CASE-BASED LEARNING COLLABORATIVE ON STIMULANTS

CME BI-WEEKLY SERIES

CENTER FOR BEHAVIORAL AND ADDICTION MEDICINE

UCLA DEPARTMENT OF FAMILY MEDICINE

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

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Medications with Evidence for Stimulant Use Disorder

Case-Based Learning Collaborative on Stimulants CME Series

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UCLA Department of Family Medicine

Friday, October 20, 2023

Disclosures

- None of the planners for this educational activity have relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients, except:
- Dr. Shoptaw, speaker and faculty for this educational event has received clinical supplies for research from: Alkermes, Inc, Indivior, Inc, and Gilead Sciences, Inc. He provides consultation services to Aelis, Inc and to Clear Scientific, Inc.
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Poll

1. Which of the following medications has an FDA approval for treatment of cocaine use disorder?
   a) Naltrexone
   b) Sertraline
   c) Mirtazepine
   d) Prazosin
   e) None of the above.

2. Which of the following medications has evidence for treatment of methamphetamine use disorder but is not technically FDA approved for this use?
   a) Mirtazepine
   b) Buprenorphine
   c) Methylphenidate
   d) Vortioxetine
   e) None of the above.

Objectives

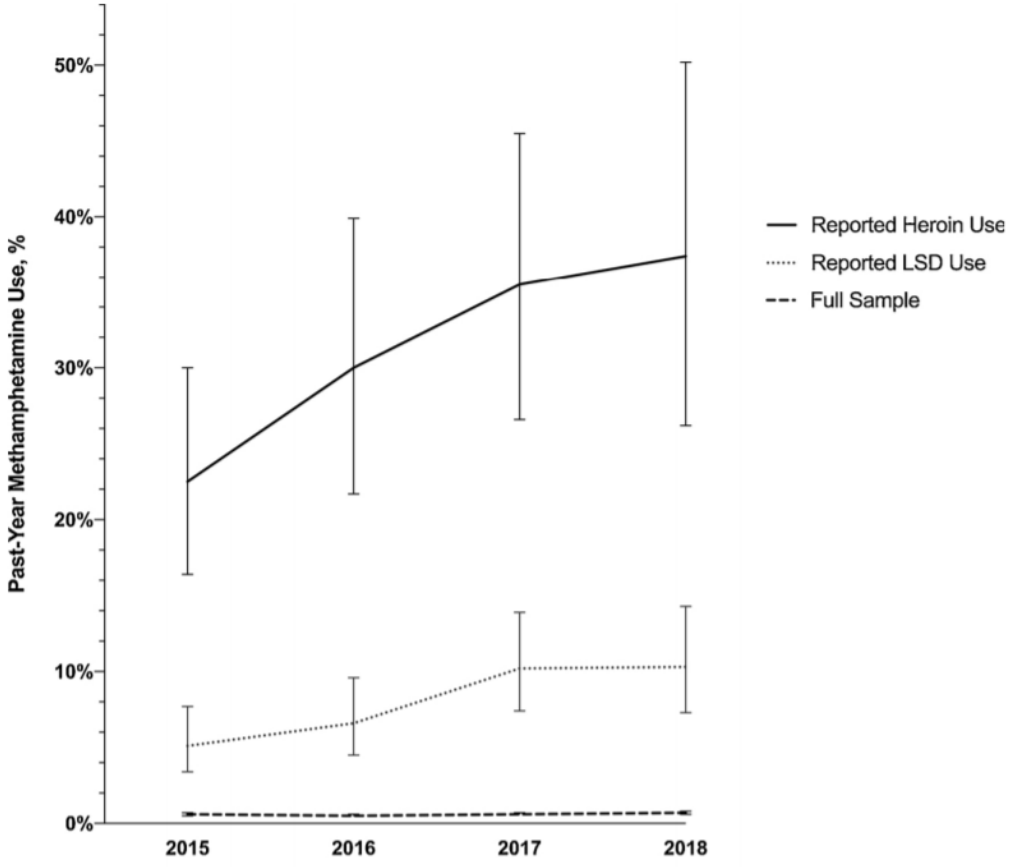
- Proficiency in:
  - Culture
  - Current epidemiology
  - Common comorbid conditions
- Understand the evidence regarding for medications for methamphetamine use disorder that have strongest data supporting use
- Understand the evidence for the range of medications that have limited evidence of efficacy for methamphetamine use disorder

Methamphetamine Effects and Function Shape Treatment Goals

Physical	Psychological
↑ Heart Rate	↑ Confidence
↑ Blood Pressure	↑ Alertness
↑ Pupil Size	↑ Mood
↑ Respiration	↑ Sex Drive
↑ Sensory Acuity	↑ Talkativeness
↑ Energy	↑ Energy
↓ Appetite	↓ Boredom
↓ Sleep	↓ Loneliness
↓ Reaction Time	↓ Timidity

- Gay Men
- Shift Workers
- Bikers – Gangs
- Women
- Rural
- Youth
- Homeless

NSDUH, Methamphetamine U.S.



- General population estimates remain low (0.7%)
- Dramatic rises in meth use among people who report using heroin and LSD

Palamar JJ. 2020. Drug Alc Dep. 2020; 3;213:108089.

ADDICTION
SSA SOCIETY FOR THE STUDY OF ADDICTION
ADDICTION OPINION AND DEBATE
doi:10.1111/add.15458

Heroin use cannot be measured adequately with a general population survey

Peter Reuter[1,2], Jonathan P. Caulkins[3] & Greg Midgette[1]

CNS Stimulant Misuse in the Past Year, 2021

Figure 20. Past Year Prescription Stimulant Misuse, Past Year Prescription Tranquilizer or Sedative Misuse, and Past Year Prescription Pain Reliever Misuse: Among People Aged 12 or Older; 2021

