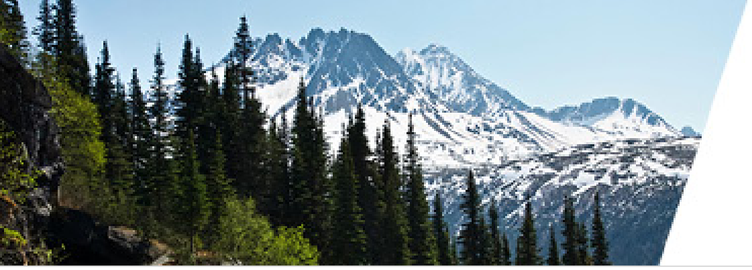


Northwest (HHS Region 10)
ATTC Addiction Technology Transfer Center Network
Funded by Substance Abuse and Mental Health Services Administration

The Northwest & Pacific Southwest ATTCs and the CTN Western States Node present:

Meth 2.0 and Opioid Use Disorder: A Collision of Epidemics

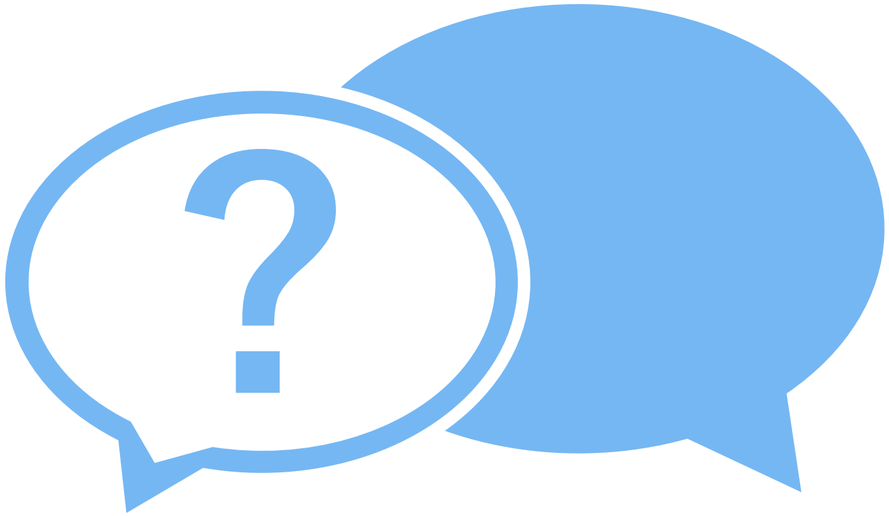
Thank you for joining us! The webinar will begin shortly.

- **Got questions?** Type them into the chat box at any time and they will be answered at the end of the presentation.
- Slides and a recording of this presentation will be made available on our website at: http://attcnetwork.org/northwest later this week

SAMHSA
Substance Abuse and Mental Health Services Administration

Q&A

Questions? Please type them in the chat box!



CME & Course Evaluation

Within three business days after the course, participants will receive an email to log in to the Stanford CME portal (stanford.cloud-cme.com) and click My CE tab to complete the course evaluation.

Within the evaluation, you will be asked to attest to your hours of participation. Upon completion of the evaluation and attestation, your transcript will be updated will then reflect the number of credit hours for the activity.

For questions about your credit following this activity, contact stanfordcme@stanford.edu.

FACULTY DISCLOSURE

Stanford Medicine adheres to ACCME Criteria, Standards and Policies regarding industry support of continuing medical education.

There are no relevant financial relationships with ACCME-defined commercial interests for anyone who was in control of the content of this activity.

For full disclosure information please go to our website:
stanford.cloud-cme.com/meth2.0

ACCREDITATION

In support of improving patient care, this activity has been planned and implemented by Stanford Medicine and Northwest Addiction Technology Transfer Center. Stanford Medicine is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

CREDIT DESIGNATION

AMERICAN MEDICAL ASSOCIATION (AMA)

Stanford Medicine designates this live activity for a maximum of 1.50 *AMA PRA Category 1 Credit(s)™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Stanford MEDICINE | Stanford Center for Continuing Medical Education

Continuing Education (CE) Credit offered by UCLA Integrated Substance Abuse Programs

- Following the web training, participating psychologists, registered nurses, LMFTs, LCSWs, and SUD counselors will receive an email from Shannon Bertea with the links to two different brief online CE course evaluations (one for PSY/RN and a second for LMFTs/LCSWs/counselors)
- Once you submit the your CE evaluation form, a CE Certificate will be emailed to you within 6-8 weeks
- Reach out to Shannon with questions (sbertea@mednet.ucla.edu)

Certificate of Attendance

If you requested a “certificate of attendance” rather than specific CME/CE, you will receive that certificate from the Northwest ATTC automatically via email within a week.

ATTC Survey, Slides, Recording

Look for our survey in your inbox!

We greatly appreciate your feedback!

Every survey we receive helps us improve and continue offering our programs.

A link to the slides and recording will also be provided in this email.

Meth 2.0 and Opioid Use Disorder

Larissa Mooney, MD

- Board-certified addiction psychiatrist & Associate Clinical Professor of Psychiatry at UCLA
- Director of the UCLA Addiction Psychiatry Clinic & Chief of the Greater LA Substance Use Disorders Section
- Co-PI of the Greater Southern California Node of the CTN

Meth 2.0 and Opioid Use Disorder: A Collision of Epidemics

Larissa Mooney, M.D.

Associate Professor of Psychiatry
Director, UCLA Addiction Psychiatry Clinic
UCLA Integrated Substance Abuse Programs

Disclosures

- Dr. Mooney has no financial disclosures or conflicts of interest

Learning Objectives

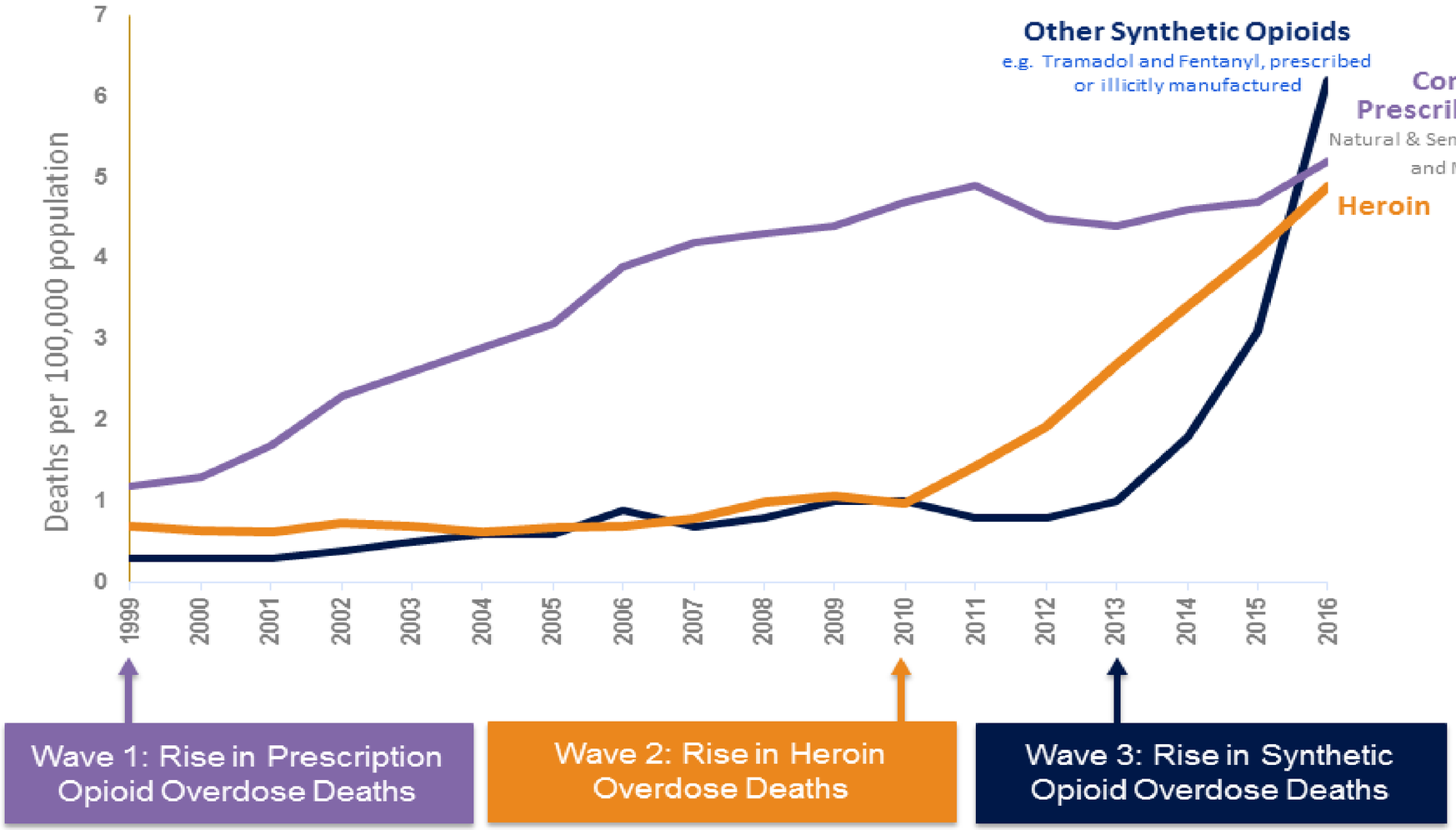
1. Describe recent epidemiological trends in methamphetamine and opioid use.
2. Identify at least three medical risks of co-occurring methamphetamine and opioid use.
3. Explain at least three evidence-based treatment approaches that can be utilized with patients who use both methamphetamine and opioids.

Outline

- Epidemiology of Opioid Epidemic
- OUD Treatment
- Meth 2.0
- Epidemiology of Stimulant Overdose
- Clinical Issues & Outcomes associated with Methamphetamine + OUD
- Methamphetamine Use D/O Treatment

Epidemiology of Opioid Epidemic

3 Waves of the Rise in Opioid Overdose Deaths



SOURCE: National Vital Statistics System Mortality File.

Source: CDC: https://www.cdc.gov/drugoverdose/epidemic/index.html

[1]https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates

Nonmedical Opioid Use and Overdose: Epidemiology

2018

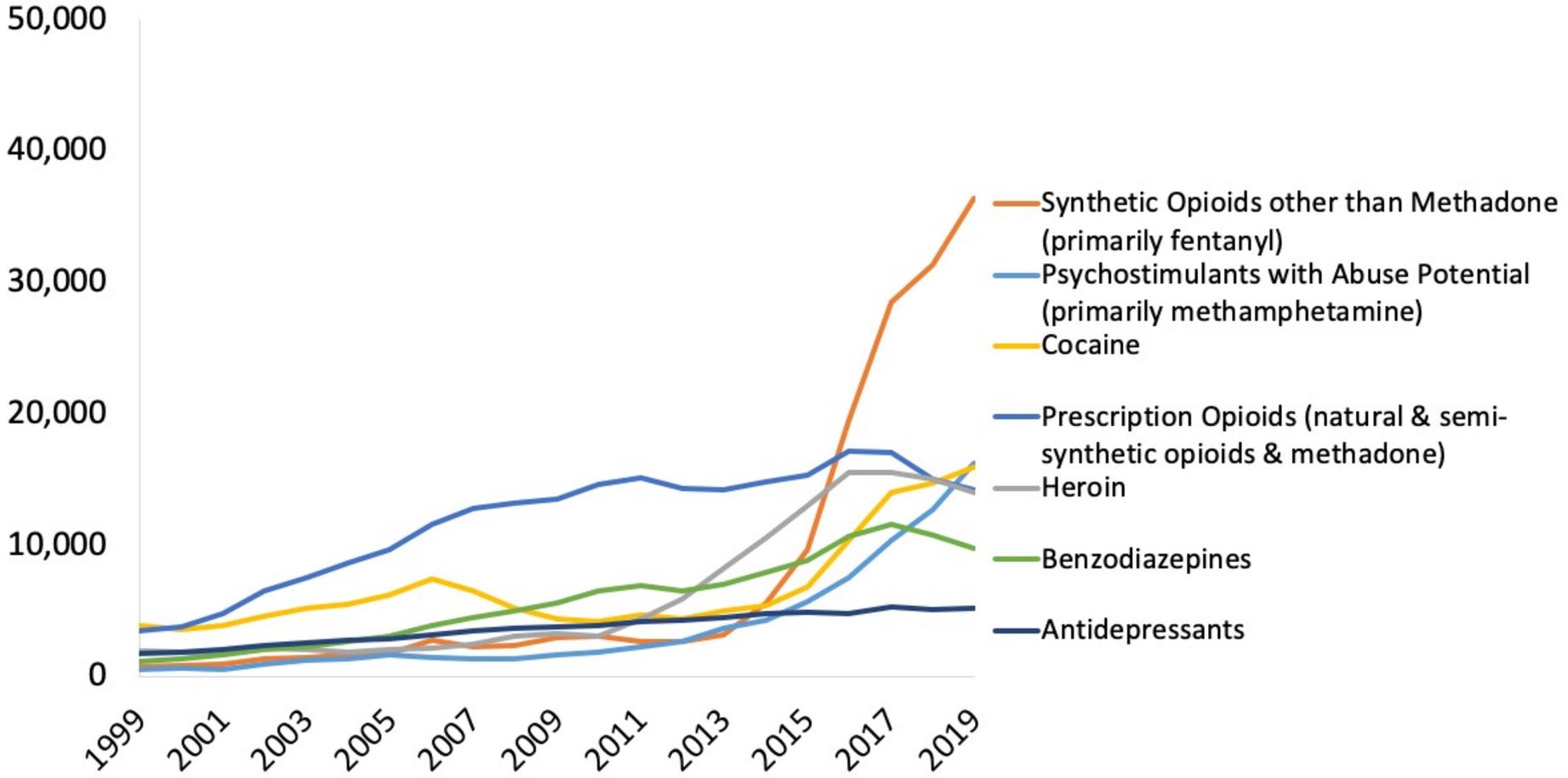
- The number of opioid-related overdose deaths was 4 times higher than in 1999
- 67,367 drug overdose deaths occurred, with more than 2/3 linked to opioids
- 10% increase in fentanyl (& analog) related deaths since from 2017 to 2018

2020

- COVID-19 hit
- >81,000 drug overdose deaths occurred between June 2019 and May 2020
- 38.4% increase in synthetic opioid overdose deaths

