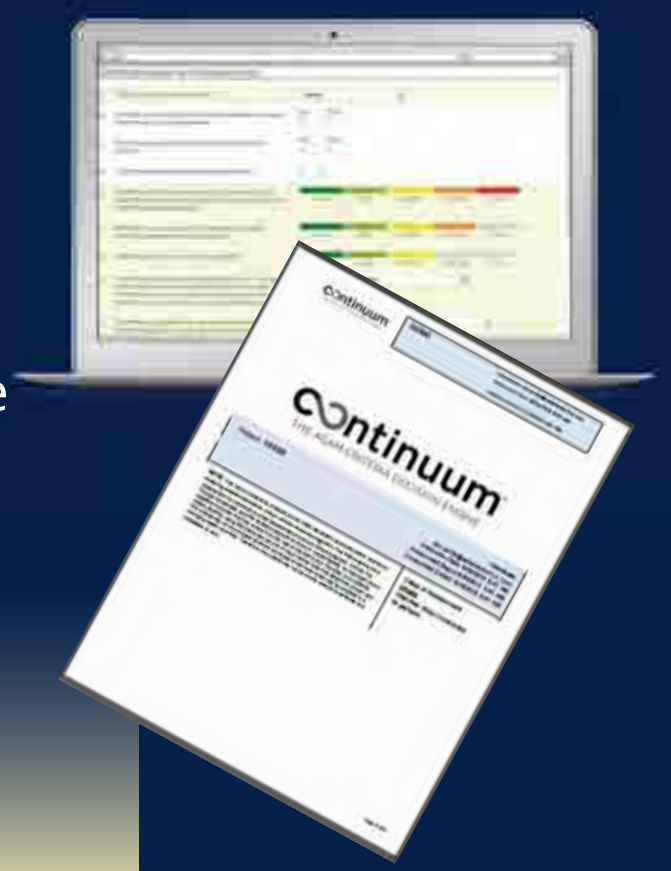
CONTINUUM™

CONTINUUM™ provides:

- DSM-5 Substance Use Disorders: Diagnoses & Criteria
- CIWA-Ar & CINA withdrawal scores (alcohol/BZs, opioids)
- Addiction Severity Index (ASI) Composite Scores
- Imminent Risk Considerations
- Access & Support Needs/Capabilities
- ASAM Level of Care recommendations



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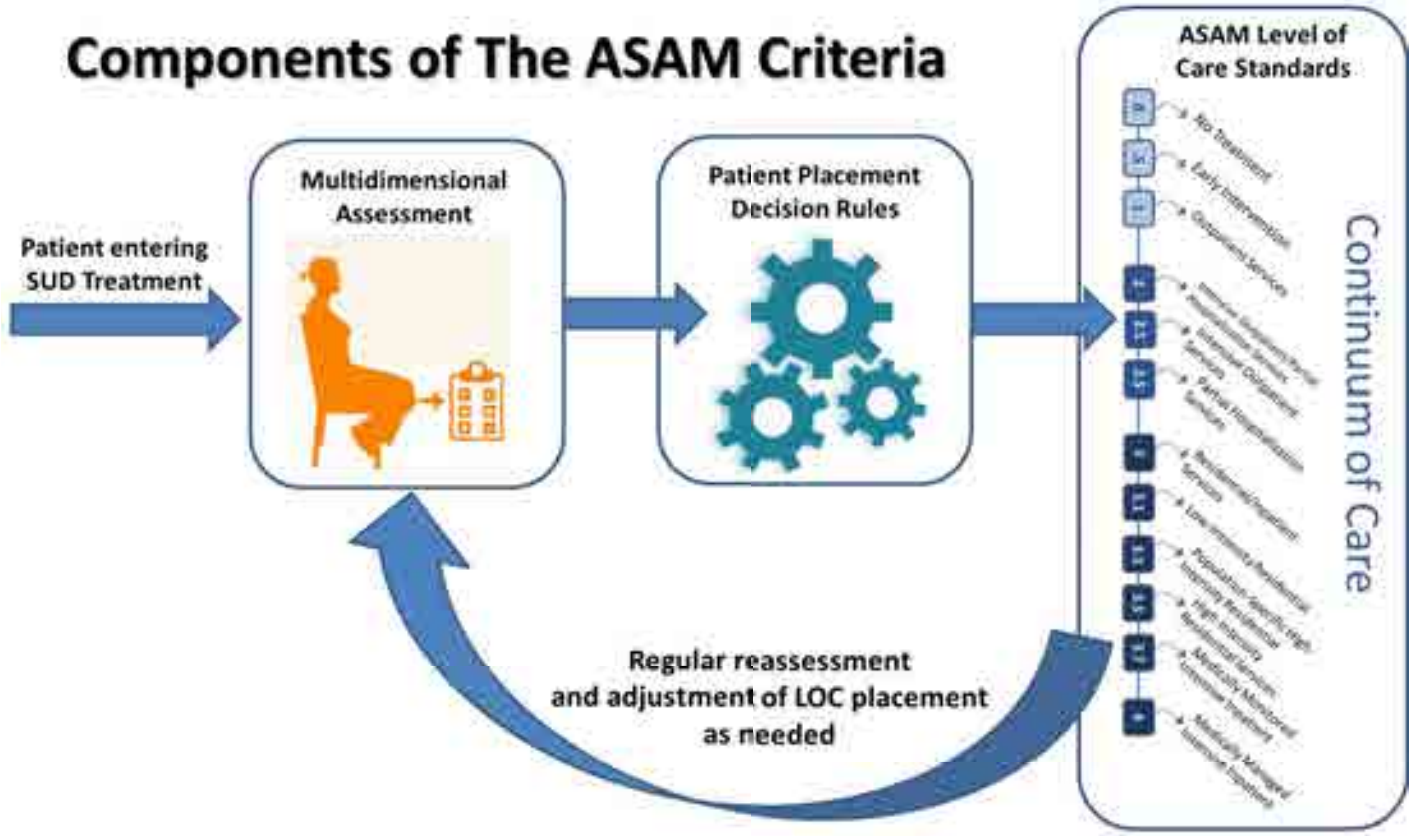
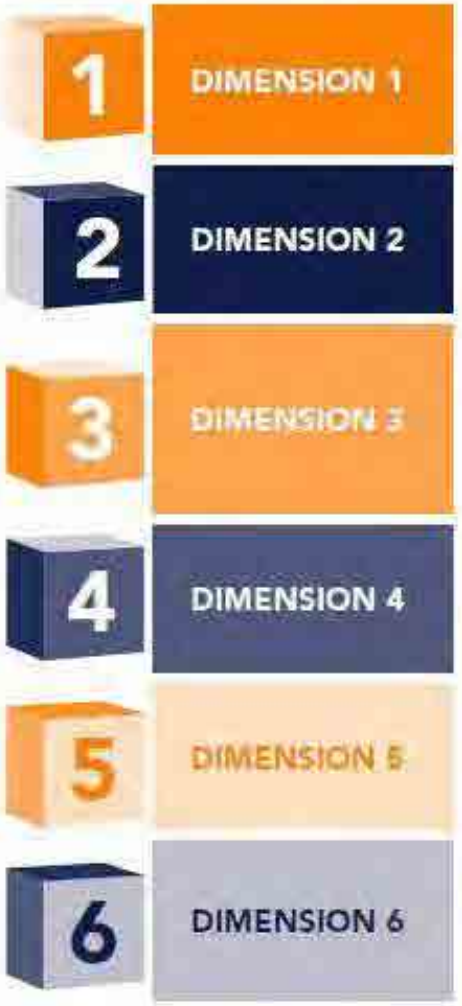
Implementation of The ASAM Criteria

