Methamphetamine Use Disorders: An Update

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Opioid Response Network

Working with communities.

- The SAMHSA-funded *Opioid Response Network (ORN)* assists states, organizations and individuals by providing the resources and technical assistance they need locally to address the opioid crisis and stimulant use.
- Technical assistance is available to support the evidence-based prevention, treatment and recovery of opioid use disorders and stimulant use disorders.

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Working with communities.

- The *Opioid Response Network (ORN)* provides local, experienced consultants in prevention, treatment and recovery to communities and organizations to help address this opioid crisis and stimulant use.
- *ORN* accepts requests for education and training.
- Each state/territory has a designated team, led by a regional Technology Transfer Specialist (TTS), who is an expert in implementing evidence-based practices.

Contact the Opioid Response Network

- To ask questions or submit a technical assistance request:
  - Visit www.OpioidResponseNetwork.org
  - Email orn@aaap.org
  - Call 401-270-5900

Learning Objectives

- Discuss historical aspects
- Describe the effects of methamphetamine use
- Discuss current trends in methamphetamine use
- Discuss methamphetamine-associated psychosis (MAP) and its management
- Describe evidence-based treatments for methamphetamine use disorder


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Historical aspects

- Ephedra is a shrub whose extract has been used in traditional Chinese medicine for over 5000years and brewed as a tea by Native American tribes/Mormons in Western USA (“Mormon Tea”, Ephedra viridis)
- In 1885, Nagai Nagayoshi – a Japanese chemist studying in Germany- identified the active chemical in ephedra, ephedrine
- He developed a method for ephedrine synthesis
- Amphetamine was created in Germany in 1887 by Romanian chemist, Lazar Edeleanu. He named it phenylisopropylamine

Historical aspects

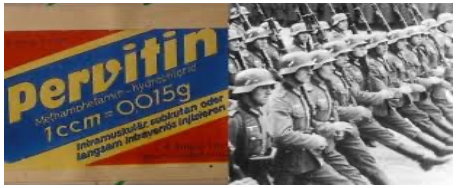
- Nagai synthesized methamphetamine from ephedrine in 1893
- Methamphetamine hydrochloride (“crystal meth”) was developed in Japan in 1919 by Akira Ogata
- In 1932 Benzedrine inhaler was marketed in the US as a nasal decongestant by Smith, Kline and French
- A few years later, Benzedrine pills were introduced for obesity, depression, narcolepsy and other conditions
- Very quickly became a drug of misuse, on the streets called “bennies”

Historical aspects

- For a period of about twenty years, from the 1930s to the 1950s, a good bit of American artistic and scientific energy was fueled by “bennies”
- Many so-called “Beat Generation” writers, including author Jack Kerouac and poet W.H. Auden, reportedly used “bennies”
- World War II probably gave the greatest impetus to date to legal medically authorized as well as illicit black-market use/misuse of amphetamine and methamphetamine on a worldwide scale

Historical aspects

- Amphetamines were given to Allied bomber pilots during WW II to sustain them by fighting off fatigue and enhancing focus during long flights
- Japanese kamikaze (“divine wind”) pilots were given methamphetamine before their suicide missions
- Pervitin, a methamphetamine brand used by German soldiers during WW II, was dispensed in tablet containers
- Blitzkrieg was guided by methamphetamine
- Post WW II Japan experienced its first methamphetamine epidemic



Historical aspects

- In the 1950s in the US, legally manufactured tablets of both dextroamphetamine (Dexedrine) and methamphetamine (Methedrine, Desoxyn) became readily available
- Amphetamines became a cure-all for such things as weight control to treating mild depression
- Obetrol, a popular diet pill in the country in the 1950s and 60s, was a combination of amphetamine and methamphetamine salts

Historical aspects

- The 1970 Controlled Substances Act severely restricted the legal production of amphetamine/methamphetamine, causing its use to decrease greatly
- Traditionally, the suppliers of methamphetamine throughout the United States have been outlaw motorcycle gangs
- Organized crime drug groups operating from Mexico currently dominate the wholesale methamphetamine trafficking in the US
- Golden Triangle is a major producer of methamphetamine and yaba tablets
- Afghanistan, one of the major producers of heroin in the world, is witnessing an unprecedented surge in production of methamphetamine (UNODC 2023)

Methamphetamine: Mechanism

- Inhibits synaptic vesicle function by inhibiting VMAT2, which prevents monoamine uptake into the vesicles and promotes their release3
- Potent full agonist of trace amine-associated receptor 1 (TAAR1). Activation of TAAR1 inhibits or reverses the transport direction of DAT,NET and SERT3
- Inhibits MAO-A and MAO-B3
- Increases the activity of Tyrosine hydroxylase3
- Two isomeric forms of methamphetamine, a dextro-isomer and a levo-isomer
  - The dextro-isomer is a CNS stimulant and is five times more biologically active, while the levo-isomer is used in over-the-counter nasal decongestants
- Half life 6-17hours

Methamphetamine: Licit forms

- Desoxyn (d-methamphetamine)
  - FDA approved for ADHD/obesity
- Didrex (benzphetamine)
  - FDA approved for obesity
- Vicks VapoRub (l-methamphetamine)
- Phentermine (dimethylphenethylamine)
  - FDA approved for obesity
  - Combination product with topiramate was FDA approved in 2012

Methamphetamine: Licit forms

- Selegeline
  - MAO-B inhibitor
  - Metabolized to l-methamphetamine
- Amphetamine Salts
  - Adderall tablets contain d-amphetamine and l-amphetamine salts in the ratio of 3:1
  - Norephedrine and 4-hydroxyamphetamine are active metabolites
  - Vyvanse is Lisdexamfetamine and gets converted to dextroamphetamine
- Addition of a methyl group to amphetamine renders methamphetamine more lipophilic, resulting in increased blood-brain barrier penetration

Methamphetamine: Illicit Forms/Routes

- Smoked
- Snorted (“Tooting”)
- Injection
- Oral (“Parashooting”)
- Rectal (“Booty bump”)

Methamphetamine: Short-term effects

- Increased attention and decreased fatigue
- Increased activity and wakefulness
- Decreased appetite
- Euphoria and rush
- Tachypnea/Tachycardia/Hyperthermia
- Loss of inhibition and heightens libido

Methamphetamine: Long-term effects

- Most significant morbidity/mortality is cardiovascular (CV)
- CV effects
  - Hypertension/arrhythmias/MIs/CAD/cardiomyopathy
- Psychiatric
  - Psychosis/depression/anxiety/insomnia/suicidality/aggression
- Neurologic
  - Seizures/stroke/cerebral vasculitis/hyperkinetic movements/cognitive impairment
- Other effects
  - Dental issues /PE/pulmonary hypertension/acne-like lesions/HIV& Hepatitis C
  - Dental issues are secondary to xerostomia/bruxism/poor care/consumption of sugary beverages

Methamphetamine: High risk populations

- Men who have sex with men (MSM)13
  - High risk sexual behaviors
  - Increased HIV seroconversion
- Women13
  - Target of violence
  - Pregnant women who use methamphetamine more likely to be Caucasian, young and single
  - Seek prenatal care late in pregnancy and experience poor weight gain
- Criminal Justice13
  - Impulsive behaviors, violent crime (high homicide rates), psychosis

Methamphetamine: Use among MSM

- MSM is a broad term which includes gay, bisexual men and heterosexual men who have sex with other men
- “Chemsex” is the use of drugs in conjunction with planned sexual activity
- Besides MA other drugs used for Chemsex include
  - Cocaine/Alcohol
  - Inhaled nitrites (“poppers”)
  - Gamma-hydroxybutyrate (GHB)/Gamma-butyrolactone (GBL)
  - Ketamine
  - Medications for erectile dysfunction
- MSM who use MA have higher prevalence of trauma as compared to MSM who do not use MA