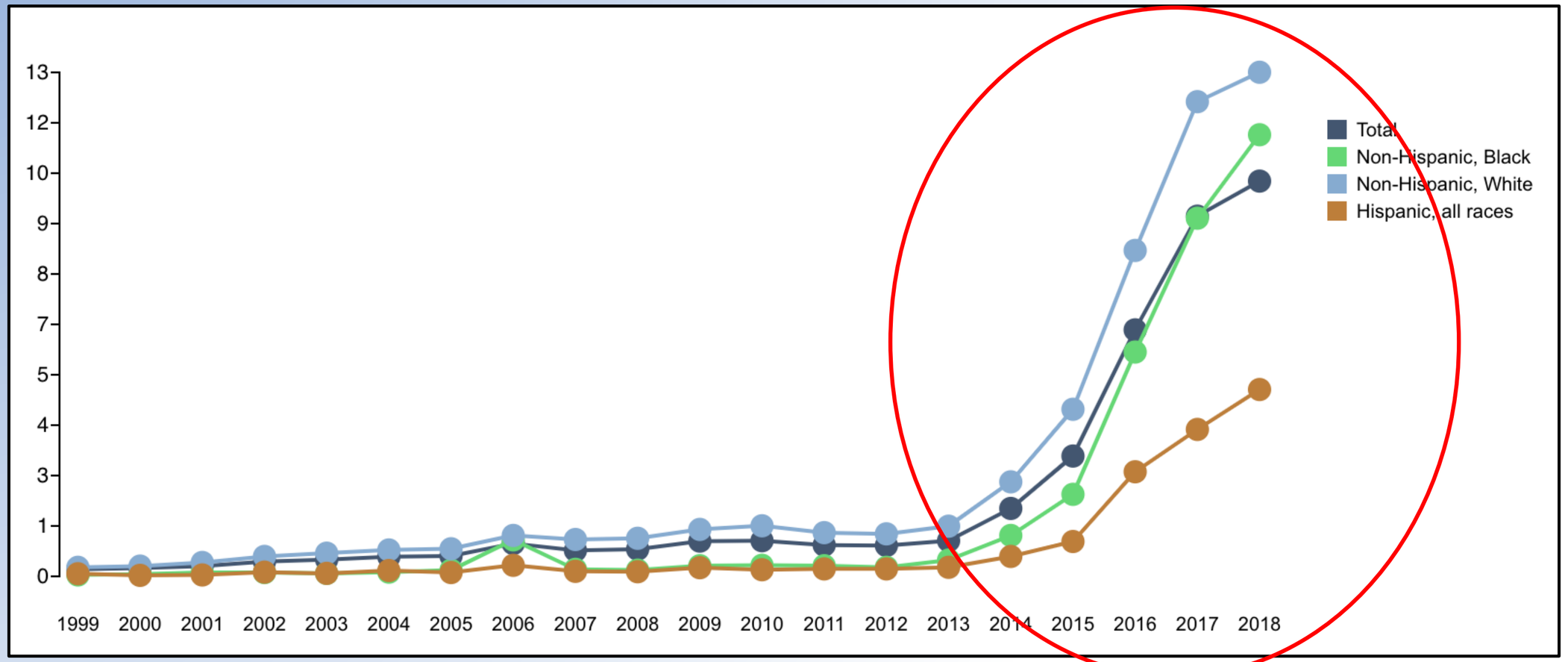
CDC 2020

Figure 2. National Drug-Involved Overdose Deaths*, Number Among All Ages, 1999-2019



*Includes deaths with underlying causes of unintentional drug poisoning (X40–X44), suicide drug poisoning (X60–X64), homicide drug poisoning (X85), or drug poisoning of undetermined intent (Y10–Y14), as coded in the International Classification of Diseases, 10th Revision.
Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2019 on CDC WONDER Online Database, released 12/2020.

Drug Overdose Deaths Involving Synthetic Opioids, Excluding Methadone, Per 100,000 Resident Population Per Year, 1999-2018

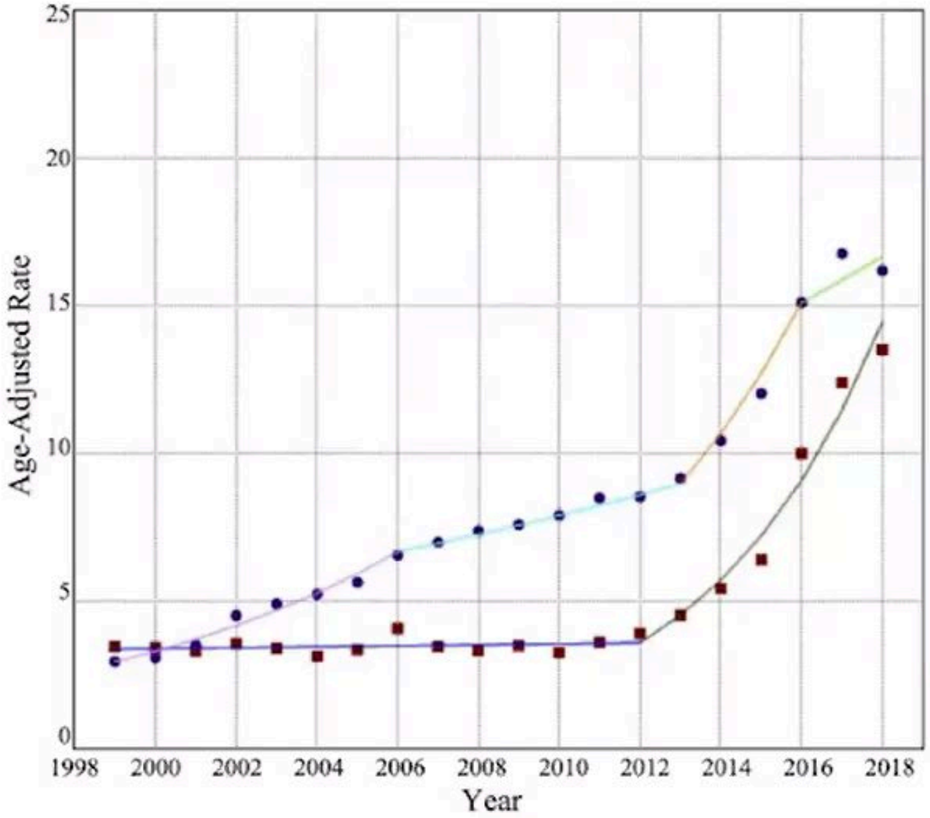


Source: Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System - Mortality.

African Americans Now Outpace Whites in Opioid-Involved Overdose Deaths

African American
APC = 0.47 from 1999 to 2012
APC = 26.16* from 2012 to 2018

White
APC = 12.43* from 1999 to 2006
APC = 4.34* from 2006 to 2013
APC = 18.96* from 2013 to 2016
APC = 5.07 from 2016 to 2018



*Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.

Furr-Holden, et al., Addiction, 2021

Opioid Use Disorder Treatment

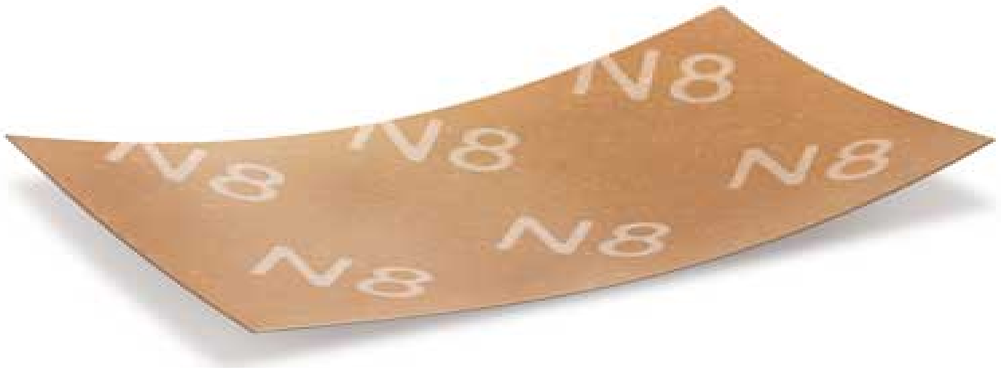
Opioid Use Disorder Treatment Approaches

- Medically assisted withdrawal management (detox):
  - Opioid-based (methadone, buprenorphine)
  - Non-opioid based (clonidine, lofexidine, supportive meds)
- Relapse prevention:
  - Agonist maintenance (methadone)
  - Partial agonist maintenance (buprenorphine)
  - Antagonist maintenance (IM naltrexone)
- Psychosocial treatment
  - To promote behavior change, skills, social support

Why Not Detoxification?

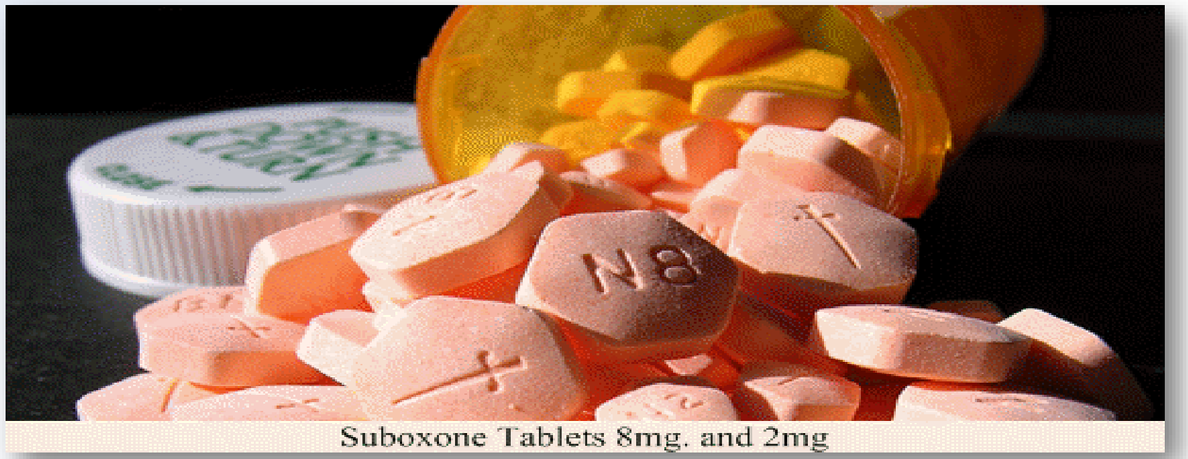
POST-DETOXIFICATION RELAPSE RATES APPROACH 100% WITHIN THE FIRST 90 DAYS FOLLOWING COMPLETION OF DETOXIFICATION.

Buprenorphine

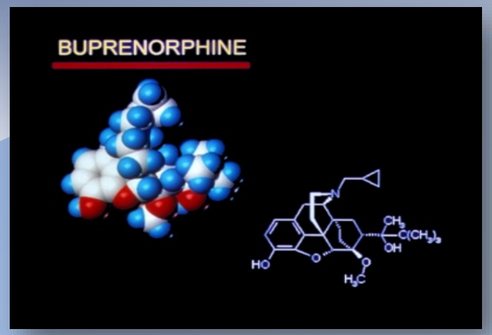


Buprenorphine for Opioid Use Disorder

- FDA approved 2002, age 16+
- Mandatory certification from DEA (100 pt. limit, or 275 with certifications)
- Mechanism: partial mu agonist
- Office-based, expands availability
- Analgesic properties
- Ceiling effect
- Safer in overdose



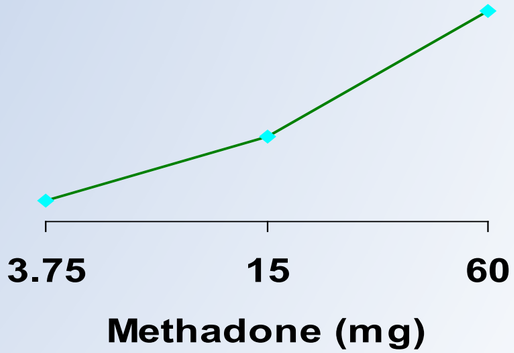
Suboxone Tablets 8mg. and 2mg

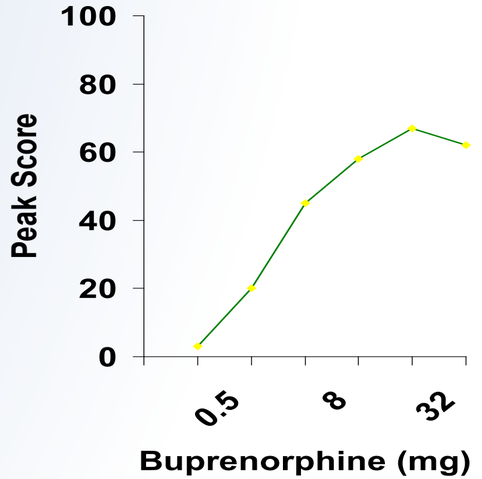


Buprenorphine: Pharmacological Characteristics

Partial Agonist (ceiling effect)

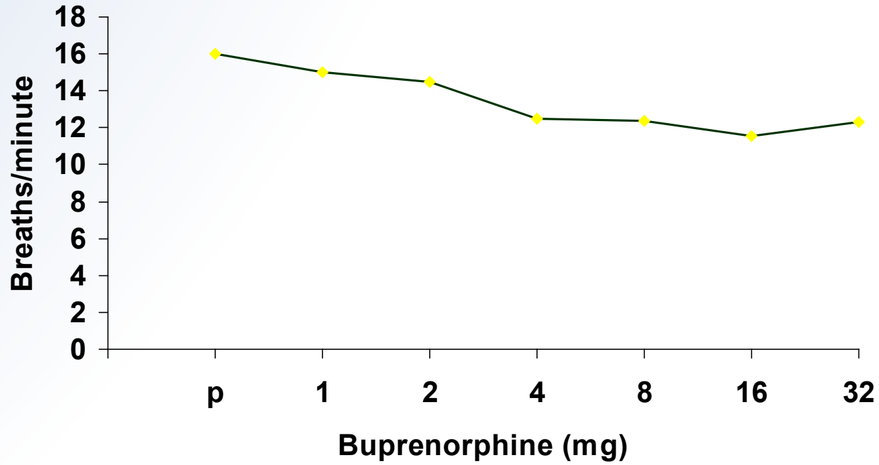
- less euphoria
- safer in overdose





Strong Receptor Affinity

- long duration of action
- 1st dose given during withdrawal



Transmucosal Buprenorphine Formulations

- **Sublingual dose**: 2mg-24mg/day
- **Subutex** (buprenorphine) (2mg, 8mg)
- **Suboxone** (4:1 bup:naloxone)

  -2mg/0.5 mg , 8mg/2mg

  -(now also in 4mg/12mg)
- **Zubsolv** (4:1 bup:naloxone)

  -(1.4/0.36mg- 11.4/2.9mg)
- **Bunavail** (6:1 buccal film bup:naloxone)

  -(2.1/0.3mg, 4.2/0.7mg, 6.3/1mg)
- **Belbuca** (75-900mcg buccal film for pain)

Buprenorphine Injection: Sublocade

- Sublocade is a monthly injectable formulation of buprenorphine approved in 2017 for the treatment of moderate to severe OUD in individuals who have initiated a transmucosal buprenorphine product and have been stabilized on treatment for at least seven days.
- The approved dosing regimen is 300 mg administered subcutaneously for the first two months, followed by maintenance doses of 100 mg/month.
- It must be prescribed as part of a Risk Evaluation and Mitigation Strategy to ensure that the product is not distributed directly to patients.