Implementation of The ASAM Criteria can improve the addiction treatment system, but only if it is **<u>implemented comprehensively and effectively</u>**



AT A GLANCE: THE SIX DIMENSIONS OF MULTIDIMENSIONAL ASSESSMENT

ASAM's criteria uses six dimensions to create a holistic, biopsychosocial assessment of an individual to be used for service planning and treatment across all services and levels of care. The six dimensions are:



Acute Intoxication and/or Withdrawal Potential

Exploring an individual's past and current experiences of substance use and withdrawal

Biomedical Conditions and Complications

Exploring an individual's health history and current physical condition

Emotional, Behavioral, or Cognitive Conditions and Complications

Exploring an individual's thoughts, emotions, and mental health issues

Readiness to Change

Exploring an individual's readiness and interest in changing

Relapse, Continued Use, or Continued Problem Potential

Exploring an individual's unique relationship with relapse or continued use or problems

Recovery/Living Environment

Exploring an individual's recovery or living situation, and the surrounding people, places, and things

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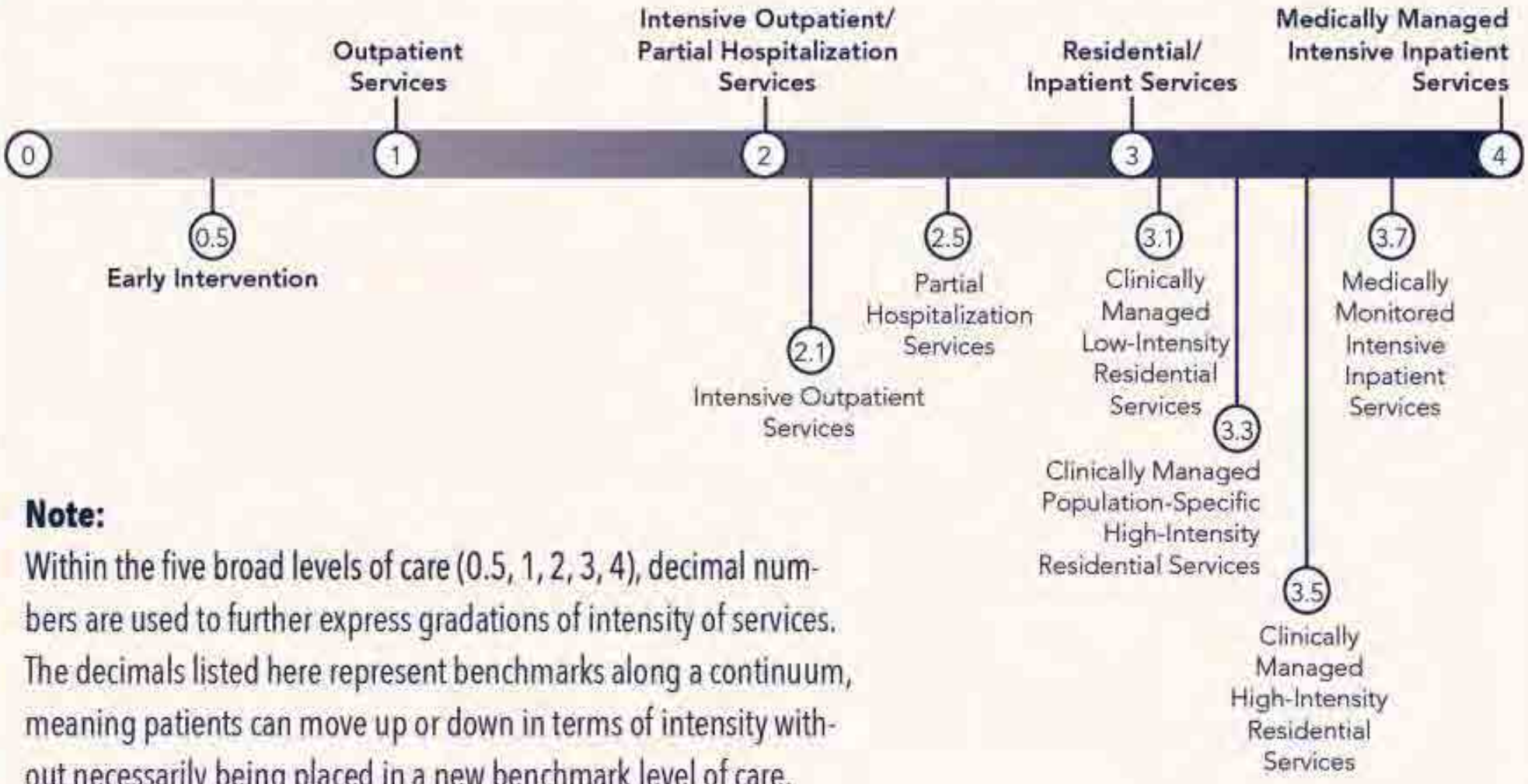
REFLECTING A CONTINUUM OF CARE