Methamphetamine: Use among MSM

- Associated with multiple sexual partners
- Inconsistent use of condoms
- Poor adherence to preexposure prophylaxis or antiviral treatment generally
- Identified as a factor contributing to rising rates of HIV transmission and other STIs
- Associated with increased rectal inflammatory cytokines (interleukin-6 and tumor necrosis factor)
  - May explain increased HIV-1 risk seen in MA users and contribute to increased inflammation among HIV+ users

Methamphetamine: Effects on Pregnancy and Infant Outcomes

- Current studies do not support increase in birth defects
- Consistently associated
  - Small for gestational age (SGA) infants
  - Neonatal and childhood neurodevelopmental abnormalities
  - Continued surveillance is indicated
- Amphetamines/MA inhibit prolactin release and reduce breast milk supply
  - Concentration of amphetamines found in breast milk is 2.8-7.5x higher than maternal plasma
  - Infants who ingest breast milk of women using amphetamines/MA exhibit increased irritability, agitation and crying

Methamphetamine: Cardiomyopathy

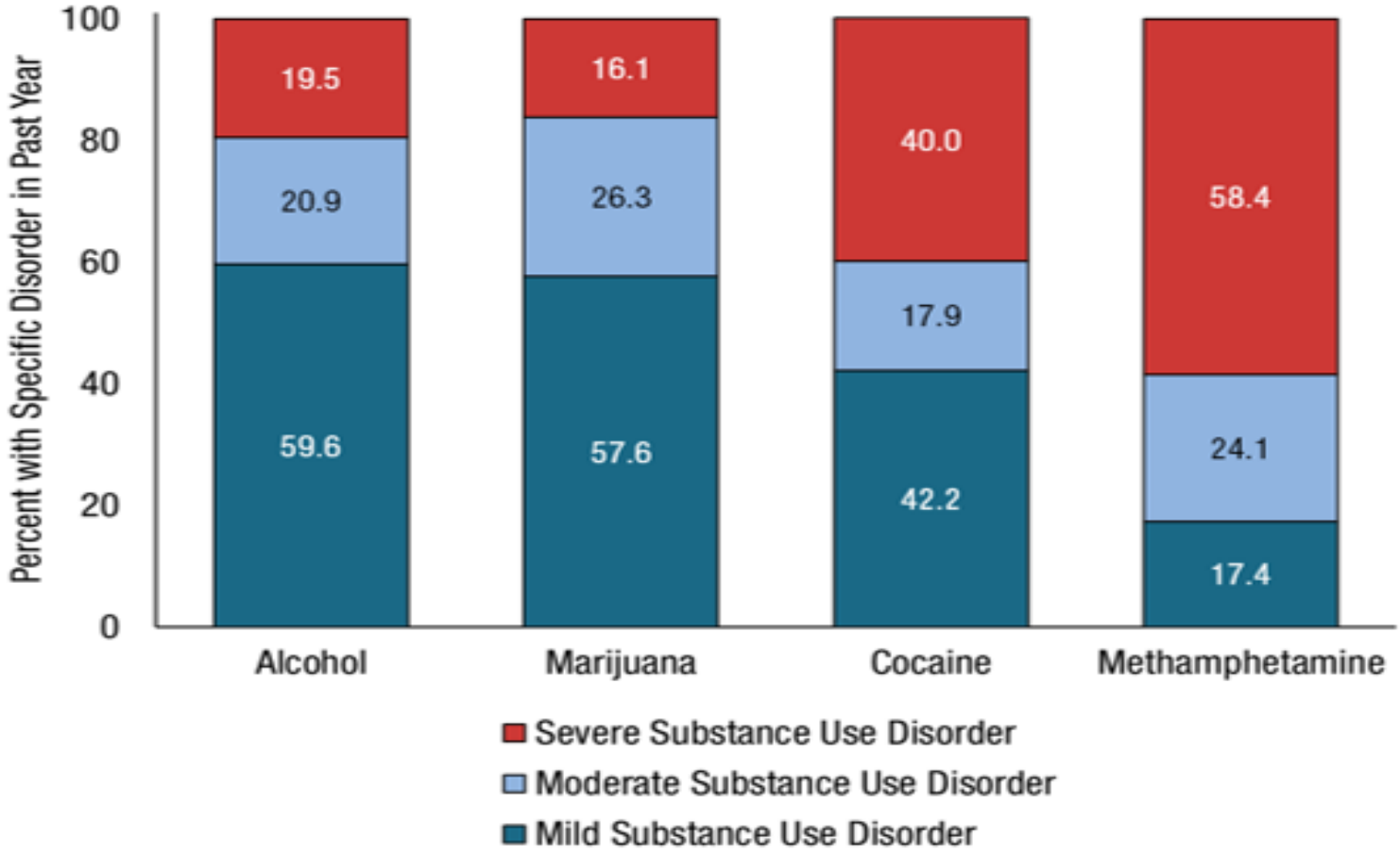
- The mechanisms for methamphetamine associated cardiomyopathy (MACM) are most likely multifactorial
- Proposed etiologies for cardiac injury include14,18
- Catecholamine excess
- Coronary vasospasm and ischemia
- Increases in reactive oxygen species (ROS)
- Mitochondrial injury and changes in myocardial metabolism
- Reduced NO-mediated vasodilatation
- Direct toxic effects

Methamphetamine: Cardiomyopathy

- Pathologically, ventricular hypertrophy and dilation, fibrosis, and contraction-band necrosis commonly have been found
- Clinically denoted as dilated cardiomyopathy and heart failure with reduced ejection fraction
- Patients with MACM tend to be of younger age compared with patients with cardiomyopathy attributable to other causes and affects men predominantly[18]
- Genetic predisposition to development of cardiomyopathy in methamphetamine users may exist via the CYP2D6 enzyme, the initial and rate-limiting step during metabolism of methamphetamine[18]
- A single study involving 56 patients showed a trend toward increased dilated cardiomyopathy among extensive metabolizers after adjusting for age and sex[18]

"Sometimes I like to circle someone perfectly healthy just to mess with their head."

Substance Use Disorder Severity Level for Specific Substances in the Past Year: NSDUH 2021