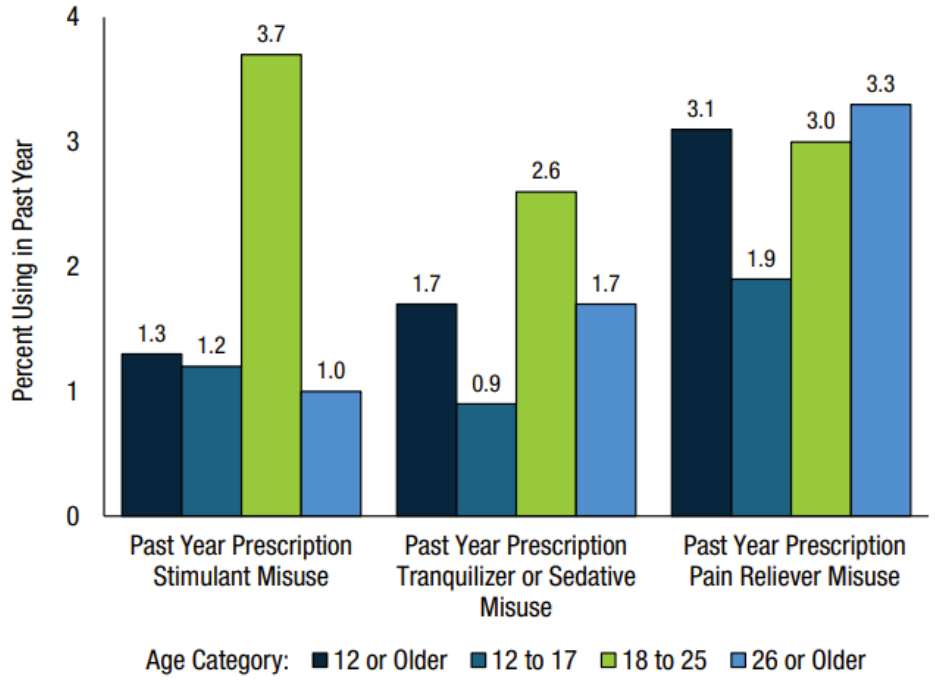
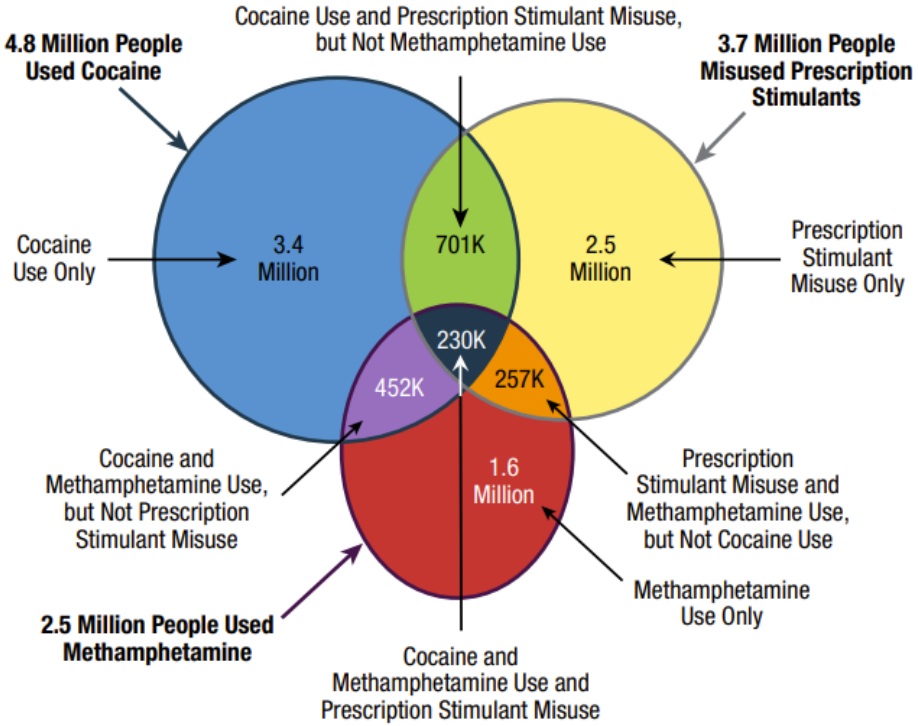


Figure 25. Past Year Central Nervous System (CNS) Stimulant Misuse: Among People Aged 12 or Older; 2021

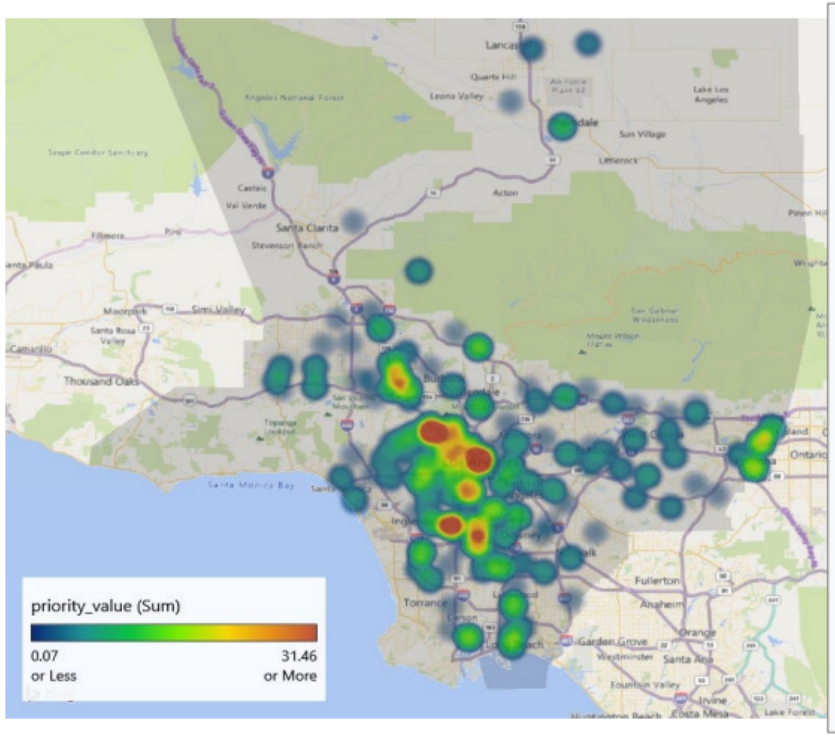


9.2 Million People Aged 12 or Older with Past Year CNS Stimulant Misuse

Substance Abuse and Mental Health Services Administration. (2023) PEP22-07-01-005, NSDUH Series H-57

Syphilis, methamphetamine and HIV incidence in LA County - Syndemics

Figure 26: Molecular HIV cluster cases by zip code and priority level, LAC, 2018-2020



