CASE-BASED LEARNING COLLABORATIVE ON STIMULANTS

CME SERIES

1st and 3rd - Fridays at 12pm-1pm PT

The Center For Behavioral And Addiction Medicine
UCLA Department Of Family Medicine
Los Angeles County Substance Abuse Prevention and Control
UT Southwestern Clinical Trials Network Big South/West Node

cbam center for behavioral & addiction medicine

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SAPC | Substance Abuse Prevention and Control

Unraveling Complexities in the Diagnosis & Management of Stimulant-Induced Psychosis

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Disclosures

Consultant, American Academy of Addiction Psychiatry – Opioid Resource Network Stimulant Work Group

Disclaimer: Off-label use of medications will be discussed during this presentation.

Objectives

1. Understand prevalence, risk factors, and clinical manifestations of psychostimulant-induced psychosis

2. Compare & contrast stimulant-induced psychosis with other types of psychotic disorders

3. Develop a treatment approach for management of stimulant-induced psychosis in both acute and chronic settings

Case

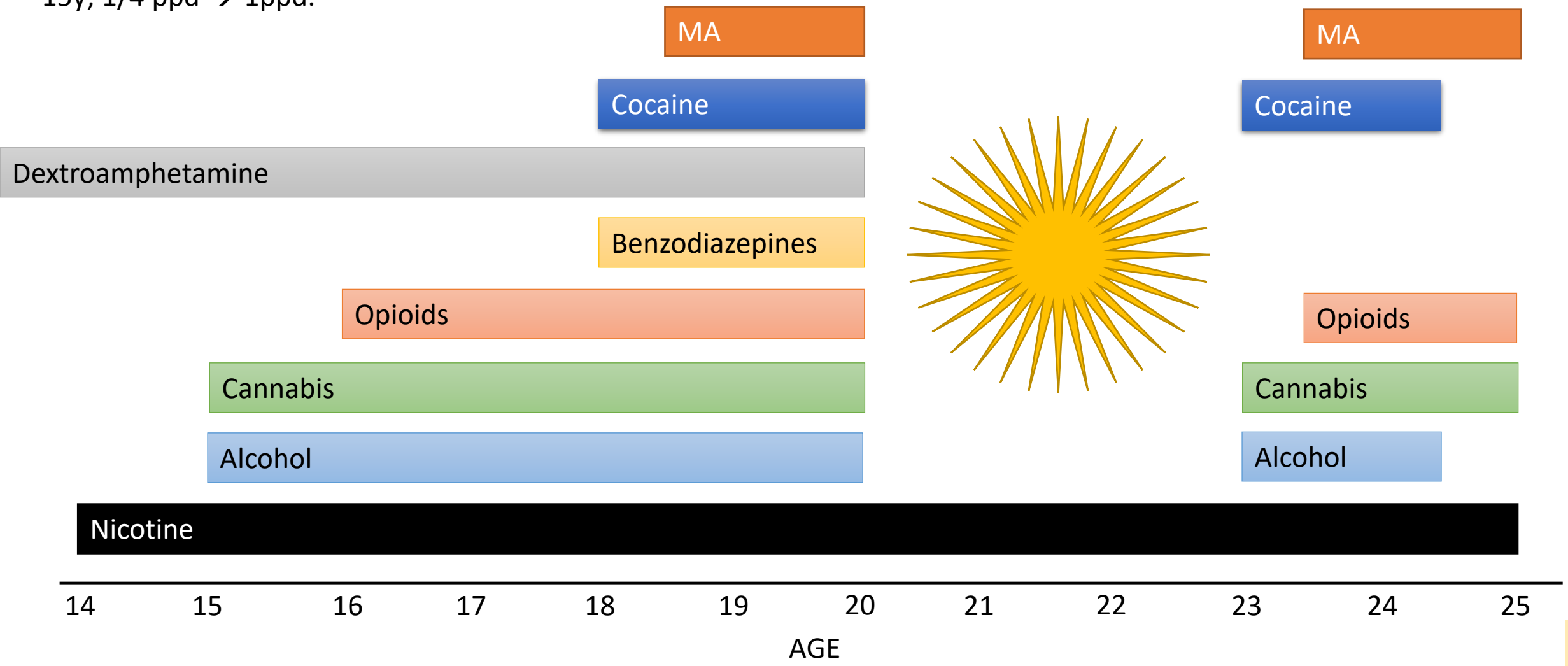
- 25-year-old Caucasian male admitted voluntarily to hospital

- Endorses two-week history of manic symptoms (**fluctuant mood, decreased sleep need, and racing thoughts**) in context of stimulant use. The patient also endorses a history of severe depressive symptoms in the past and is currently reporting **depressed mood, feelings of guilt & worthlessness, low energy (exhaustion), and passive suicidal ideation**.

- The patient also believes he and his family have been the victims of an elaborate **cyber attack via mobile device** & the perpetrator is trying to extort them.

- **Motivated for treatment** because wife kicked him out and is planning divorce

1st use: 14y, Cigarettes since 15y; 1/4 ppd → 1ppd.



