

Methamphetamine Use Disorders: An Update

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June 20, 2024



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.

Funding for this initiative was made possible (in part) by grant no. 1H79TI085588-2 from SAMHSA. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.



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





Historical aspects

- ✧ Ephedra is a shrub whose extract has been used in traditional Chinese medicine for over 5000 years 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”



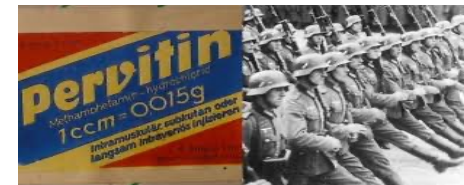
Historical aspects

- ✧ 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



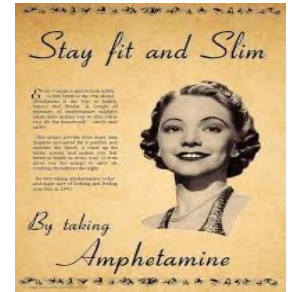
Historical aspects

- ✧ 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 include^{14,18}
- ✧ 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 predominantly¹⁸
- Genetic predisposition to development of cardiomyopathy in methamphetamine users may exist via the CYP2D6 enzyme, the initial and rate-limiting step during metabolism of methamphetamine¹⁸
- A single study involving 56 patients showed a trend toward increased dilated cardiomyopathy among extensive metabolizers after adjusting for age and sex¹⁸

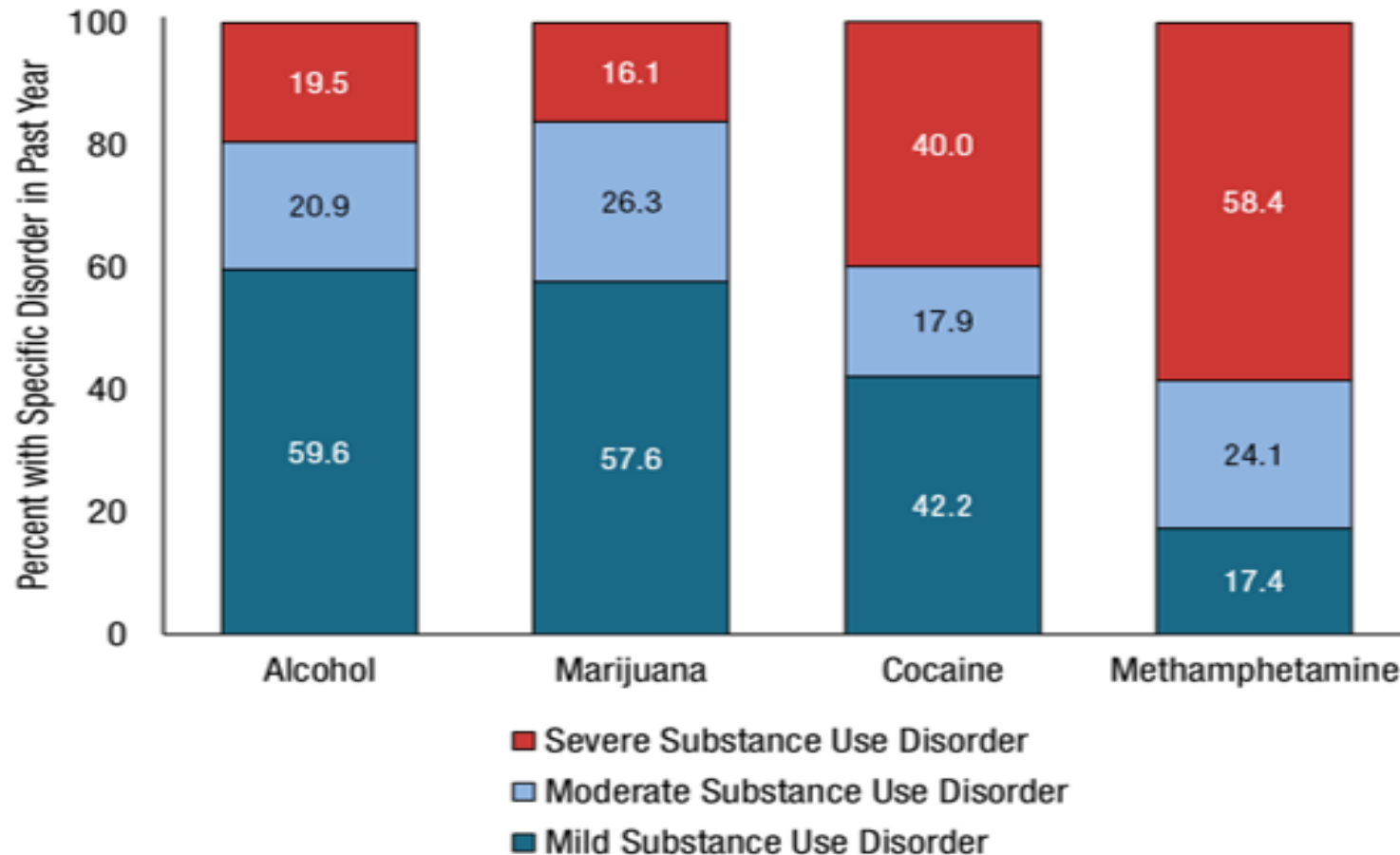




"Sometimes I like to circle someone perfectly healthy just to mess with their head."