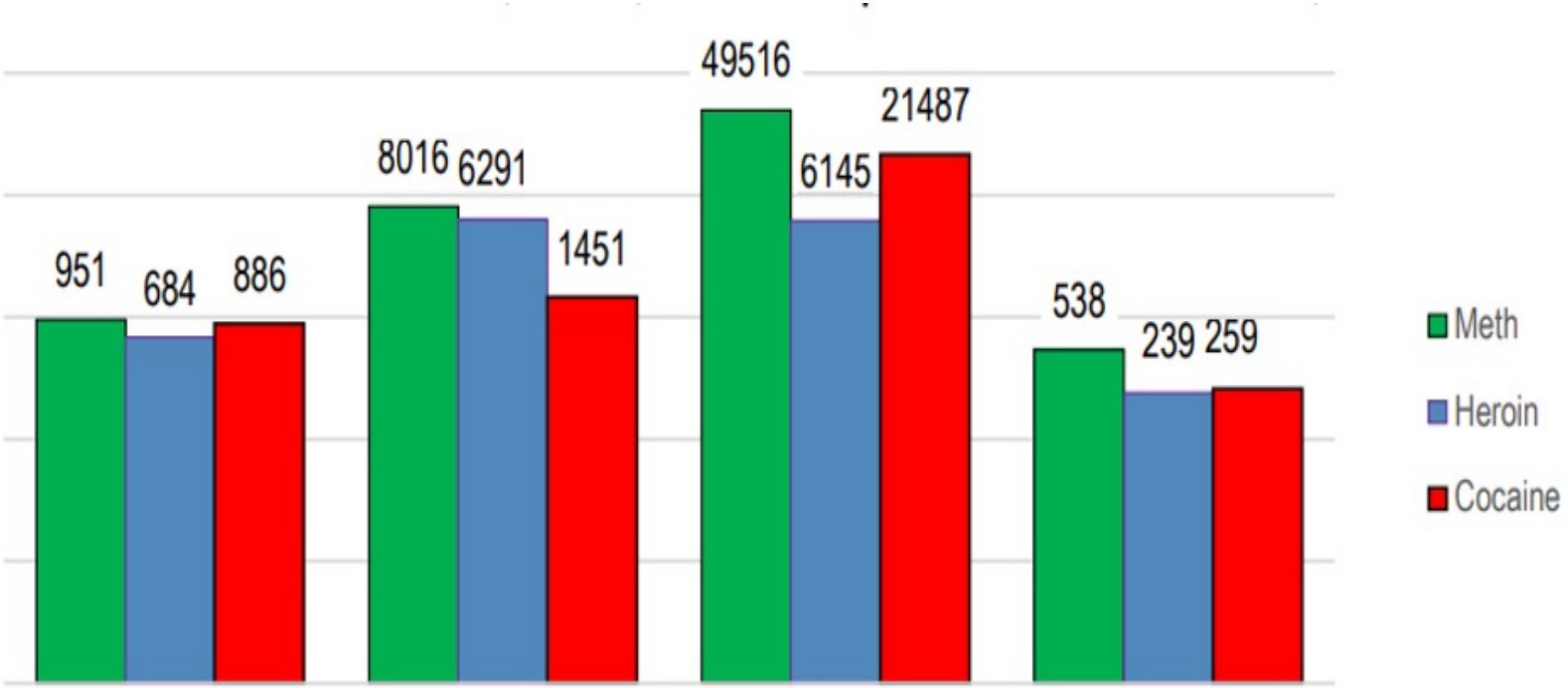
Methamphetamine: Epidemiology

- 2.5 million people ages 12 and older reported using methamphetamine in the past year (NSDUH 2021)12
- 1.6 million people ages 12 and older had a methamphetamine use disorder in the past year (NSDUH 2021)12
- In 2022, an estimated 0.2% of 8th graders, 0.3% of 10th graders, and 0.5% of 12th graders reported using methamphetamine in the past 12 months (2022 Monitoring the Future survey)
- In 2021, approximately 53,495 people died from an overdose involving cocaine and psychostimulants (primarily methamphetamine)1

Methamphetamine: Trends in Texas

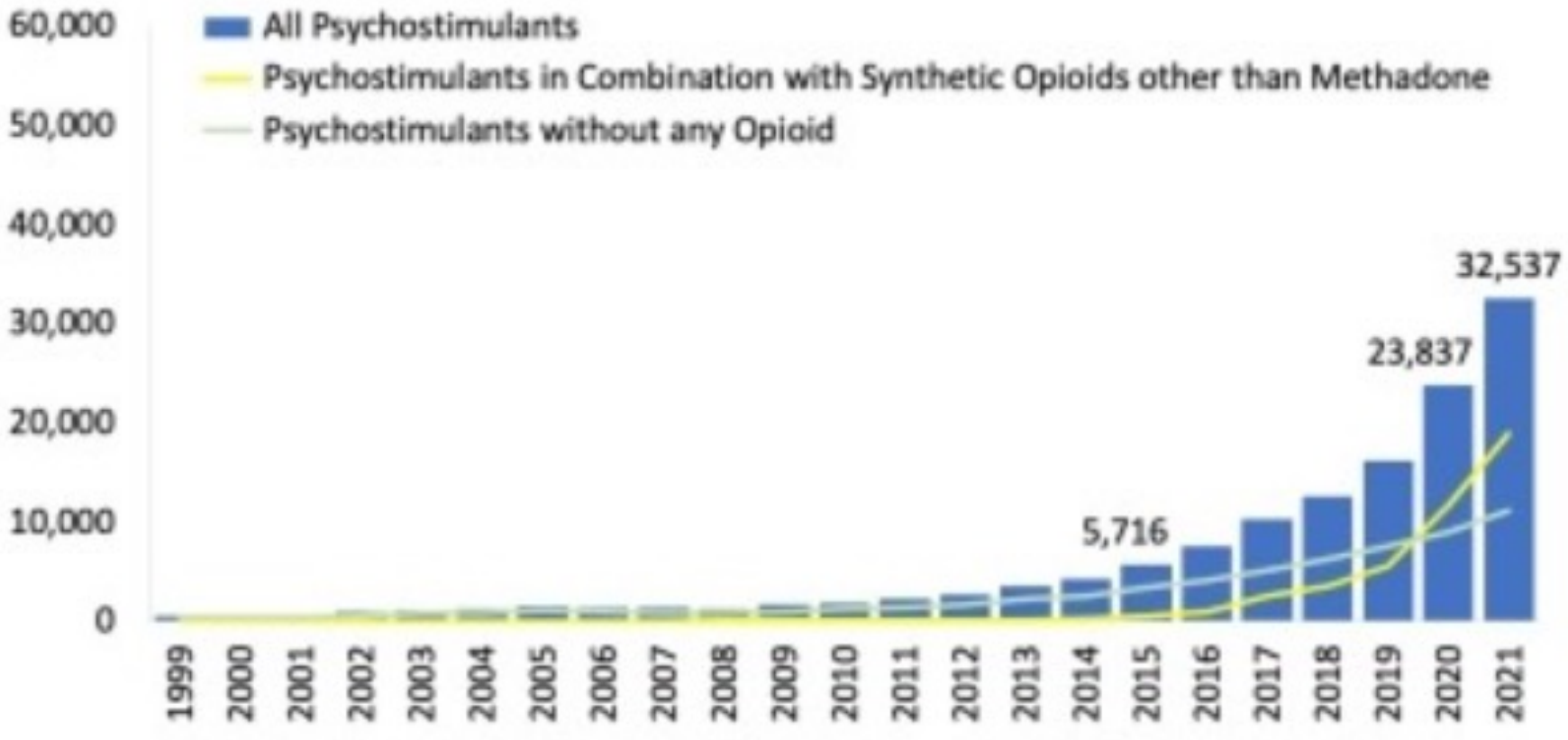
- Methamphetamine is the top drug threat in the state
- Methamphetamine outnumbers other drugs in the four drug reporting systems, and it continues to increase (TESS/TEDS/NFLIS/DSHS)
- There is high availability and reduced price since the cartels took over the methamphetamine drug trade
- Methamphetamine is trafficked into the U.S. is made from phenyl-2-propanone (P2P)