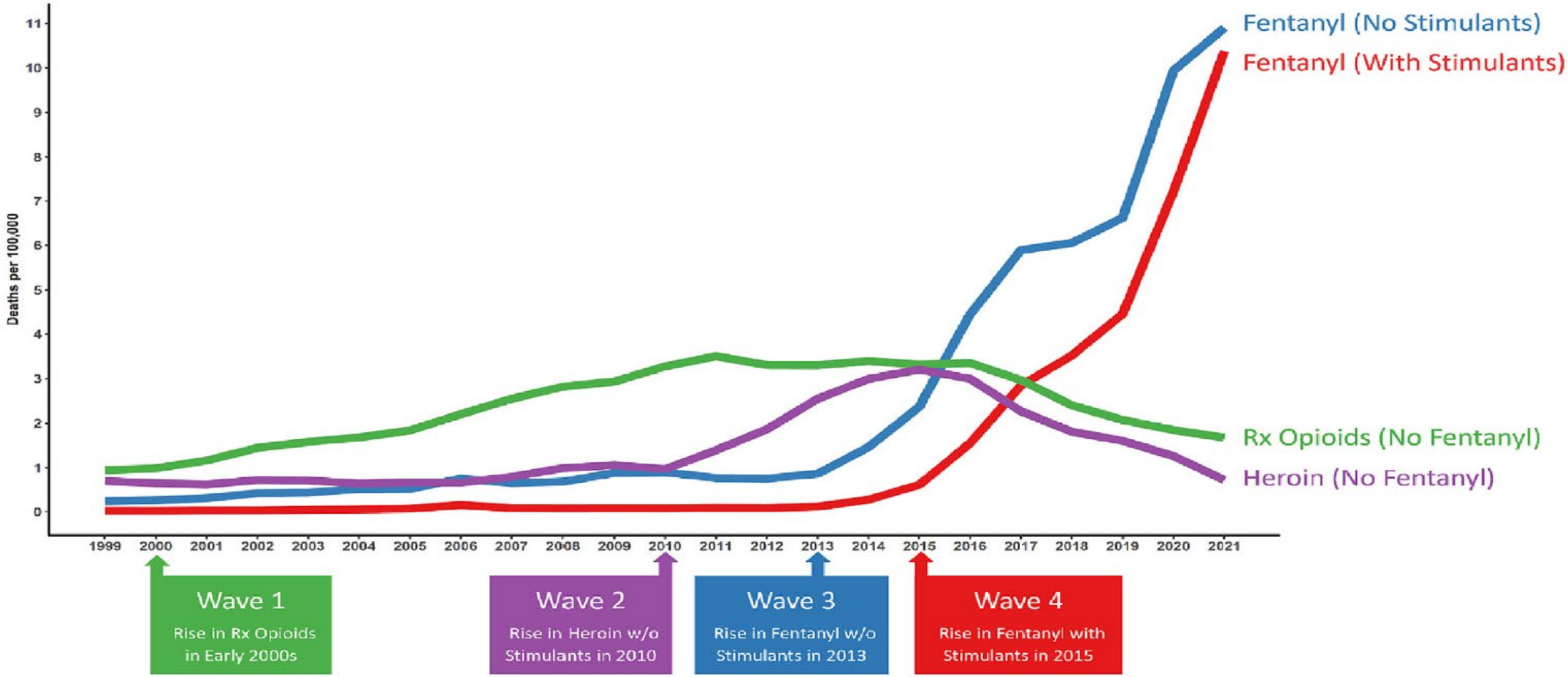
Note: Clusters are colored as low priority (blue: < 5 persons with new HIV diagnoses between 2018-2020), medium priority (green: ≥ 5 persons with new HIV diagnoses between 2018-2020), and high priority (orange/red: ≥ 5 cases diagnosed in 2020). Among 282 persons identified in high priority clusters, 195 (69%) were interviewed through Partner Services where additional behavioral and clinical information was collected.

Among persons in high priority clusters, 18% had a history of methamphetamine use, 11% had a history of being unhoused, 66% reported anonymous sex partners, and 49% had co-infection with syphilis.

The highest number of high priority clusters were in West Hollywood, Downtown, and South Los Angeles zip codes.

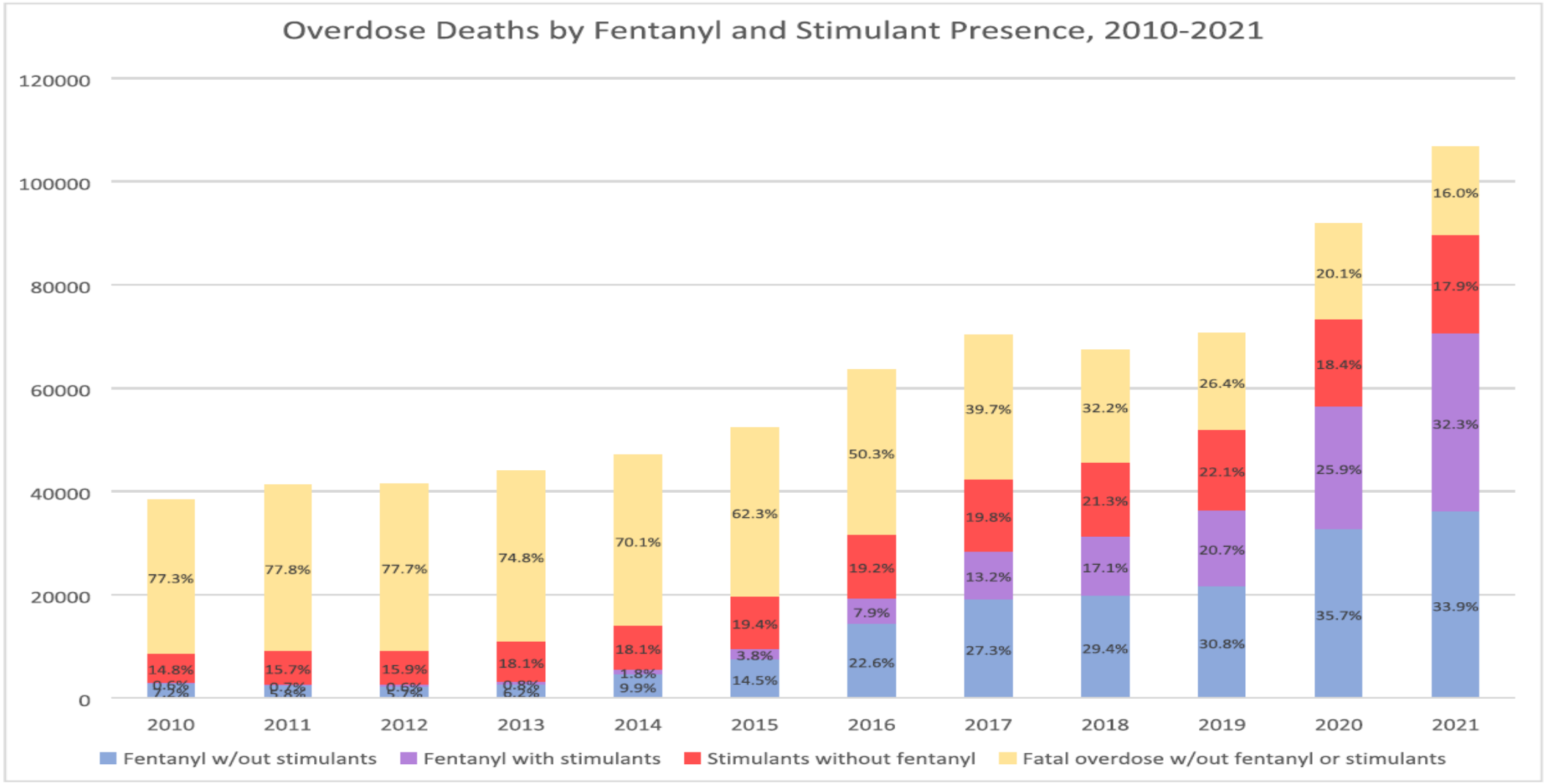
http://publichealth.lacounty.gov/dhsp/Reports/HIV/2020AnnualHIVSurveillanceReportUpdated9-2021_fig1fig2update.pdf