Note:

Within the five broad levels of care (0.5, 1, 2, 3, 4), decimal numbers are used to further express gradations of intensity of services. The decimals listed here represent benchmarks along a continuum, meaning patients can move up or down in terms of intensity without necessarily being placed in a new benchmark level of care.

Ok, so you've determined the "Dose" of Care…

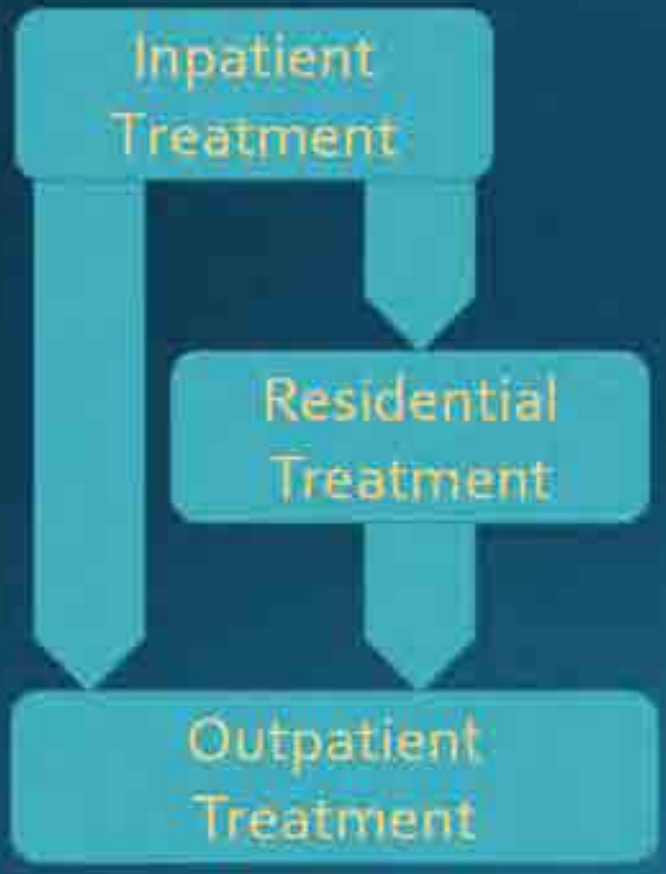
- There is currently NO WAY to know whether a treatment program even has the capability to deliver that care!!
- Programs licensed by state – no consistent criteria
  - One state even made their own "ASAM Level" and built it into regulations
- Data on use of Medication for Addiction Treatment in opioid addiction indicate most treatment programs do not offer minimal, baseline evidence based treatment

ASAM CRITERIA DEFINE FOR EACH LOC:

- Staffing (type, number)
- Assessment and treatment planning process
- Hours and types of modalities of care delivered (individual, group, medication, care coordination, etc)

- ASAM and CARF partnered to develop the ASAM Level of Care certification program
  - Beginning with residential programs; Levels of Care 3.1, 3.5, and 3.7
  - Provide patients and families, and other stakeholders with confidence that a program has the capacity to provide the appropriate level of care

Current treatment framework for PSUD



- Medical/psychiatric stabilization – "detox"
- Short-term medication use
- No effect on drug use, high relapse rates

- Drug rehab or TC model
- Only psychosocial interventions, high cost
- Large decrease of use, but high relapse rates