Methamphetamine, Cocaine and Heroin: Trends in Texas 2020

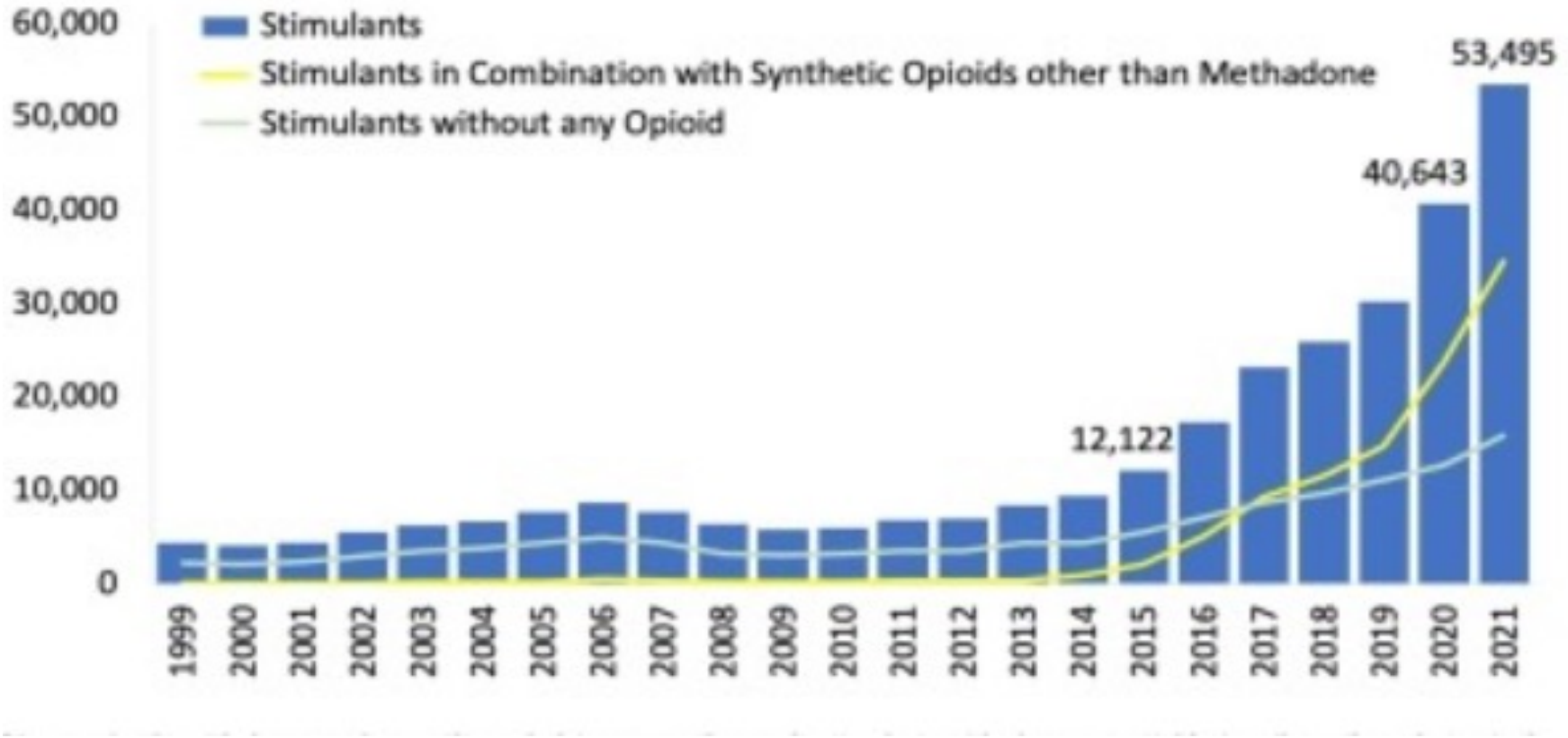


Sources: NFLIS, TESS, TEDS, DSHS

Overdose deaths: Psychostimulants primarily Methamphetamine, 1999-2021 (CDC Wonder Database)



Overdose deaths: Psychostimulants and Cocaine by Opioid involvement, 1999-2021(CDC Wonder database)



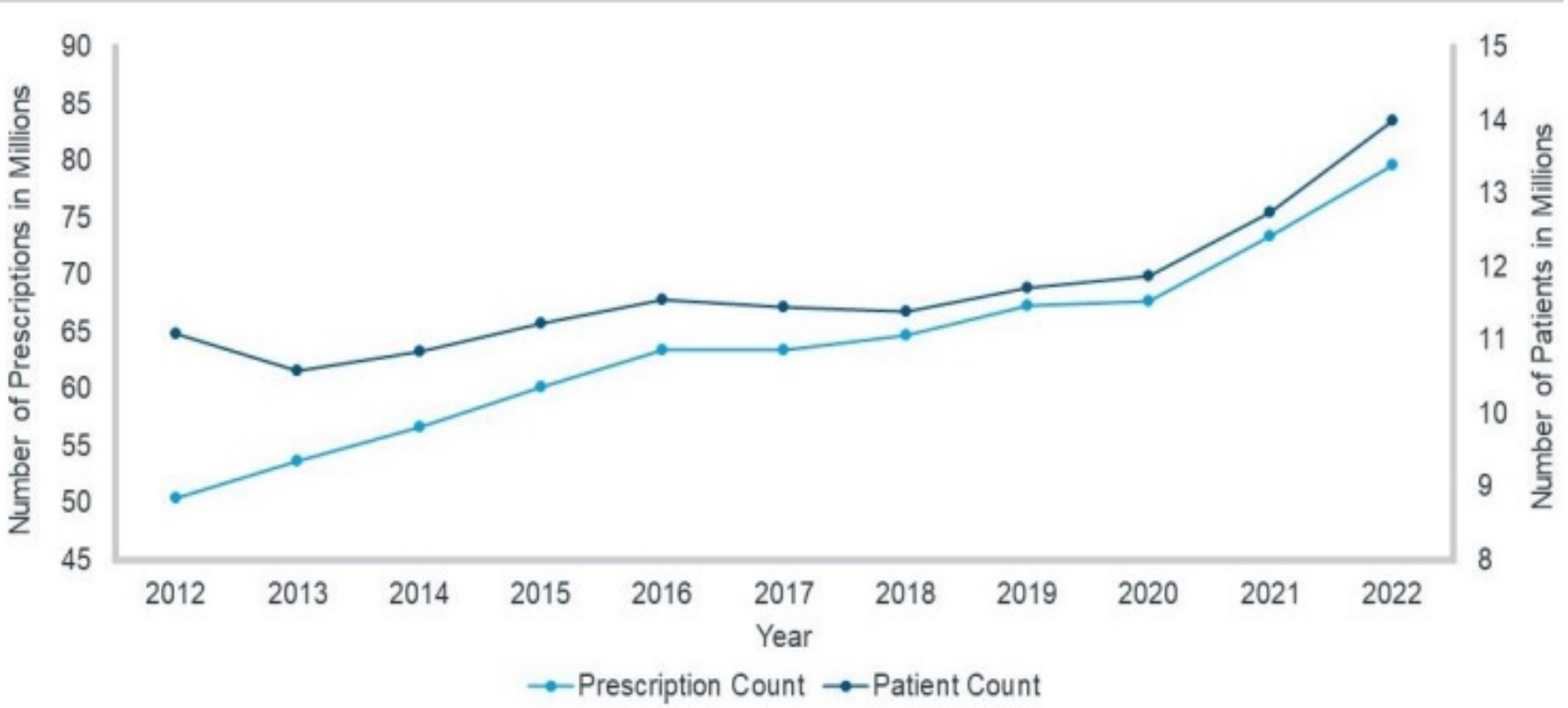
Stimulant Prescribing: Trends in the Country 2012-2022 (IQVIA Report)

- Prescriptions for stimulants have steadily increased since 2012[17]
- From 2012 to 2022, overall dispensing of stimulants in the US increased by **57.9%**[17]
- During the COVID-19 pandemic, policies enacted to minimize barriers to treatment combined with increased health seeking behavior likely expanded access to stimulants via telehealth[17]
- The highest annual increase in prescription stimulants dispensed was from 2021 to 2022[17]

Stimulant Prescribing: Trends in the country 2012-2022 (IQVIA Report)