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

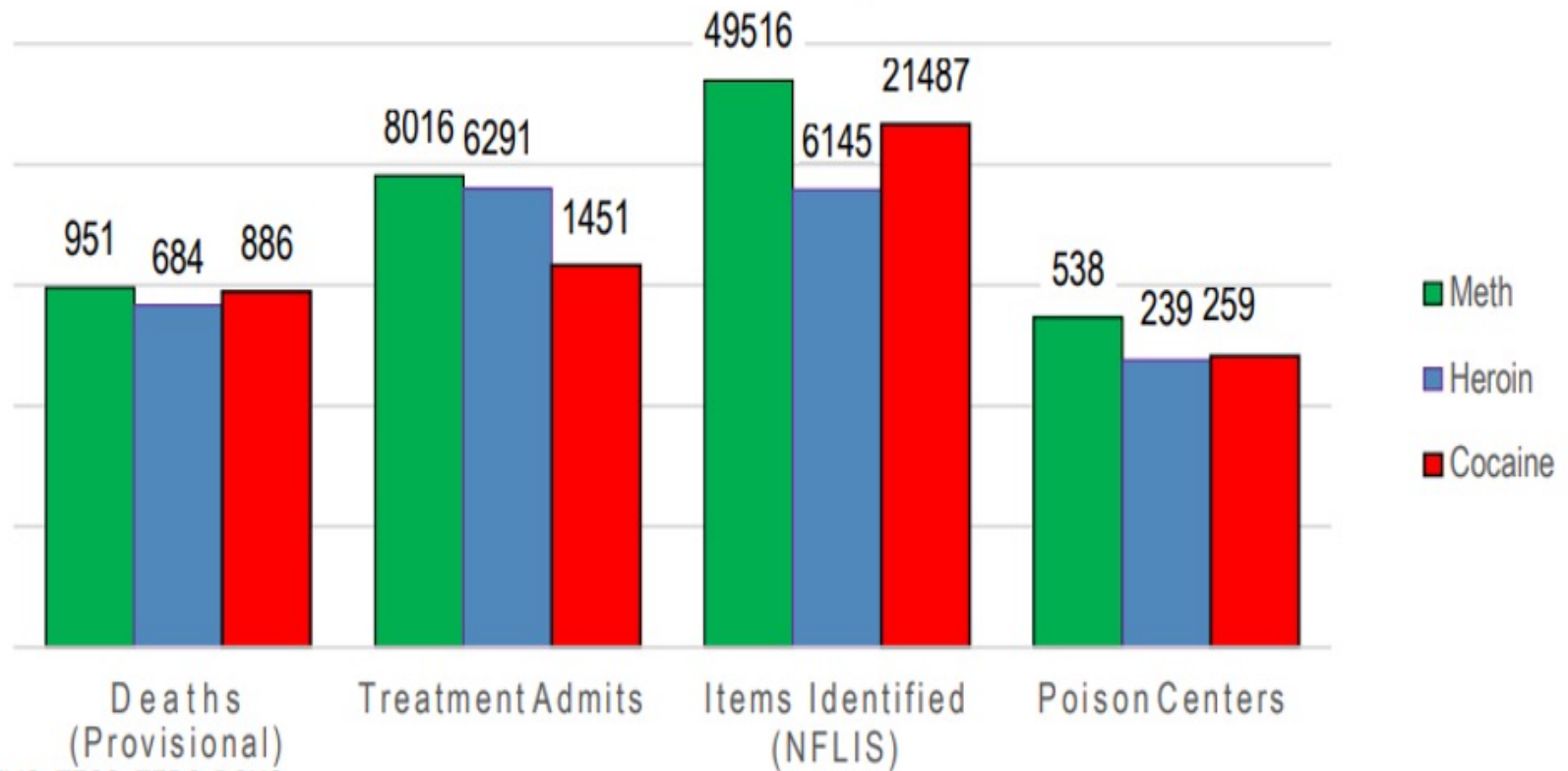


Methamphetamine: Trends in Texas

- 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)



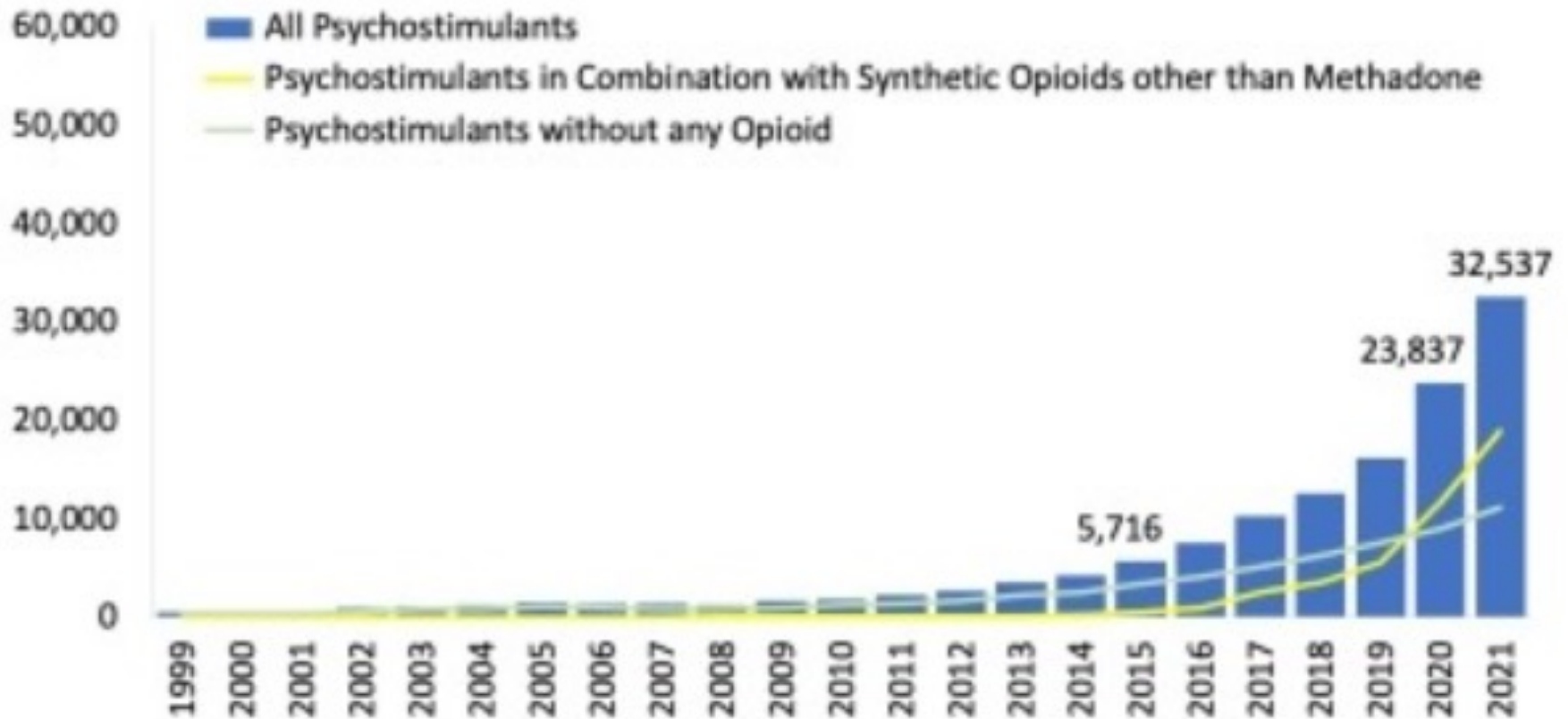
Methamphetamine, Cocaine and Heroin: Trends in Texas 2020