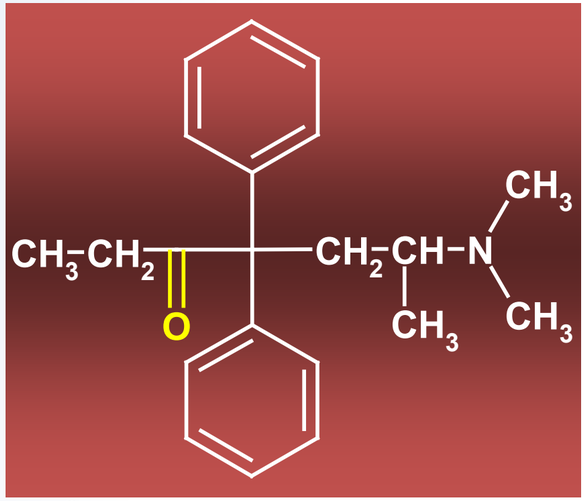
Extended-Release Injectable Naltrexone for OUD

Extended-Release Naltrexone

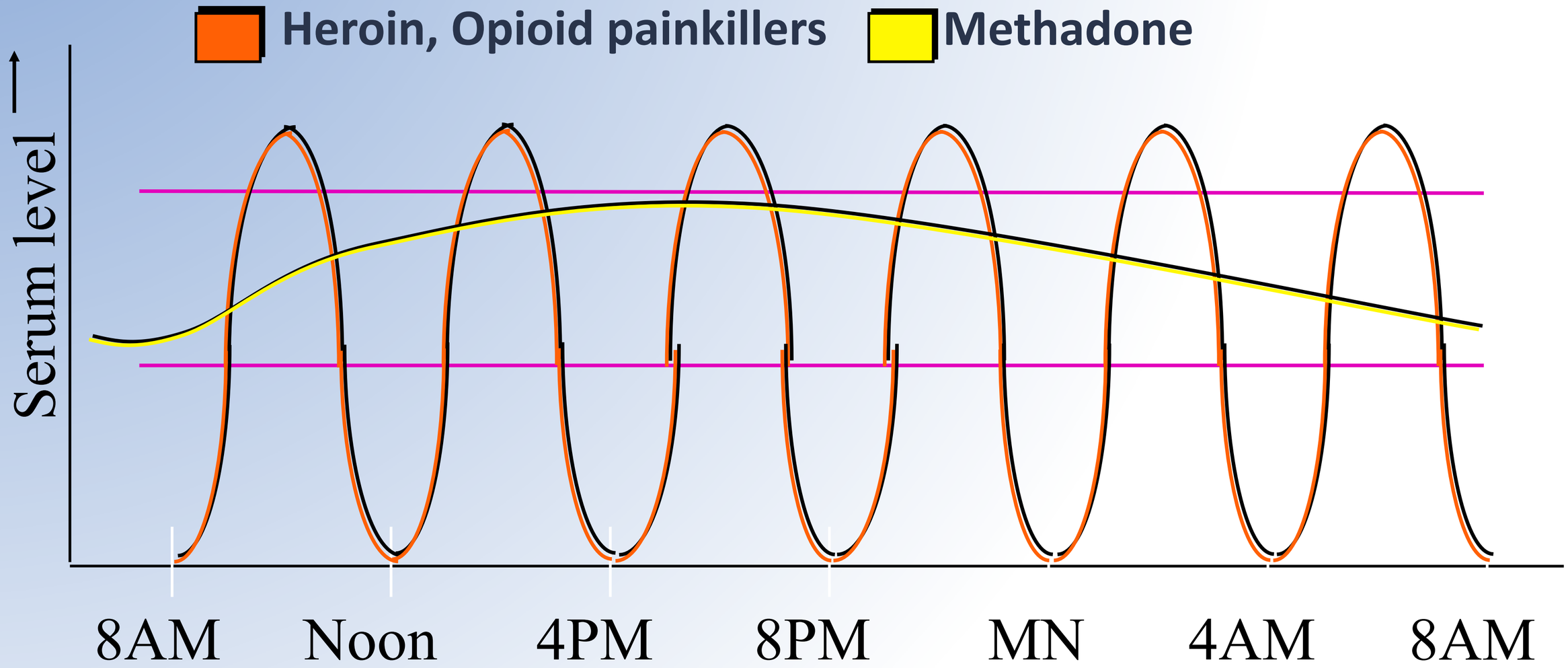
- **Dosing:** 380mg injection in deep gluteal muscle every 4 weeks; alternate sides each month.
- Blocks opioid receptors for **one entire month** compared to approximately 28 doses of oral naltrexone.
- **Adverse effects:** injection site reactions, nausea/vomiting, precipitated opioid withdrawal, depression, elevated LFTs
- ***Note:*** *Large doses of opioids may be required to override the blockade in a medically monitored setting*.

Methadone: Clinical Properties

- Orally active synthetic μ agonist
- Action: CNS depressant/ analgesic
- Long half-life, slow elimination
- Effects last 24 hours
- Once daily dosing maintains constant blood level
- Prevents withdrawal, reduces craving and use
- Facilitates rehabilitation
- Clinic dispensing limits availability



Blood levels: methadone vs. short-acting opioids



Treatment Outcome Data: Methadone

- 8-10 fold reduction in death rate
- Reduction in drug use
- Reduction in criminal activity
- Increased treatment retention
- Engagement in socially productive roles; improved family and social function
- Increased employment
- Improved physical and mental health
- Reduced spread of infectious disease/HIV

Comparative Medication Effectiveness

- Meta-analyses: methadone slightly more effective than buprenorphine in retaining patients in treatment; equally effective in reducing opioid use *(Mattick et al., 2014)*
- X:BOT trial *(Lee et al., 2018)* - XR-naltrexone (NTX) vs. buprenorphine (BUP) for 24 weeks (n=570): induction rates lower for NTX than BUP (72% vs. 94%), but relapse rates equivalent once inducted
- Retrospective comparative effectiveness using claims data (Optum Labs), N=40,855 w/ OUD *(Wakeman et al., 2020):* methadone and buprenorphine associated with reduced OD and OUD-related morbidity at 3 and 12 mos compared w/ NTX, inpatient tx, IOP.

Naloxone

Short-acting opioid antagonist

- High affinity for mu opioid receptor
- Displaces opioids from receptor
- Rapidly reverses effects of opioid overdose (minutes)
- Effects last 20-90 mins
- FDA approved for IV, SC, IM, intranasal use

- Opioid overdose-related deaths can be prevented when naloxone is administered in a timely manner.
- **www.PrescribeToPrevent.org**

Overdose Risk Factors

- History of prior overdose
  - Release after emergency care for overdose
- Opioid use disorder
- Prescribed more than 50 mg of oral morphine equivalents daily
- Recent release from incarcerated or residential setting
- Combining opioids with other central nervous system depressants (e.g. alcohol, benzos)
- Medical conditions (e.g. pulmonary diseases)

Psychosocial Treatment Modalities

- May be combined effectively with medication treatment and mutual support groups (e.g. AA, NA):
  - Cognitive behavioral therapy
  - Contingency management
  - Motivational interviewing
  - 12-step facilitation

- Individuals with OUD have elevated rates (80%) of other substance use disorders *(NSDUH)*
- Higher rates of depressive disorders, anxiety disorders and personality disorders than general population

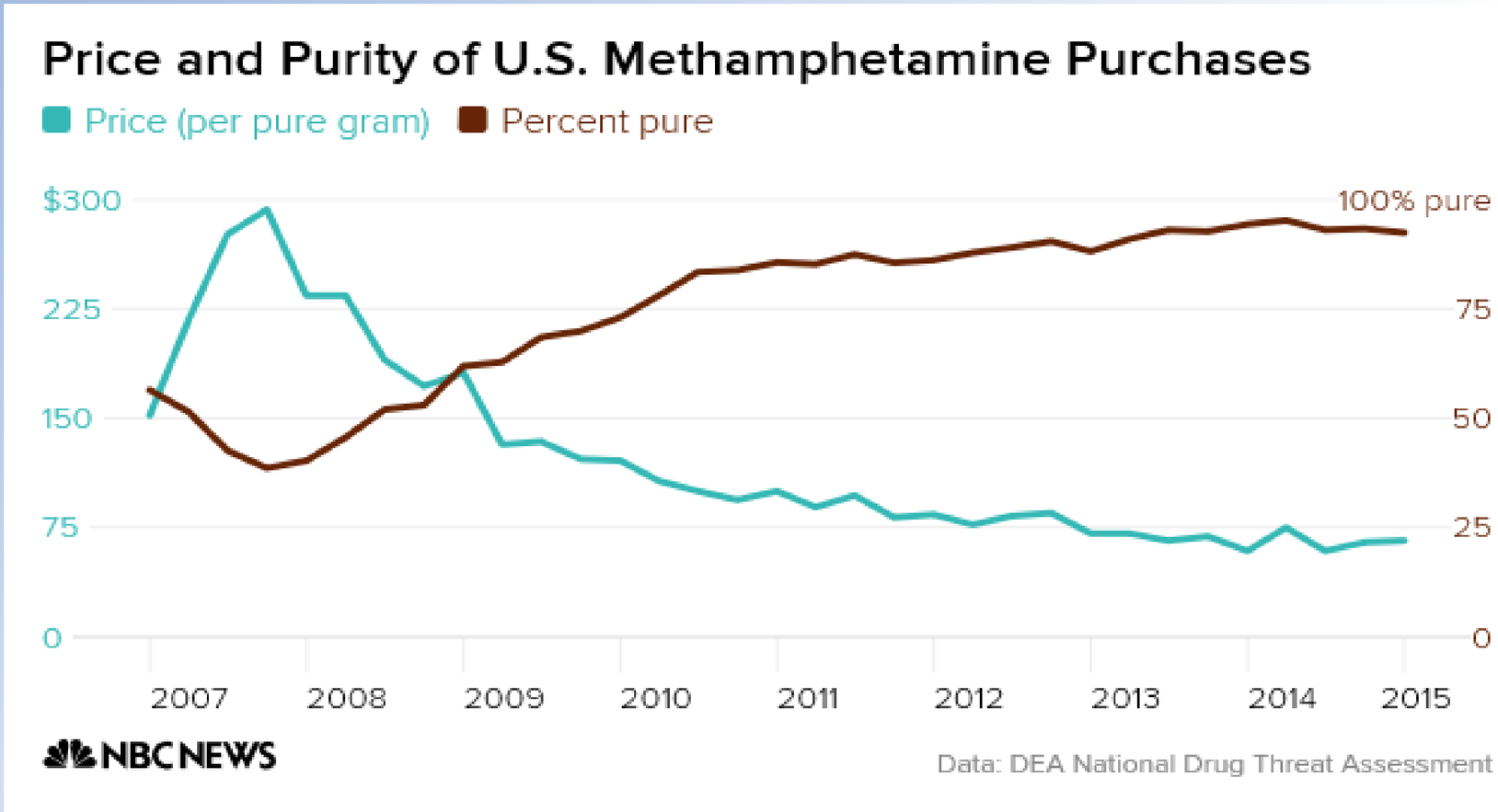
Source: Dutra, et al., 2008, Am J Psychiatry; Kidorf et al., 2004; Wu et al., 2016, Drug Alcohol Depend.

ED Bridge: Patients who obtained Bup Rx in ED were twice as likely to be engaged in addiction tx 1 month later relative to those given referrals. This model is similar to other chronic medical conditions such as hypertension, diabetes, and asthma in which ED clinicians initiate or restart treatment.

Source: D'Onofrio et al., 2015, *JAMA*.; Srivastada et al., 2019, *Can Fam Physician*

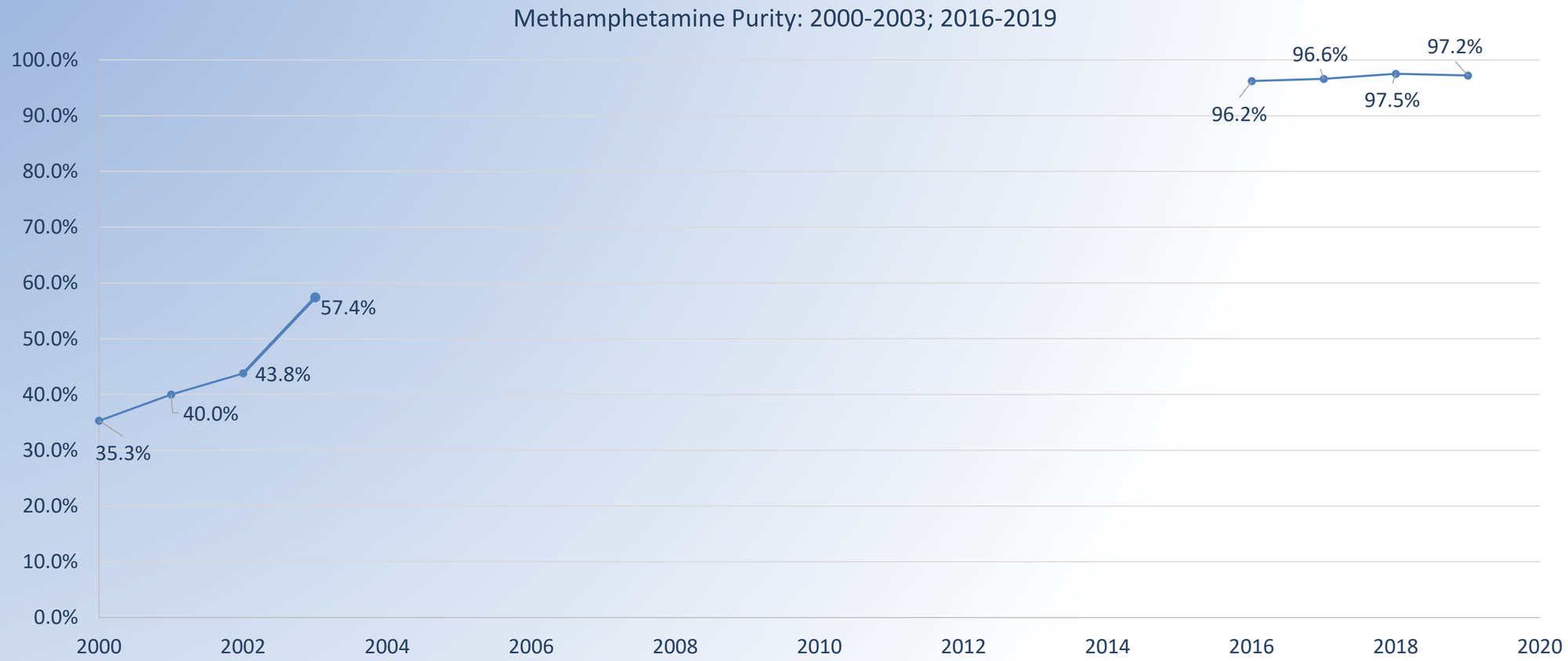
Methamphetamine 2.0

Purity of meth produced in Mexico has surged from 39% in 2007 to 97% today



Source: The Economist, 2019

Methamphetamine Purity 2000-2003 and 2016-2019



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

Meth 2.0

Extremely pure (~97%)