- Psychosocial-only, "abstinence-based"
- Low cost
- Small reductions of use

Adam Bisaga, MD. 2019 ISAM conference, Delhi, India

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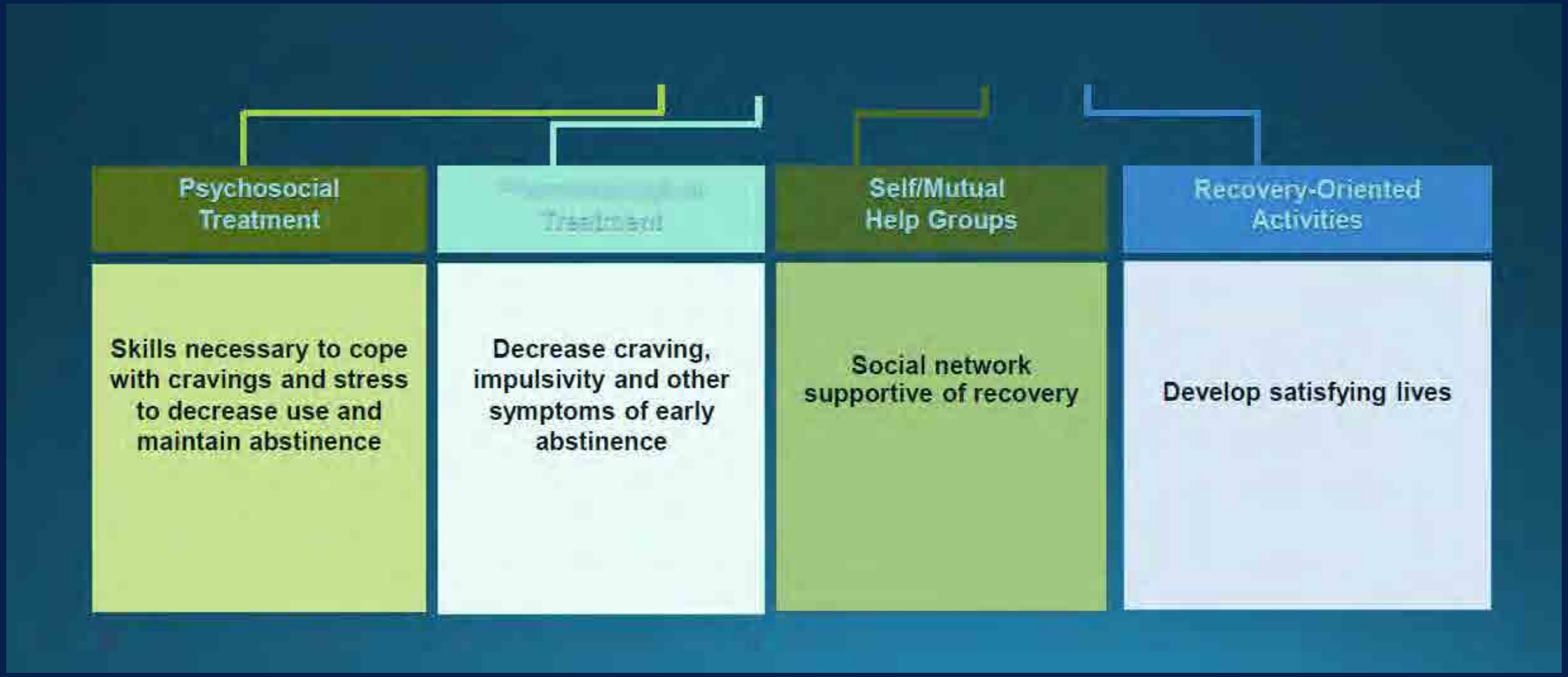
Current Modalities of Care (Stimulant)



Adam Bisaga,, MD> 019 ISAM conference, Delhi, India

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Psychosocial Treatment Modalities

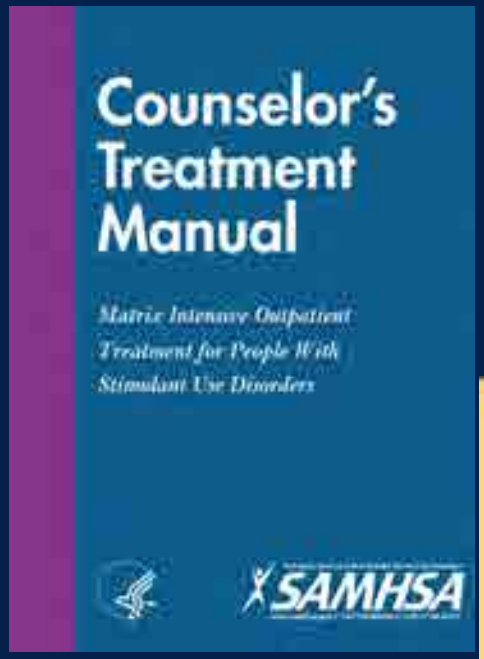
- The Matrix Model
- Contingency Management (CM)
  - motivational incentives

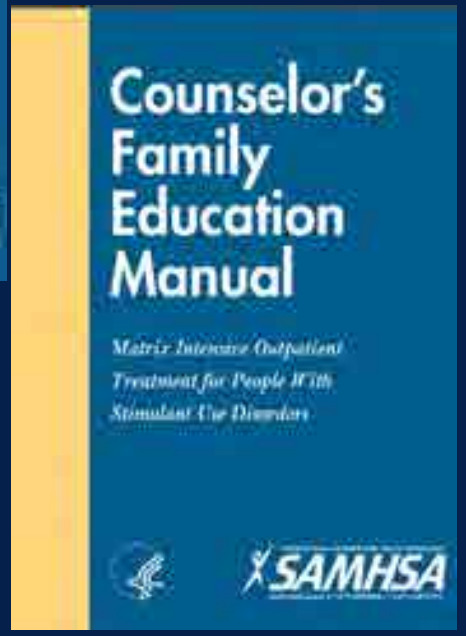
- Cognitive-behavioral therapy (CBT)
- 12-Step facilitation therapy
- Mobile medical application: reSET®