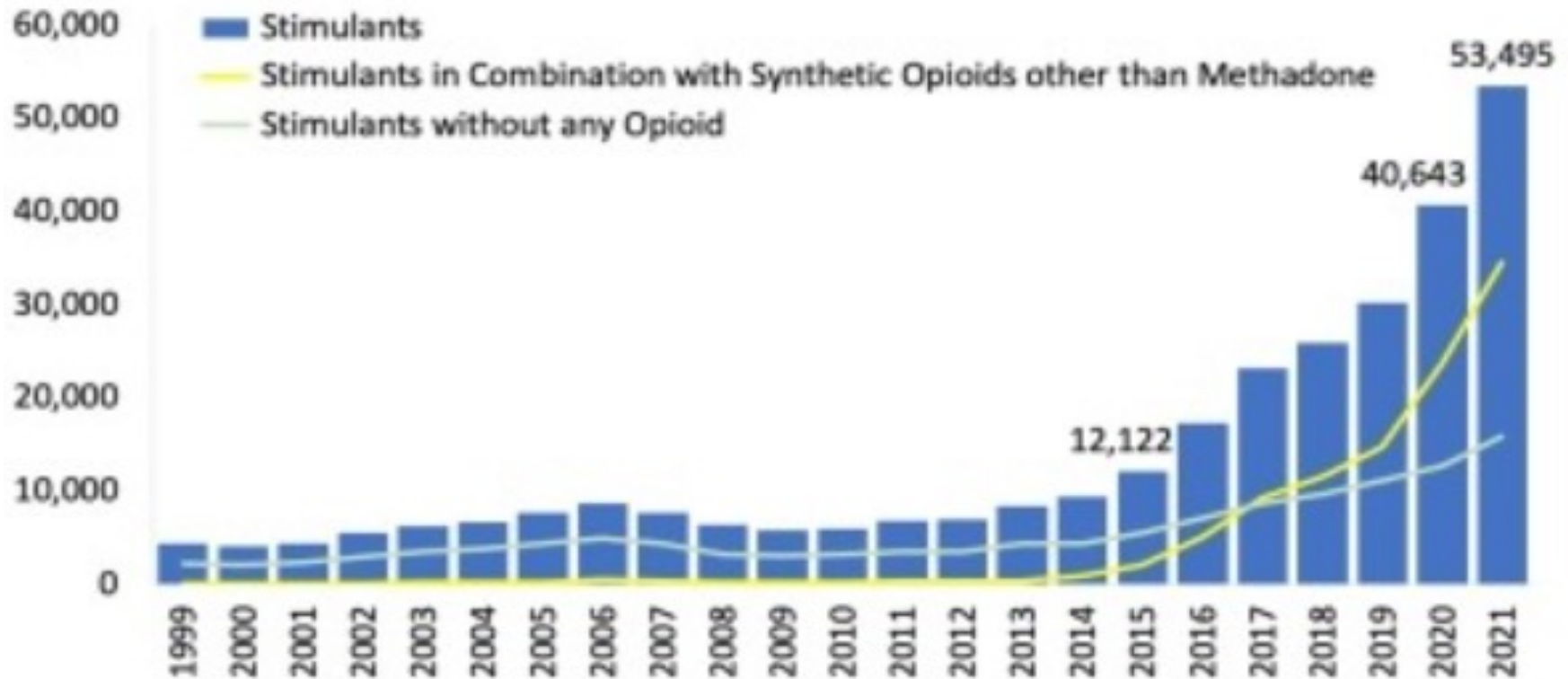
Sources: NFLIS, TESS, TEDS, DSHS



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 2012¹⁷
- ✧ 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 telehealth¹⁷
- ✧ The highest annual increase in prescription stimulants dispensed was from 2021 to 2022¹⁷