High potency → high addictive potential

Increased cardiotoxicity, psychiatric effects

Mass produced in Mexico → inexpensive

Readily available, easily accessible

The P2P Method

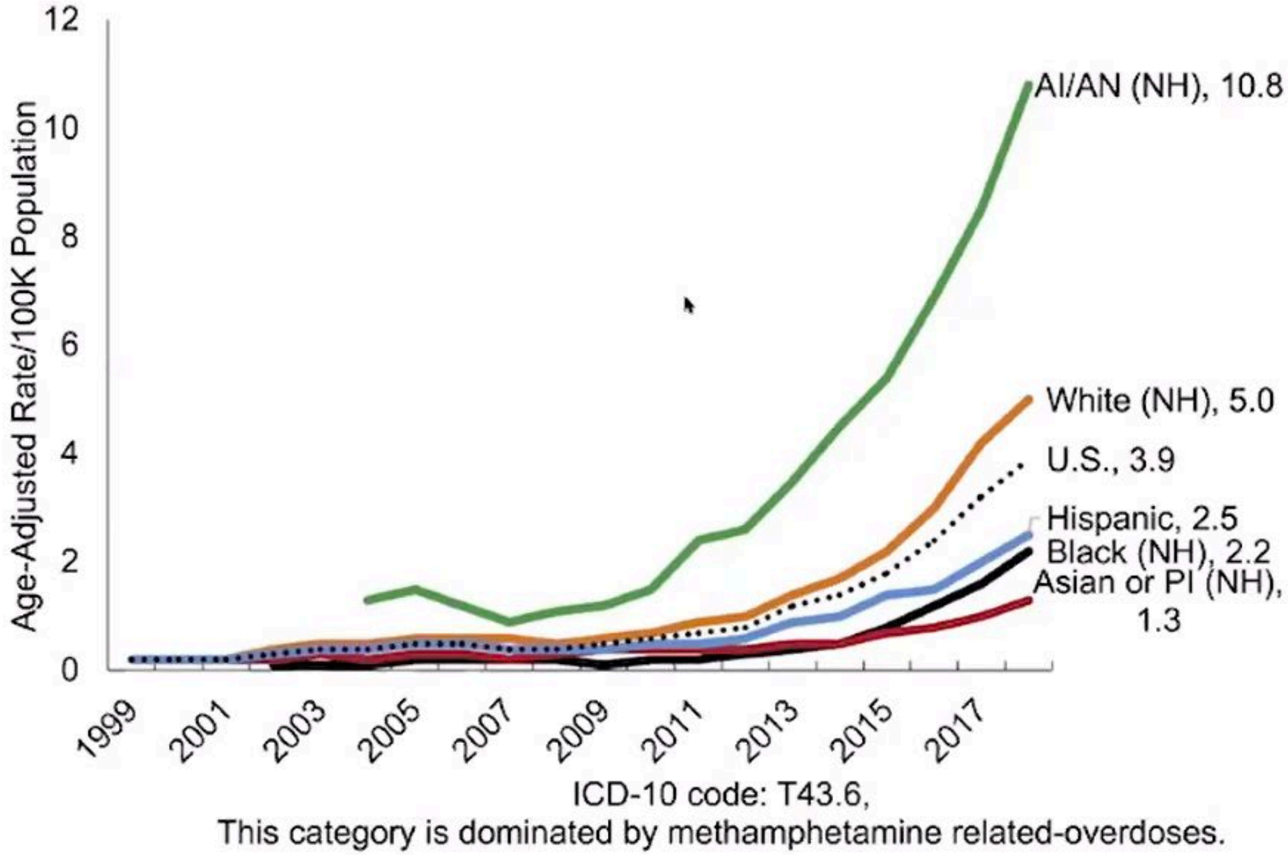
- Manufacturers/chemists begin using different formula to make meth without pseudoephedrine
  - 1-phenyl-2-propanone (P2P)
  - Altered ratio of L- to D-meth

- DEA profiling program:
  In 2010 → 43% seized meth made using P2P
  In 2011 → 79%
  In 2013 → 95%

Source: Maxwell, 2014

Deaths Involving Psychostimulants, by Race

U.S. Overdose Deaths Involving Psychostimulants (Mostly Methamphetamine), by Race

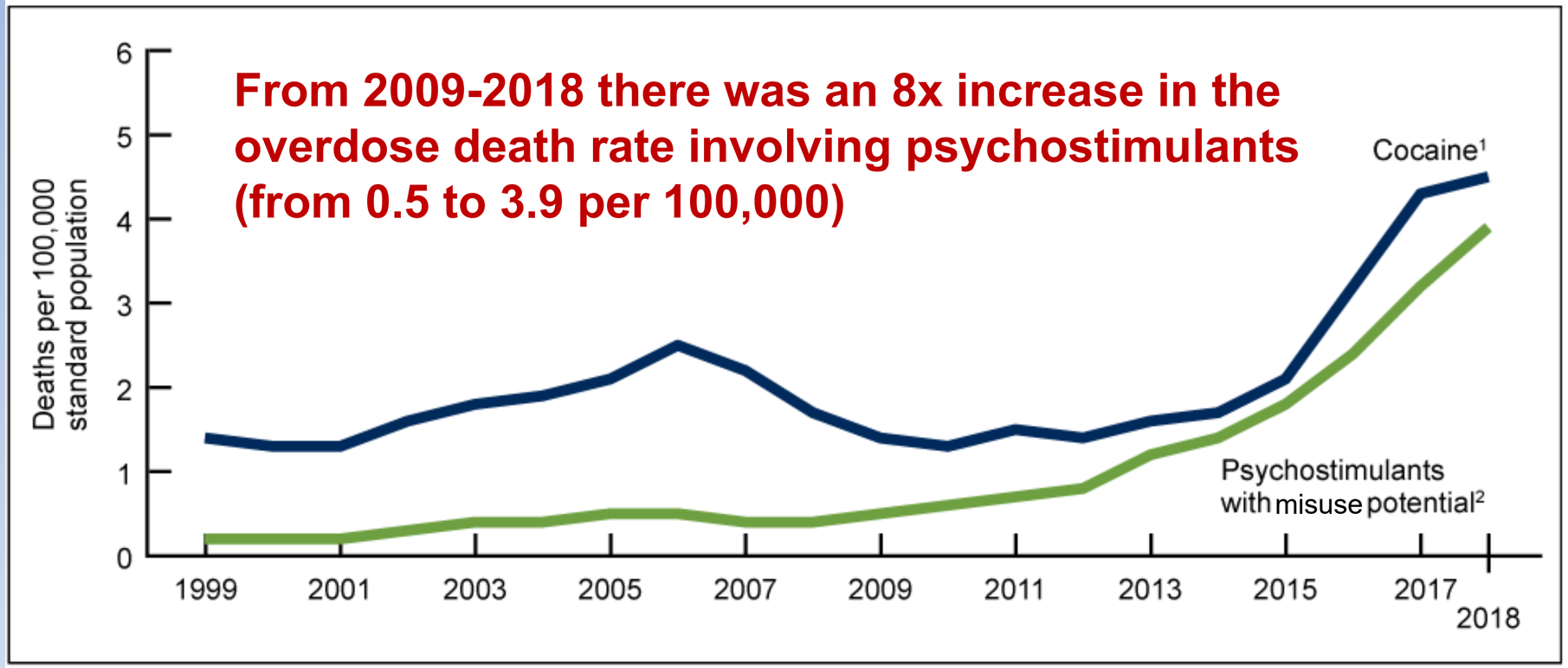


Source: CDC WONDER

Epidemiology of Methamphetamine/Stimulant and Meth+ OUD Overdose

Methamphetamine 2.0 overdoses

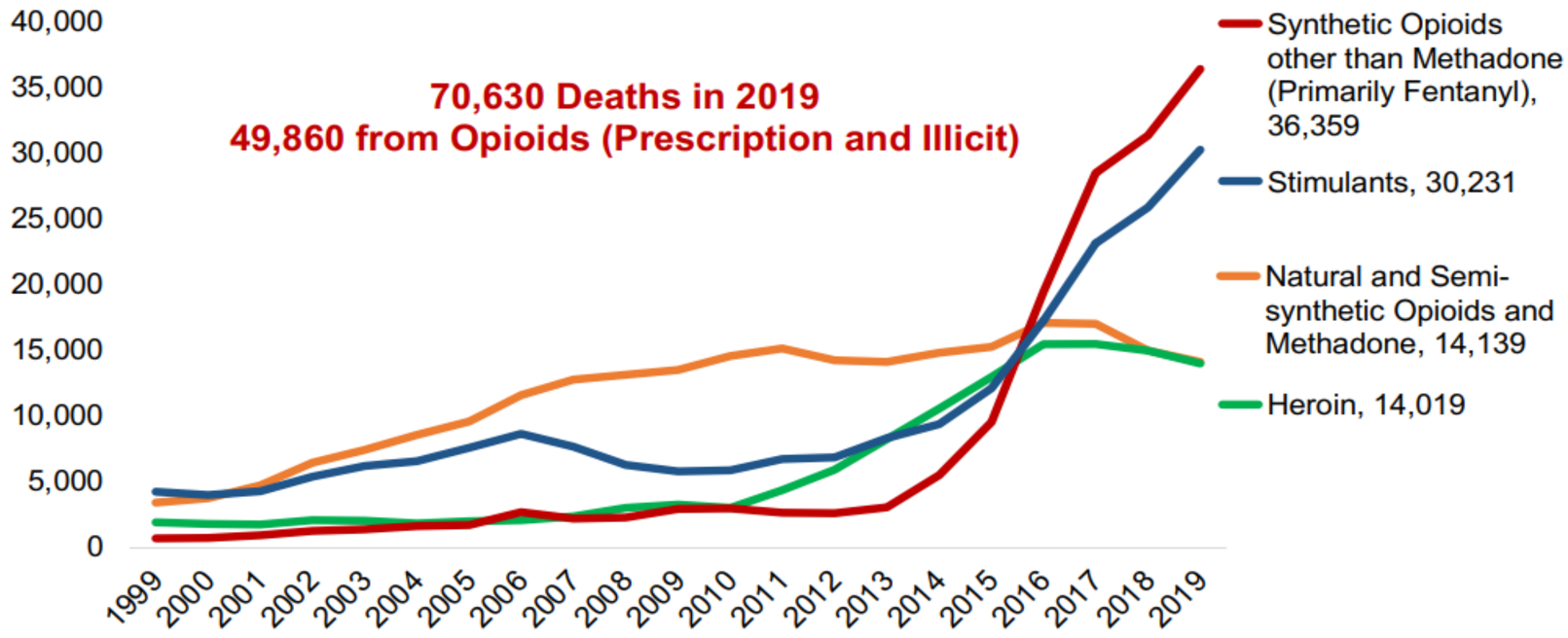
Figure 4. Age-adjusted drug overdose death rates involving stimulants, by type of stimulant: United States, 1999–2018



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

Evolution of Drivers of Overdose Deaths, All Ages

Analgesics → Heroin → Fentanyl → Stimulants

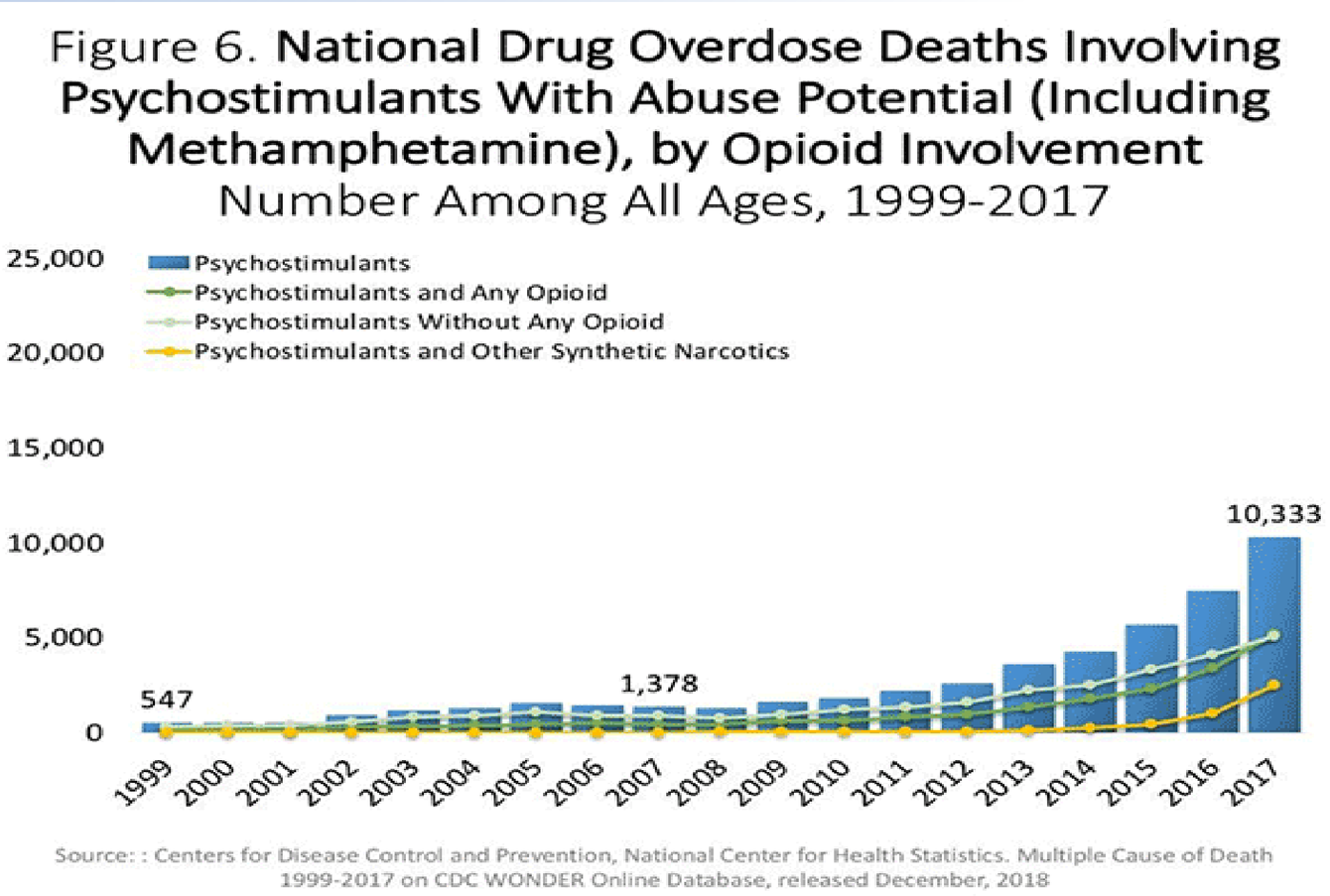


Source: The Multiple Cause of Death data are produced by the Division of Vital Statistics, National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC), United States Department of Health and Human Services (US DHHS).