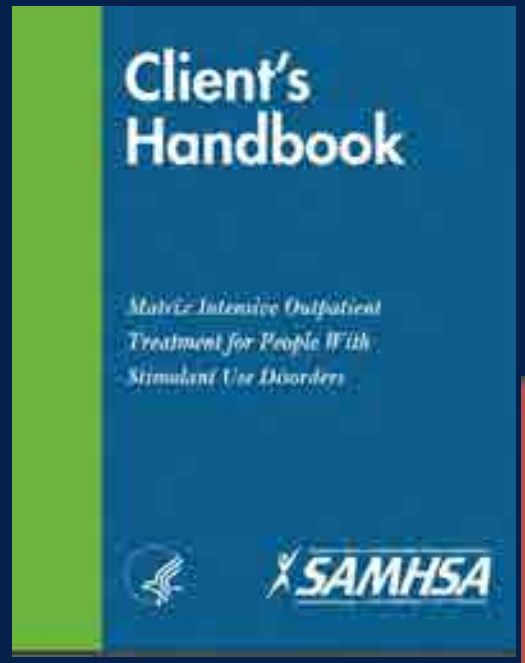
Matrix Model

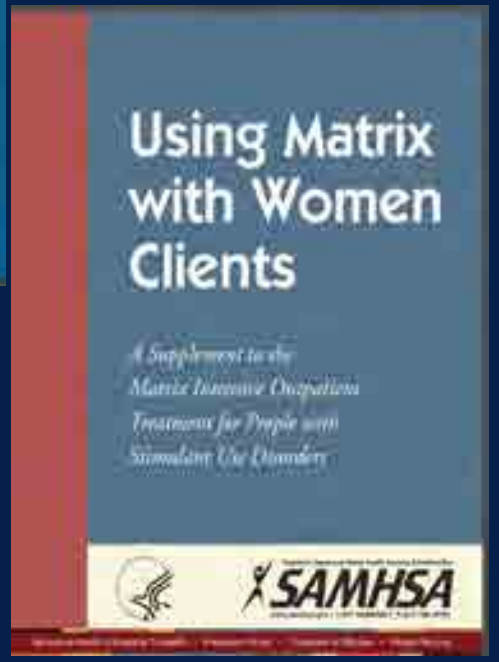
- 16 week Manualized outpatient treatment
  - CBT (36 sessions)
  - Family education (12 sessions)
  - Individual counseling (4 sessions)\
  - 12-step facilitation (4 sessions)
  - Drug Testing

Help in Developing and Running Program









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State of the Data: Matrix Approach

- Significantly better retention in treatment than TAU
- Significantly more methamphetamine negative drug test during the treatment
- In-treatment superiority of Matrix approach was not maintained after treatment

(R.Rawson et al. Addiction 2004)

Diagnosis and then……

- Lack of Infrastructure / Capacity of Evidence Based treatment
- Few Matrix Programs actually being offered throughout the US
- Matrix-type programs can be utilized as a TAU in the treatment of ANY drug of abuse within treatment programs….this is rarely done

Cochrane Review (2016)

- The most studied and promising psychosocial approach: Contingency Management

- Compared to TAU, any psychosocial treatment may improve adherence but may not improve abstinence after treatment.

A comparison of CM and CBT approaches for stimulant dependent individuals

- During the Study period:
  - CM Group had better retention
  - CM Group had better rates of stimulant use

- Longer term results after treatment (study went 1 year out)
  - CM and CBT had comparable outcomes
  - No evidence of additive effects when both approaches used together

Throwing in the Kitchen Sink can be a waste of resources
Treating a Chronic Brain Disease with an Acute Model does NOT Produce Long-Term Efficacy

R.Rawson MD, Addiction. 2006)

Regulatory Issues with CM

- OIG has a open-comment period on CM
- OIG current proposal would allow a Safe Harbor protection from Anti-Kickback statute for "patient engagement tools and supports" – but OIG has proposed to exclude cash, git cards and other cash equivalents

- IT IS CASH , GIFT CARDS AND CASH EQUIVALENTS THAT WORK!

- OIC would like comment on allowing, for example, a $25 check, or gift cards.
-
- https://www.federalregister.gov/documents/2019/10/17/2019-22027/medicare-and-state-healthcare-programs-fraud-and-abuse-revisions-to-safe-harbors-under-the

Shameless Plug

- ASAM has developed Standards of Care, Quality Metrics, Practice Guidelines on Medication Treatment of Opioid Addiction, and is completing a Practice Guideline for Alcohol Withdrawal Management.

- The development of a Practice Guideline for the Treatment of Psychostimulant Use Disorder is a potential topic for ASAM's next topic. If this does emerge as the next topic, ASAM would welcome support from FDA or other federal stakeholders to develop the document.

Bottom Line

- Lack of infrastructure - treatment workforce and programs
- Lack of providers adhering to evidence-based care
- Lack of requirements for use of Evidence based care
  - Medication for opioid, alcohol, and nicotine addiction\
  - Proven Matrix and CM approaches
  - Lack of licensing and certification requirement
  - Lack of health plan requirements

Even if we have a medication: Prescribers and Patients and Treatment Programs are not using them