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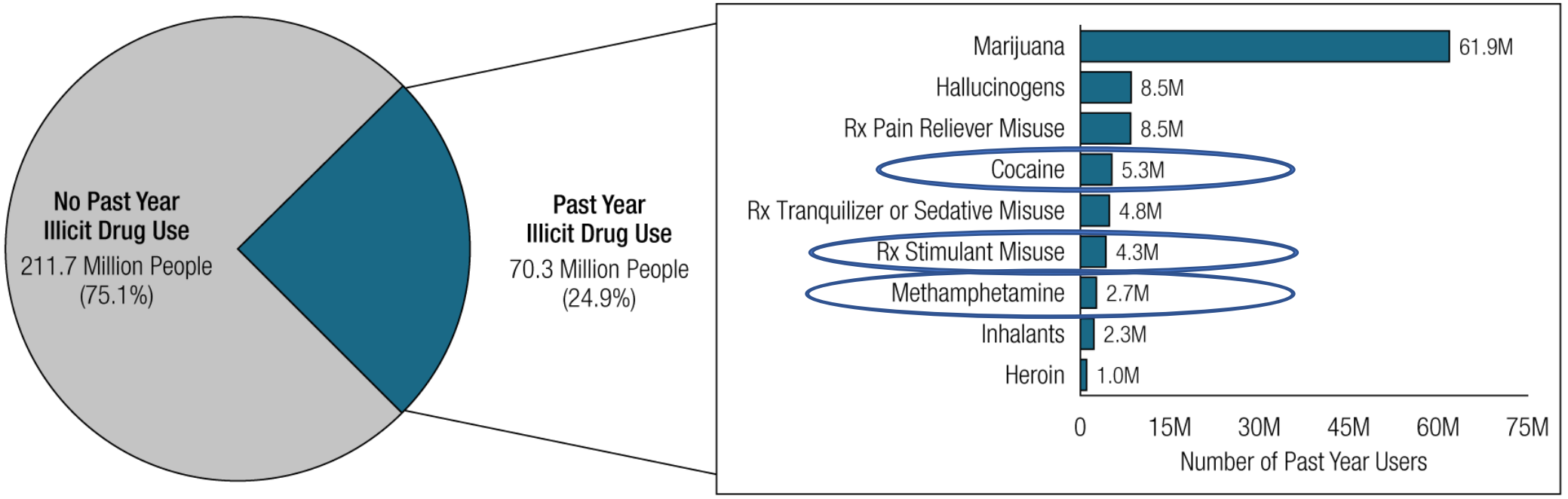
Preliminary Considerations

- ADHD

- Cannabis
- Alcohol, Opioids, Benzodiazepines
- Psychostimulants

- Period of abstinence

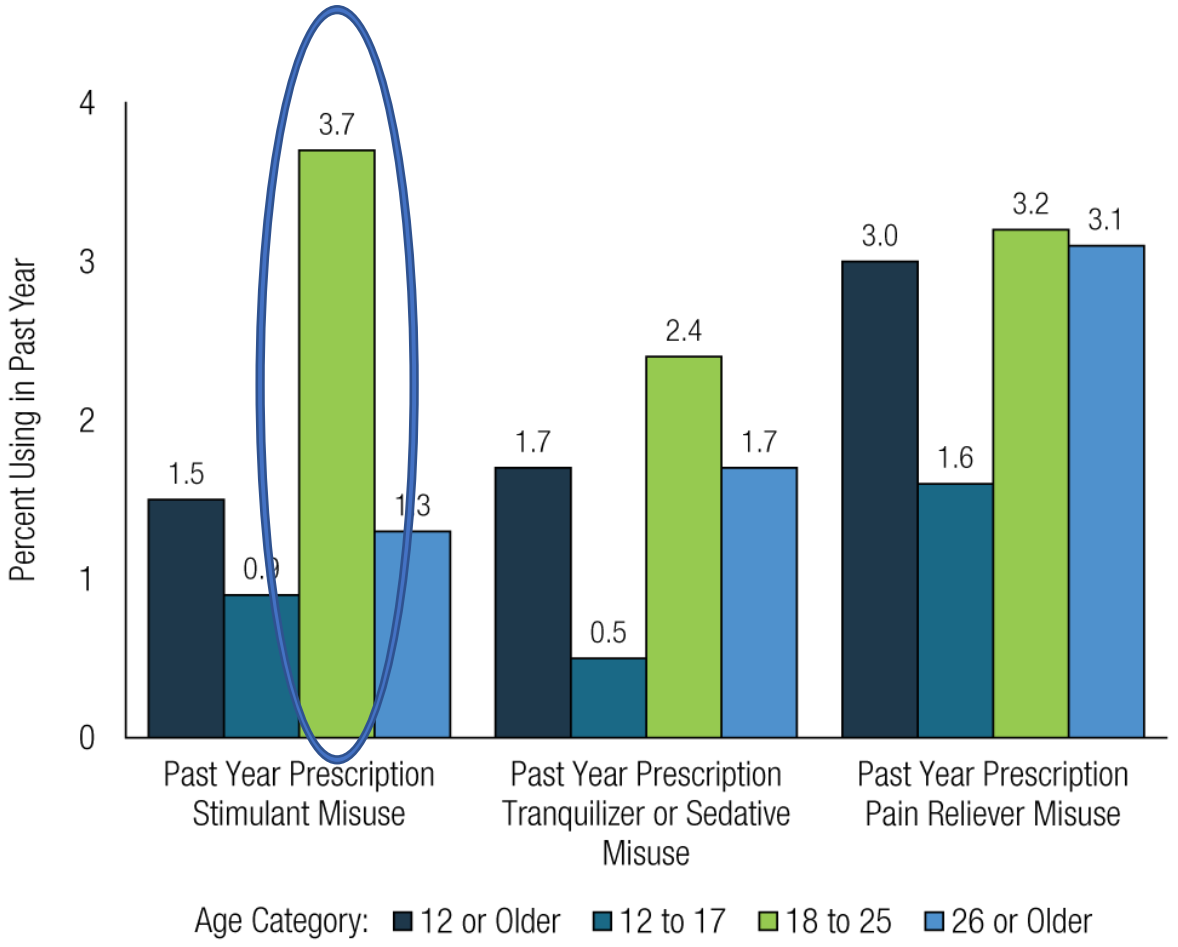
Past Year Illicit Drug Use: Among People Aged 12 or Older; 2022