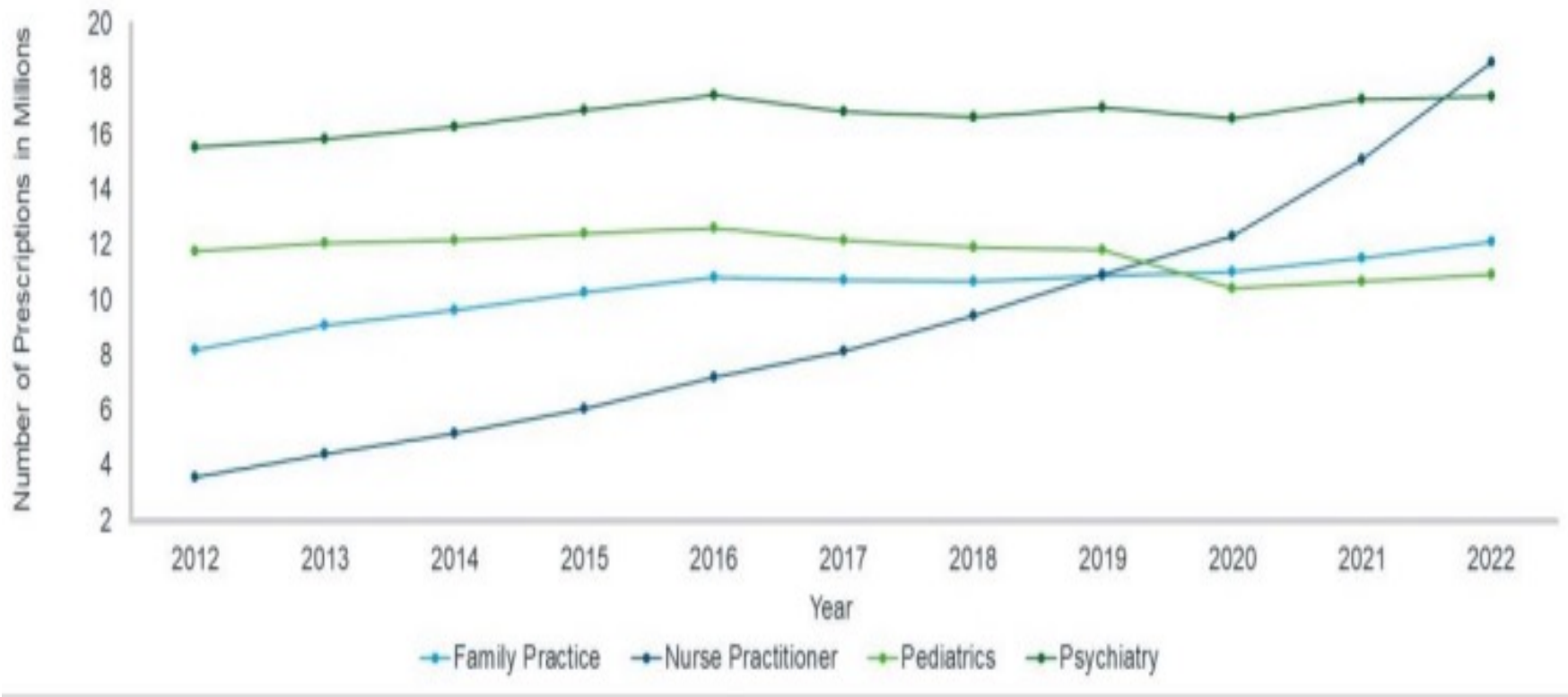
- From 2012 to 2021, adults between the ages of 31-40 years, particularly women, and older patients (71-80 years old) had the highest increase in prescription stimulants dispensed[17]
- In 2022, women surpassed men in dispensed prescriptions for stimulants[17]
- Overall, psychiatrists and pediatricians had most prescription stimulants dispensed; however, annual increases have been much higher among nurse practitioners[17]

Stimulant Prescribing: Prescriptions and Patients from 2012 to 2022



Stimulant Prescribing: By Treatment Category from 2012-2022

Stimulant Prescribing: Top Prescriber Specialty from 2012 to 2022



Methamphetamine Induced Psychosis (MAP)

- Biologic basis
  - Higher dopaminergic signaling in the mesolimbic, nigrostriatal and mesocortical pathways causes elevated glutamate levels that damage GABAergic interneurons
  - This leads to glutamate dysregulation and impairment of NMDA receptors, resulting in damage to the cortex and onset of psychotic symptoms
- Clinical types
  - Rapid resolution of psychotic symptoms
  - Persistent psychosis

MAP: Acute Agitation and Psychosis

- Comprehensive work up to rule out any organic etiology
- IV fluids
- Benzodiazepines
  - Lorazepam 2mg PO/IV/IM
- Ketamine 1-2 mg/kg IV or 3-4 mg/kg IM
- Antipsychotics
  - Haloperidol 5-10mg PO/IM/IV; Olanzapine 5-10mg PO/IM/SL; Risperidone 1-2mg PO

MAP: Persistent Psychosis

- Antipsychotics
  - Risperidone 1-2mg BID
  - Aripiprazole 10mg daily
  - Quetiapine 100-200mg daily

- If depressive symptoms persist
  - Consider Bupropion XL 300-450mg daily
  - Consider Mirtazapine/SNRIs/SRIs if trial of Bupropion XL fails

Methamphetamine: Evidence Based Treatments

- Psychosocial Interventions
  - Matrix Model
  - Contingency management (CM)
- Pharmacological Interventions
  - ADAPT-2:Accelerated Development of Additive Pharmacotherapy Treatment for Methamphetamine Use Disorder[7]
  - Mirtazapine
  - Buprenorphine

Methamphetamine: Psychosocial Interventions

- Matrix Model
  - 16-week comprehensive behavioral treatment approach
  - Integrates principles of CBT, Motivational Interviewing
  - Combines behavioral therapy, family education, individual counseling, 12-Step support, drug testing, and encouragement for non-drug-related activities
- Contingency Management (CM)
  - Incentives provided contingent on treatment attendance, abstinence[5,6]

Methamphetamine: NIDA Clinical Trials Network Study 2010

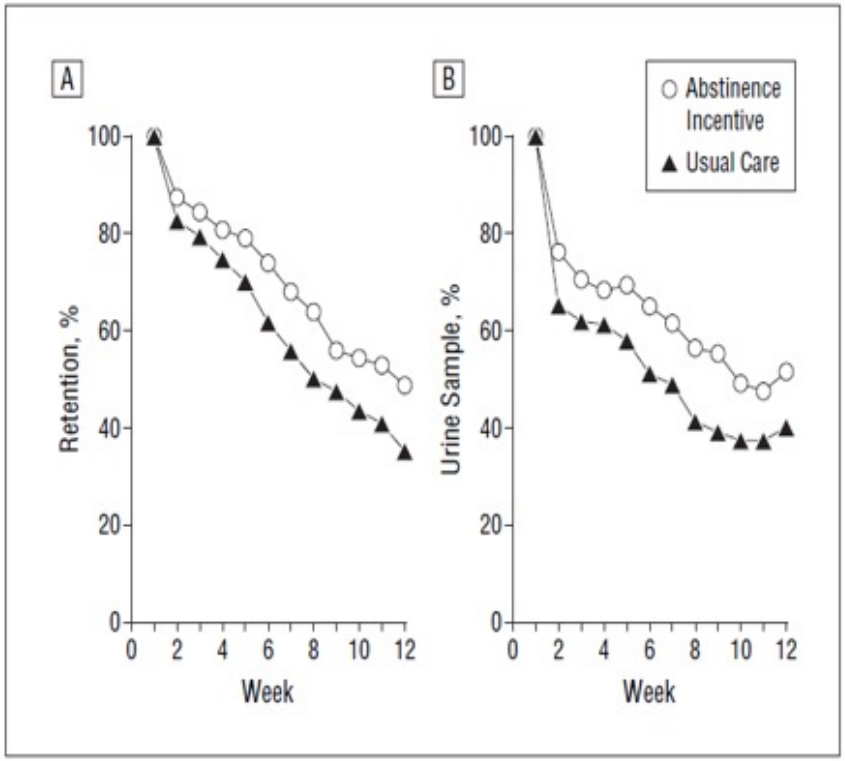
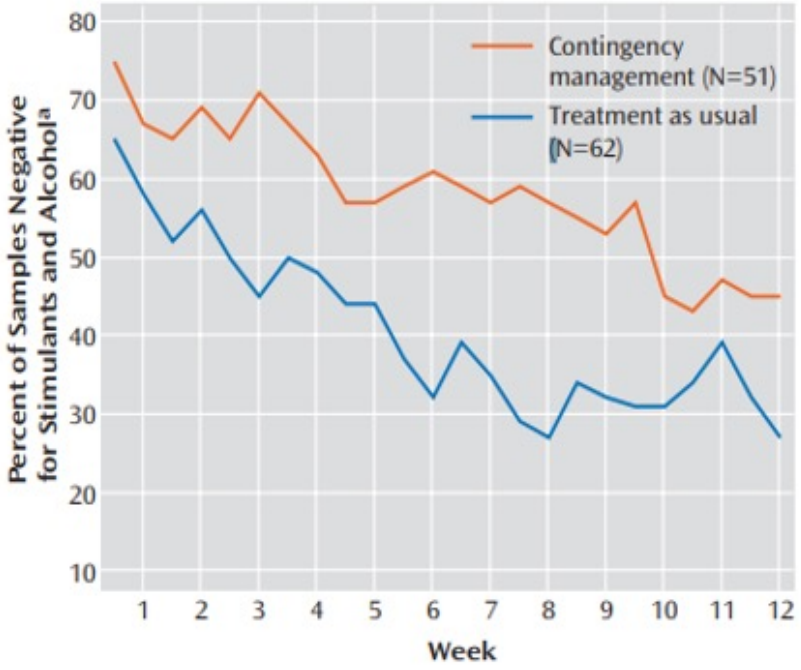
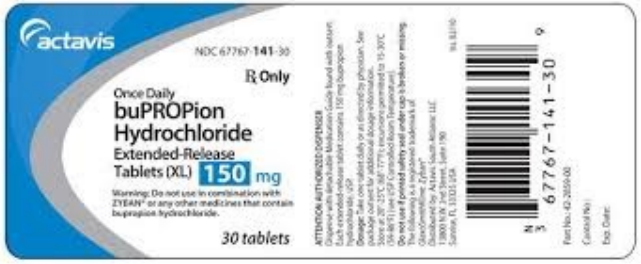