Meth +/- Opioids Overdose Deaths

In 2017 ~15% of all drug overdose deaths involved methamphetamine and **50%** of those deaths also involved an opioid

Misuse



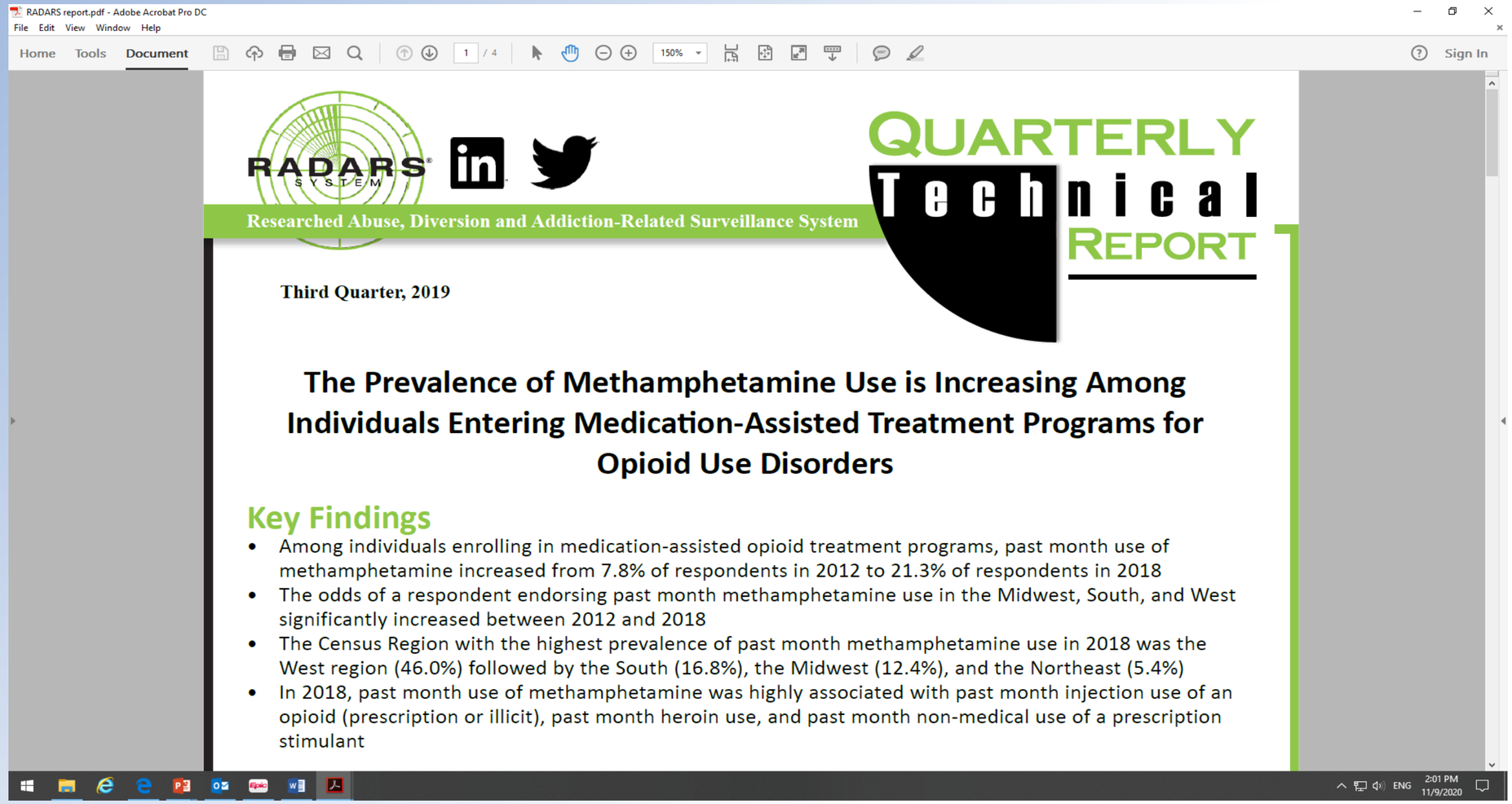
Increased Overdose Death Rates During COVID-19 Pandemic
12-months Ending June 2020 Compared to 12-months Ending June 2019

	ALL DRUGS	HEROIN	NAT & SEMI – SYNTHETIC	METHADONE	SYNTHETIC OPIOIDS	COCAINE	OTHER PSYCHO-STIMULANTS (mainly meth)
June-19	68,711	14,856	12,148	2,863	33,164	14,894	14,583
June-20	83,335	14,480	12,966	3,195	48,006	19,215	20,318
% Change	**21.3%**	**-2.5%**	**6.7%**	**11.6%**	**44.8%**	**29.0%**	**39.3%**

*Predicted Number of Deaths
Source: NCHS Provisional Drug Overdose Death Counts:
https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm (Accessed on 1-18-2021)

Clinical Issues and Outcomes Associated with Methamphetamine + OUD

Meth use with MOUD

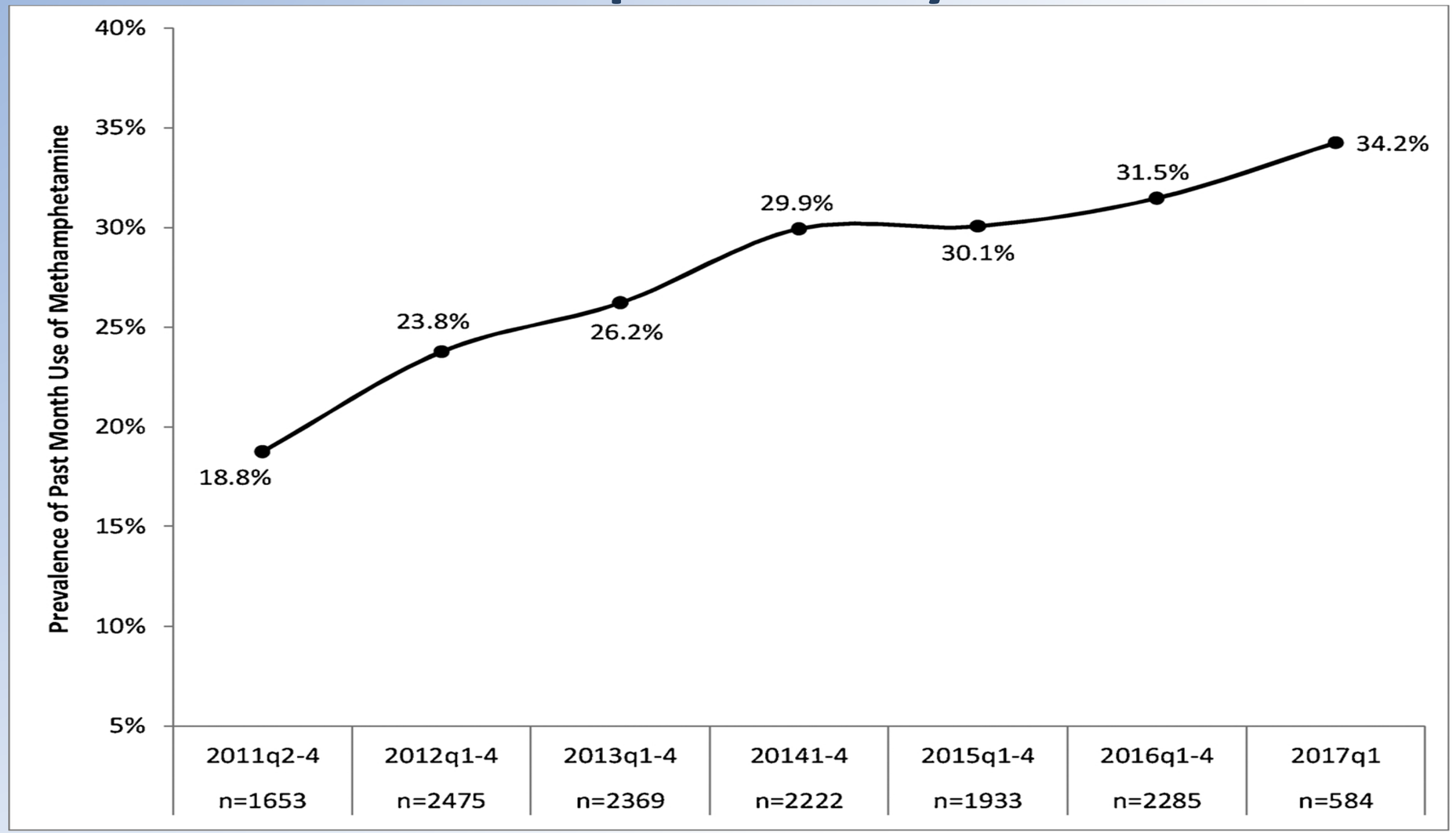


Twin Epidemics: The surging rise of methamphetamine use in chronic opioid users.

- Past-month use of methamphetamine significantly increased among treatment-seeking opioid users (+82.6%, $p < .001$),
  - From 18.8% in 2011 to 34.2% in 2017.

Source: Ellis, M. Kasper, A., Cicero, T. (2018) Drug and Alcohol Dependence, 2018, 14-20

% of respondents reporting use of meth in past 30 days



Source: Ellis et al. 2018

Methamphetamine and Opioid Co-Ingestion – What are the Issues?

- A synergistic effect occurs when using meth and an opioid together (i.e., the result is greater than either alone)
- May use together to diminish side effects of the other
- Increased overdose risk (respiratory depression + cardiac arrest)
- The most potent effect seems to be in the first 90 minutes of co-ingestion

Source: Ellis, Kasper, & Cicero, 2018; Trujillo et al., 2011

Dropout rates of in-person psychosocial substance abuse treatment: a systematic review and meta-analysis

- Meta-analysis of in-person psychosocial SUD treatment.
- Drop out rates in first 90 days of treatment
- 151 studies, with 26,243 participants.
- Results yielded overall average dropout rates, and predictors of dropout.

Source: Lappan et al., *Addiction*, 2020

Substance Targeted and Dropout

Treatment Target	Dropout Rate
Heroin	25.1
Tobacco	25.5%
Alcohol	26.1%
Cocaine	48.7%
Methamphetamine	53.5%

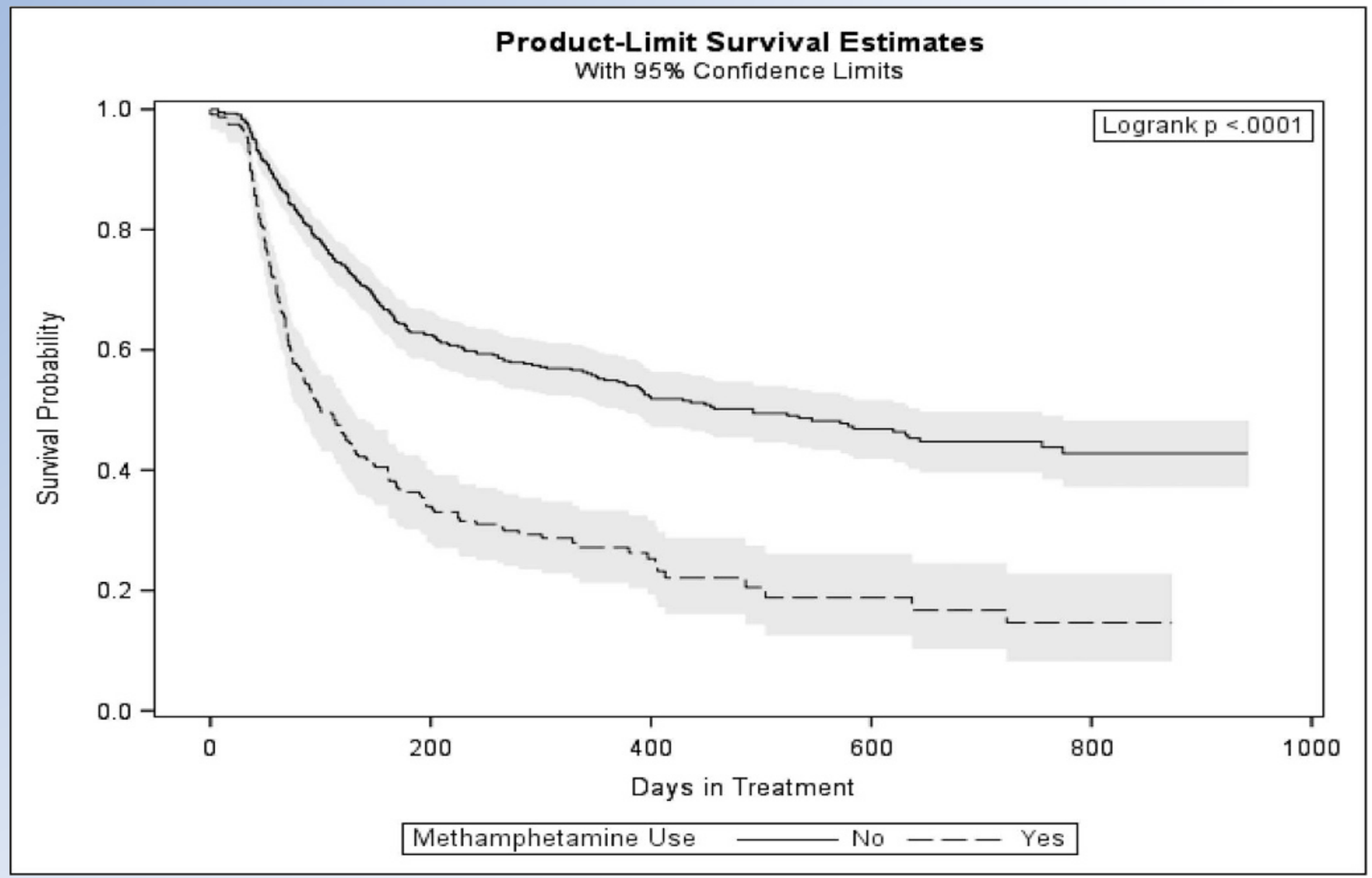
Source: Lappan et al., *Addiction*, 2020

Association between methamphetamine use and retention among patients with OUD treated with buprenorphine

- Adults receiving buprenorphine from Washington State MAT-Drug and Opioid Addiction program clinics between 2015-2018 (N=799)
  - Past 30-day substance use data were collected at baseline and 6-months, as well as date of program discharge.
- 30% (n=237) individuals reported meth use at admission. Baseline methamphetamine use was associated with more than twice the relative hazards for discharge in adjusted models (aHR=2.39; 95% CI: 1.94–2.93).

Source: Tsui, et al., 2020

Association between methamphetamine use and retention among patients with opioid use disorder treated with buprenorphine



Source: Tsui, et al., 2020

Interest in Reducing Meth and Opioid Use among Syringe Services Program Participants in Washington State

- In a sample of 583 participants at a Washington State syringe exchange program (443 opioids; 140 methamphetamine), survey data were collected on their attitudes about stopping drug use.
- **82%** of the individuals who reported opioids as their primary drug expressed an interest in reducing/stopping opioid use
- **46%** of individuals who reported methamphetamine as their primary drug expressed an interest in reducing/stopping their meth use.