Overdose Crisis 4th Wave: Poly-Substance Use



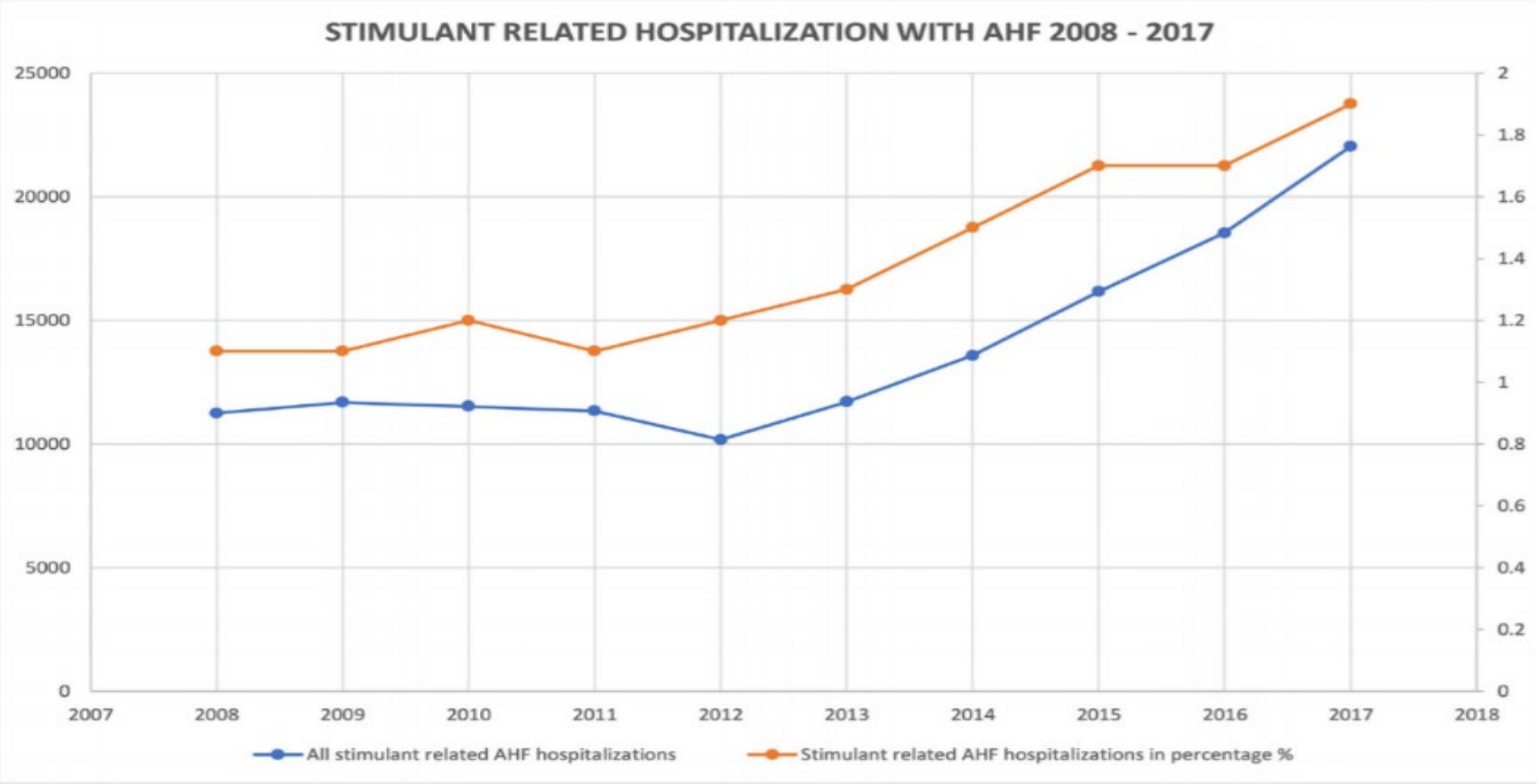
Friedman J, Shover CL. Addiction. 2023 Sep 13. DOI: 10.1111/add.16318

Overdose Deaths



Friedman J, Shover CL. Addiction. 2023 Sep 13. DOI: 10.1111/add.16318

Increase in Prevalence of Acute Heart Failure by Stimulant Use; National Inpatient Sample

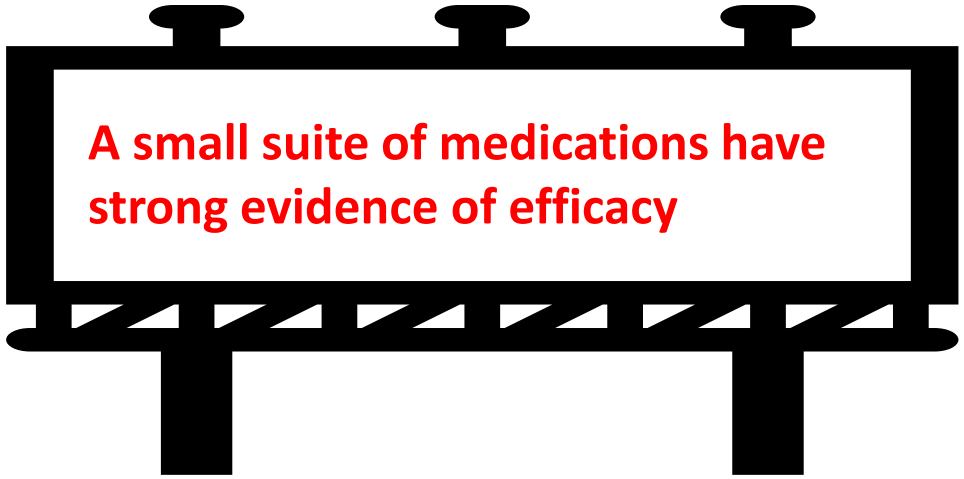


Shetty et al. 2021 *Int J Cardiology. 331:* 158-163

Status of Medication Development for Stimulant Use Disorder

There are no FDA approved medications for stimulant use disorder

No medications that might be FDA approved within the next five years



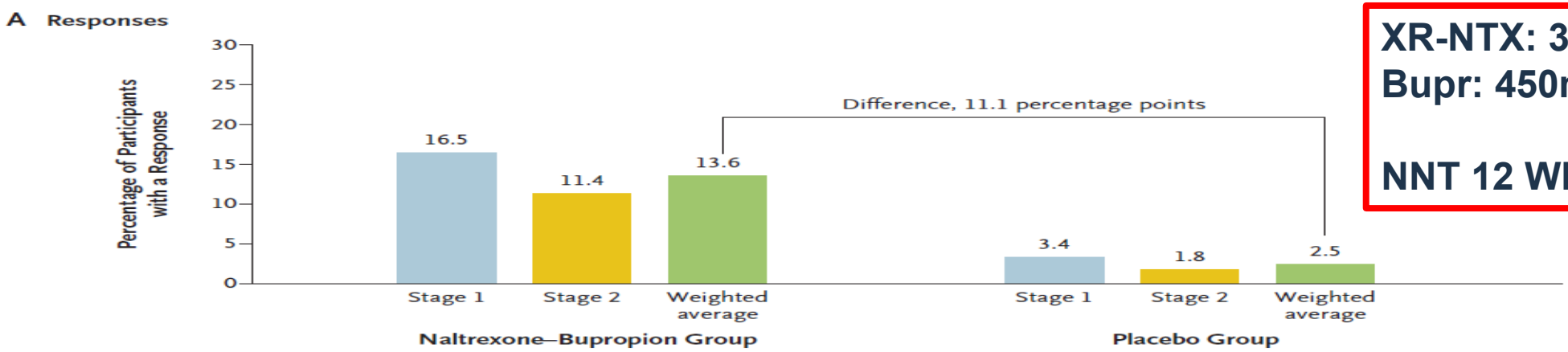
Strongest Evidence for Use: Methamphetamine Use Disorder