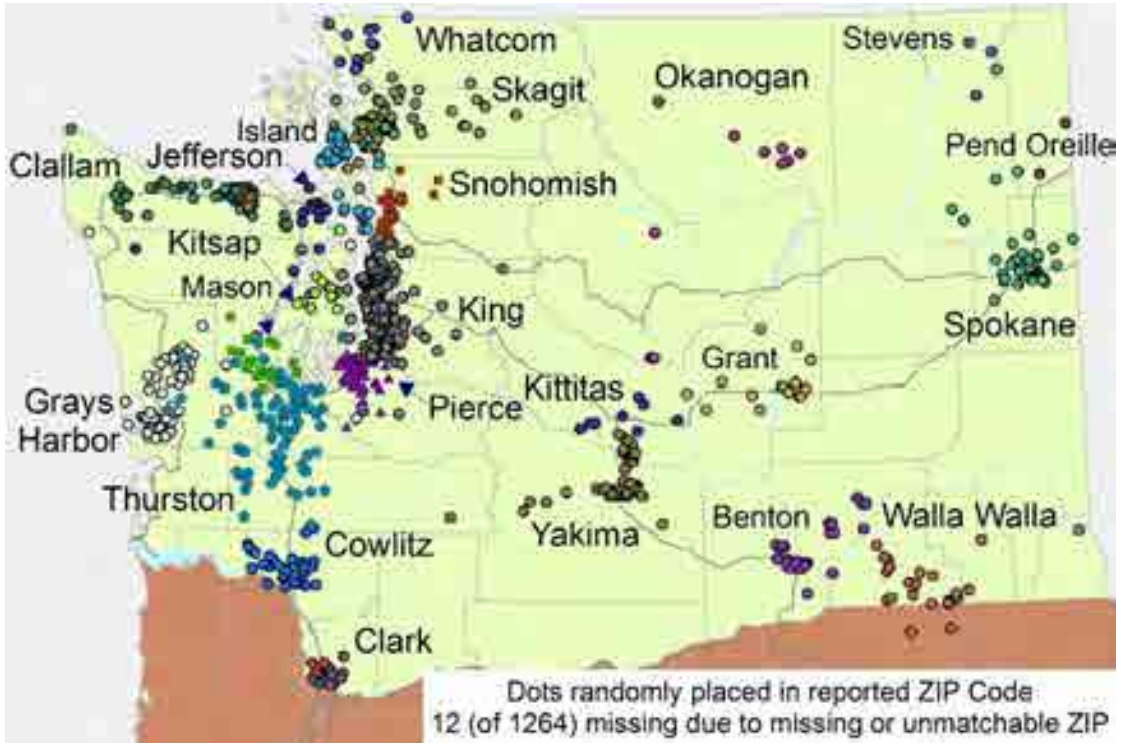
Gratitude

Thanks to Dr. Margaret Jarvis for use of some slide components

ASAM American Society of Addiction Medicine

Session IV: Current Treatment Paradigms