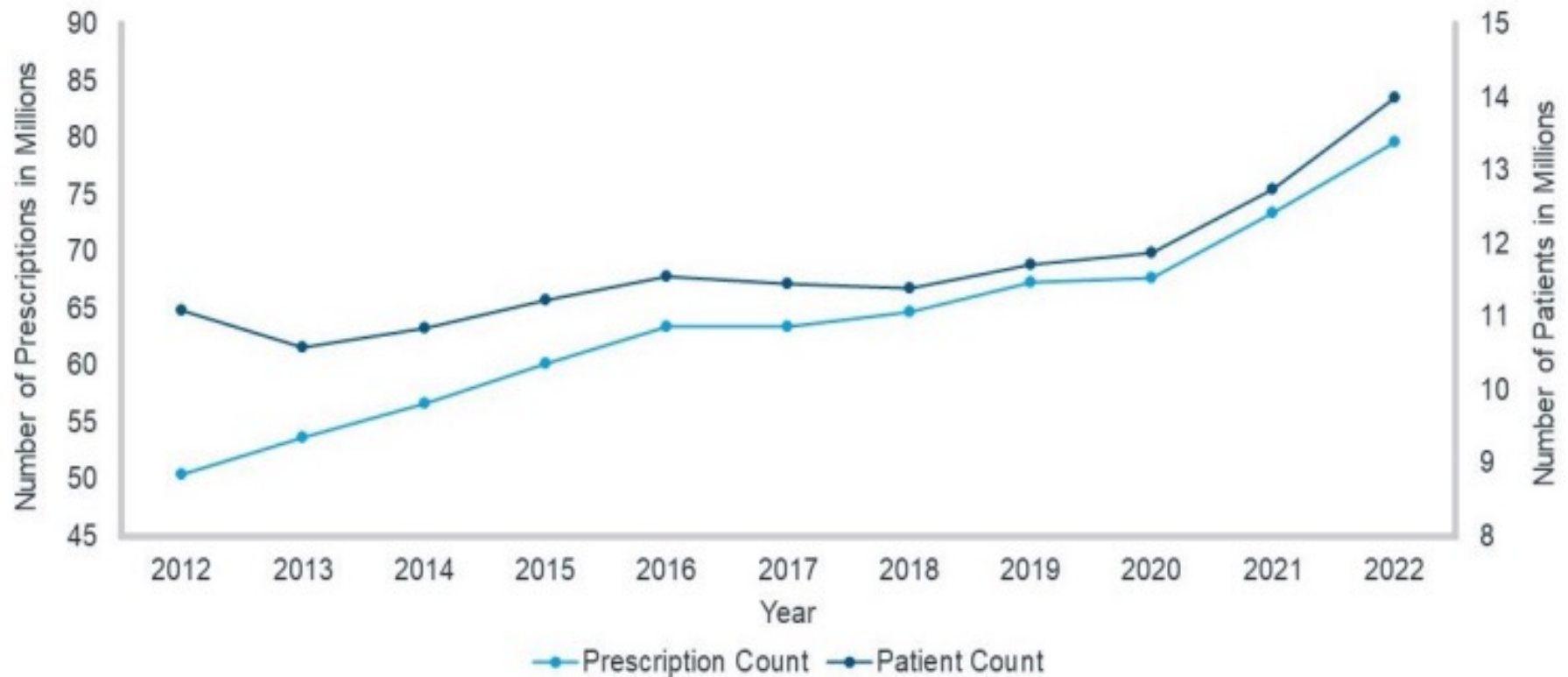


Stimulant Prescribing: Trends in the country 2012-2022 (IQVIA Report)

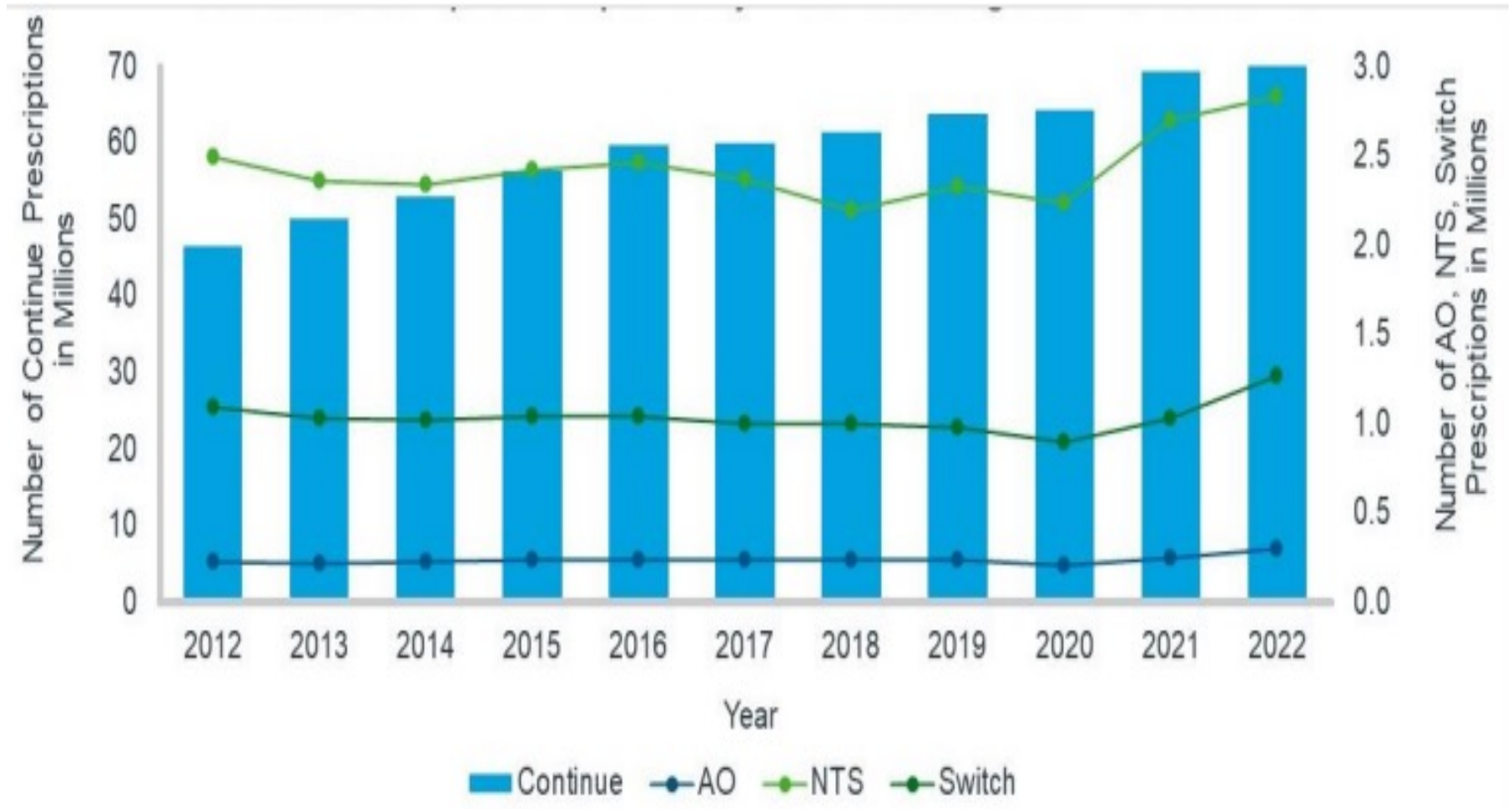
- ✧ From 2012 to 2021, adults between the ages of 31-40 years, particularly women, and older patients (71-80 years old) had the highest increase in prescription stimulants dispensed¹⁷
- ✧ In 2022, women surpassed men in dispensed prescriptions for stimulants¹⁷
- ✧ Overall, psychiatrists and pediatricians had most prescription stimulants dispensed; however, annual increases have been much higher among nurse practitioners¹⁷



