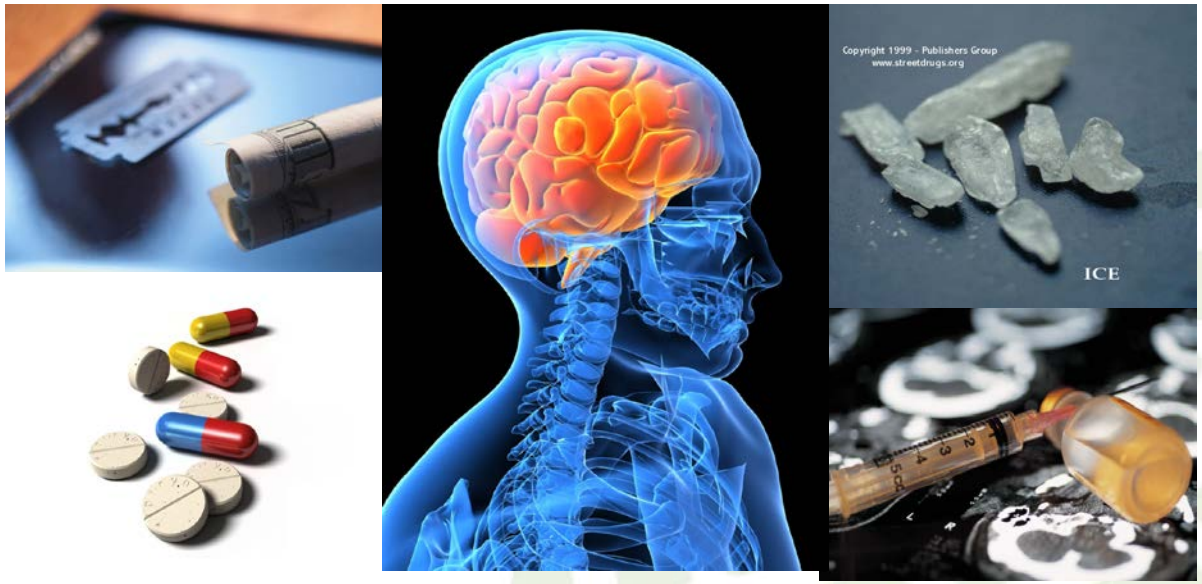
Stimulant Use by Patients on Medication for Opioid Use Disorder: *Do We Have Any Answers?*



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April 27 2020

No Disclosures

Learning Objectives

- Participants will be able to explain the current epidemiology of cocaine and methamphetamine in the US
- Participants will be able to describe the most common clinical challenges in treatment people with stimulant use disorders.
- Participants will be able to review and discuss the current evidence-based practices for the treatment of individuals on MOUD with stimulant use disorder.

Forms of Methamphetamine

Methamphetamine Powder

Description: Beige/yellowy/off-white powder

Crystalline Methamphetamine

Description: White/clear crystals/rocks; ‘crushed glass’ / ‘rock salt’

Methamphetamine Today

- **The market is inundated with so much pure, low-cost meth that dealers have more of it than they know what to do with.**
- **2018 - United States border agents seizing 10 to 20 times the amounts they did a decade ago.**
- **Methamphetamine, experts say, has never been purer, cheaper or more lethal.**
- **2014–2018- Fentanyl-contaminated meth and cocaine**

Figure 76. Two Milligrams of Fentanyl - A Potential Lethal Dose

Source: Network Environmental Systems (NES)

A lethal dose of carfentanil 1/100th of the amount shown next to the penny.

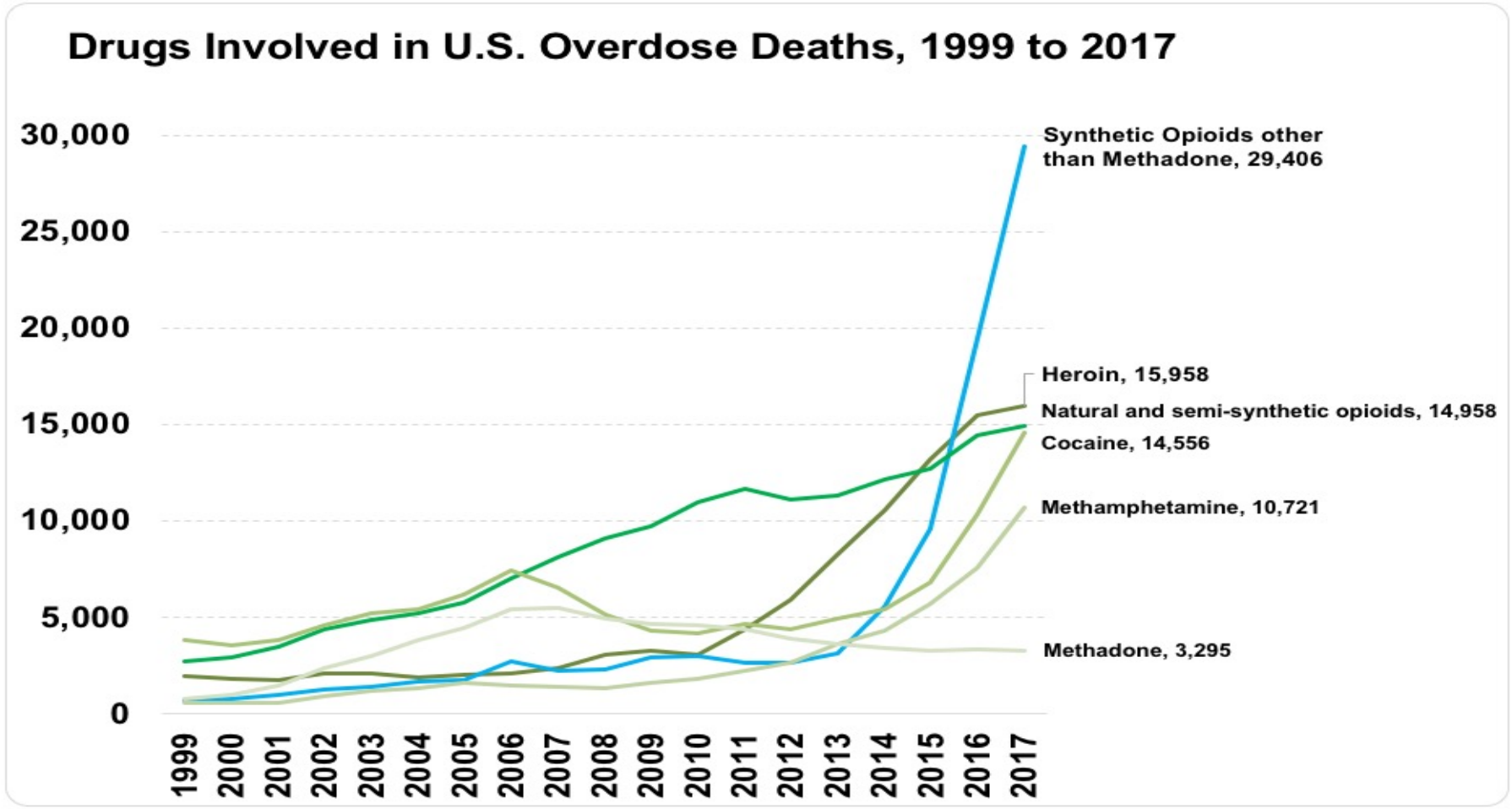
Covid-19 and Drug Supply

Cartels are scrambling': Virus snarls global drug trade MUSTIAN and BLEIBERG AP News April 19, 2020