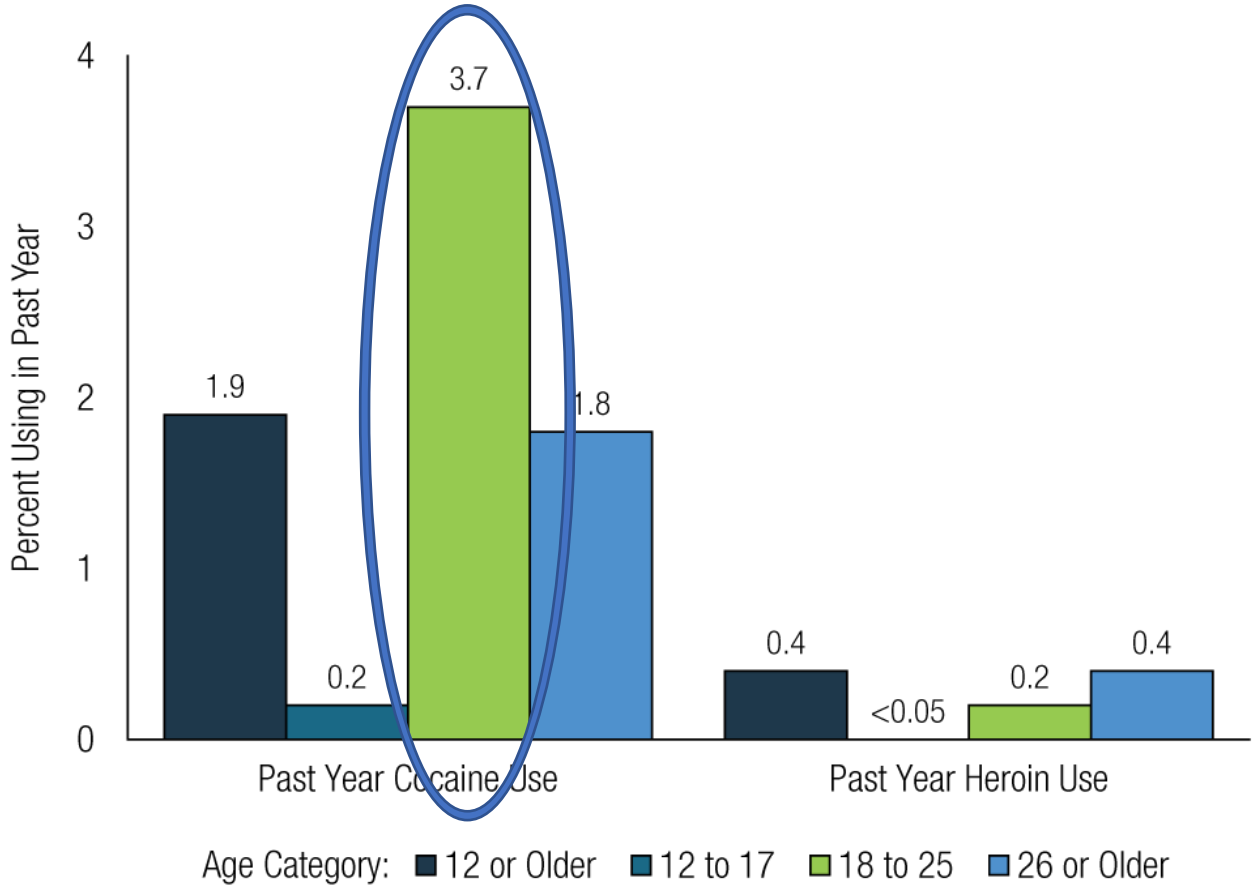
Rx = prescription.

Note: The estimated numbers of past year users of different illicit drugs are not mutually exclusive because people could have used more than one type of illicit drug in the past year.

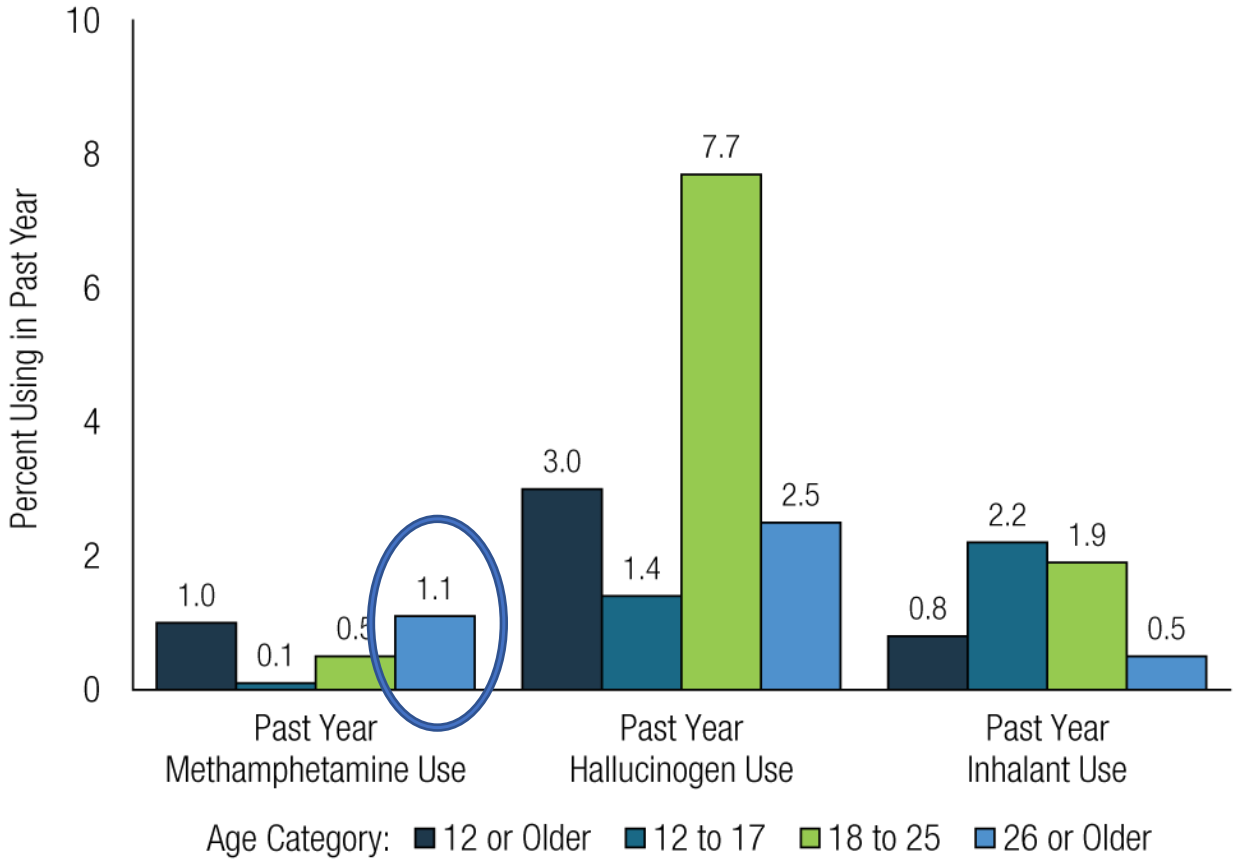
Past Year Prescription Stimulant Misuse, Past Year Prescription Tranquilizer or Sedative Misuse, or Past Year Prescription Pain Reliever Misuse: Among People Aged 12 or Older; 2022