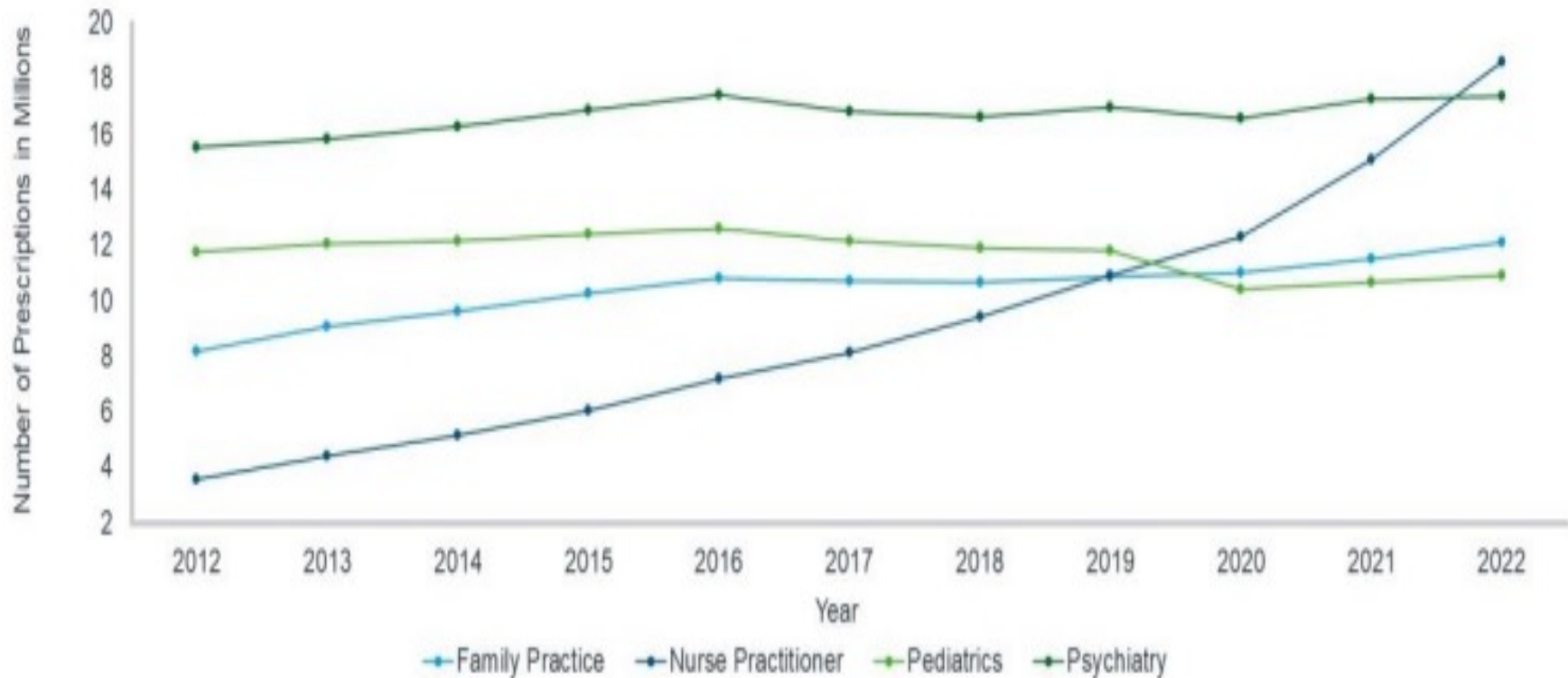
Stimulant Prescribing: Prescriptions and Patients from 2012 to 2022



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 Addictive Pharmacotherapy Treatment for Methamphetamine Use Disorder⁷
- 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