WA Syringe Services Program Survey 2019

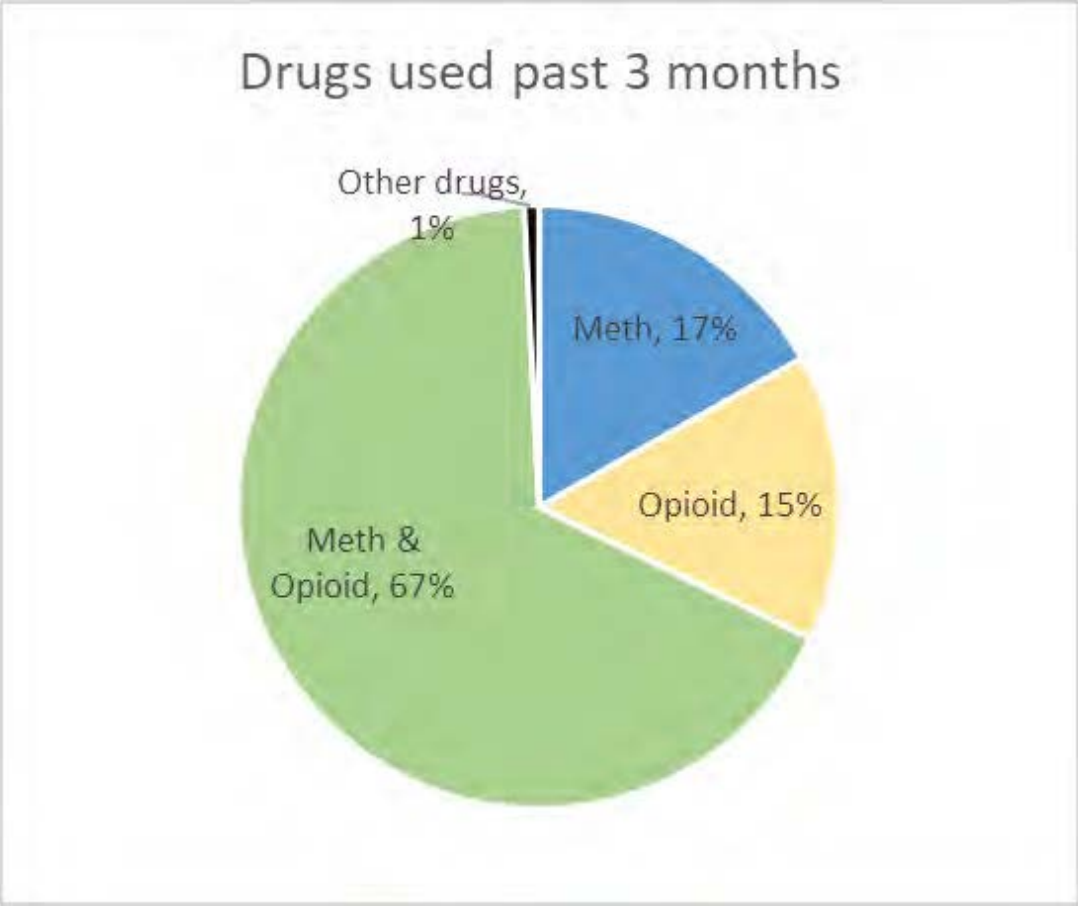


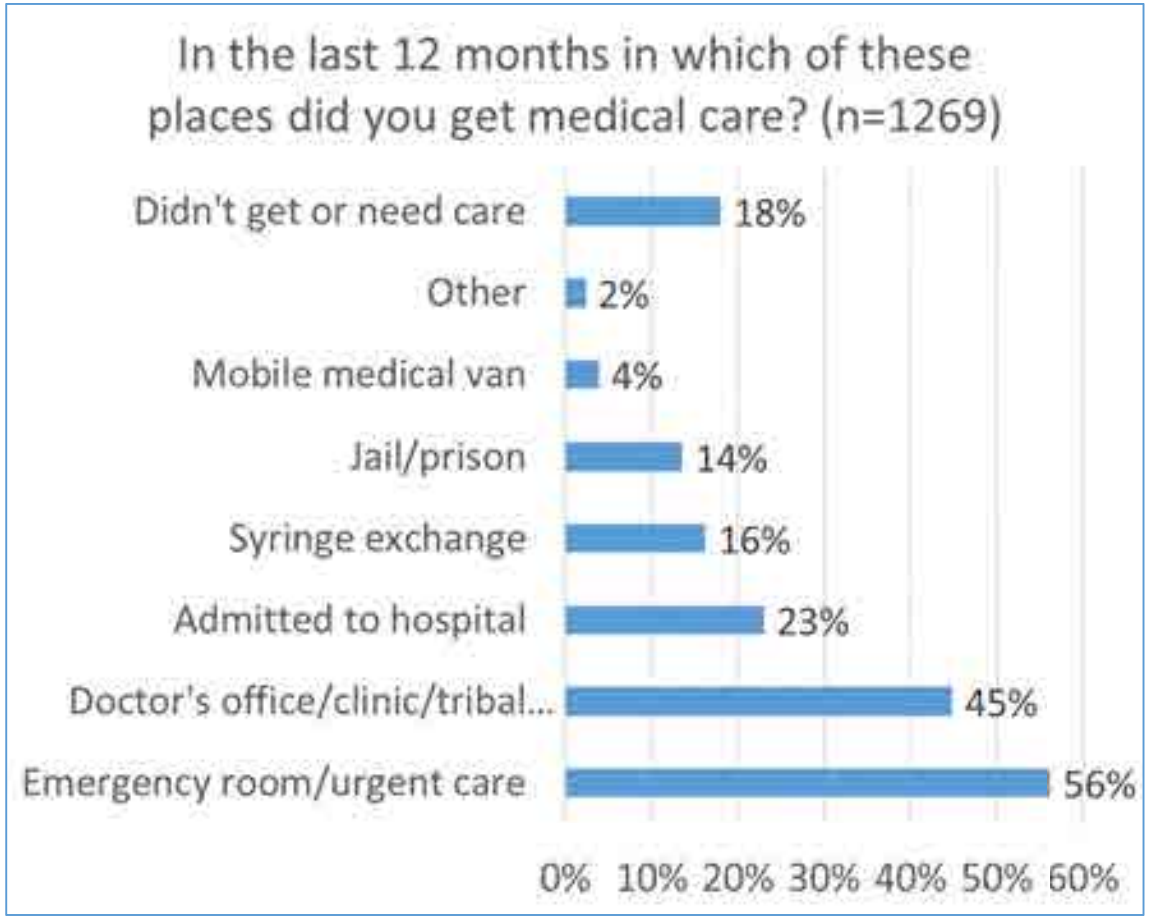
Caleb-Banta Green, Susan Kingston, Alison Newman, Sara Glick