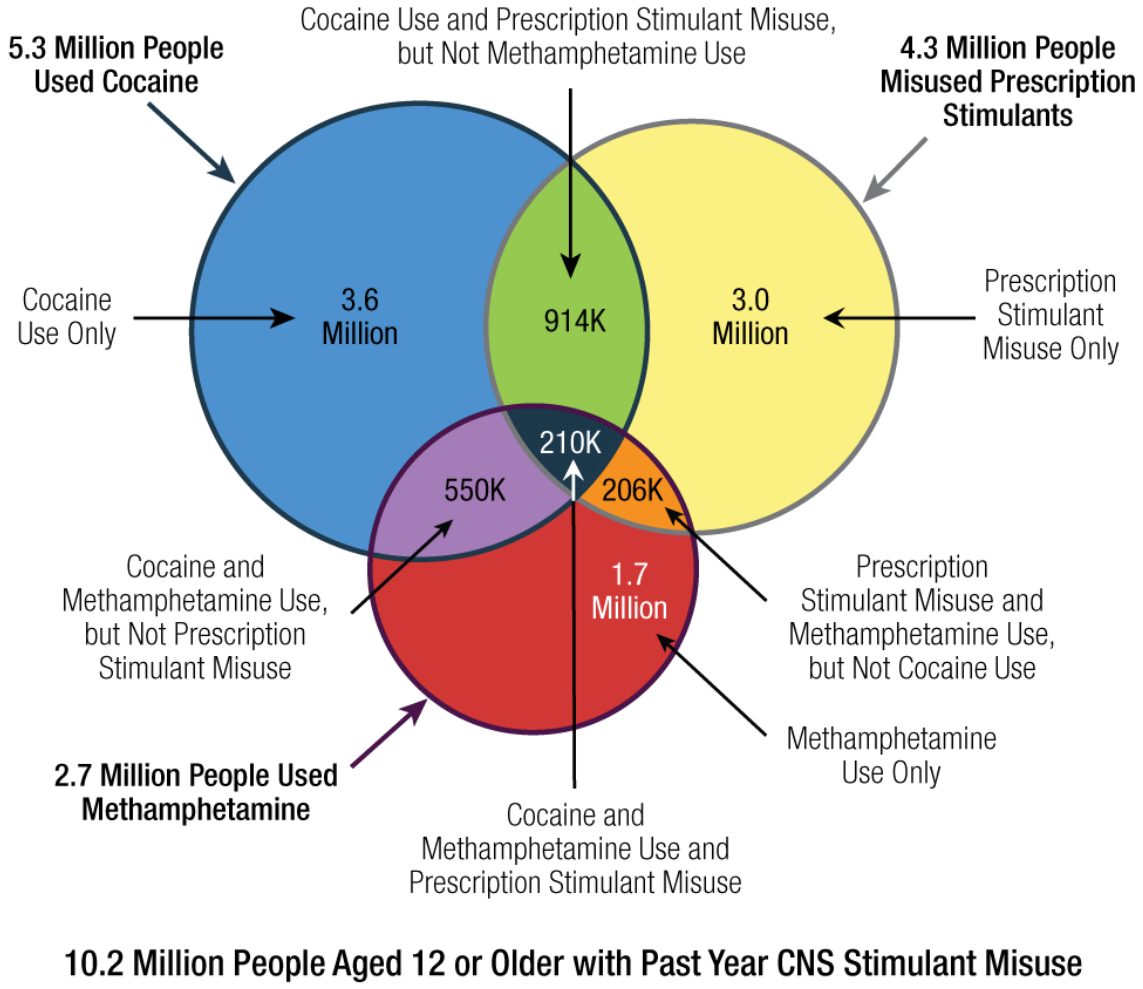
Past Year Cocaine Use or Past Year Heroin Use: Among People Aged 12 or Older; 2022



Past Year Methamphetamine Use, Past Year Hallucinogen Use, or Past Year Inhalant Use: Among People Aged 12 or Older; 2022



Past Year Central Nervous System (CNS) Stimulant Misuse: Among People Aged 12 or Older; 2022



1,88M (18%) with some form of combined stimulant use

Schizophrenia (DSM-5)