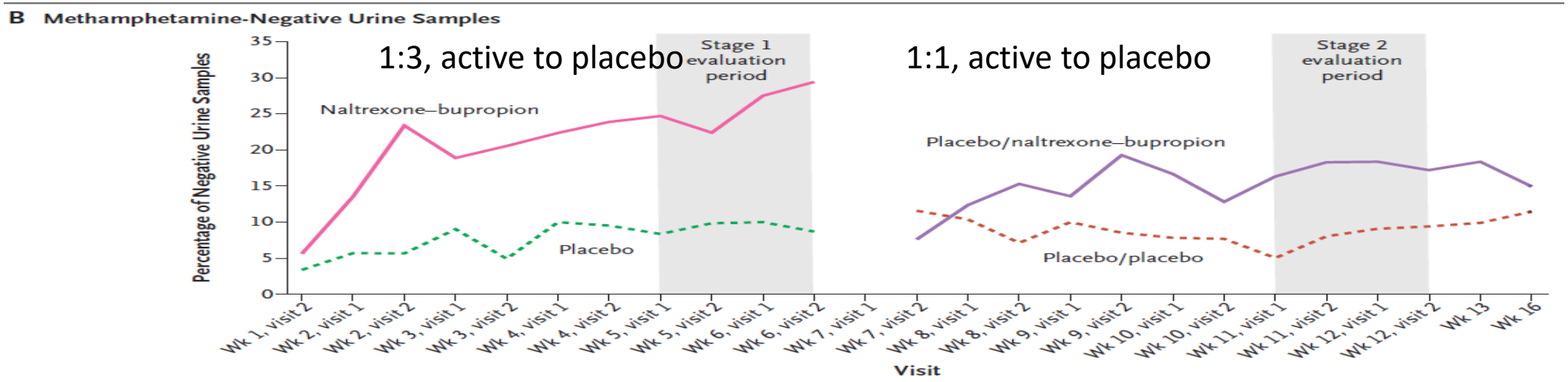
XR-NTX @ 3 weeks + bupropion @ 450 q d
Mirtazapine @ 30mg q d

Broadly Effective Medication for Meth Use Disorder

XR-NTX: 380mg @ 3 wks
Bupr: 450mg @ day

NNT 12 Wks=9





Trivedi MH et al., N Engl J Med. 2021 Jan 14;384(2):140-153.

Benefits of XR-NTX+Bupropion Continue to Accrue

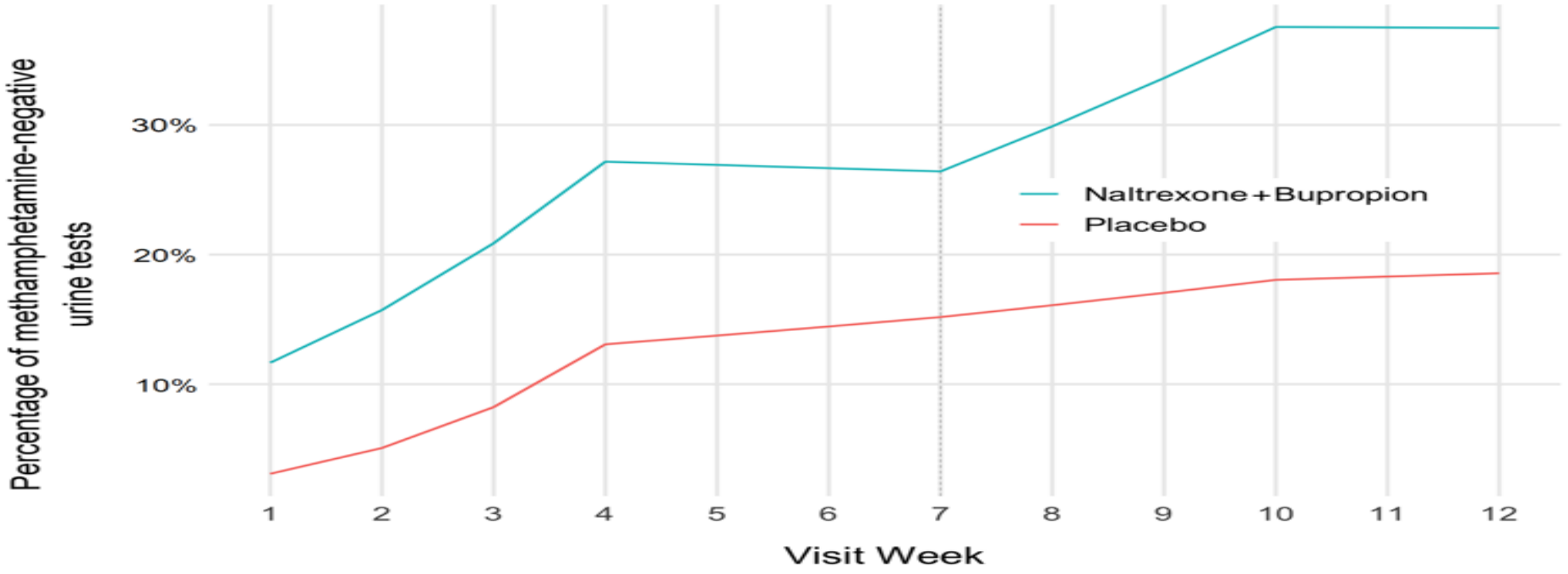


Figure 1. Marginal predicted mean percentage of methamphetamine-negative urine tests over 12 weeks while on naltrexone plus bupropion versus placebo

Li MJ et al. Submitted

Culture Links with Medication Effects: MSM vs MSW

Table 3

Comparison of the adjusted treatment effect for extended-release naltrexone plus bupropion (XR-NTX + BUP) versus placebo for MSM/W and MSW participants.

	Stage 1			Stage 2			NTX-BUP vs Placebo Treatment Effect*			
Subgroup	# Randomized	Placebo Responder Rate	XR-NTX + BUP Responder Rate	# Re-randomized	Placebo Responder Rate	XR-NTX + BUP Responder Rate	Treatment Effect (*h*)	Standard Error of *h*	Number Needed to Treat	p-value
MSM/W	151	(3/108) 0.0278	(6/43) 0.1395	90	(2/47) 0.0426	(10/43) 0.2326	0.1479	0.0357	6.7	0.04
MSW	95	(4/69) 0.0580	(2/26) 0.0769	50	(0/22) 0.0000	(1/28) 0.0357	0.0227	0.0484	41.3	

MSM/W: men who have sex with men only or with both men and women.

MSW: men who have sex exclusively with women.

Treatment Effect (*h*): between-group difference (active medication vs placebo) in the weighted average of Stage 1 and Stage 2 respond rates.