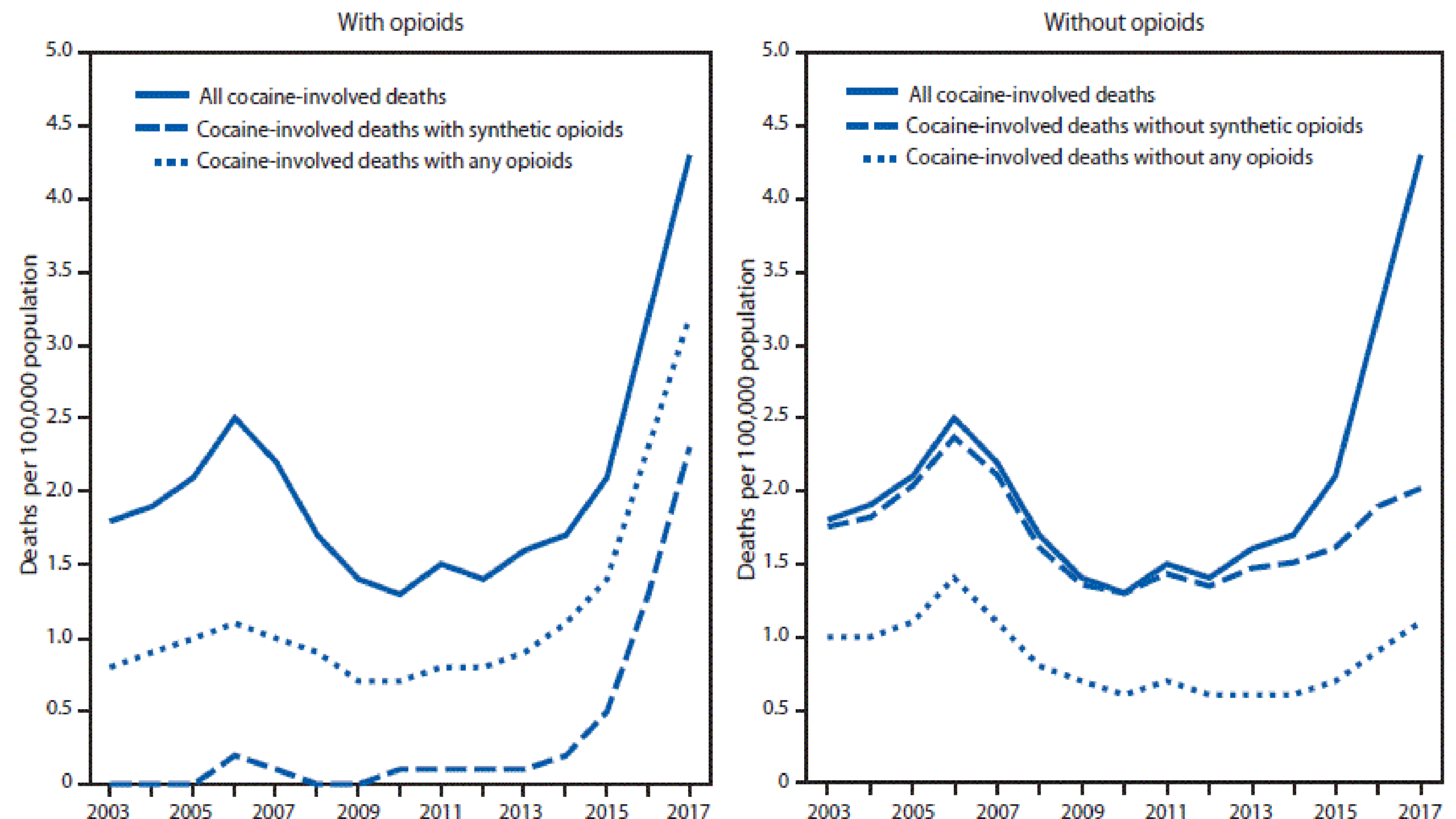
- Virtually every illicit drug has been impacted, with supply chain disruptions at both the wholesale and retail level. Traffickers are stockpiling narcotics and cash along the border, and the U.S. Drug Enforcement Administration even reports a decrease in money laundering and online drug sales on the so-called dark web.
- Cocaine prices are up 20 percent or more in some cities. Heroin has become harder to find in Denver and Chicago, while supplies of fentanyl are falling in Houston and Philadelphia. In Los Angeles, the price of methamphetamine has more than doubled in recent weeks to $1,800 per pound.

Cartels are scrambling': Virus snarls global drug trade MUSTIAN and BLEIBERG AP News April 19, 2020

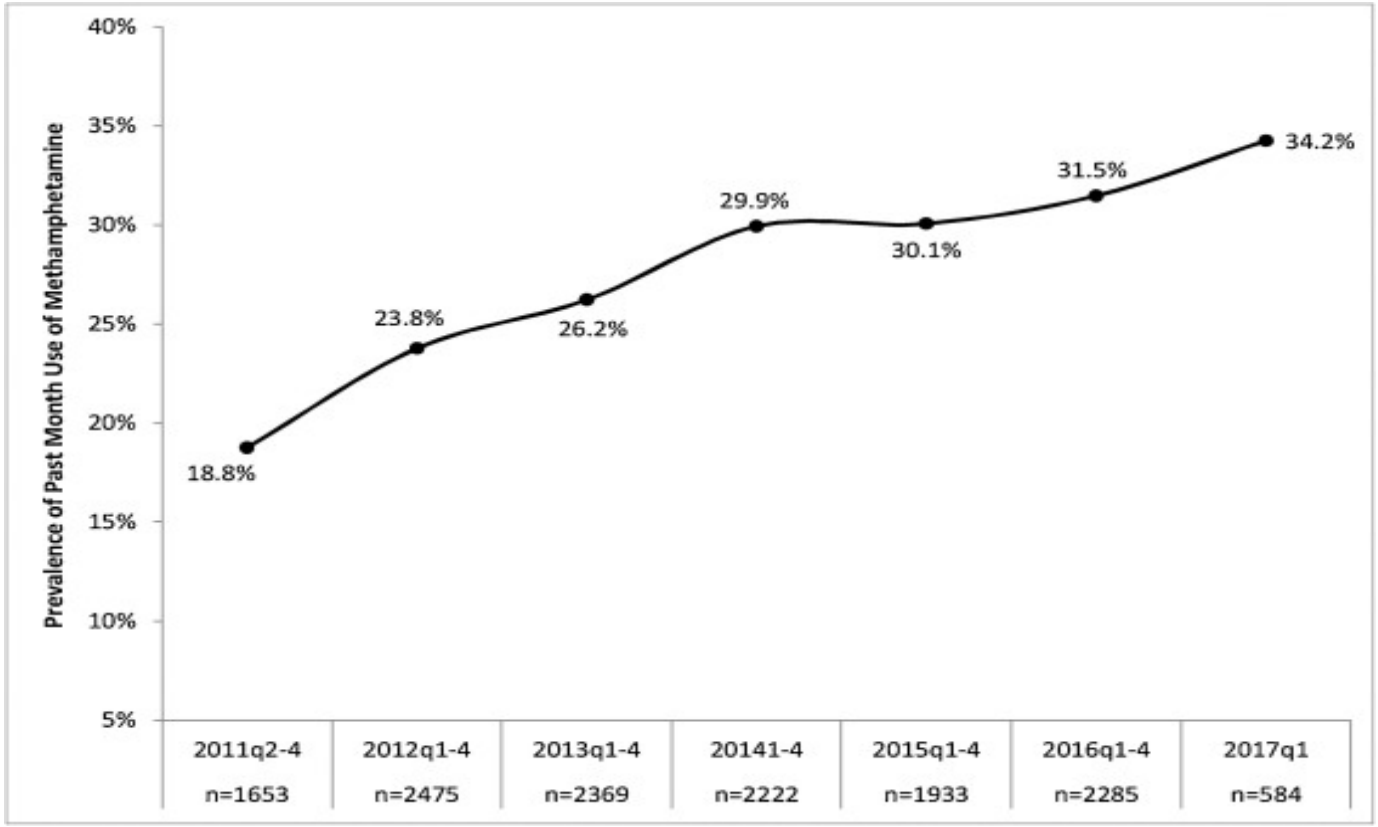
- Cartels are increasingly shifting to synthetic opioids such as fentanyl, which can be cooked 24/7 throughout the year, are up to 50 times more powerful than heroin and produce a greater profit margin.
- Though some clandestine labs that make fentanyl from scratch have popped up sporadically in Mexico, cartels are still very much reliant upon Chinese companies to get the precursor drugs.
- Huge amounts of these mail-order components can be traced to a single, state-subsidized company in Wuhan that shut down after the outbreak earlier this year, said Louise Shelley, director of the Terrorism, Transnational Crime and Corruption Center at George Mason University, which monitors Chinese websites selling fentanyl.