Substance-Induced Psychosis

A. Presence of one or both:
   - Delusions
   - Hallucinations

B. Historical evidence sx developed during, or within a month of, intoxication or withdrawal

C. Etiological relationship of substance to psychosis

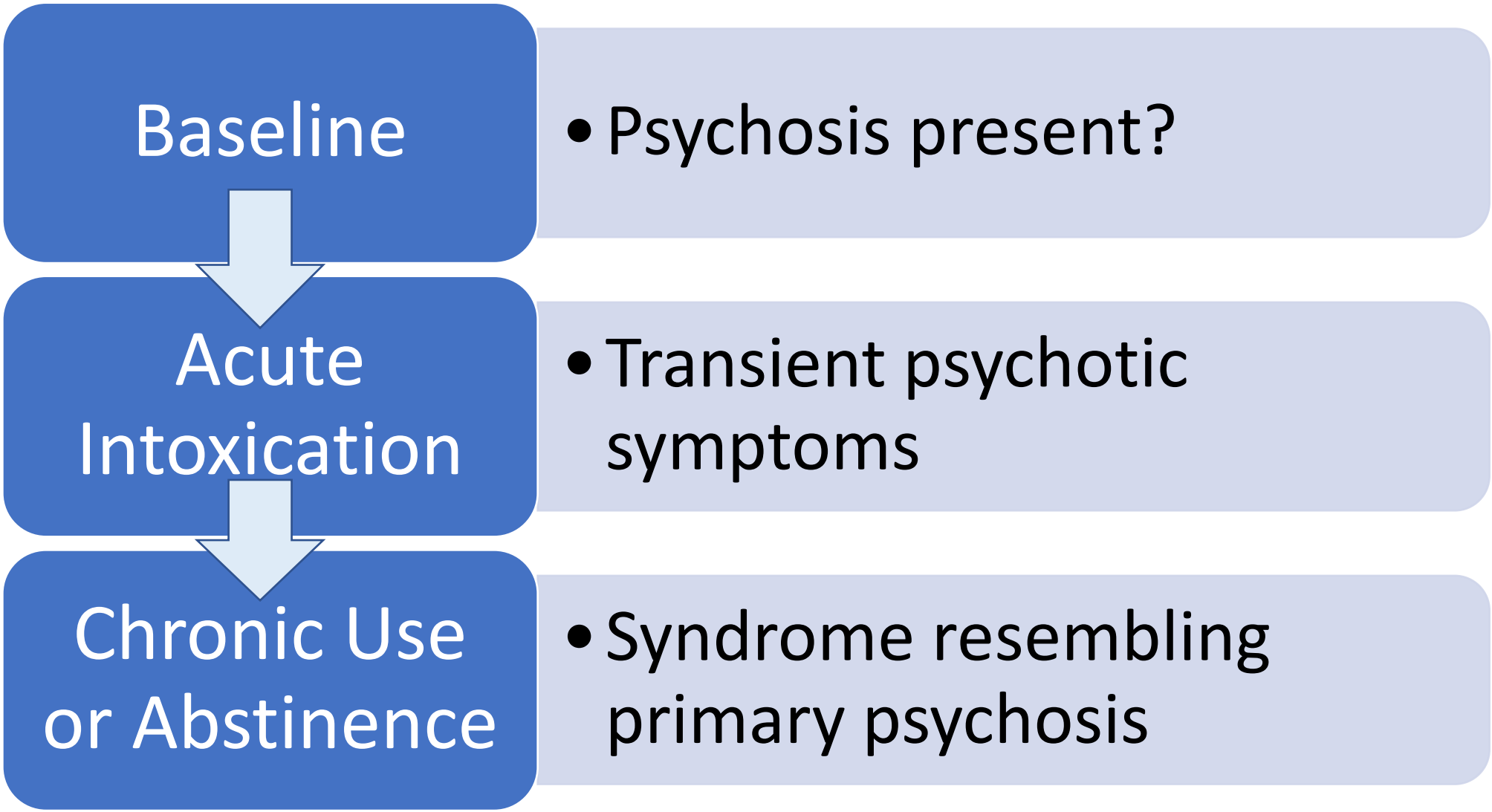
D. Symptoms not during delirium

E. Clinical distress

Pathogenesis of SIP

- Higher central dopamine activity
  - ***Stimulants***
  - Cathinones
- Cannabinoid CB-1 receptor agonism
- 5HT2A-receptor agonism
  - Hallucinogens
  - Phenylethylamines (e.g., 2C)
- NMDA antagonism
  - Phencyclidine (PCP)
  - Ketamine
- K-opioid receptor activation
  - Salvia divinorum
  - Kratom (Mitragyna speciosa)

Stimulant-Induced Psychosis



	Schizophrenia	Cocaine	Methamphetamine

Symptom profile	• Positive symptoms
	• Negative symptoms
	• Thought disorder
		• Hallucinations (96%)
		  • Auditory > Visual
		• Paranoid delusions (90%)
		• Behavioral abnormalities (29%)
		• Tactile hallucinations
		  • Parasitosis
			• Persecutory delusions (84%)
			• Hallucinations
			  • Auditory (69%) > Visual (65%)
			• Hostility (53%)
			• Conceptual disorganization (36%)
			• Depression (31%)

Duration	Chronic	1. Ccn-Induced Psychotic Symptoms 2. Ccn-Induced Psychotic Disorder	
Prevalence		Current users = 50.2% (40-66%) • CIPD = 40% (95% CI: 14.9-71.7) • CIPS = 55.2% (95% CI: 32.8-75.7) Lifetime users = 55.6% (9.6–91%) • CIPD = 16% (95% CI: 10.6-23.2) • CIPS = 68.4% (95% CI: 62.8-73.5)	Current = 22.1% Lifetime = 42.7% Only MUD = 43.3% MUD & MA users = 23.2%
Relationship to drug		Quantity/dose → symptom severity	

Prevalence of Cocaine Induced Psychosis

Current users (3 studies, n=102)

- Pooled prevalence of CIP (sx + SIPD) = 50.2% (95% CI: 32.0-68.4)
  - Excluding one study gave lower prevalence of 41.4% (29.5-54.4)
  - CIPD = 40% (14.9-71.7)
  - CIPS = 55.2% (32.8-75.7)

- Lifetime users (17 studies, n=5286)
- Pooled prevalence of CIP = 55.6% (50.2-61.0)
  - CIPD = 16% (10.6-23.2)
  - CIPS = 68.4% (62.8-73.5)

Cannabis as Risk Factor?