FIGURE 2. Negative Drug Samples[a] Over 12 Weeks for Patients With Methamphetamine Use Disorders Receiving Usual Treatment With or Without Contingency Management

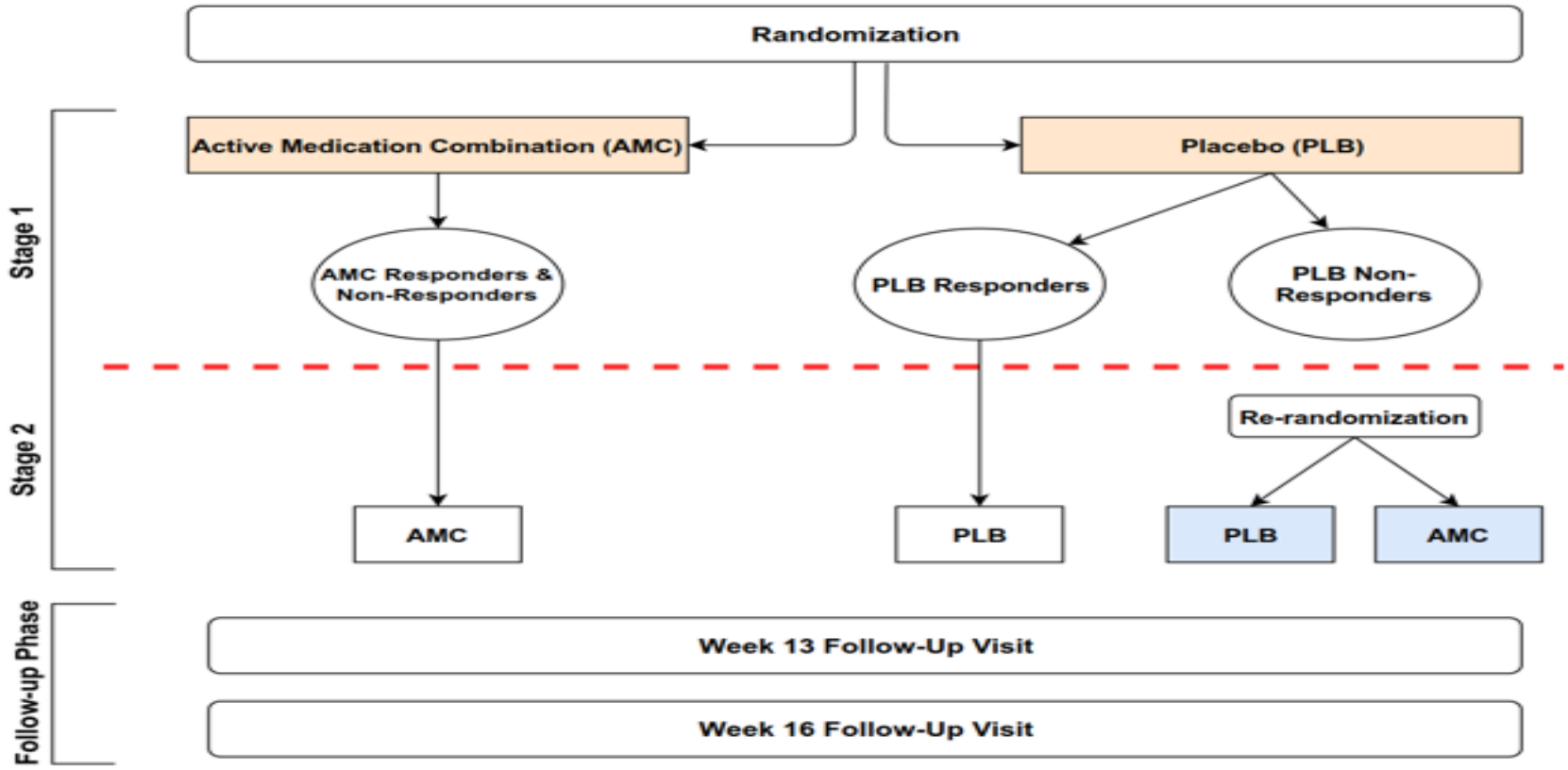


Methamphetamine: ADAPT-2

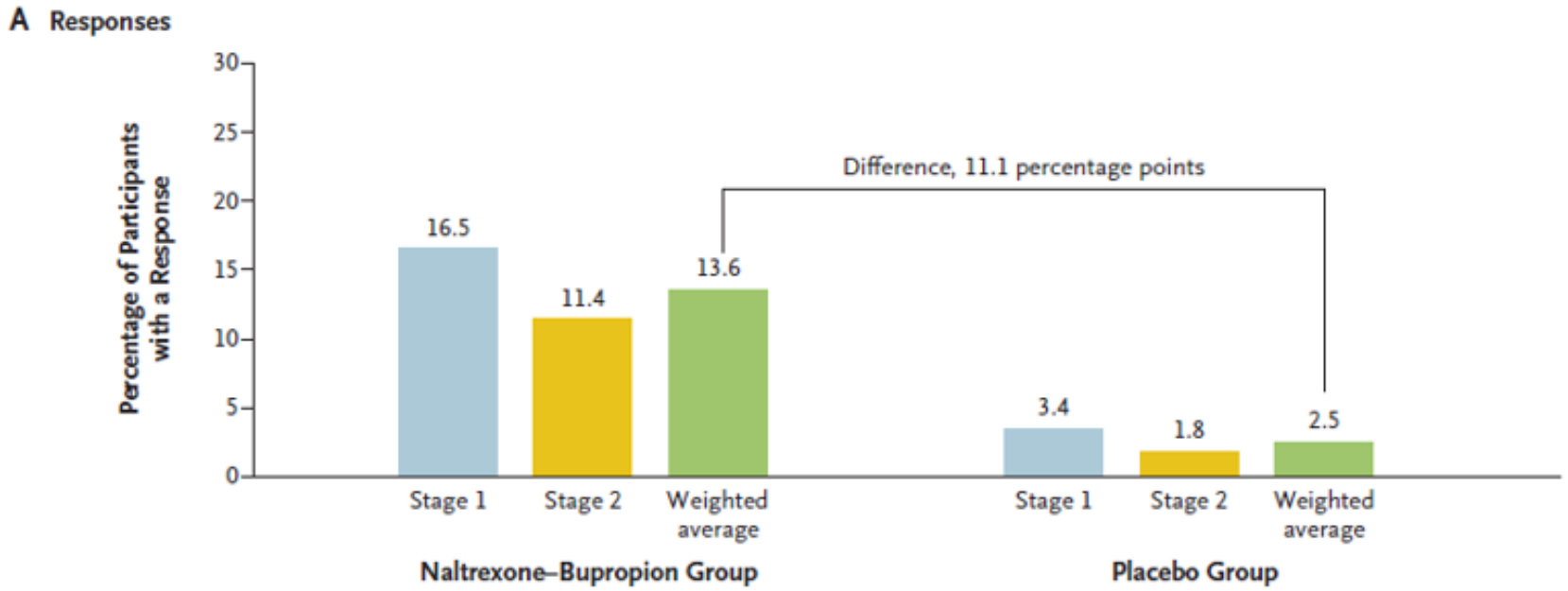
- 12 week double-blind, placebo-controlled, randomized sequential parallel comparison design (SPCD) clinical trial evaluating the efficacy of extended-release naltrexone plus bupropion as a combination pharmacotherapy for methamphetamine use disorder
- Extended-release naltrexone 380mg administered intramuscularly every 3 weeks plus bupropion XL titrated within 7days to 450mg daily
- Overall, 13.6% of people who received the medications responded to treatment, compared to only 2.5% who received the placebo. Side effects of the treatment were mild