Source: McMahan et al., 2020

Methamphetamine Use D/O Treatment + OUD Treatment

Behavioral Interventions for SUD – Gold Standard for Stimulant Use Disorder

- Contingency management (CM)
- Cognitive behavioral therapy (CBT)
  - Matrix Model
- Community Reinforcement Approach (CRA)
- Motivational interviewing
- 12-step facilitation
- Exercise

- Behavioral interventions may be combined with 12-step mutual support
- Consider level of care:
  - General outpatient
  - Intensive outpatient
  - Residential treatment

Non-Pharmacological Interventions for Methamphetamine Use Disorder: A Systematic Review Drug and Alcohol Dependence

- 44 Studies reviewed.
- Conclusions: While contingency management (CM) interventions showed the strongest evidence favoring the outcomes assessed, tailored CBT alone or with CM was also effective in the target population.

Source: AshaRani, PV, et al. 2020

Current Status of Treatment Approaches for Stimulant Use Disorder

- **Contingency management unanimously supported in reviews** (6 recent systematic reviews and meta-analyses) found to have best evidence of effectiveness.
- Other approaches with less but clear evidence of support: Cognitive Behavioral Therapy (CBT) and Community Reinforcement Approach (CRA).
- Approach with evidence for treatment of a broad variety of SUD: Motivational Interviewing (MI).
- Approach with recent studies showing benefit to methamphetamine users: Physical Exercise (PE).

AshaRani, PV, et al. 2020; Rawson et al., 2015; Trivedi et al., 2017

Contingency Management

- A technique employing the systematic delivery of positive reinforcement for desired behaviors, effective to facilitate reduced use of stimulants.
- In the treatment of methamphetamine use disorder, vouchers or prizes or gift cards can be “earned” for submission of methamphetamine-free urine samples or other behaviors that promote recovery (eg. attendance at treatment sessions).

A comparison of contingency management and cognitive-behavioral approaches during methadone maintenance treatment for cocaine dependence.

- The purpose of this study was to compare the effectiveness of CM and CBT alone or in combination for cocaine dependence for patients receiving methadone treatment.
- N=120 random assignment to CM, CBT, CM+CBT, or MMTP (standard methadone tx only, TAU).
- Interventions were 16 weeks, 3 research visits per week.

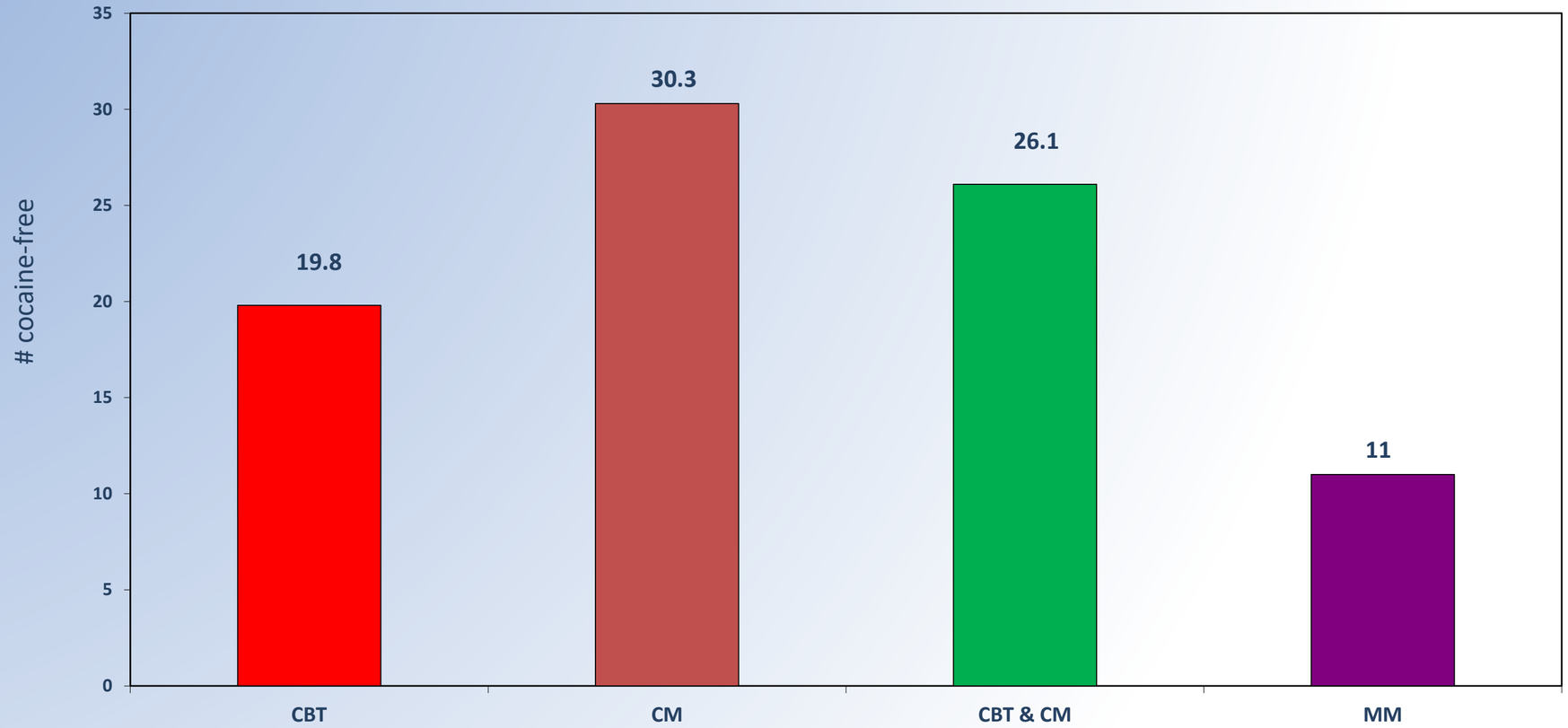
Source: Rawson et al., *Arch Gen Psychiatry*. 2002

Cocaine-free Urine Samples During Study

P<.001

CM>MM

CBT & CM>MM



Source: Rawson et al., *Arch Gen Psychiatry*. 2002

Discussion

- During study period, the CM conditions were associated with significantly more cocaine free UDS than the control group.
- CBT did not produce a substantial suppression of cocaine use during the study period.
- CBT and CM did not show an additive effect.
- Self reported data supported significant reductions in cocaine use from baseline to week 17 for all groups except MMTP.
- At the 26- and 52-week follow-up points self-reports and urine results reflect an improvement in all 3 intervention groups compared to MMTP alone.

Source: Rawson et al., *Arch Gen Psychiatry*. 2002

Effects of lower-cost incentives on stimulant abstinence in methadone maintenance treatment: a National Drug Abuse Treatment Clinical Trials Network study

- Contingency management (CM) has been shown to effective in research settings, but cost has limited real world implementation.
- This NIDA Clinical Trials Network study addressed cost with an intermittent reinforcement approach (“fishbowl approach”).
- Sites were 6 community-based, methadone maintenance clinics in locations across the United States.
- Stimulant use was the primary target.

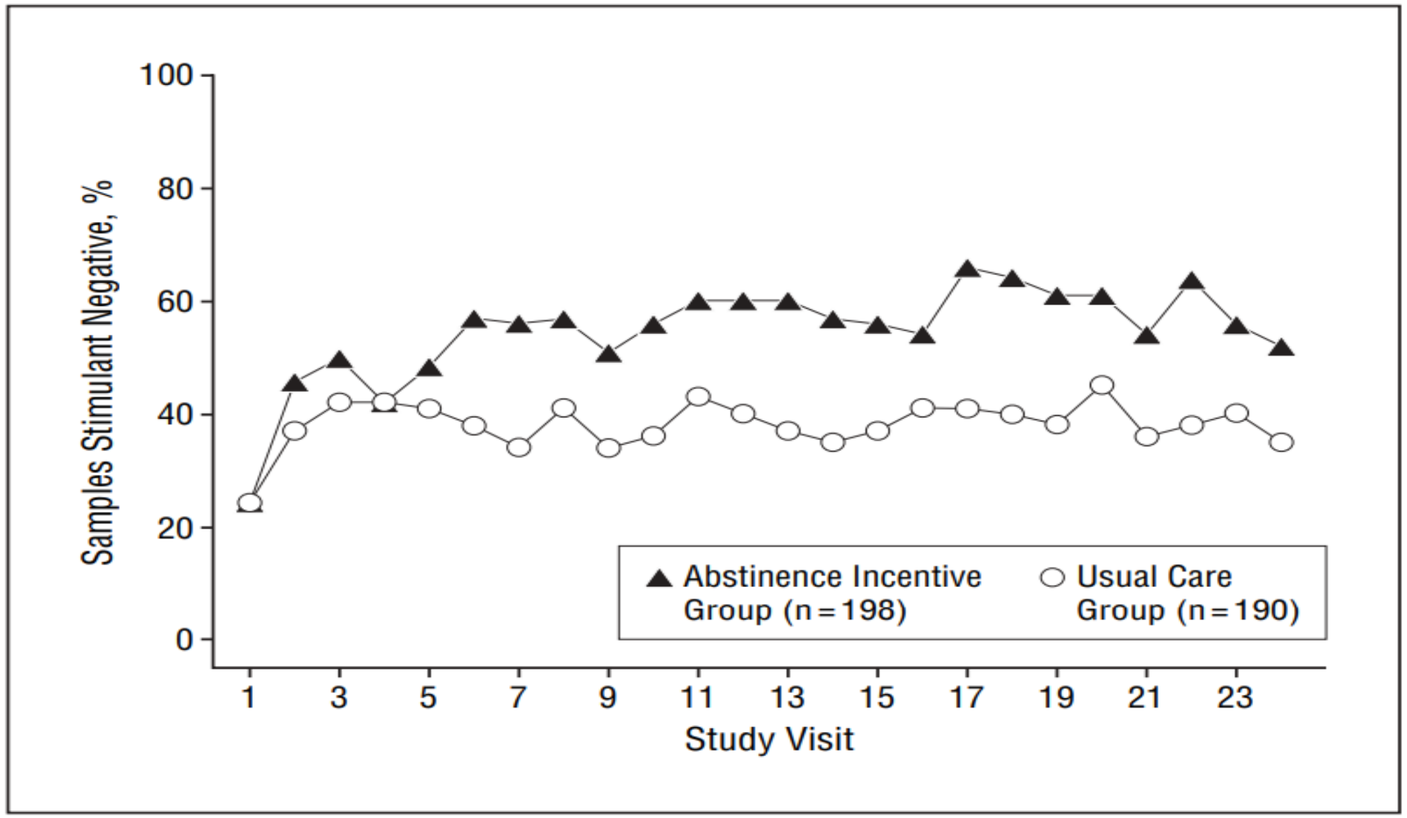
Source: Peirce et al., *Arch Gen Psychiatry.* 2006

Effects of lower-cost incentives on stimulant abstinence in methadone maintenance treatment: a National Drug Abuse Treatment Clinical Trials Network study

- 388 participants across 6 OTPs were randomly assigned to either the CM condition (intermittent reinforcement, “fishbowl”) or treatment as usual (TAU).
  - On methadone, submitted stimulant-positive UDS within 2 weeks
- Submission of negative samples was twice as likely for CM as for the TAU group.
- Achieving 4 or more, 8 or more, and 12 weeks of continuous abstinence was approximately 3, 9, and 11 times more likely for CM vs TAU participants.
- The average cost of prizes was $120 per participant.

Source: Peirce et al., *Arch Gen Psychiatry.* 2006

Percent Samples Stimulant Negative



Target drug use. The mean percentage of submitted samples testing negative for target drugs (stimulants and alcohol) is shown for abstinence incentive and usual care participants at each of 24 study visits.

Source: Peirce et al., *Arch Gen Psychiatry.* 2006

Desipramine and contingency management for cocaine and opiate dependence in buprenorphine-maintained patients.

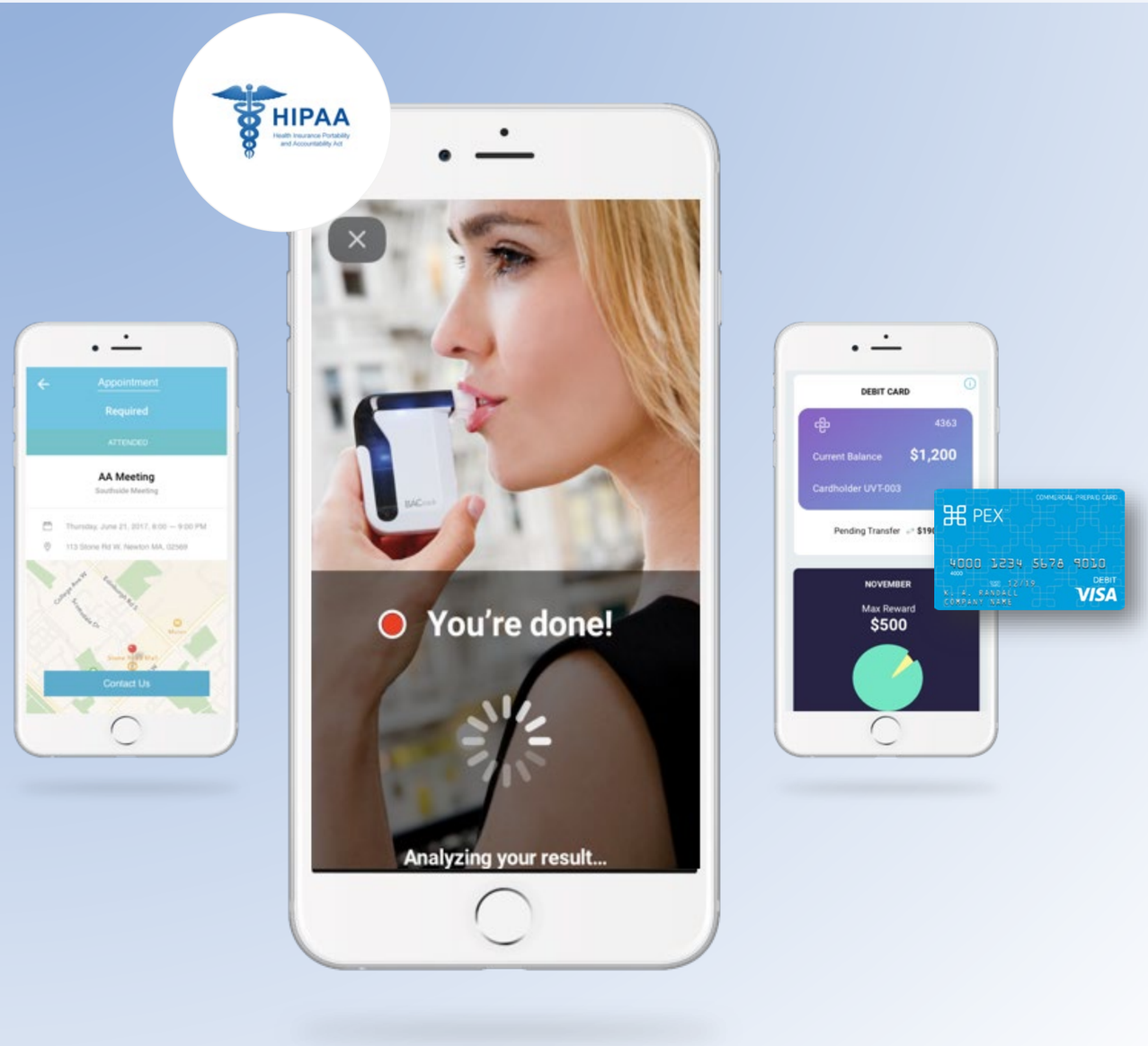
- A 12-week, randomized, double blind, four cell trial evaluating DMI (150 mg/day) or placebo plus CM or a non-contingent voucher control in 160 cocaine users maintained on buprenorphine (median 16 mg daily)
- Cocaine-free and combined opiate and cocaine free urines increased more rapidly over time in those treated with either DMI or CM, and those receiving both interventions had more drug-free urines (50%) than the other three treatment groups (25/29%)
- DMI and CM had independent and additive effects in facilitating cocaine-free urines in buprenorphine-maintained patients

Source: Kosten et al., *Drug and Alcohol Dependence*. 2003

App-based CM?