Drugs Involved in U.S. Overdose Deaths, 1999 to 2017
30,000
25,000
20,000
15,000
10,000
5,000
0
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
Synthetic Opioids other than Methadone, 29,406
Heroin, 15,958
Natural and semi-synthetic opioids, 14,958
Cocaine, 14,556
Methamphetamine, 10,721
Methadone, 3,295

Kariisa M, et al. *MMWR Morb Mortal Wkly Rep*. 2019;68(17):388-395


With opioids
Without opioids
All cocaine-involved deaths
Cocaine-involved deaths with synthetic opioids
Cocaine-involved deaths with any opioids
Cocaine-involved deaths without synthetic opioids
Cocaine-involved deaths without any opioids
Deaths per 100,000 population
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
2003
2005
2007
2009
2011
2013
2015
2017

Methamphetamine use among patients with chronic opioid use is on the rise



Ellis, MS, Kasper, ZA, Cicero, TJ (2018). Twin epidemics: The surging rise of methamphetamine use in chronic opioid users. Drug and Alcohol Dependence, v193, 1 Dec 2018, 14-20.

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The Prevalence of Methamphetamine Use is Increasing Among Individuals Entering Medication-Assisted Treatment Programs for Opioid Use Disorders

Severtson SG, Kreider SED, Olsen H, Ellis MS, Cicero TJ, Dart RC (2019). RADARS® System Technical Report, 2019-Q3

The Prevalence of Methamphetamine Use is Increasing Among Individuals Entering Medication-Assisted Treatment Programs for Opioid Use Disorders

- **Data from the RADARS® System Opioid Treatment Program were used to assess the change in the prevalence of past month methamphetamine use among individuals entering medication-assisted treatment programs for opioid use disorders. Data from 39,312 valid surveys given to individuals entering treatment facilities from January 2012 through December 2018 were assessed.**

The Prevalence of Methamphetamine Use is Increasing Among Individuals Entering Medication-Assisted Treatment Programs for Opioid Use Disorders

- **The number of respondents reporting past month use of methamphetamine increased from 402 (7.8%) in 2012 to 1,166 (21.3%) in 2018. Areas with the greatest increases in the number of cases appeared to be in the West (California, Montana, Nevada), the Midwest (Indiana) and South (Oklahoma) .**

- **The Census Region with the highest prevalence of past month methamphetamine use in 2018 was the West region (46.0%) followed by the South (16.8%), the Midwest (12.4%), and the Northeast (5.4%)**

Heroin and Methamphetamine Injection: An Emerging Drug Use Pattern

- Alia Al-Tayyib, Stephen Koester, Sig Langegger & Lisa Raville (2017) Heroin and Methamphetamine Injection: An Emerging Drug Use Pattern, Substance Use & Misuse, 52:8, 1051-1058, DOI: 10.1080/10826084.2016.1271432
-

Heroin and Methamphetamine Injection: An Emerging Drug Use Pattern

- Persons who inject drugs (PWID) were recruited as part of the National HIV Behavioral Surveillance (NHBS) system in Denver, Colorado. Differences between those who reported only heroin injection, only methamphetamine injection, and combined heroin and methamphetamine injection were assessed.

Heroin and Methamphetamine Injection: An Emerging Drug Use Pattern

Table 4. Association between overdose and drug injection pattern in the past 12 months in a sample of persons who inject drugs.

	Overdosed at least once *n* (%)	**Unadjusted prevalence ratio (95% CI)**	**Adjusted prevalence ratio* (95% CI)**
Drug injection pattern			
Heroin only	20 (11.6)	1.0 (ref)	1.0 (ref)
Metham-phetamine only	9 (7.4)	0.63 (0.30, 1.35)	0.64 (0.29, 1.43)
Both heroin and metham-phetamine	99 (33.6)	2.89 (1.85, 4.49)	2.80 (1.72, 4.53)

Heroin and Methamphetamine Injection: An Emerging Drug Use Pattern

“Goofballing” : The practice of injecting both methamphetamine and heroin was associated is associated with a 2.8 times higher risk of overdose in the past 12 months than heroin injection alone. *

* These data are from 2015. With the rapid emergence of fentanyl, this OD death rate is likely now much higher.

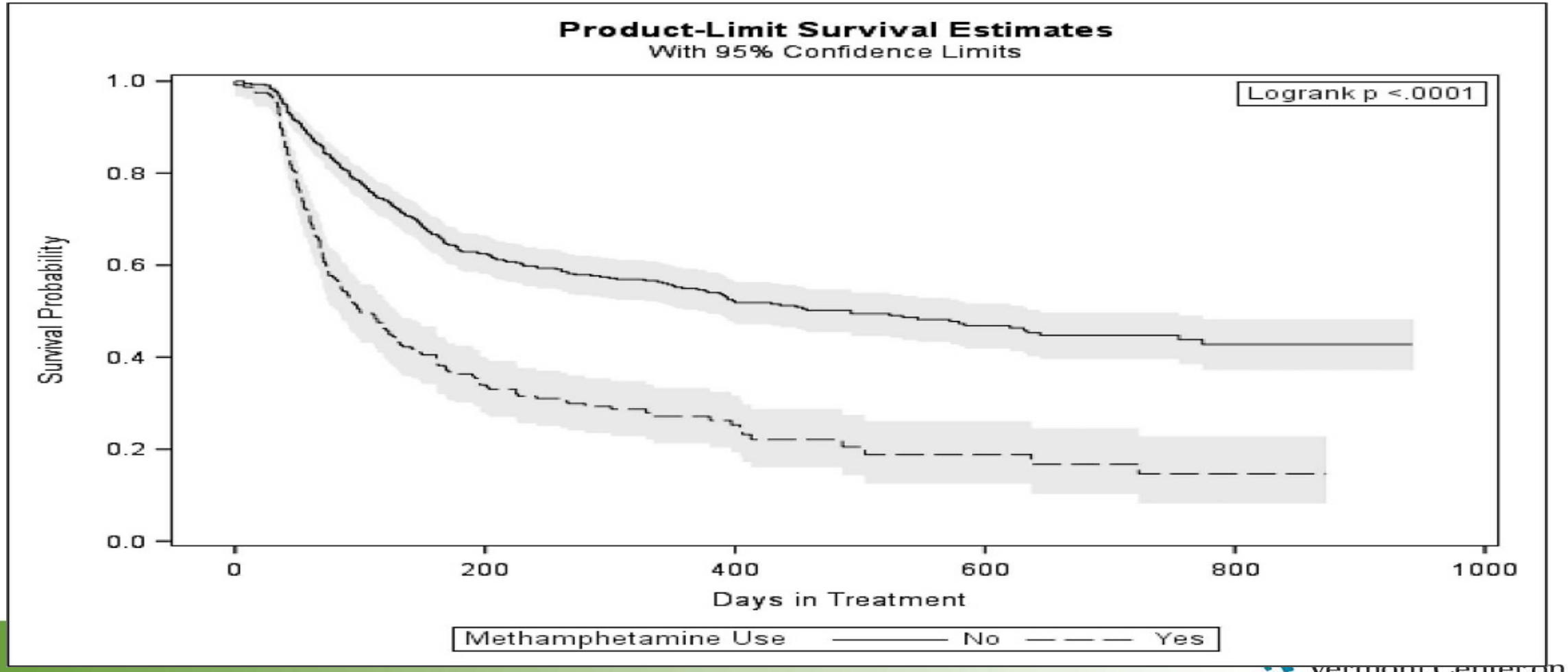
Association between methamphetamine use and retention among patients with opioid use disorders treated with buprenorphine

Journal of Substance Abuse Treatment
109 (2020) 80–85
Judith I. Tsui, et al.

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

- The study utilized data on adult patients receiving buprenorphine from Washington State Medication Assisted Treatment-Prescription Drug and Opioid Addiction program clinics between November 1, 2015 and April 31, 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).

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



Clinical Challenges

Clinical Challenges with Stimulant Dependent Individuals

- Overdose death
- Limited understanding of stimulant addiction
- Ambivalence about need to stop use
- Impulsivity/Poor judgement
- Cognitive impairment and poor memory
- Anhedonia
- Hypersexuality
- Violence and psychosis
- Powerful Pavlovian trigger-craving response
- Very poor retention in outpatient treatment
- Elevated rates of psychiatric co-morbidity

Methadone vs Buprenorphine: Is there a different response to stimulant use?