Methamphetamine: ADAPT-2 Study Design



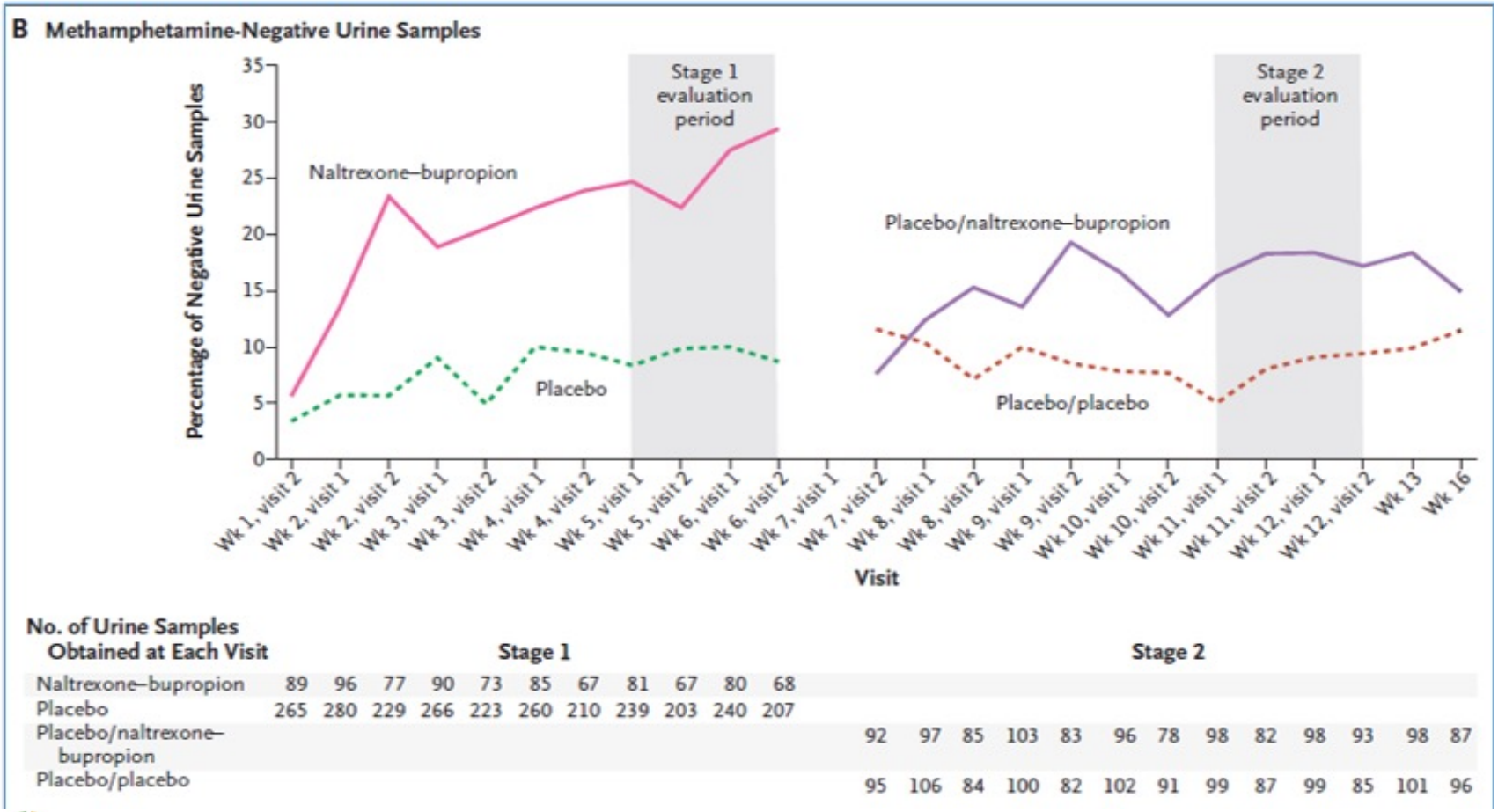
Methamphetamine: ADAPT-2 Study Results



Trivedi MH, et al. *N Engl J Med*. 2021;384(2):140-153.

Methamphetamine: ADAPT-2 Study Results

Methamphetamine Negative UDS Results in Stage 1 and Stage 2 in ITT Population



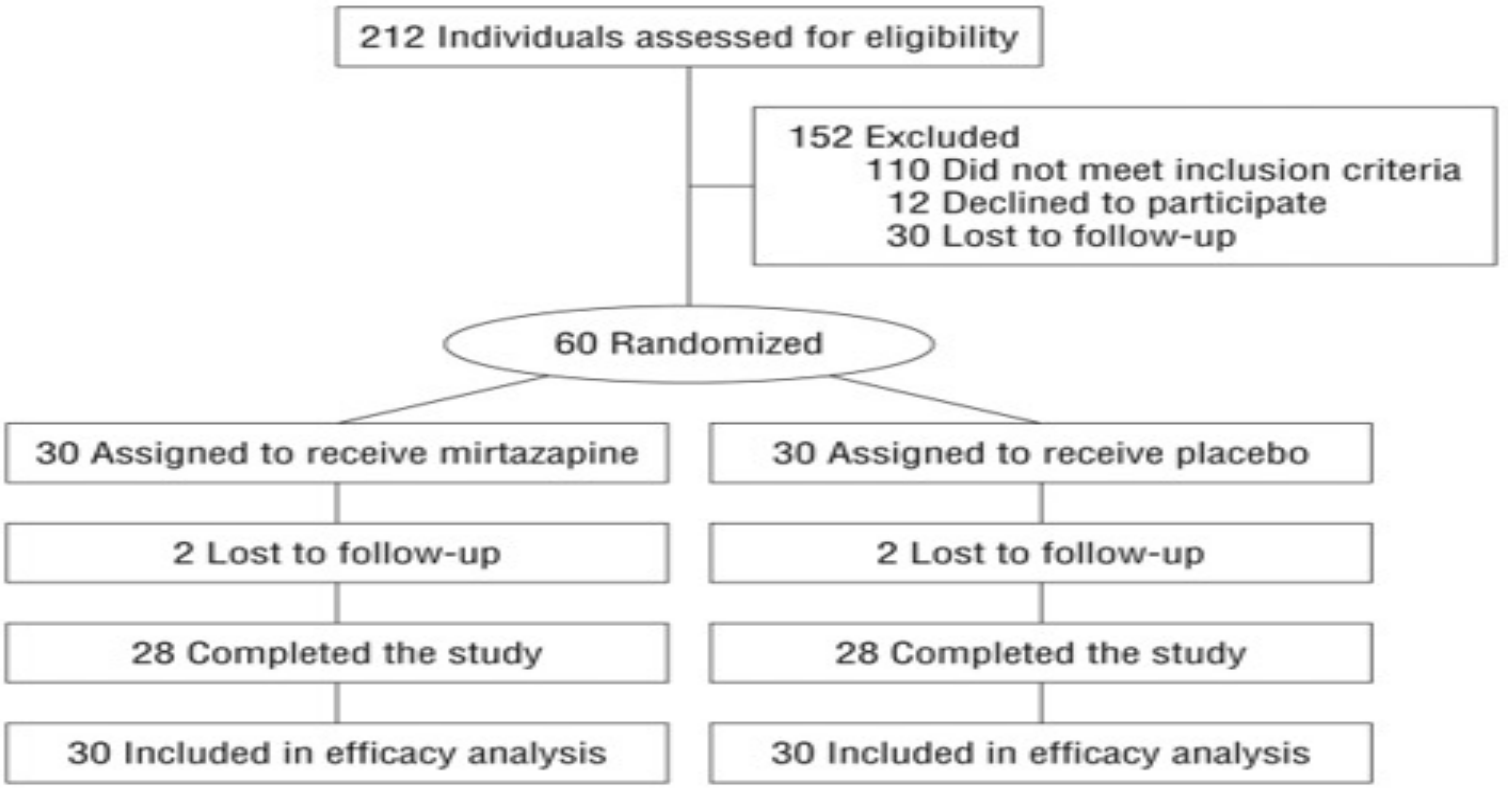
No. of Urine Samples Obtained at Each Visit	Stage 1											Stage 2												
Naltrexone–bupropion	89	96	77	90	73	85	67	81	67	80	68													
Placebo	265	280	229	266	223	260	210	239	203	240	207													
Placebo/naltrexone–bupropion												92	97	85	103	83	96	78	98	82	98	93	98	87
Placebo/placebo												95	106	84	100	82	102	91	99	87	99	85	101	96