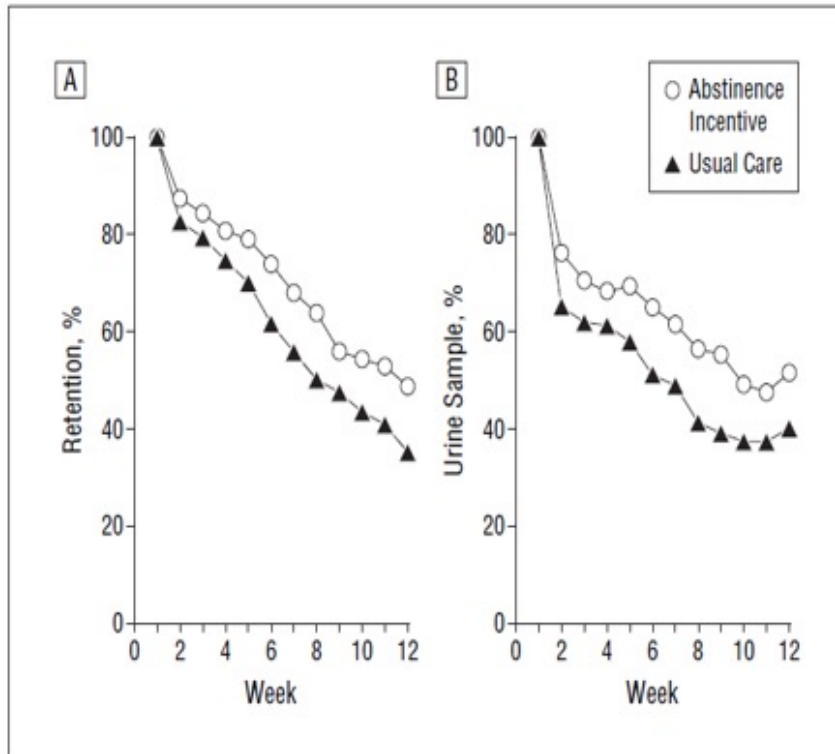
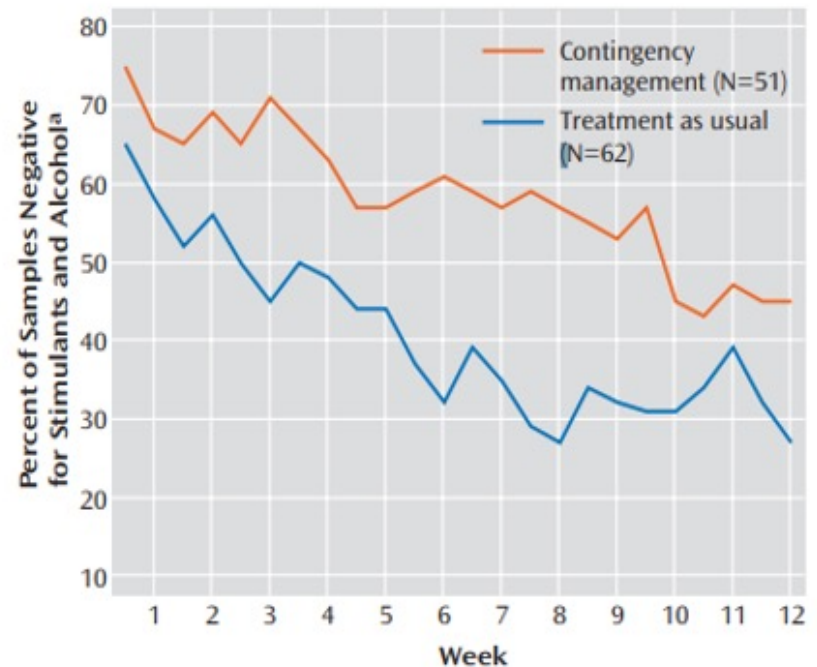
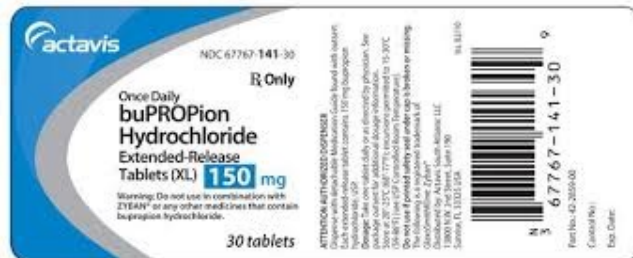


FIGURE 2. Negative Drug Samples^a Over 12 Weeks for Patients With Methamphetamine Use Disorders Receiving Usual Treatment With or Without Contingency Management