- **Don't know. We do not have good data on rates of stimulant use comparing patients on methadone with those on buprenorphine.**
- **Preclinical and laboratory research in the 80s and 90s suggested that buprenorphine may be useful in reducing stimulant use.**
- **Several studies (Strain et al 1994; Schottenfeld et al 1997) compared methadone and buprenorphine for the treatment of individuals who used opioids and cocaine. Results of both studies showed that both medications reduced opioid use but did not affect cocaine use.**
- **Ling et al 2016 reported mixed results when buprenorphine was used to treat cocaine dependent individuals. Some measures indicated a reduction of cocaine use, other measures concluded no effect. The jury is still out.**

Cocaine use by patients on methadone: We've been here before

- **In the late 1980s and 1990s, the cocaine epidemic seriously damaged the treatment progress of many patients on methadone.**
- **In many OTPs, 70% + of UAs were positive of cocaine.**
- **The treatment progress for many patients on methadone and who had not used illicit drugs for years was seriously degraded by high levels of cocaine use. This was particularly true once crack became available.**
- **Dramatic increases in injection drug use, HIV, Hep C and drug-related crime were associated with the elevated cocaine use. Premature treatment termination/drop-out rates increased dramatically.**
- **Many OTPs became locations for cocaine dealing and associated behaviors**

Acute Clinical Strategies

Clinical Management of Stimulant Users: *Acute Psychosis*

- **Symptoms of acute psychosis: Auditory hallucinations, and visual (flashing lights, peripheral artifacts), olfactory, and tactile sensations. Powerful paranoia and persecutory delusions are extremely common, ideas of reference, stereotypy and compulsive acts, blunt affect, poverty of speech, delirium, and violence.**
- **Stimulant-induced psychosis is generally transient and may require use of either a benzodiazepine or an antipsychotic, both of which should be discontinued when acute symptoms have resolved.**

Clinical Management of Stimulant Users: *Intoxication*

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

Clinical Management of Stimulant Users: *Withdrawal*

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

Harm Reduction Strategies for Stimulant Users

- Information about medical and psychiatric effects of meth
- Syringe Exchanges/Recommendations to change route of administration
- Naloxone (for opioid overdose)
- Quiet rooms and washup/shower rooms
- Condoms/safe sex education
- Topical antibiotic creams and ointments for injection sites
- Water (dehydration)
- Tooth paste/tooth brush

Research on “What Works”

First, What Doesn't Work

- **Intensive, process group therapy sessions discussing stimulant use or emotionally volatile content.**
- **Confrontation**
- **Medications**
- **Insight-oriented psychotherapy**
- **Generic CBT**
- **Kicking people out of treatment (Really, really bad idea).**

What do patients on MAT say about stimulant use?

- VERY modest exploratory interview project in Vermont with 25 patients on MAT who were current, or recent users of stimulants.
- 15 men; 10 women
- 19 use or used cocaine; 6 meth
- 12 injected; 12 smoked
- 15 were current users; 10 had stopped for at least 3 months.
- 14 on methadone; 11 on buprenorphine

What did the patients say?

- Reported availability of cocaine (and more recently meth) has greatly increased in past year. Is available from people who previously only sold opioids
- Drug history: 22 of 25 had used cocaine before using opioids. 3 of those individuals said they started opioids (pills) to “mellow out” from cocaine effects.
- 16 reported that they felt the effects of stimulants were more “addicting” than opioids. (They were referring to the fact that their opioid use was driven to avoid withdrawal. Their stimulant use was driven by a response to craving and desire for drug effect.)

What did the patients say?

- What are/were the challenges of stopping stimulant use?
  - Love the drug effect and in a perfect world would use all the time
  - Craving/desire is very powerful and ambivalent about stopping
  - Drug is widely available in inexpensive dosage forms
  - Craving is triggered by many things
    - Coming to the clinic
    - Standing in long dosing lines with drug conversations
    - Parts of town
    - Drug using friends
    - Dealers phone calls
    - Boredom

What did the patients say?

- **What helped them with stopping?**
  - **Group and individual general counseling.. NO**
  - **Groups discussing stimulant use… NO NO NO**

  (not unusual to go and use after group, with other group members)
  - **Changing dose…NO**
  - **Not carrying cash and limiting handling of money…YES**
  - **Avoiding drug using friends.. YES**
  - **Avoiding parts of town….YES**
  - **Changing phone numbers… YES**
  - **Coming to clinic when less crowded…Yes**
  - **Staying busy with activities**
    - **Kids**
    - **Exercise/sports**
    - **Animal rescue**

What did the patients say?

- Has any form of treatment been useful?
- 4 people reported that drug court was the key to their stopping
- 5 people had previously been in a study of contingency management and found it very useful
- With both of these “interventions” patients said the immediate certain consequences resulting from the results of a UA gave them something to “hold on to”. Although in drug court the main focus is on the negative contingency, the 2 patients talked about how rewarding it was to get the praise from the drug court folks and the judge for giving stimulant free samples.

Effective Treatment Strategies

PLOS | MEDICINE

RESEARCH ARTICLE

Comparative efficacy and acceptability of psychosocial interventions for individuals with cocaine and amphetamine addiction: A systematic review and network meta-analysis

Franco De Crescenzo[1,2,3], Marco Ciabattini[4], Gian Loreto D'Alò[4], Riccardo De Giorgi[1,2], Cinzia Del Giovane[5], Carolina Cassar[6], Luigi Janiri[3], Nicolas Clark[7], Michael Joshua Ostacher[8,9], Andrea Cipriani[1,2]*

1 Department of Psychiatry, University of Oxford, Oxford, United Kingdom, **2** Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, United Kingdom, **3** Institute of Psychiatry and Clinical Psychology, Catholic University of the Sacred Heart, Rome, Italy, **4** School of Hygiene and Preventive Medicine, University of Rome Tor Vergata, Rome, Italy, **5** Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland, **6** Department of Dynamic and Clinical Psychology, Sapienza University of Rome, Rome, Italy, **7** Mental Health and Substance Abuse, World Health Organization, Geneva, Switzerland, **8** Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California, United States of America, **9** Department of Psychiatry, VA Palo Alto Health Care System, Palo Alto, California, United States of America

Meta-Analysis Findings

Network meta-analysis was used to analyze 50 clinical studies (6,943 participants) on 12 different psychosocial interventions for cocaine and/or amphetamine addiction.

The combination of contingency management and community reinforcement approach, was the most efficacious and most acceptable treatment both in the short and long term.

Psychosocial Interventions for Cocaine and Psychostimulant Amphetamines Related Disorders.

Werner Paulo Knapp, Bernardo Soares, Michael Farrell, Maurício Silva deLima. (2009)
The Cochrane Collaboration.

Twenty-seven randomized controlled studies (3663 participants) fulfilled inclusion criteria and had data that could be used for at least one of the main comparisons.

- **The comparisons between different type of behavioral interventions showed results in favor of treatments with <u>some form of contingency management in respect to both reducing dropouts and lowering cocaine use</u>.**

Responding to global stimulant use: Challenges and opportunities Lancet (Farrell et al, 2019)

Psychosocial **interventions other than contingency management have weak and non-specific effects** on stimulant problems and there are no effective pharmacotherapies. Substantial research investment is needed to develop more effective, innovative, and impactful prevention and treatment.

Contingency Management

(Also known as Motivational Incentives)

Contingency Management

A technique employing the systematic delivery of positive reinforcement for desired behaviors. In the treatment of methamphetamine dependence, vouchers or prizes can be "earned" for submission of methamphetamine-free urine samples.