- Initiation of cannabis use during adolescence is a risk factor for occurrence & severity of CIP in ccn-dependent individuals
- Lifetime & recent use of cannabis associated w/CIP
- Phenomenological diffs b/w cocaine- & cannabis-induced psychoses
- May interact, but distinct

Other Risk Factors for CIP

- Younger age of cocaine use onset
- ADHD
- Previous psychosis
- Personality (ASPD, BPD)
- Genetics (DAT; COMT)

Risk Factors for MIP

- More frequent MA use, quantity of MA used; greater severity of MA addiction
- Polydrug use
- Earlier onset of substance use; longer duration of MA use
- Higher MA use dose
- Nature of MA (crystal meth versus other forms)
- Comorbid depression or anxiety
- Family history of psychosis → persistent MA psychosis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Treatment Approach: Identify & Reduce Harm

- Harm 1: Medical
  - Serologic testing
  - HIV Post-Exposure (PEP)/Pre-Exposure Prophylaxis (PrEP)
  - Hepatitis A & B Vaccination
  - COVID Vaccination
  - Screening for chronic medical conditions

- Harm 2: Substance Use
  - Assess relationship to all substances, determine stages of change
  - Identify patient goal(s)
  - Provide referral to treatment
  - Pharmacotherapy

Treatment Approach: Identify & Reduce Harm

- Harm 3: Mental Health
  - Assess safety, depression/mania, anxiety, trauma, psychosis
  - Pharmacotherapy
  - Counseling/psychotherapy
  - Behavioral activation

- Harm 4: Psychosocial
  - Housing insecurity, undomiciled status
  - Food insecurity
  - Employment/vocational rehabilitation
  - Development of social support

Medications for Methamphetamine Use Disorder

Positive Signals

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

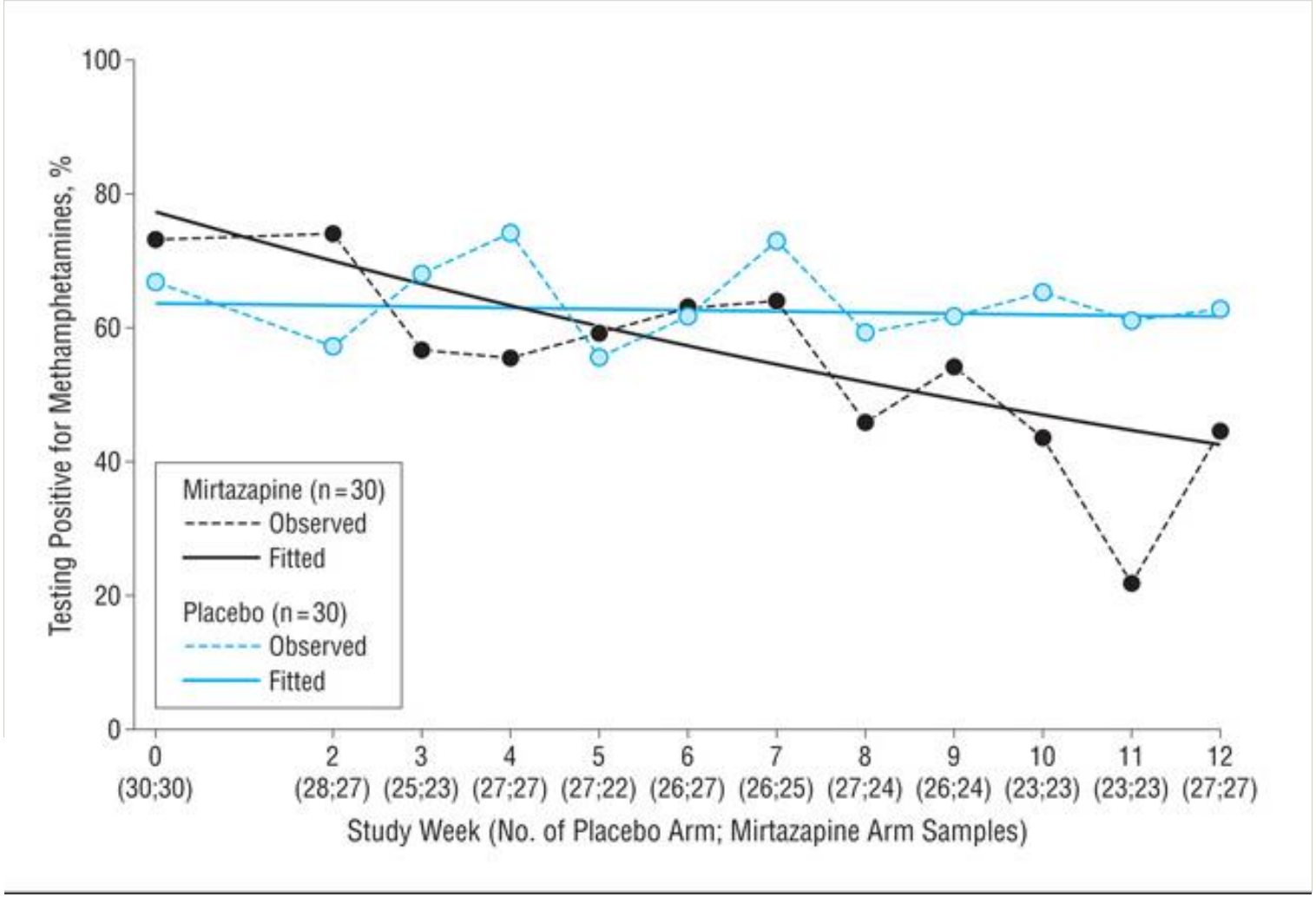
1. Elkashef et al., 2008; Shoptaw et al., 2008; Heinzerling et al., 2014; Anderson et al., 2015; 2. Colfax et al., 2012; Coffin et al., 2020; 3. Jayaram-Linstrom et al., 2008; 4. Tilhonen et al., 2007; Ling et al., 2014; 5. Galloway et al., 2011; 6. Elkashef et al., 2011; 7. Heinzerling et al., 2010;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