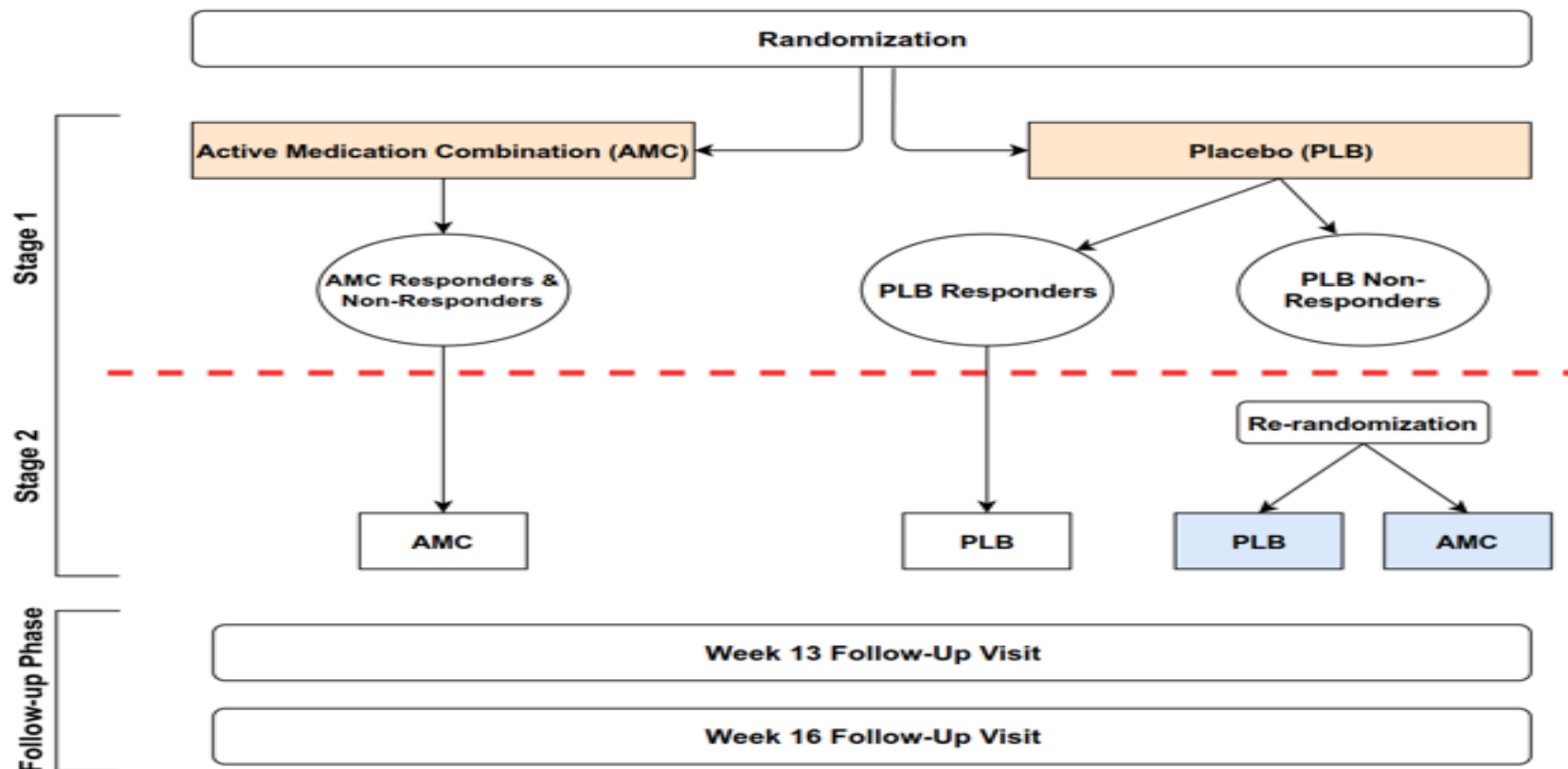


Methamphetamine: ADAPT-2

- ✧ 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

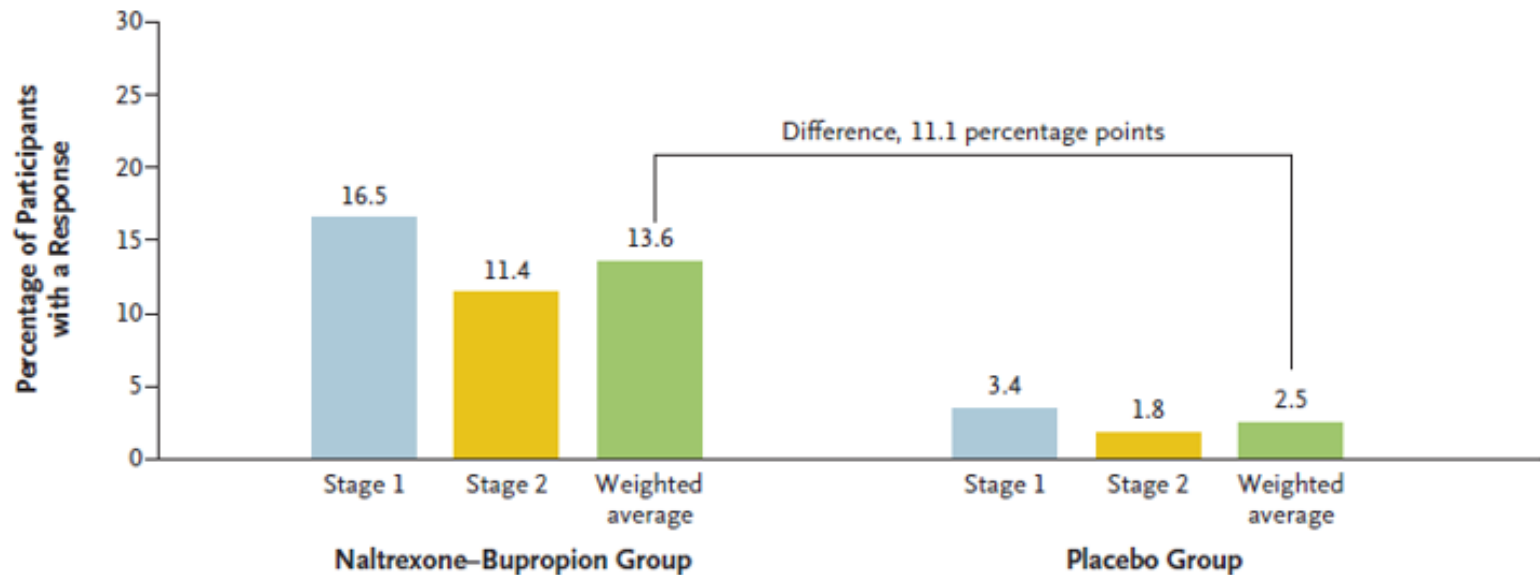


Methamphetamine: ADAPT-2 Study Design



Methamphetamine: ADAPT-2 Study Results

A Responses

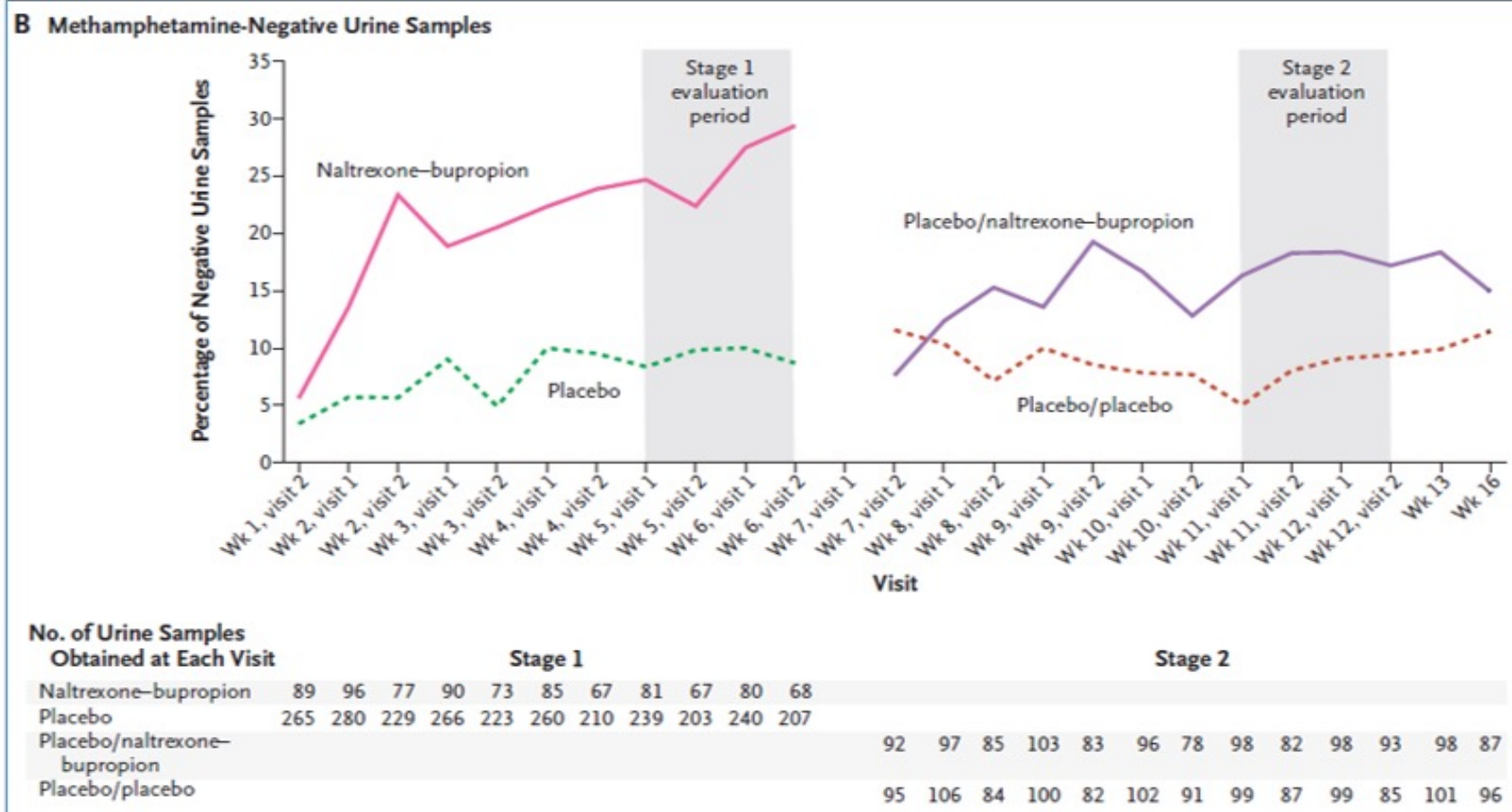


Trivedi MH, et al. *N Engl J Med*. 2021;384(2):140-153.