Basic Behavioral Principles

1. **Frequently monitor target behavior**

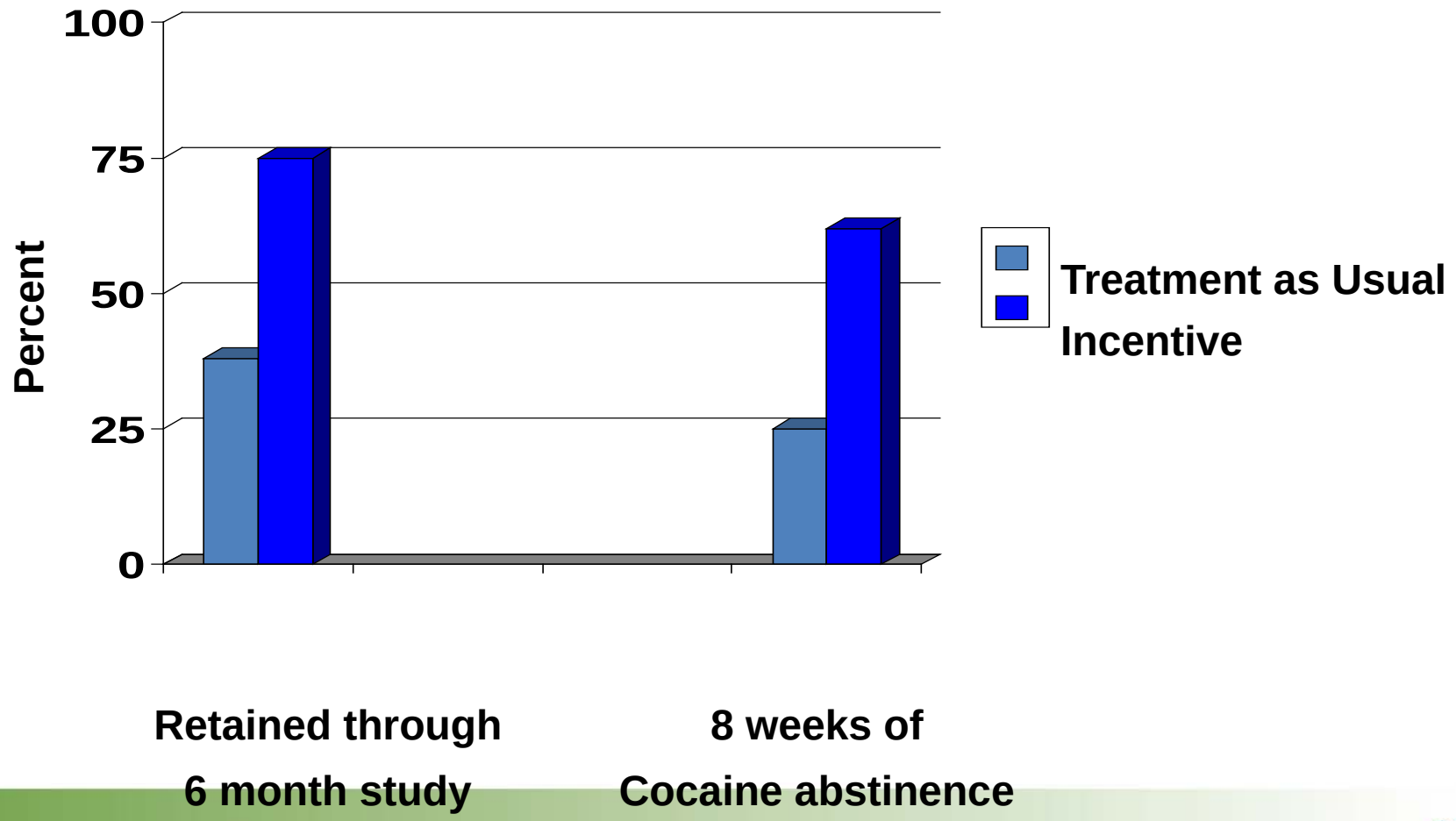
2. **Provide incentive when target behavior occurs**

3. **Remove incentive when target behavior does not occur**

Research on Contingency Management/Motivational Incentives

Treatment of Cocaine Dependence

Higgins et al 1994



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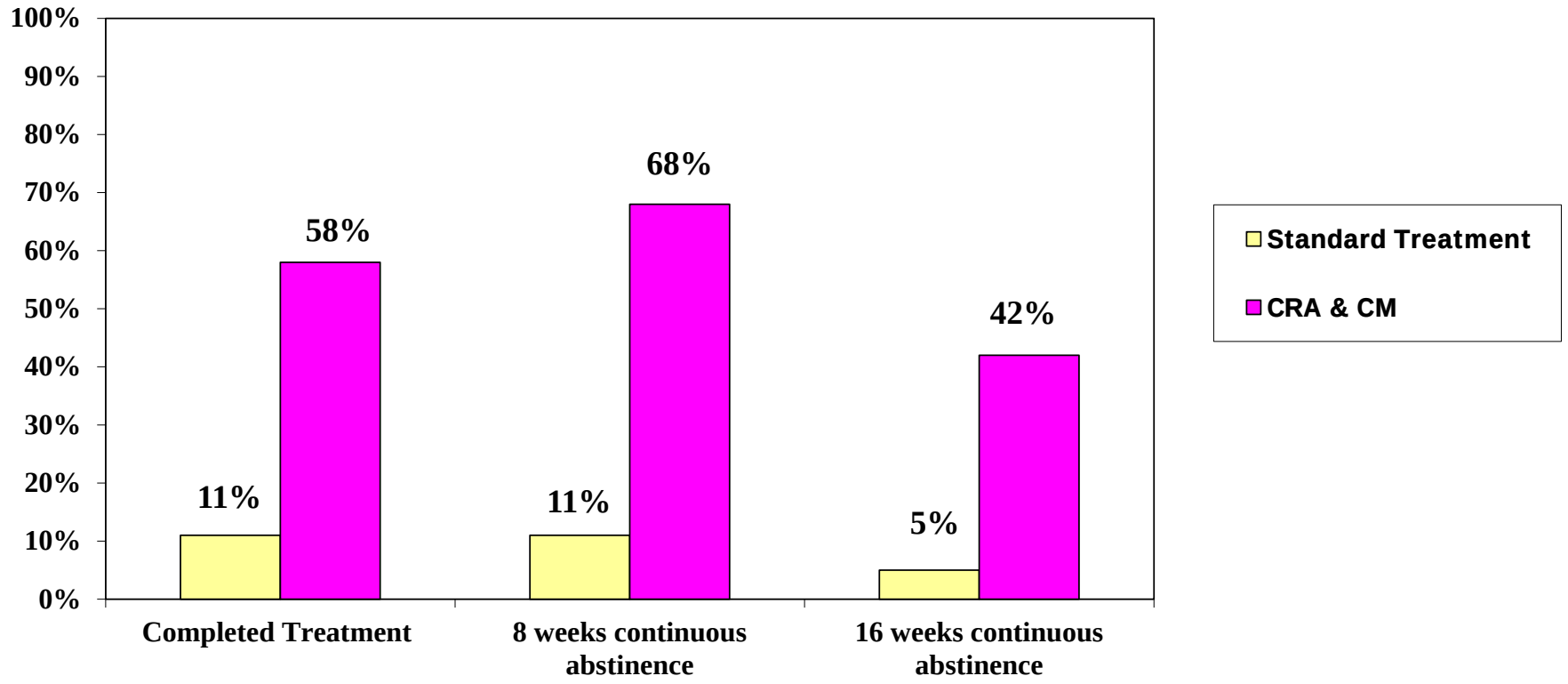
Contingency Management:

Higgins et al., 1993



Contingency Management for the Treatment of Methamphetamine Dependence. ***Roll, John, et al. American Journal of Psychiatry. 163: 1993-1999, 2006.***

- **METHOD: The authors report data on 113 participants who were diagnosed with methamphetamine abuse or dependence. They were randomly assigned to receive 12 weeks of either treatment as usual (Matrix) or treatment as usual plus contingency management.. The reinforcers for drug-negative samples were plastic chips, some of which could be exchanged for prizes.**