Methamphetamine: Mirtazapine Study

Mirtazapine To Reduce Methamphetamine Use: A Randomized Controlled Trial[3]

- Objective—To determine whether mirtazapine would reduce methamphetamine use among MSM who are actively using methamphetamine
- Design—Double-blind, randomized, controlled, 12-week trial of mirtazapine vs placebo conducted from September 5, 2007, to March 4, 2010
- Setting—San Francisco Department of Public Health
- Participants—Participants were actively using, methamphetamine-dependent, sexually active MSM seen weekly for urine sample collection and substance use counseling.
- Interventions—Random assignment to daily oral mirtazapine (30 mg) or placebo; both arms included 30-minute weekly substance use counseling
- Main Outcome Measures—The primary study outcome was reduction in methamphetamine positive urine test results. Secondary outcomes were study medication adherence (by self-report and medication event monitoring systems) and sexual risk behavior

Methamphetamine: Mirtazapine Study Assessment



Methamphetamine: Study Results

- Mirtazapine To Reduce Methamphetamine Use: A Randomized Controlled Trial
  - Participants assigned to the mirtazapine group had fewer methamphetamine-positive urine test results
  - Urine positivity decreased from 67% (20 of 30 participants) to 63% (17 of 27) in the placebo arm and from 73% (22 of 30) to 44% (12 of 27) in the mirtazapine arm
  - Adherence was 48.5% by medication event monitoring systems and 74.7% by self-report; adherence measures were not significantly different between arms
  - Most sexual risk behaviors decreased significantly more among participants taking mirtazapine compared with those taking placebo

Methamphetamine: Buprenorphine Studies

- Buprenorphine for Methamphetamine use disorder
  - Salehi M et al: The Effect of Buprenorphine on Methamphetamine Cravings14
  - Kheirabadi GR et al: The Effect of Add-on Buprenorphine to Matrix Program in Reduction of Craving and Relapse Among People With Methamphetamine Use Disorder: A Randomized Controlled Trial15
- Rationale is utilizing the kappa antagonism of Buprenorphine in suppressing withdrawal, dysphoria and negative affect

Methamphetamine Studies: Application in Practice (Triple drug regimen)

- Week 1: Start Naltrexone 25mg at bedtime for 7days and then titrate to 50mg at bedtime
- Week 2: Start Bupropion XL 150mg every morning for 7days and then increase to 300mg daily
- May titrate to Bupropion XL 450mg daily if partial response to the above regimen after 6 weeks
- May consider augmentation with Mirtazapine 15mg at bedtime and titrate to 30mg at bedtime if needed if partial response to Naltrexone 50mg daily plus Bupropion XL 450mg daily after 3-4 months

Methamphetamine: Ongoing Studies

- Stimulus CTN 0108: Transcranial Magnetic Stimulation for the Treatment of Methamphetamine/Cocaine Use Disorder
- This study aims to
  - Determine the feasibility and effect size for 20 sessions of repetitive transcranial magnetic stimulation (rTMS) versus sham in adults with a DSM 5 methamphetamine use disorder (MUD) or a cocaine use disorder (CUD)
  - Evaluate the safety of rTMS compared to sham in participants with CUD/MUD at the end of treatment and at a 12-week follow-up

Methamphetamine: Ongoing studies

- CURB-2 CTN 0109: Randomized, Placebo-Controlled Trial of Injectable Naltrexone and Monthly Injectable Buprenorphine for Cocaine Use Disorder (CURB-2)
  - The study aims to evaluate the safety and efficacy of combined monthly injections of XR-NTX and injectable BUP for CUD compared to placebo
- Recent research suggests that a kappa opioid receptor antagonist can curb the negative emotional states associated with stimulant withdrawal that leads to increased craving and drug-seeking behaviors

ORN Survey

To better improve our services, we respectfully request you complete this brief survey about your experience with the Opioid Response Network.

Thank you!

Questions & Discussion

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References

1. Han B, Cotto J, Etz K, Einstein EB, Compton WM, Volkow ND. Methamphetamine overdose deaths in the US by sex and race and ethnicity. JAMA Psychiatry. 2021;78(5):564-567. doi:10.1001/ jamapsychiatry.2020.4321
2. Colfax GN, Santos GM, Das M, Santos DM, Matheson T, Gasper J, Shoptaw S, Vittinghoff E. Mirtazapine to reduce methamphetamine use: a randomized controlled trial. Arch Gen Psychiatry. 2011; 68:1168–1175. [PubMed: 22065532]
3. Cruickshank CC, Dyer KR. A review of the clinical pharmacology of methamphetamine. Addiction. 2009; 104:1085–1099. [PubMed: 19426289]
4. Petry et al. Effect of prize-based incentives on outcomes in stimulant abusers in outpatient psychosocial treatment programs. Archives General Psychiatry. 2005; 62:1148-1156
5. Roll et al. Contingency management for the treatment of methamphetamine use disorders. Am J Psychiatry. 2006; 163:1993-1999
6. Trivedi M. H. et al. Bupropion and Naltrexone in Methamphetamine Use Disorder. N Engl J Med 2021;384:140-53. DOI: 10.1056/NEJMoa2020214

References

12. Substance Abuse and Mental Health Services Administration. National Survey on Drug Use and Health (NSDUH). Accessed January 14, 2022. https://www.samhsa.gov/data/data-we-collect/ nsduh-national-survey-drug-use-and-health

13. Palamar JJ, Han BH, Keyes KM. Trends in characteristics of individuals who use methamphetamine in the United States, 2015-2018. Drug Alcohol Depend. 2020;213:108089. doi:10.1016/j.drugalcdep.2020.108089 Won S et al. Methamphetamine-Associated Cardiomyopathy. Clin. Cardiol. 36, 12, 737–742 (2013) 737 Published online in Wiley Online Library (wileyonlinelibrary.com) DOI:10.1002/clc.22195

14. Salehi M et al. The Effect of Buprenorphine on Methamphetamine cravings. Journal of Clinical Psychopharmacology 35(6):p 724-727, December 2015. *DOI:* 10.1097/JCP.0000000000000408

15. Kheirabadi GR et al. The Effect of Add-on Buprenorphine to Matrix Program in Reduction of Craving and Relapse Among People With Methamphetamine Use Disorder: A Randomized Controlled Trial. Journal of Clinical Psychopharmacology 2021;41(1):45-48.doi: 10.1097/JCP.0000000000001320.

References

17.https://www.deadiversion.usdoj.gov/drug_chem_info/stimulants/IQVIA_Report_on_Stimulant_Trends_from_2012-2022.pdf

18. Reddy PV et.al. Clinical Characteristics and Management of Methamphetamine Associated Cardiomyopathy: State-of-the-Art Review. JAHA;2020 Jun 2;9(11):e016704. doi: 10.1161/JAHA.120.016704