*All models were adjusted for study site, age, race, ethnicity, education, employment, HIV serostatus, and baseline methamphetamine use.

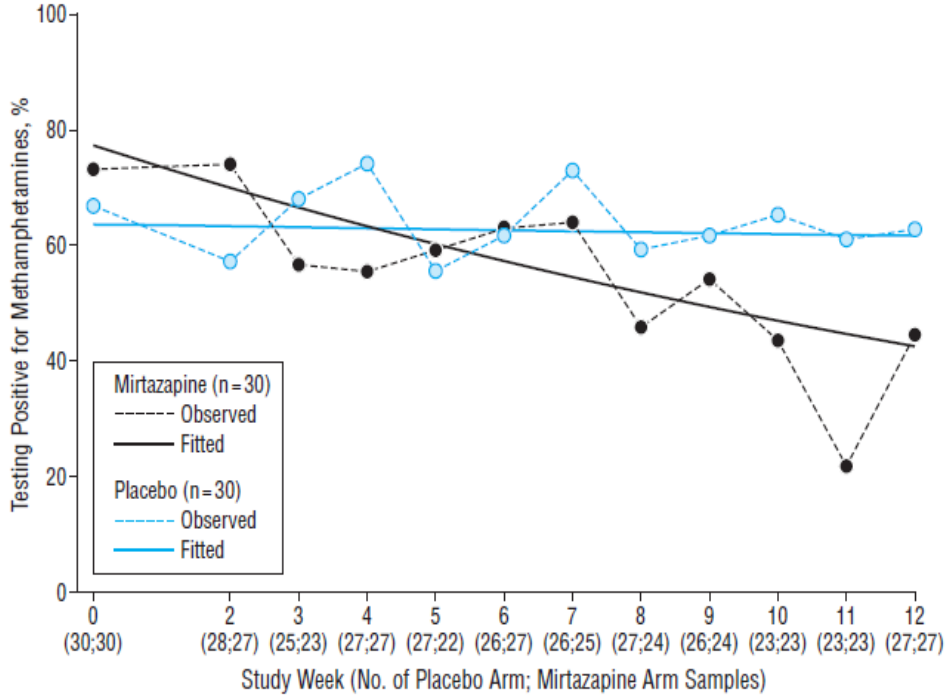
4

Kidd JD, Smiley SL, et al. Drug Alcohol Depend. 2023 Sep 1;250:110899.

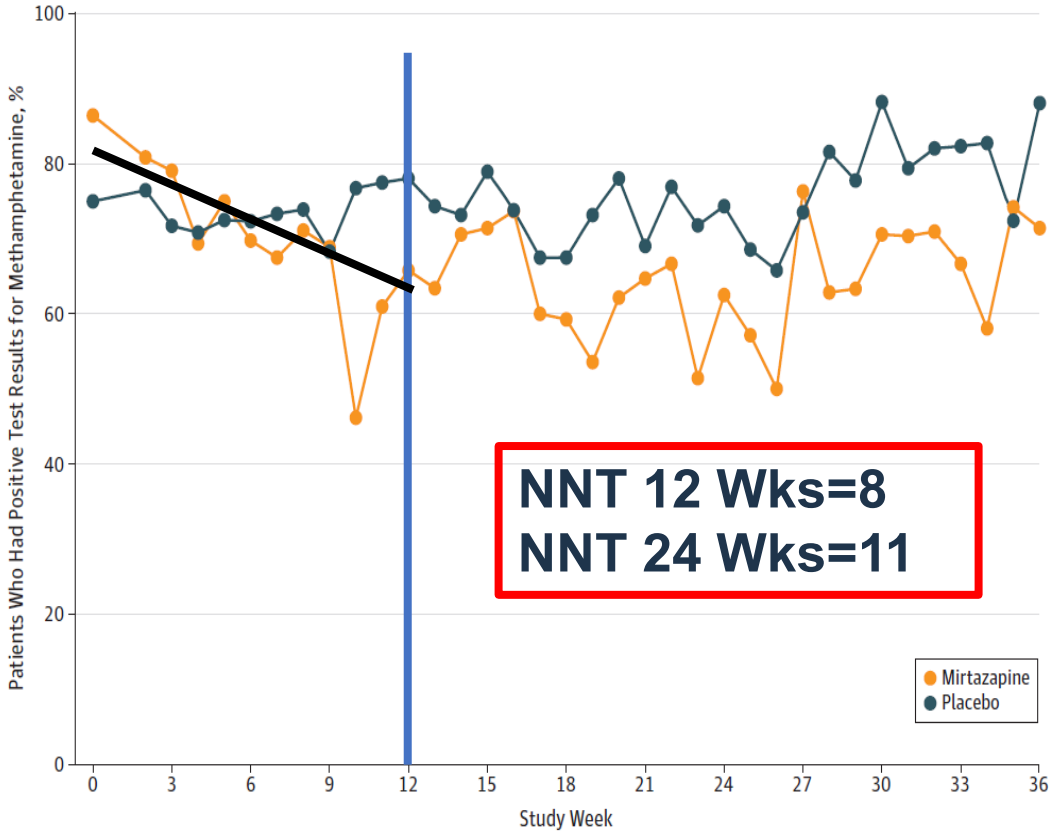
Findings and Targets

- Mechanism for combination medication is unknown – but the combination produces the strongest signal of efficacy in over 30 years of addiction research
- Fully powered trial: 403 participants randomized
- Primary outcome response: # participants with two weeks of meth-negative urine screens in weeks 5+6; weeks 11+12
- 450 mg bupropion is a significant dose of a weak stimulant
- XR-NTX produces a significant dose full mu opioid antagonist and kappa opioid antagonist
- Combination produces synergized effect
  - Similarly, lower doses efficacious for weight loss (Contrave™)

Pharmacotherapy for Stimulant Use in MSM: Mirtazapine 30 mg/day



Colfax et al. *Archives Gen Psych,* 2011 *68*: 1168-1175



Coffin et al., doi:10.1001/jamapsychiatry.2019.3655

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Mirtazapine Meta-Analysis

Study or Subgroup	Mirtazapine Events	Mirtazapine Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
Coffin et al 2019	25	38	32	41	76.8%	0.84 [0.64, 1.12]
Colfax et al 2011	12	27	17	27	23.2%	0.71 [0.42, 1.18]
Total (95% CI)		**65**		**68**	**100.0%**	**0.81 [0.63, 1.03]**
Total events	37		49			

Heterogeneity: $Chi^2 = 0.36$, $df = 1$ ($P = 0.55$); $I^2 = 0\%$
Test for overall effect: $Z = 1.69$ ($P = 0.09$)

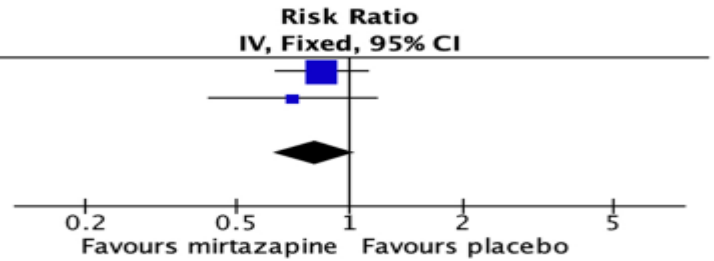

Fig. 2. : Forest plot and meta-analysis of reduction in methamphetamine positive urine toxicology screens at 12 weeks.