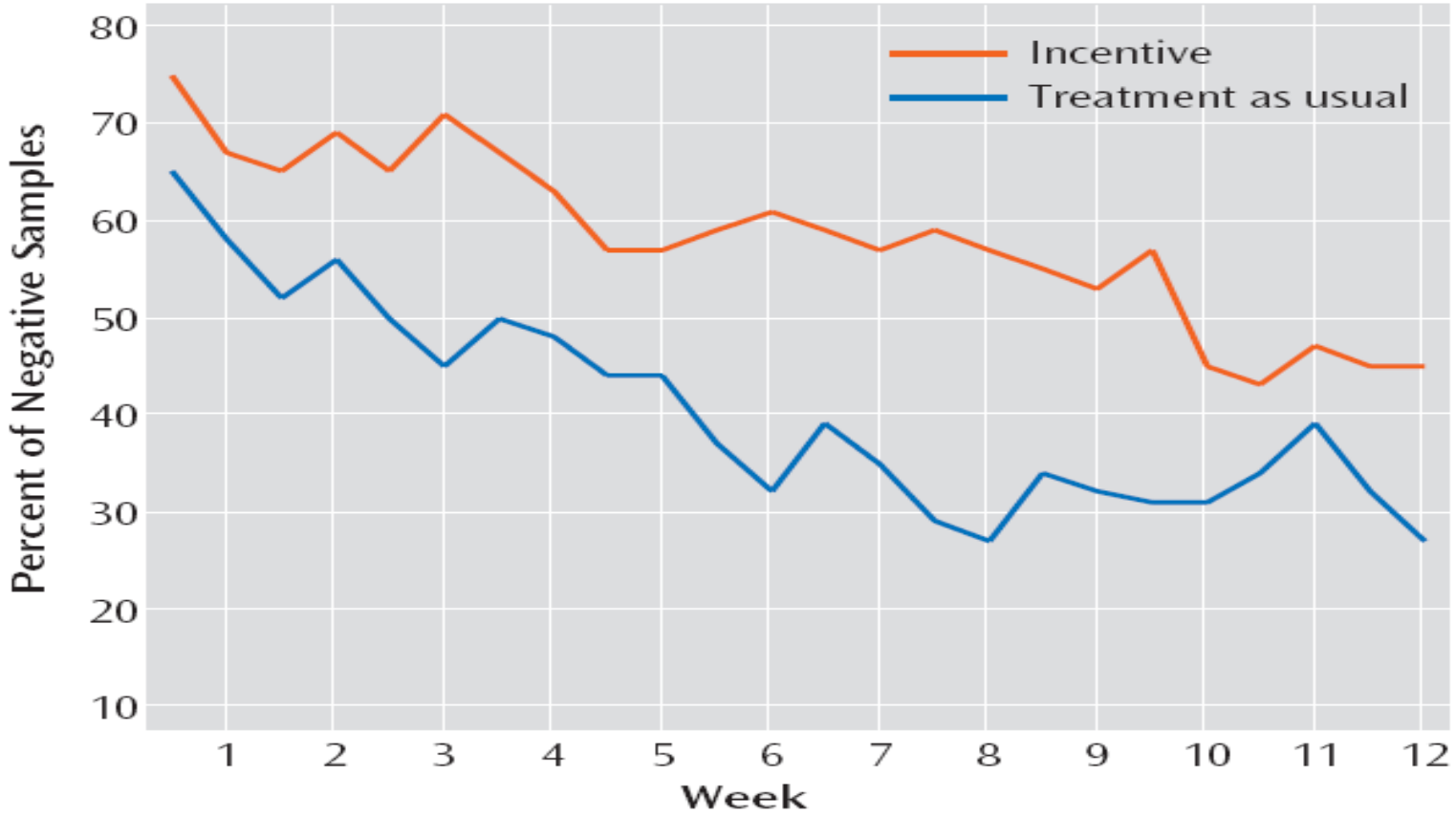
- **RESULTS: The participants in both groups remained in treatment for equivalent times, but those receiving contingency management in addition to usual treatment submitted significantly more negative samples, and they were abstinent for a longer period of time (5 versus 3 weeks).**

CM with Methamphetamine Users

Roll et al, 2006

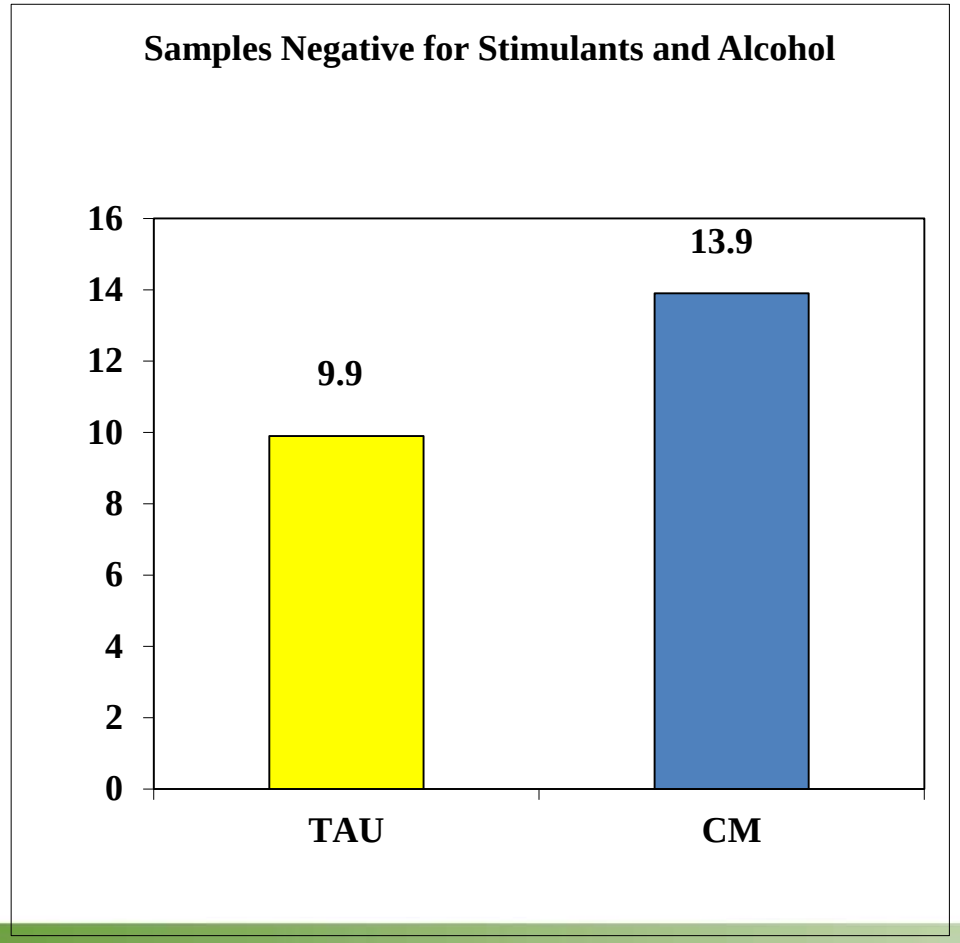
- NIDA Clinical Trials Network
- 113 methamphetamine users
- TAU, or TAU plus CM
- 12 week; 2 urine samples per week
- Fishbowl drawings (50% “good job”; 42% worth $1-$5; 8% worth $20; 1 worth $80-$100)
- Max possible about $400