Methamphetamine Pharmacotherapy

	FDA	MOA	Target Effects
Bupropion	No	Dopamine/Norepinephrine reuptake inhibition	Reduce meth use in LOW severity users
Mirtazapine	No	Enhance dopamine/norepinephrine via blocking presynaptic A2 adrenergic and/or 5HT2C receptors	Reduce meth use; HIV risk behaviors
Methylphenidate	No	Enhance dopamine and norepinephrine via reuptake inhibition at DAT/NET	Craving reduction?
Naltrexone	No	Opioid Antagonist	Reduce meth use; craving reduction
Naltrexone IM plus Bupropion	No	Combination Therapy	Reduce meth use; low attrition for treatment?

Mirtazapine

Figure: Observed & fitted weekly urinalysis results by treatment arm



Mirtazapine 30mg daily vs PBO in METH-dependent MSM (N=60)

<u>Findings</u>

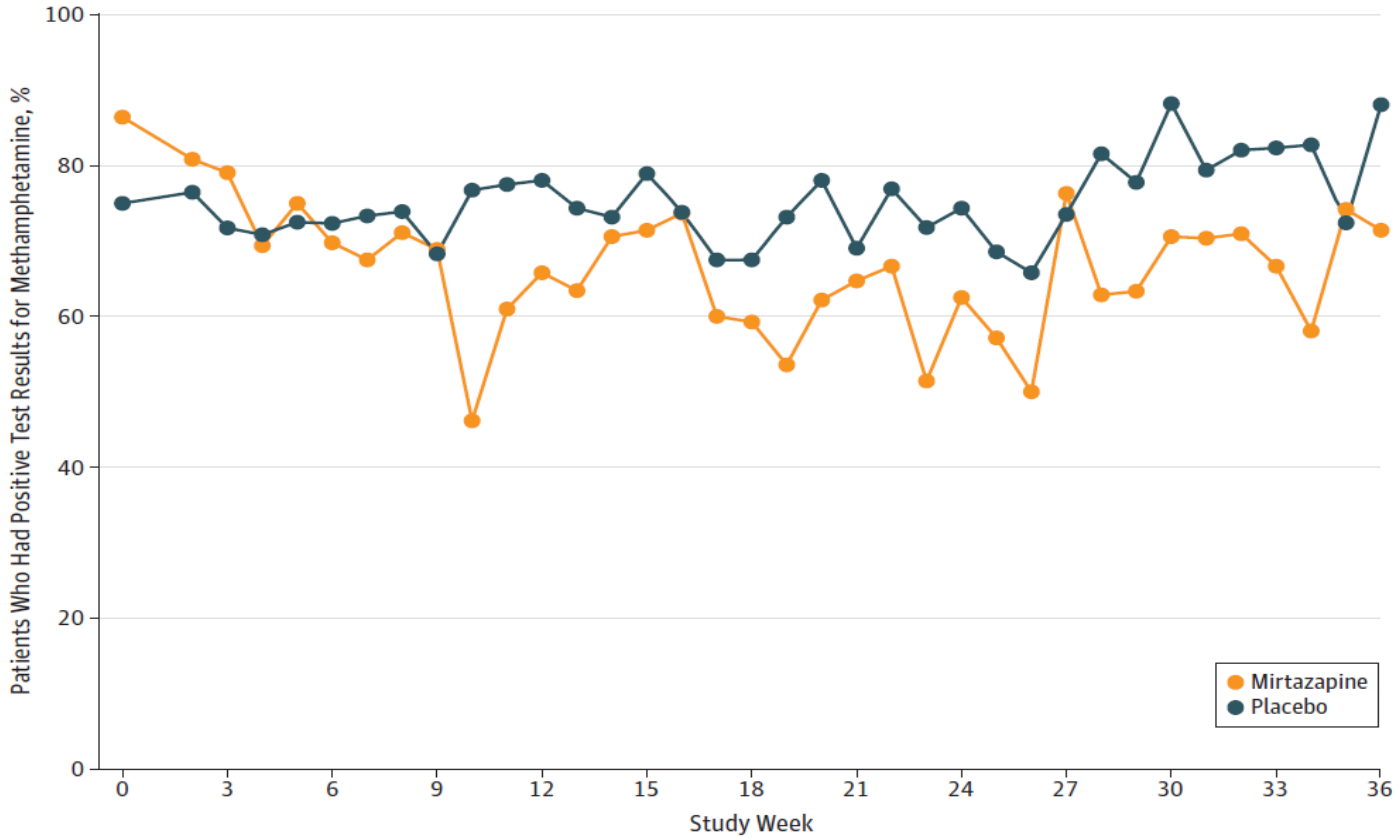
- METH-positive urines lower for mirtazapine relative to PBO (p=0.02)