Study or Subgroup	Mirtazapine Events	Mirtazapine Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
Coffin et al 2019	49	60	48	60	37.6%	1.02 [0.86, 1.22]
Colfax et al 2011	28	30	28	30	62.4%	1.00 [0.87, 1.14]
Total (95% CI)		**90**		**90**	**100.0%**	**1.01 [0.91, 1.12]**
Total events	77		76			

Heterogeneity: $Chi^2 = 0.03$, $df = 1$ ($P = 0.85$); $I^2 = 0\%$
Test for overall effect: $Z = 0.14$ ($P = 0.89$)

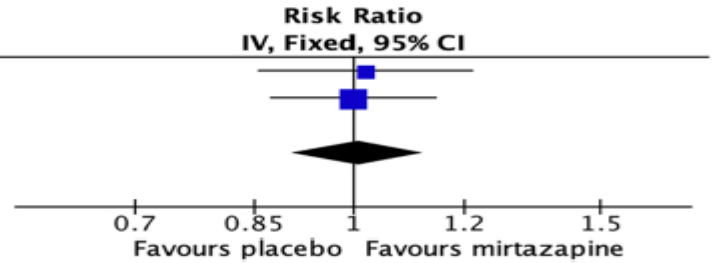

Fig. 3. : Forest plot and meta-analysis of retention in treatment at 12 weeks.

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
Coffin et al 2019	-0.28	2.2143	58.9%	-0.28 [-4.62, 4.06]
Colfax et al 2011	1.5	2.6531	41.1%	1.50 [-3.70, 6.70]
Total (95% CI)			**100.0%**	**0.45 [-2.88, 3.78]**

Heterogeneity: $Chi^2 = 0.27$, $df = 1$ ($P = 0.61$); $I^2 = 0\%$
Test for overall effect: $Z = 0.27$ ($P = 0.79$)

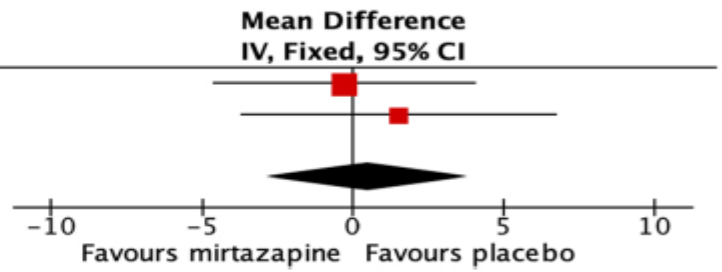

Fig. 4. : Forest plot and meta-analysis of reduction in depression symptom severity as measured by the CES-D scale at 12 weeks.

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Naji L et al. Drug Alcohol Depend. 2022 Mar 1;232:109295. doi: 10.1016/j.drugalcdep.2022.109295.

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Findings and Targets

- Main strengths for mirtazapine for methamphetamine
  - Study findings replicate! Hardest thing to do in science is the same thing twice
  - Slopes of meth reduction measured by positive urine drug screens over time are parallel in the two trials
- Mechanism of response
  - FDA approved antidepressant – so may be reducing depressive symptoms during discontinuation of methamphetamine
  - More likely mechanism is restoration of sleep architecture – participants all recognized better sleep during the trial; sleep disturbance also is a common depressive symptom
- Potential downsides
  - Weight gain significant, which may be unacceptable for some MSM and for some women
  - Both studies conducted so far are in MSM and trans women; need replication in general broad groups – trial ongoing in Australia to advise use in outpatient clinic settings
    - Many of study assessments in that multisite trial are conducted using telehealth visits

ASAM Stimulant Guideline Systematic Review

Psychiatric Medications

Medication/Class	Conditions	Outcomes	Reference
Bupropion	6 studies	No significant signal to reduce MA use 2^o ↓ for 150mg bid in lower use (5) ↓ ad libitum smoking (6)	1-6
Sertraline	Sert 50mg bid, CM	Sertaline less likely to achieve MA 3 wk abstinence	7
Atomoxetine	80mg/d	In OUD+ATS; ↓ MA use, but weak signal	8
Aripiprazole, methylphenidate	Arip = 15mg/d Methyl = 54mg/d	Arip ↑ MA+ UDS vs placebo Methyl ↓ MA+ UDS vs placebo	9
Topiramate	Top 200mg/d	In OUD+ATS; ↓ MA+ UDS at 6, not 12 weeks, ASI drug use severity and need; no diff crav or dep	10
Oxytocin	40 IU (4 weeks)	↓ depression, craving; ↓ ACTH, ↓cortisol	11

For systematic review, see Siefried KJ, et al. CNS Drugs. 2020 Apr;34(4):337-365.
For Practice Guideline: https://www.asam.org/quality-care/clinical-guidelines/stimulant-use-disorders

Psychostimulants

Medication/Class	Conditions	Outcomes	Reference
d-Amphetamine	30mg/d, 60mg/d	↓ in craving, withdrawal severity	12
	110mg/d	↓ in withdrawal severity	13
Methylphenidate	54mg/d	↑ in retention at 6 wks	14
	54mg/d	2^{o} ↓ MA use at 10 wks	15
	54mg/d	↓ craving, fewer MA+ UDS, ↓ dep	16
Modafinil	3 studies	No consistent signal	17-19
Amineptine	300mg/d	↓ withdrawal symptoms (?), now off mkt	20

For systematic review, see Siefried KJ, et al. CNS Drugs. 2020 Apr;34(4):337-365.
For Practice Guideline: https://www.asam.org/quality-care/clinical-guidelines/stimulant-use-disorders

GABA & Opioid Medications

Medication/Class	Conditions	Outcomes	Reference
Gabapentin+Baclofen	GPN – 800mg/tid B – 20mg tid	No differences	21
Buprenorphine	6mg/d SL Bupe	↓ craving, fewer MA+ UDS	22
Buprenorpine, methadone	8mg/d SL Bupe 40mg/d methadone	No differences	23
XR-NTX	380mg Injection	No differences	24, 25
Naltrexone	1000mg implant	No differences	26
Naltrexone	50mg/d	↓ MA+ UDS	27

For systematic review, see Siefried KJ, et al. CNS Drugs. 2020 Apr;34(4):337-365.
For Practice Guideline: https://www.asam.org/quality-care/clinical-guidelines/stimulant-use-disorders

Other Mechanisms

Medication/Class	Conditions	Outcomes	Reference
Ondansetron (5HT3)	0.5mg, 2mg, 8mg/d	No differences; 5-hour half-life	28
Varenicline	1mg bid	No differences; reduced smoking	29
Riluzole	50mg/d	↑ retention and abstinence	30
NAC+Naltrexone	NAC - 2400mg/d NTX – 200mg/d	No differences	31
NAC	NAC – 2400mg/d	No differences	32
PROMETA	Flumazenil 2mg IV Gabapentin 1200/d Hydroxyzine 50/d	2 studies; No differences	33, 34
tDCS	Active	↓ craving ↑ neurocog (35) ↓ craving ↑ memory tests (36)	35, 36
Meth Psychosis	6 antipsychotics	Olanzapine, Quetiapine preferred for antipsychotic effects; no effect on MA	37