- At least three companies are marketing app-based treatment programs that deliver CM remotely:
  - DynamiCare - CM delivered for stimulant-free saliva tests
  - reSET - FDA cleared, CM delivered for completion of treatment modules
  - WeConnect - CM delivered for adherence to treatment plan activities

An Integrated, Wrap-around Toolkit, Powered by CM



- Recovery Coaching
- Remote Substance Testing
- Medication Adherence
- Appointment Tracking
- CBT Modules
- Virtual Recovery Support
- FINANCIAL REWARDS

Net Promoter Score: **72**

Medications for MUD - 1

Positive Signals

- Bupropion (better in low severity users)[1]
- Mirtazapine[2]
- Naltrexone[3]
- Methylphenidate[4]
- d-amphetamine (craving/WD)[5]
- Topiramate (better if abstinent at tx entry)[6]
- Modafinil (better in hi-severity users)[7]

[1]Elkashef et al. 2008, Shoptaw et al., 2008; Heinzerling et al., 2014; Anderson et al., 2015; [2]Colfax et al., 2012; Coffin et al., 2020; [3]Jayaram-Linstrom et al., 2008; [4]Tiihonen et al., 2007; Ling et al., 2014; [5]Galloway et al., 2011; [6]Elkashef et al., 2011; [7]Heinzerling et al., 2010; Anderson et al., 2012.

Medications for MUD - 2

(Mostly) Negative Results

- Imipramine
- Desipramine
- Tyrosine
- Ondansetron
- Fluoxetine
- Sertraline, paroxetine
- Aripiprazole
- Gabapentin
- N-acetylcysteine
- Varenicline

Bupropion: dopamine-norepinephrine re-uptake inhibitor for meth?

Randomized trial of bupropion SR 150 mg twice daily versus placebo for 12 weeks in methamphetamine users with ***less than daily meth use***

Total sample	Bupropion (N=41)	Placebo (N=43)	P value
End of treatment abstinence	29% (12)	14% (6)	0.087

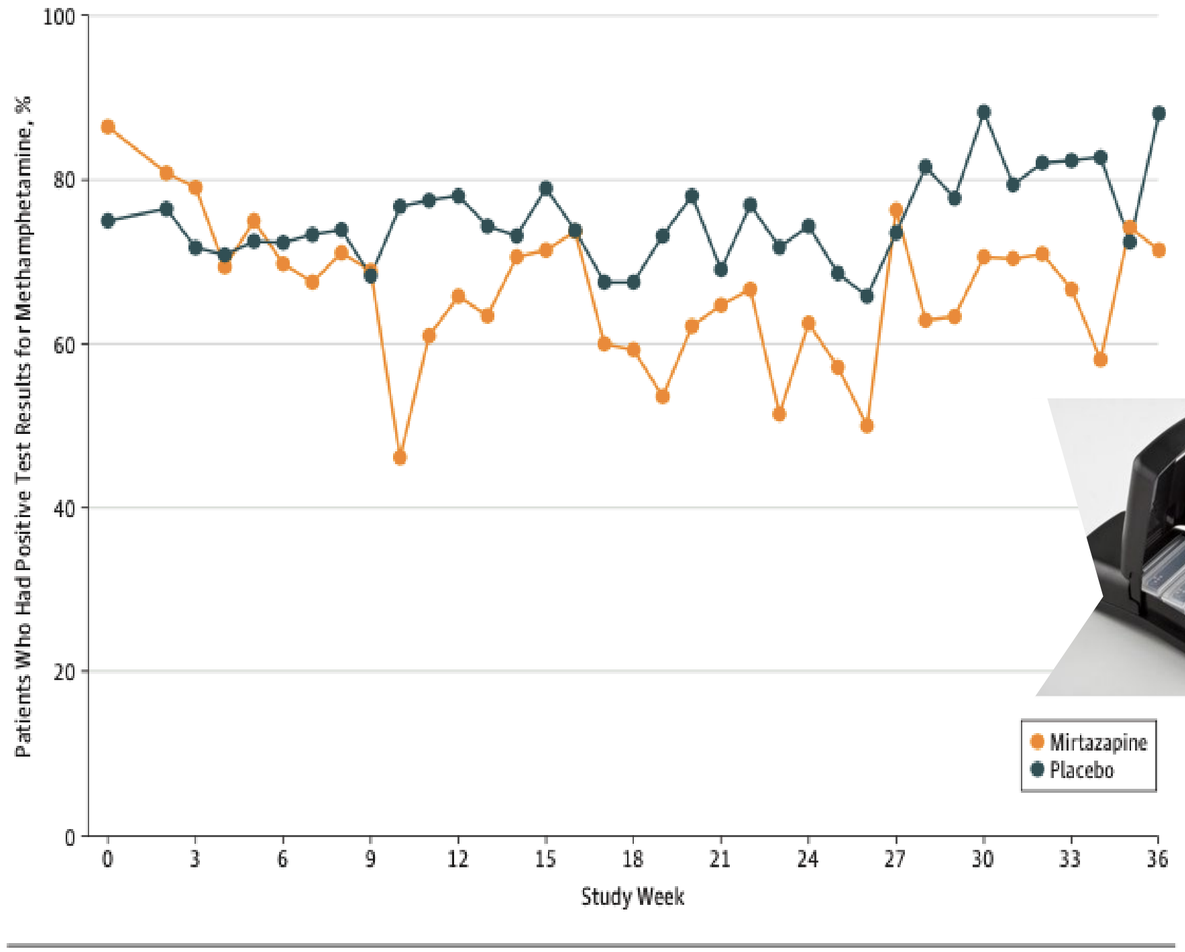
Only 32% (13/41) of bupropion participants were deemed medication adherent via week 6 plasma bupropion level. Adherence was strongly associated with end of treatment meth abstinence.

Bupropion only	Adherent (N=13)	Non-adherent (N=28)	P value
End of treatment abstinence	54% (7)	18% (5)	0.018

Source: Heinzerling KG. 2014, *Addiction*

MIRTAZAPINE

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



Colfax GN, et al. (2011) *Arch Gen Psychiatry;* Coffin PO et al. (2019) *JAMA Psychiatry*.

Summary:

- Double blind, RCT, n=120 cis men, transgender men, transgender women who have sex with men and MA use disorder, actively using MA
- Mirtazapine 30 mg vs placebo, plus counseling, for 24 weeks, and 12 weeks of f/u
- ~40% adherence in both groups (used WisePill dispenser)
- Significant reductions in positive UDS in the mirtazapine group at all time points

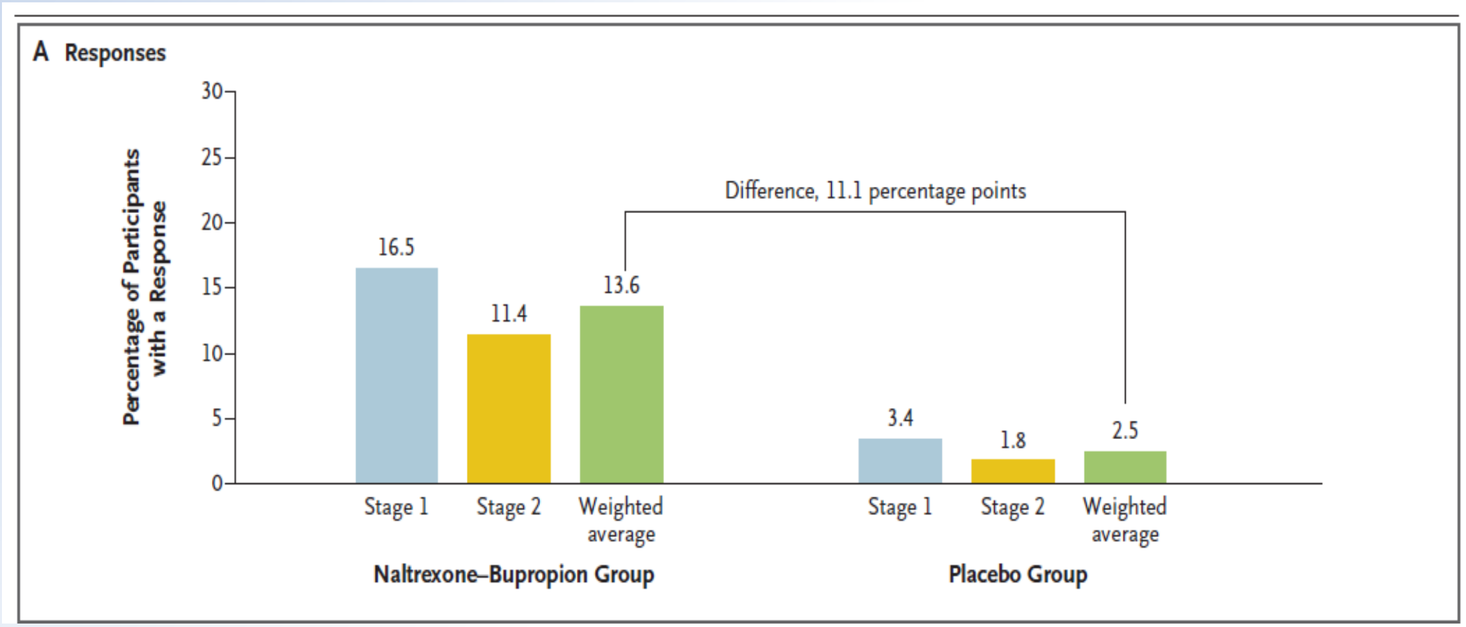
Sustained-Release Methylphenidate for MUD

- Sustained-release methylphenidate (MPH) titrated to 54mg/day to reduce methamphetamine (MA) use (N=90).
- 10 weeks active med (MPH vs. PLB), then 4 weeks single-blind PLB
- CBT platform with motivational incentives (MA-neg UDS)
- MPH associated with significantly fewer self-reported days of MA use over the active treatment period than PLB in MA users with >10 days use in past 30 days at baseline (not for 1° outcome)
- MPH group reduced MA use > PLB from baseline to end of active phase (6.5 vs. 3.5 days)
- No difference in proportion of +UDS across active med period

Source: Galloway, 2011

Naltrexone for MUD

- Naltrexone shown to reduce subjective effects of MA and relapse to amphetamines[1]
- NIDA CTN: open-label 8-wk pilot study (N=49) XR-naltrexone + bupropion XL 450 mg for severe MUD yielded 11 responders (6 out of 8 MA-negative UDS in last 4 weeks of meds)[2]
- f/u RCT: combination yielded significant response relative to placebo in 12-week, 2 stage trial (N= 403 Stage 1, N= 225 Stage 2) (*see fig*)[3]



Sources: [1]Jayaram-Lindstrom et al., 2008 *Am J Psych*; [2]Mooney LJ et al, 2016 *J Addict Med*. [3]Trivedi et al., 2021 *NEJM*

Clinical Management Considerations

- Treat agitation or withdrawal symptoms if indicated
- Provide/refer to evidence-based behavioral interventions
- Treat psychiatric comorbidity
- Consider medications with some evidence base
  - Think about comorbidities when selecting options (e.g., ADHD, depression, anxiety)
  - Consider severity of use (e.g., frequency, duration)

Summary of Pharmacotherapy Evidence – Methamphetamine

- Underpowered studies, high attrition
- Bupropion may be more effective in individuals with lower use disorder severity
  - May be better in individuals with depression, males
- Low strength evidence that methylphenidate and topiramate may facilitate reduction in use
  - Topiramate better if negative urine screen at baseline
  - Standard dosing ranges generally studied

Source: Chan et al., 2018

Summary of Off-Label Pharmacotherapy Options Cont'd

- Methamphetamine: bupropion 300 mg/day, topiramate 300 mg/day, naltrexone, mirtazapine 30 mg/day, methylphenidate 54 mg/day
- Evidence for effects of prescription stimulants on abstinence most robust for cocaine use d/o; influenced by dose and potency
- Safety considerations: seizure threshold, h/o prescription stimulant use disorder, medical/psych/substance comorbidities

Source: Buchholz & Saxon, 2019. *Curr Opin Psychiatry*; Tardelli VS et al., 2020, *Psychopharmacology.*

Naloxone for Users of Methamphetamine?

- Patients with co-occurring stimulant use disorder and opioid use disorder should be maintained on medication treatment for opioid use disorder (MOUD), even if stimulant use is ongoing.
- With increasing rates of fentanyl mixed into samples of methamphetamine (and cocaine), stimulant users are at much higher risk for overdose death due to their lack of tolerance for opioids.
- Stimulant users should be educated about the dangers of fentanyl and offered naloxone in case of opioid overdose.
- Fentanyl has greater affinity for the opioid receptor than naloxone = more difficult to reverse overdose.

What are some treatment implications for MUD + OUD?

- **Prescribe naloxone** for overdose prevention
  - May require more than one dose to counteract the effects of meth and heroin/fentanyl
- Combine **medication treatment for OUD with contingency management** for meth
- Assess and treat psychiatric comorbidity
- Refer to other **evidence-based behavioral tx interventions**: CBT, CRA
- Emerging considerations: exercise? rTMS? Digital therapeutics?

Thank you!