- HIV risk behaviors also reduced on mirtazapine
  - # of partners with whom METH used
  - Episodes of anal sex with serodiscordant partners
  - Episodes of unprotected and insertive anal sex with serodiscordant partners

Colfax et al., Arch Gen Psychiatry. 2011

Mirtazapine (2)

Proportion of Participants With Positive Urine Test Results for Methamphetamine During Follow-Up, by Arm



Mirtazapine 30mg daily vs PBO in METH-using MSM, cis men, trans men & women (N=120)

Findings

- Significant reductions in MA+ urine tests at wk 24 & wk 36 in Mirtazapine group
- Reductions in # sexual partners, fewer episodes of condomless anal sex with serodiscordant partners, fewer episodes of condomless receptive anal sex with serodiscordant partners at wk 24
- Net reduction in depression, insomnia severity at wk 24

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Coffin et al., JAMA Psychiatry. 2020

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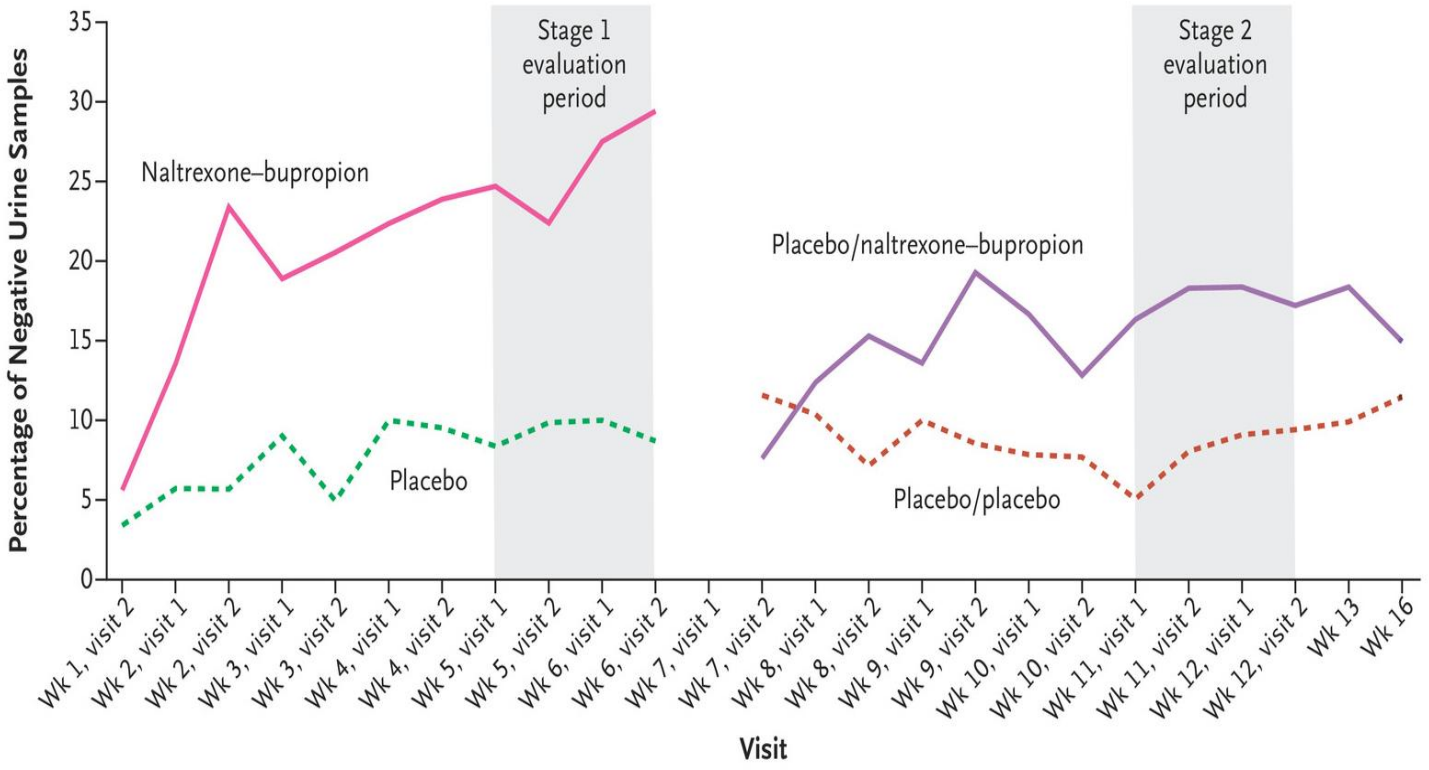
Naltrexone-Bupropion

Naltrexone IM 380mg + Bupropion 450mg/day vs PBO in METH-dependent persons (N=403)

Findings

- Stage 1: 16.5% of NTX-Bup group w/response vs 3.4% of PBO (defined as 3 out of 4 METH-neg urines)
- Stage 2: 11.4% of NTX-Bup group w/response vs 1.8% of PBO
- Low response, but higher than that among PBO group

Figure: METH-negative urine samples – NTX/BUP vs PBO



Trivedi et al., NEJM. 2021.

Methamphetamine Pharmacotherapy in MSM

- **Bupropion XL 300mg/d** showed greater ↓ in MA+ urine samples; ↓ sexual risk behaviors in both med & pbo groups
- **Modafinil (up to 200mg/d)** ↓ in MA use > 50% (in trial completers), intervention combined w/CBT
- **Mirtazapine 30mg/d** showed greater ↓ in MA+ urines (incl TGW)
  - Greater ↓ sexual risk behaviors (#partners, #episodes condomless AI)
  - ↓ Depression, insomnia severity
- **XR-NTX** – no advantage c/w PBO, ↓ sexual risk in both groups

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Das, 2010; McElhiney, 2009; Coffin, 2018, 2020

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