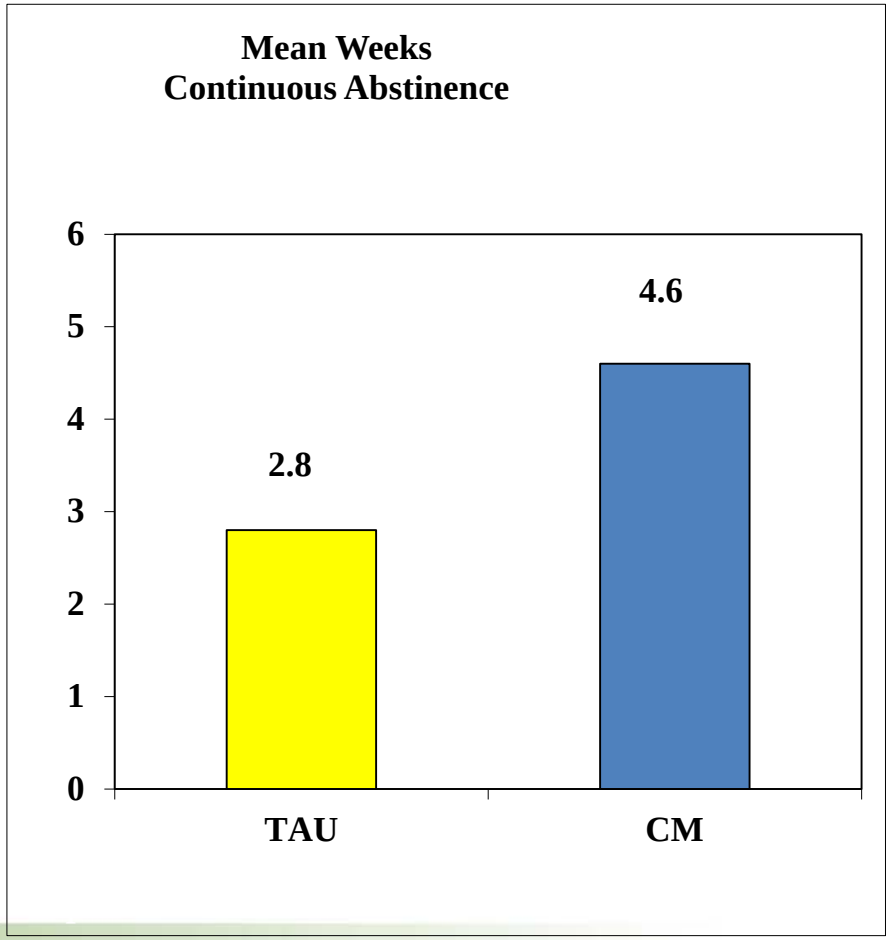
Retention Rate: Roll et al 2006



CM with Methamphetamine Users

Roll et al, 2006





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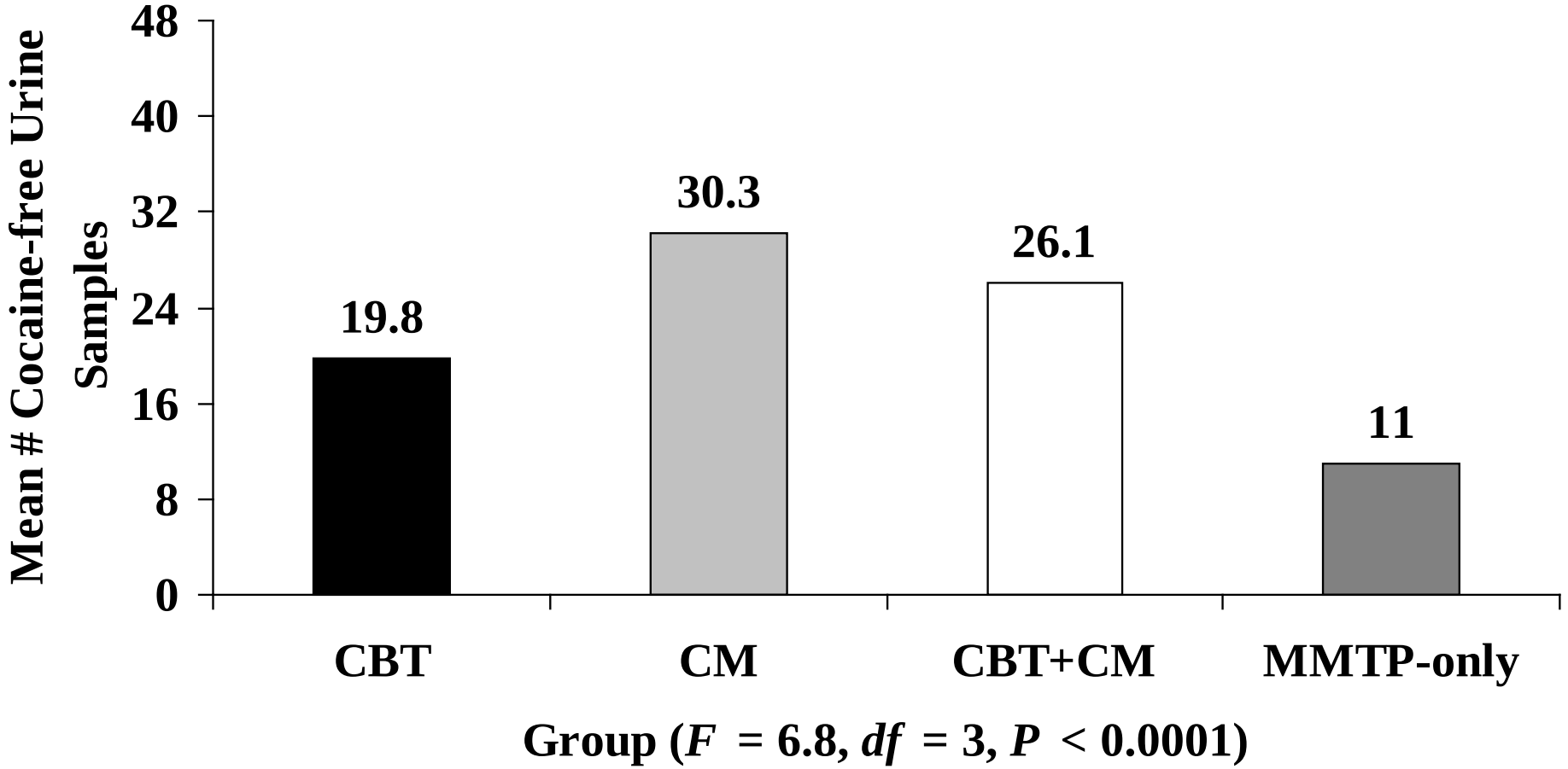
A Comparison of Contingency Management and Cognitive-Behavioral Approaches During Methadone Maintenance Treatment for Cocaine Dependence. *R. Rawson, et al. Archives of General Psychiatry 2002;59:817-824*

- **DESIGN:** Randomized clinical trial.
- **PARTICIPANTS:** Patients with cocaine dependence receiving methadone maintenance treatment (n=120).
- **INTERVENTIONS:** Participants were randomly assigned to 1 of 4 conditions: CM, CBT, combined CM and CBT or methadone treatment as usual. The active study period was 16 weeks, requiring 3 clinic visits per week.
- **RESULTS: Urinalysis results during the 16-week treatment period show that participants assigned to the 2 groups featuring CM had significantly superior in treatment urinalysis results, whereas urinalysis results from participants in the CBT group were not significantly different than those from the MMTP-only group.**
- **CONCLUSIONS:** Study findings during treatment provide solid evidence of efficacy for CM (with and without CBT. There was no evidence of a combined effect.

Stimulant-Free Uas Rawson et al, 2002



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Incentives Improve Retention of Patients Who Use Stimulants

MIEDAR Study

- 400 patients enrolled in NIDA's CTN Study
- Patients who reported cocaine, methamphetamine or amphetamine use were enrolled in one of two treatment conditions
  - Treatment as usual plus abstinence-based incentives
  - Treatment as usual (no incentives)
- Patients receiving incentives and treatment as usual attended more counseling sessions and had longer periods of abstinence than patients in the treatment as usual condition

Petry et al., 2005

Incentives Improve Outcomes in Patients With Methamphetamine Use Disorders

MIEDAR Study

- Patients receiving incentives plus treatment as usual submitted more stimulant- and alcohol-negative samples than patients who only received treatment as usual

Roll et al., 2006

Lower-Cost Incentives Improve Stimulant Abstinence for Patients in Methadone Maintenance Treatment