Methamphetamine: ADAPT-2 Study Results

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



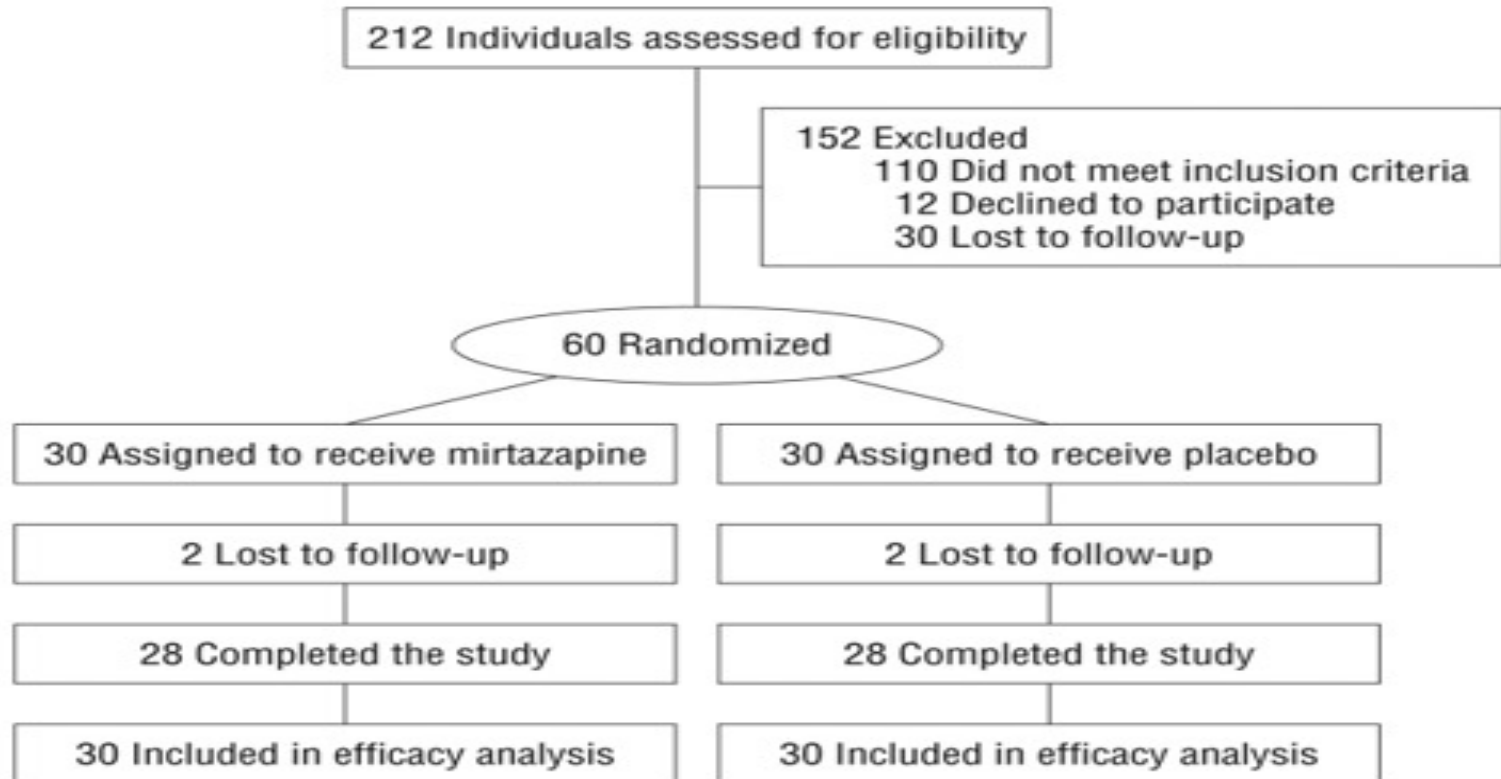
Methamphetamine: Mirtazapine Study

Mirtazapine To Reduce Methamphetamine Use: A Randomized Controlled Trial³

- ✧ 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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