Larissa Mooney, M.D.
lmooney@mednet.ucla.edu

References

- Buchholz J, Saxon AJ. Medications to treat cocaine use disorders: current options. *Curr Opin Psychiatry*. 2019;32(4):275-281. doi:10.1097/YCO.0000000000000518
- Chan B, Kondo K, Ayers C, Freeman M, Montgomery J. Pharmacotherapy for Stimulant Use Disorders: A Systematic Review. Published online 2019. Accessed February 25, 2021. https://europepmc.org/article/med/30715830
- Charlotte W, Loshak H, Dulong C. Withdrawal Management and Treatment of Crystal Methamphetamine Addiction in Pregnancy: A Review of Clinical Effectiveness and Guidelines. Published online 2019. Accessed February 25, 2021. https://europepmc.org/article/nbk/nbk546255?report=printable&client=bot&client=bot&client=bot
- Coffin PO, Santos G, Hern J, et al. Effects of Mirtazapine for Methamphetamine Use Disorder Among Cisgender Men and Transgender Women Who Have Sex With Men: A Placebo-Controlled Randomized Clinical Trial. *JAMA Psychiatry.* 2020;77(3):246–255. doi:10.1001/jamapsychiatry.2019.3655
- Colfax GN, Santos G, Das M, et al. Mirtazapine to Reduce Methamphetamine Use: A Randomized Controlled Trial. *Arch Gen Psychiatry.* 2011;68(11):1168–1175. doi:10.1001/archgenpsychiatry.2011.124
- Comer SD, Sullivan MA, Yu E, et al. Injectable, Sustained-Release Naltrexone for the Treatment of Opioid Dependence: A Randomized, Placebo-Controlled Trial. *Arch Gen Psychiatry*. 2006;63(2):210–218. doi:10.1001/archpsyc.63.2.210.
- Dackis, Charles A, et al. “A Double-Blind, Placebo-Controlled Trial of Modafinil for Cocaine Dependence.” *Neuropsychopharmacology*, vol. 30, no. 1, 2005;20(1):205–211. doi:10.1038/sj.npp.1300600.
- Dackis, Charles A, et al. “A Double-Blind, Placebo-Controlled Trial of Modafinil for Cocaine Dependence.” *Journal of Substance Abuse Treatment.* 2012;43(3):303–312. doi:10.1016/j.jsat.2011.12.014.
- Decisions in Recovery: Treatment for Opioid Use Disorder. https://mat-decisions-in-recovery.samhsa.gov/. Accessed February 2021.
- D’Onofrio G, O’Connor PG, Pantalon MV, et al. Emergency Department–Initiated Buprenorphine/Naloxone Treatment for Opioid Dependence: A Randomized Clinical Trial. *JAMA*. 2015;313(16):1636–1644. doi:10.1001/jama.2015.3474

References

- Dutra L, Stathopoulou G, Basden SL, Leyro TM, Powers MB, Otto MW. A meta-analytic review of psychosocial interventions for substance use disorders. Am J Psychiatry. 2008;165(2):179-187. doi:10.1176/appi.ajp.2007.06111851
- Ellis MS, Kasper ZA, Cicero TJ. Twin epidemics: The surging rise of methamphetamine use in chronic opioid users. Drug and Alcohol Dependence. 2018;193:14-20. doi:10.1016/j.drugalcdep.2018.08.029
- Galloway GP, Buscemi R, Coyle JR, et al. A randomized, placebo-controlled trial of sustained-release dextroamphetamine for treatment of methamphetamine addiction. Clin Pharmacol Ther. 2011;89(2):276-282. doi:10.1038/clpt.2010.307
- Garbutt J, Kranzler H, O'Malley S, Jama DG-, 2005 undefined. Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. jamanetwork.com. Accessed February 25, 2021. https://jamanetwork.com/journals/jama/article-abstract/200637
- Garbutt J, West S, Carey T, Lohr K, Jama FC-, 1999 undefined. Pharmacological treatment of alcohol dependence: a review of the evidence. jamanetwork.com. Accessed February 25, 2021. https://jamanetwork.com/journals/jama/article-abstract/189443?casa_token=p5BdWwV8plwAAAAA:N30nColM8Rwm_VGy0xwCTiXe_PdveWCqQuJOsYRRLAjriyShj3HE-src2YNLrzB7JZOh2hJI9A
- Gerra G, Fantoma A, Zaimovic A. Naltrexone and buprenorphine combination in the treatment of opioid dependence. *Journal of Psychopharmacology*. 2006;20(6):806-814. doi:10.1177/0269881106060835
- Goodnough A, Katz J, Sanger-katz M. Drug Overdose Deaths Drop in U.S. for First Time Since 1990. The New York Times. https://www.nytimes.com/interactive/2019/07/17/upshot/drug-overdose-deaths-fall.html. Published July 17, 2019. Accessed February 17, 2021.
- Gorelick, David A., et al. "Transcranial Magnetic Stimulation in the Treatment of Substance Addiction." *Annals of the New York Academy of Sciences*, 2014, doi:10.1111/nyas.12479.

References

- Hedegaard H, Warner M, Miniño AM. Drug overdose deaths in the United States, 1999–2015. NCHS data brief, no 273. Hyattsville, MD: National Center for Health Statistics. 2017.
- Heinzerling, Keith G, et al. Randomized, Placebo-Controlled Trial of Bupropion in Methamphetamine-Dependent Participants with Less than Daily Methamphetamine Use. *Addiction.* 2014;109(11):1878–1886. doi:10.1111/add.12636.
- Johnson B, Rosenthal N, Capece J, Jama FW-, 2007 undefined. Topiramate for treating alcohol dependence: a randomized controlled trial. jamanetwork.com. Accessed February 25, 2021. https://jamanetwork.com/journals/jama/fullarticle/vol/298/pg/1641
- Johnson BA, Rosenthal N, Capece JA, et al. Improvement of Physical Health and Quality of Life of Alcohol-Dependent Individuals With Topiramate Treatment US Multisite Randomized Controlled Trial. Accessed February 25, 2021. https://jamanetwork.com/
- Kidorf M, Disney ER, King VL, Neufeld K, Beilenson PL, Brooner RK. Prevalence of psychiatric and substance use disorders in opioid abusers in a community syringe exchange program. Drug Alcohol Depend. 2004;74(2):115-122. doi:10.1016/j.drugalcdep.2003.11.014
- Kiefer F, Jahn H, Tarnaske T, et al. Comparing and combining naltrexone and acamprosate in relapse prevention of alcoholism: A double-blind, placebo-controlled study. *Archives of General Psychiatry*. 2003;60(1): 92–99
- Krupitsky E, Zvartau E, Woody G. Use of Naltrexone to Treat Opioid Addiction in a Country in Which Methadone and Buprenorphine Are Not Available. Springer. doi:10.1007/s11920-010-0135-5
- Krystal, JH, Cramer, JA, Krol, WF, Kirk, GF, Rosenheck, RA. Veterans Affairs Naltrexone Cooperative Study 425 Group. Naltrexone in the treatment of alcohol dependence. New England Journal of Medicine. 2001; 345(24):1734–1739.
- Jayaram-Lindström N, Hammarberg A, Beck O, Franck J. Naltrexone for the Treatment of Amphetamine Dependence: A Randomized, Placebo-Controlled Trial. American Journal of Psychiatry. 2008;165(11):1442-1448. doi:10.1176/appi.ajp.2008.08020304
- Levin, FR, et al. Extended Release Mixed Amphetamine Salts and Topiramate for Cocaine Dependence: A Randomized Clinical Replication Trial with Frequent Users. *Drug and Alcohol Dependence*.2020; 206:107700. doi:10.1016/j.drugalcdep.2019.107700.

References

- Ling W, Hillhouse MP, Saxon AJ, et al. Buprenorphine + naloxone plus naltrexone for the treatment of cocaine dependence: the Cocaine Use Reduction with Buprenorphine (CURB) study. Wiley Online Library. 2016;111(8):1416-1427. doi:10.1111/add.13375
- Mariani JJ, Pavlicova M, Bisaga A, Nunes EV, Brooks DJ, Levin FR. Extended-release mixed amphetamine salts and topiramate for cocaine dependence: a randomized controlled trial. Biol Psychiatry. 2012;72(11):950-956. doi:10.1016/j.biopsych.2012.05.032
- Mason BJ, Quello S, Goodell V, et al. Gabapentin treatment for alcohol dependence: a randomized clinical trial. *JAMA Internal Med.* 2014;174(1): 70-7.
- Maxwell JC. A new survey of methamphetamine users in treatment: who they are, why they like 'meth' and why they need additional services. *Substance Use & Misuse.* 2014;49(6): 639-644. DOI 10.3109/10826084.2013.841244
- McMahan V, et al. Interest in Reducing Methamphetamine and Opioid Use among Syringe Services Program Participants in Washington State. *Drug and Alcohol Dependence.* 2020
- Mooney LaJ, et al. Utilizing a Two-Stage Design to Investigate the Safety and Potential Efficacy of Monthly Naltrexone Plus Once-Daily Bupropion as a Treatment for Methamphetamine Use Disorder. Journal of Addiction Medicine.2016;10(4):236–243., doi:10.1097/adm.0000000000000218.
- NIAAA 2014, NIH Publication No. 14-7974. Accessed from https://pubs.niaaa.nih.gov/publications/treatment/treatment.htm on Oct. 12, 2017.
- O'Malley SS, Garbutt JC, Gastfriend DR, Dong Q, Kranzler HR. Efficacy of extended-release naltrexone in alcohol-dependent patients who are abstinent before treatment. *Journal of Clinical Psychopharmacology*.2007;27(5):507–512.
- PrescribeToPrevent. https://prescribetoprevent.org/. Accessed February 2021.
- Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: Results from the 2019 National Survey on Drug Use and Health (HHS Publication No. PEP20-07-01-001, NSDUH Series H-55). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration.2020. Retrieved from https://www.samhsa.gov/data/

References

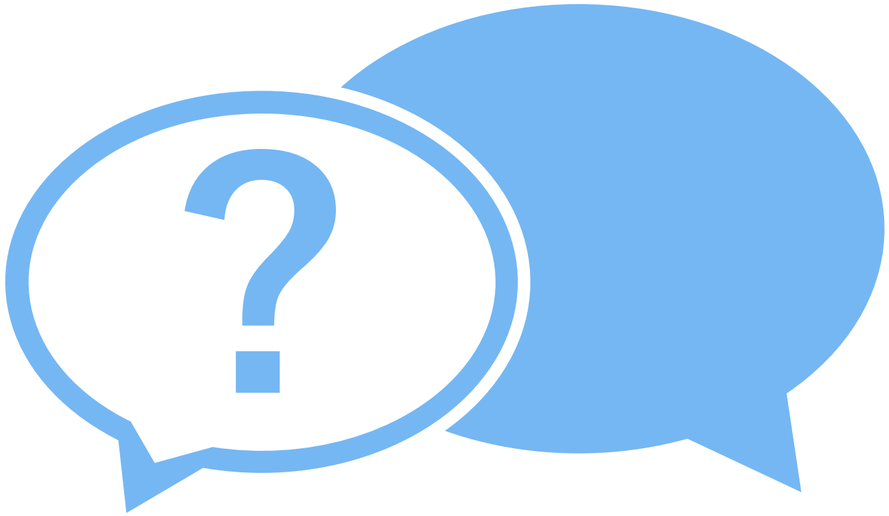
- Suchting R, et al. Preliminary Examination of the Orexin System on Relapse-Related Factors in Cocaine Use Disorder. Brain Research. 2019;1731: 146359.doi:10.1016/j.brainres.2019.146359.
- Tardelli VS et al. Prescription psychostimulants for the treatment of stimulant use disorder: A systematic review and meta-analysis. Psychopharmacology (Berl). 2020;237:2233.doi.org/10.1007/s00213-020-05563-3
- Trivedi MH, Walker R, Ling W, et al. Bupropion and Naltrexone in Methamphetamine Use Disorder. N Engl J Med. 2021;384(2):140-153. doi:10.1056/NEJMoa2020214
- Tsui, et al. Association between methamphetamine use and retention among patients with opioid use disorders treated with buprenorphine. Journal of Substance Abuse Treatment.2020;109:80–85
- Volkow, ND, et al. Therapeutic Doses of Oral Methylphenidate Significantly Increase Extracellular Dopamine in the Human Brain. The Journal of Neuroscience.2001;21(2).doi:10.1523/jneurosci.21-02-j0001.2001.
- Volpicelli J, Alterman AI, Hayashida M, & O'Brien CP. Naltrexone in the treatment of alcohol dependence. Archives of Gen Psychiatry.1992;49(11: 867-880.
- Volpicelli J, Rhines K, Rhines J, Volpicelli LA, Alterman AI, O'Brien CP. Naltrexone and alcohol dependence: Role of subject compliance. (1997). Archives of General Psychiatry.1997;54(8):737–742.
- West SL, Garbutt JC, Carey TS, Lux LJ, Jackman AM, Tolleson-Rinehart S,…Crews, FT.Pharmacotherapy for alcohol dependence. Evidence Report No. 3. (AHCPR Pub. No. 99-E004) Rockville, MD: U.S. Department of Health and Human Services; Public Health Service, Agency for Health Care Policy and Research.1999
- Wu LT, Zhu H, Swartz MS. Treatment utilization among persons with opioid use disorder in the United States. Drug Alcohol Depend. 2016;169:117-127. doi:10.1016/j.drugalcdep.2016.10.015
- Wright C, Moore RD. Disulfiram treatment of alcoholism. American Journal of Medicine.1990;88(6):647–655.

References

- AshaRani PV, Aditi H, Esmond S, Wei J, Jit HT, and Mythily S. Non-pharmacological interventions for methamphetamine use disorder: a systematic review. Drug and Alcohol Dependence. 2020 May;212. doi:108060.
- Lappan SN, Brown AW, Hendricks PS. Dropout rates of in-person psychosocial substance use disorder treatments: a systematic review and meta-analysis. Addiction. 2020 Feb;115(2):201-217. doi: 10.1111/add.14793.
- National Drug Threat Assessment, 2020. DEA Methamphetamine profiling program.
- Peirce JM, Petry NM, Stitzer ML, Blaine J, Kellogg S, Satterfield F, Schwartz M, Krasnansky J, Pencer E, Silva-Vazquez L, Kirby KC, Royer-Malvestuto C, Roll JM, Cohen A, Copersino ML, Kolodner K, Li R. Effects of lower-cost incentives on stimulant abstinence in methadone maintenance treatment: a National Drug Abuse Treatment Clinical Trials Network study. Arch Gen Psychiatry. 2006 Feb;63(2):201-8. doi: 10.1001/archpsyc.63.2.201. PMID: 16461864.
- Rawson RA, Huber A, McCann M, Shoptaw S, Farabee D, Reiber C, Ling W. A comparison of contingency management and cognitive-behavioral approaches during methadone maintenance treatment for cocaine dependence. Arch Gen Psychiatry. 2002 Sep;59(9):817-24. doi: 10.1001/archpsyc.59.9.817. PMID: 12215081.
- Thomas Kosten , Alison Oliveto , Alan Feingold, James Poling , Kevin Sevarino , Elinore McCance-Katz, Susan Stine, Gerardo Gonzalez, Kishor Gonsai (2003) Desipramine and contingency management for cocaine and opiate dependence in buprenorphine maintained patients. Drug and Alcohol Dependence. 70, 315-325.
- The National Threat Assessment, 2005, National Drug Intelligence Center, U.S. Dept. of Justice DEA Methamphetamine Profiling Program.

Q&A

Questions? Please type them in the chat box!



gracias cảm ơn bạn ধন্যবাদ 고맙습니다

شكرا جزيلا salamat благодарю вас 谢谢

Dziękuję Ci **Thank** ευχαριστώ

quyana tack **you!** አመሰግናለሁ

धन्यवाद danke asante grazie

hík’ʷu? merci תודה obrigado ขอบคุณ

ありがとうございました спасибі mahalo