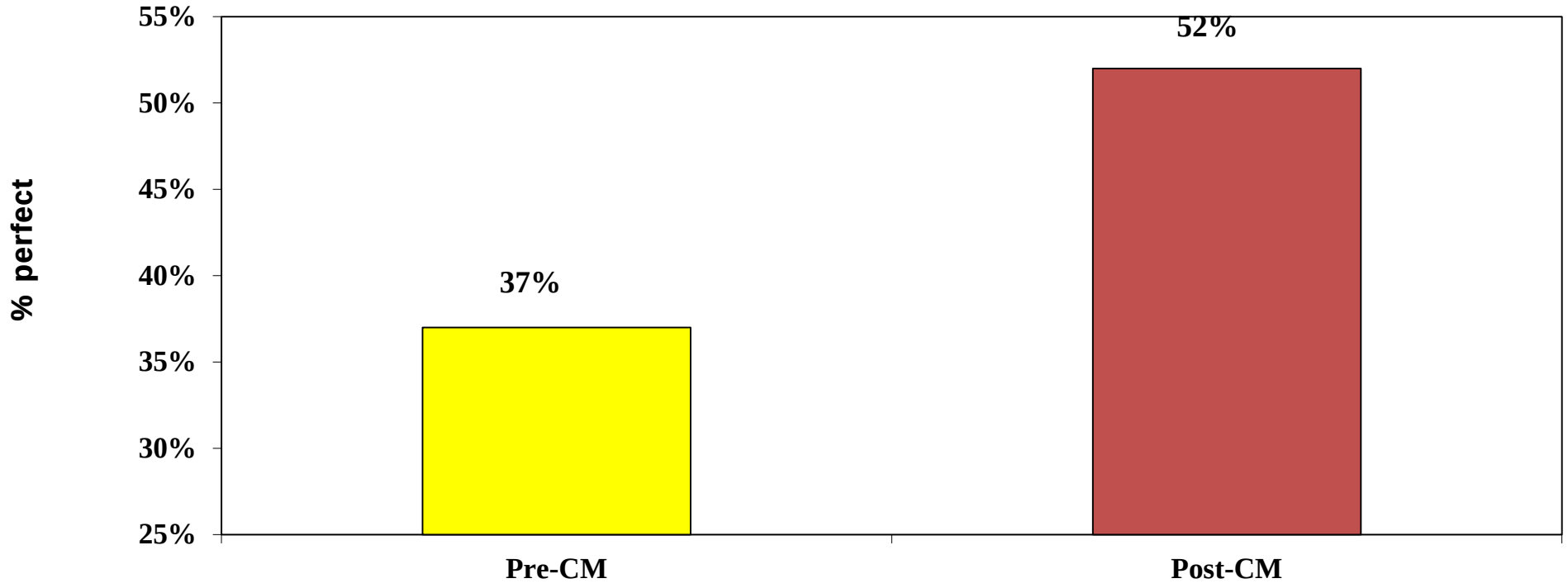
MIEDAR Study

- Patients in methadone maintenance treatment reduced their alcohol and stimulant use when given lower-cost incentives
- Patients receiving incentives submitted more stimulant- and alcohol-negative samples than patients who only received treatment as usual
- Patients in the incentive group received an average of $120 in incentives/per participant over 12 weeks

Peirce et al., 2006

Perfect medication attendance

n=49



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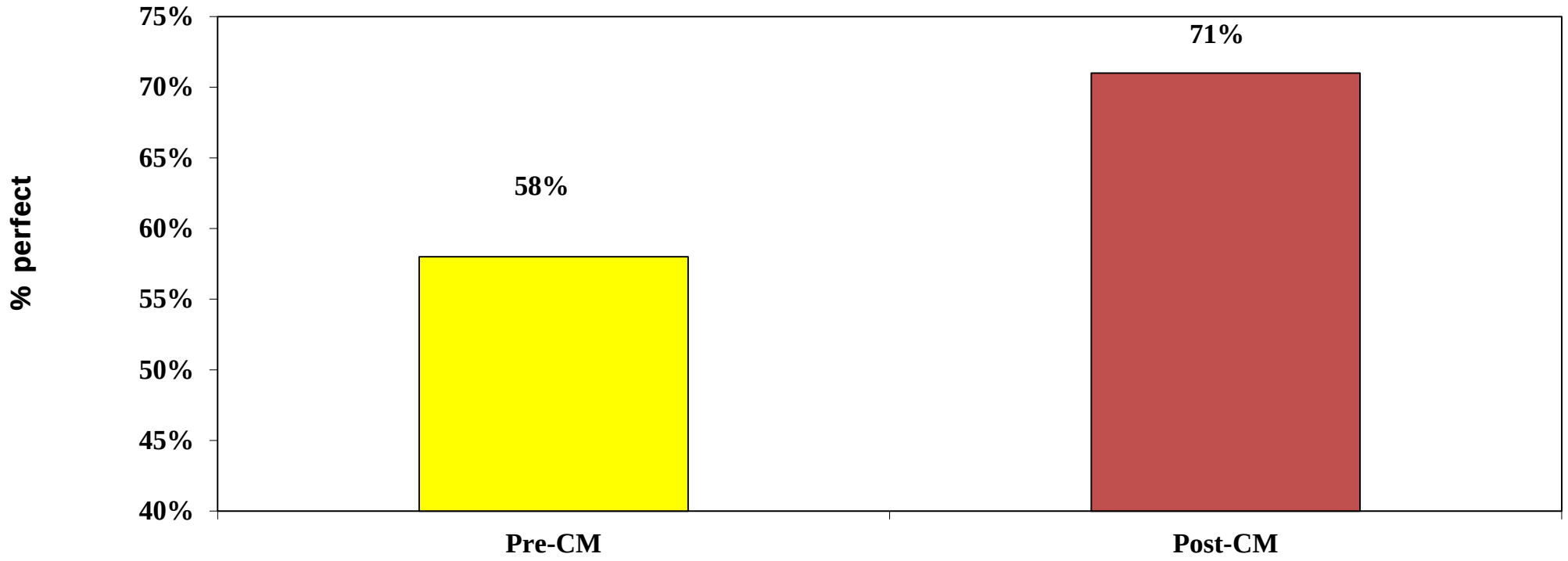
Perfect group attendance

n=49



3. Choice of Reinforcer continued

Three major types of incentive programs

- **Access to clinic privileges**
  Example: Take-home dose of methadone
- **On-site prize distribution**
  Example: A prize cabinet contains many small prizes, some large prizes and a few jumbo prizes
- **Vouchers or other token economy systems**
  Example: Points or vouchers are accumulated in an account and redeemed for retail goods or services

LOW COST INCENTIVES

Fishbowl Method

Patients select an increasing number of draws each time they display a targeted behavior.

- Get one draw for the first drug-free urine sample, two draws for the second drug-free urine sample, and so on
- Lose the opportunity to draw a prize with a positive urine screen, but are encouraged and supported
- When patients test drug-free again, they start with one draw

Fishbowl Ticket Ratios

To manage cost, ticket ratios are as follows:

TICKET	COST	CHANCE
Good Job	$0	50.0%
Small	$1	41.8%
Large	$20	8.0%
Jumbo	$80–$100	0.2%

Implementation Tips

- **Give reinforcement frequently**
- **Easy to earn initially (set the bar low)**
- **Reinforcers should be items of use and value to patients**
- **Reinforcement should be connected to specific, observable behavior**
- **Minimize delay in reinforcement delivery; greater delay, weaker effect**
- **Focus on small steps; any improvement**
- **Simple is better**

Contingency Management Apps

- **reSET** is a 90-day Prescription Digital Therapeutic (PDT) for Substance Use Disorder (SUD) intended to provide cognitive behavioral therapy (CBT), as an adjunct to a contingency management system, for patients 18 years of age and older who are currently enrolled in outpatient treatment. FDA approved. https://peartherapeutics.com/products/reset-reset-o/
- **DynamiCare** Health is a platform for families and individuals that reinforces a person's recovery from addiction and rewards healthy behavior. DynamiCare's easy-to-use technology includes random breath and saliva tests submitted through the app, verified treatment attendance check-ins, a supportive Recovery Coach, rewards for healthy progress, and a dashboard for supporters.
- www.dynamicarehealth.com.

Other Approaches with Support/Interest

- **Community Reinforcement Approach:** Improves functioning of patients in treatment with CM
- **Motivational Interviewing**: No direct evidence with meth users, but support with other SUDs.
- **Physical Exercise**: Rawson et al, 2015. Evidence of reduction of meth relapse among less severe users; enhancement of dopamine receptor recovery, reduction in depression and anxiety during early meth abstinence..
- **Transcranial Magnetic Stimulation (TMS).** Transcranial magnetic stimulation is FDA approved for treatment resistant depression and has demonstrated preliminary evidence of potential efficacy for stimulant use disorder

An Integrated Behavioral Model

An integrated, evidence-based, multi-component program for the treatment of individuals with stimulant use disorders. The contents of this program will include strategies including:

1. motivational incentives (based on contingency management research),

2. elements of cognitive behavioral therapy

3. elements of community reinforcement approach,

4. motivational interviewing skills,

5. physical exercise

6. 12-Step program participation.

In addition, an appendix will include a set of other EBPs to augment the core program at the discretion of each organization.

Medications Considered for Cocaine Use Disorder

Positive/Under Consideration

- topiramate
- modafinil
- bupropion
- amphetamine salts
- buprenorphine+naltrexone

Medications for Methamphetamine Use Disorder

Positive/Under Consideration

bupropion
mirtazapine ***
naltrexone
methylphenidate
d-amphetamine
topiramate

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