UNIVERSITY of WASHINGTON
ADAI Alcohol & Drug Abuse Institute

Unpublished data, please do not distribute

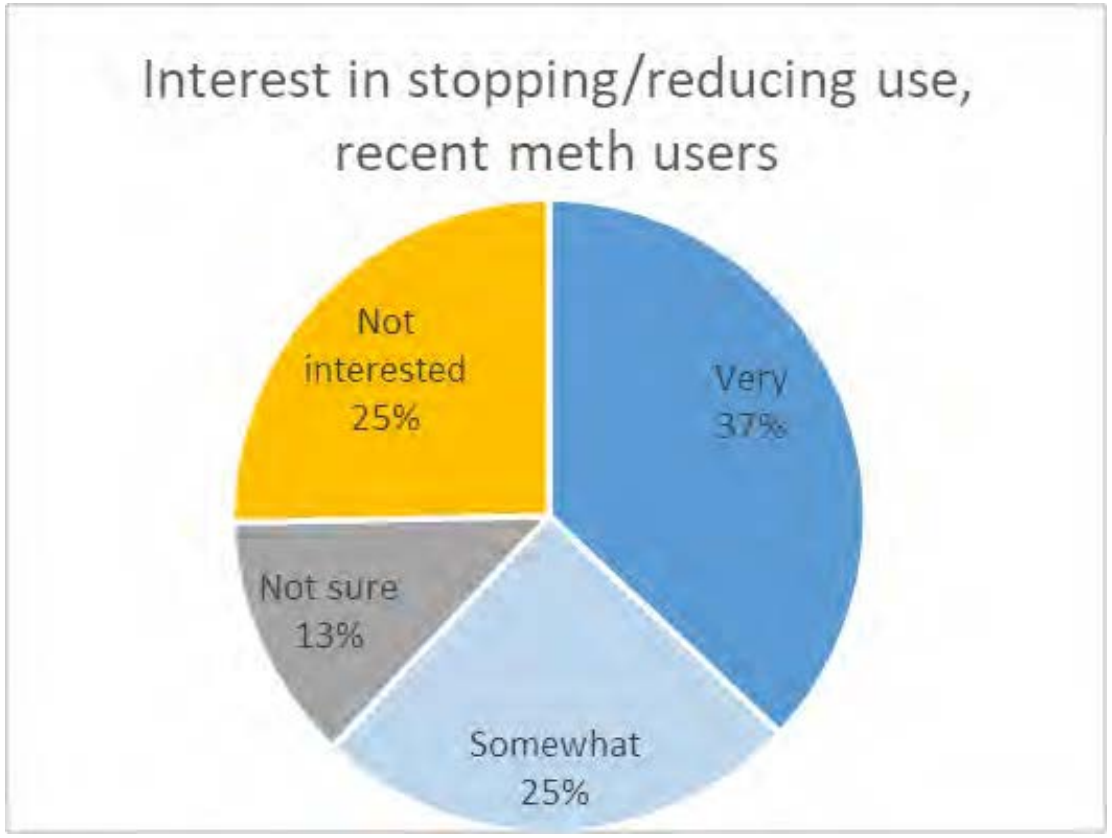
King County

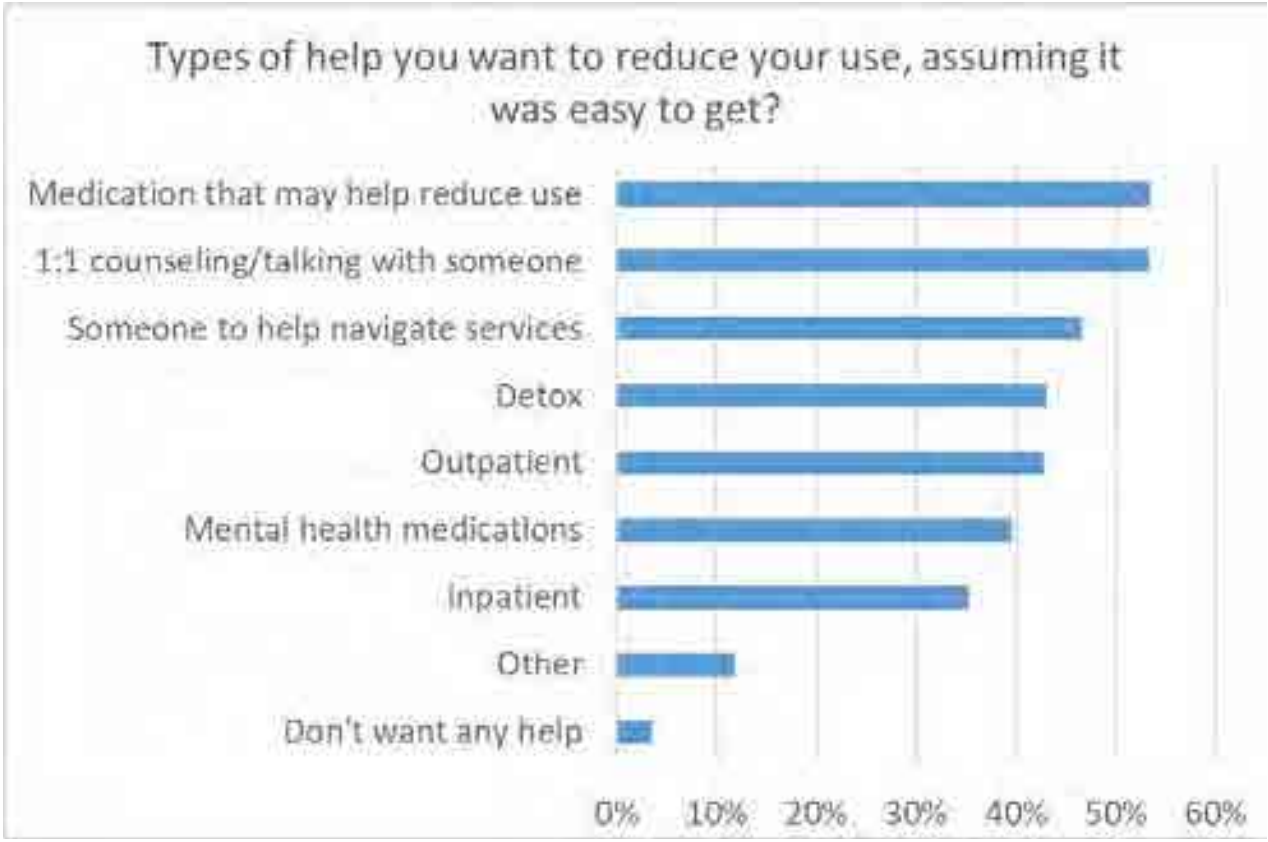




69% homeless/impermanently housed
37% incarcerated in prior year

59% needed health care in prior year, but didn’t seek it (2017 data)





Compares to 78% of opioid users

Session IV: Current Treatment Paradigms

Session V: Future Directions

Save the Date!

Public Meeting on Patient-Focused Drug Development for Stimulant Use Disorder

March 10, 2020
Silver Spring, MD and Webcast

FDA is interested in hearing perspectives from individuals with stimulant use disorder and other stakeholders on the:

- Health effects and daily impacts of their condition
- Impact (if any) of opioid and polysubstance use on their condition
- Treatment goals
- Decision factors considered when seeking out or selecting a treatment

Registration will open online in January 2020!

For more information, please visit: https://www.fda.gov/drugs/news-events-human-drugs/public-meeting-patient-focused-drug-development-stimulant-use-disorder-03102020-03102020.

Questions? PatientFocused@fda.hhs.gov

Session V: Future Directions

Closing Remarks

Adjournment