For systematic review, see Siefried KJ, et al. CNS Drugs. 2020 Apr;34(4):337-365.
For Practice Guideline: https://www.asam.org/quality-care/clinical-guidelines/stimulant-use-disorders

Withdrawal

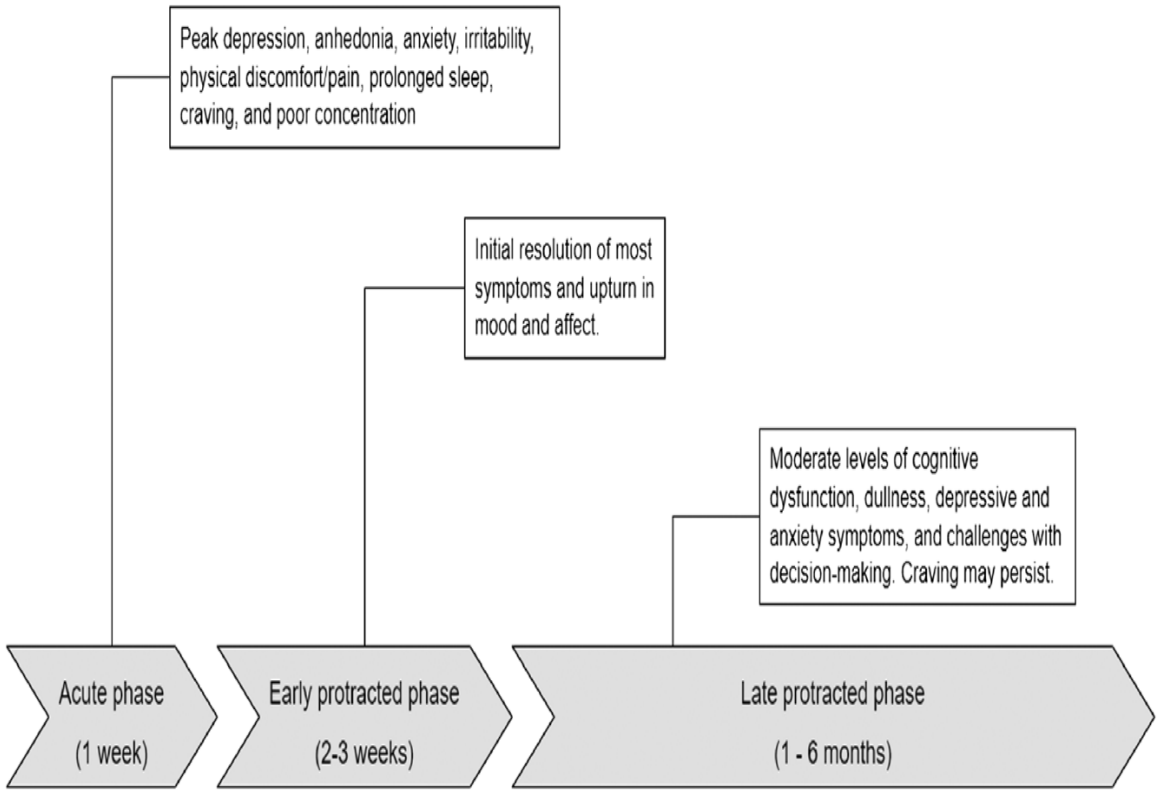

FIGURE 1 Summary of stimulant withdrawal symptoms across different phases (with time-frame following abstinence)

- Amineptine is the only medication that shows strong efficacy for withdrawal symptoms (20).
  - Strong stimulant, agonist effects
  - Still off-market in most parts of the world
- Overall, there is inconsistent signal for biomedical treatments on MA withdrawal
- Symptom relief for MA withdrawal seen for a few medications (mirtazapine, naltrexone, bupropion) and repetitive transcranial magnetic stimulation during acute (first week), early protracted (weeks 2–4) and late protracted (> 4 weeks) withdrawal phases

For Clinical Review, see Li MJ et al. Addiction. 2023 Apr;118(4):750-762.
For Systematic Review, see Acheson LS et al. Acheson LS, Drug Alcohol Rev. 2023 Jan;42(1):7-19.

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Addressing Cardiovascular Insult in People Who Use Methamphetamine

- Ongoing use of methamphetamine causes cardiovascular insult that links to increases in hospital for cardiac diseases
- Methamphetamine is causal in ~50% of cases of pulmonary arterial hypertension (Zamanian RT et al. Am J Respir Crit Care Med. 2018; 197:788-800)
- Raises the question of using statins in people actively using methampehtamine

Summary Current Evidence

After 25 years, there are some signals for efficacy, though there still is no FDA approved treatment for cocaine or methamphetamine addiction:

- Mirtazapine effects in MSM are impressive, particularly replication
  - Effect is reduction in use, not abstinence (like naltrexone for heavy alcohol drinking)
  - So far only tested in San Francisco and only in MSM
- Large trial, strong signal for XR-NTX+Bupropion over placebo for reducing methamphetamine use

Other medications with mixed mechanisms show little signal

Strong evidence for use of antipsychotics for psychosis

Some evidence for symptom relief for withdrawal

Evidence to consider medication as a *foundation* of treatment for stimulant use disorder

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Application of Knowledge and Cases

Case 1

46 yo PMH of sedative use disorder, opioid use disorder severe in early remission, stimulant use disorder severe who is brought today due to recent relapse on Xanax bars about 4 bars possibly 2mg each per day last use today about 2 hours ago; also use of methamphetamines inhaled and smoked 30 mins ago. Now starting to behave in erratic fashion, endorsing anxiety, having auditory hallucinations, paranoia, and irritability which were reasons brought in for evaluation.

- On initial assessment patient endorses mistrust from evaluator, thinks that she is at her aunt's house and questions my presence, is difficult to be redirected.
- There is no history of bipolar disorder, schizophrenia, there is history of psychosis only when under the influence per relative.
- There is history of GAD, PTSD for which patient takes clonazepam, no records found on PDMP.

Exam

- BP: 178/104 HR 108 RR: 22 T: 97.4
- Neurologic: Grossly intact, non-focal
- Behavior: irritable, anxious
- Speech: fast rate and rhythm normal volume
- Language: intact; no abnormalities noted
- Mood: anxious; sleep is generally poor, has not slept for the past 3 days
- Affect: full range and congruent with mood
- Thought process: circumpherential and not goal-directed
- Thought content: Paranoia

Orientation: alert and oriented to person and time

- Concentration and Attention: decreased attention span as there is inability to appropriately attend and answer questions throughout interview
- Intellect/Fund of Knowledge: average as evidenced by use of language and vocabulary
- Insight: poor as evidenced by lack understanding of symptoms
- Judgment: poor as evidenced by engagement in treatment

Management

- What would initial management be for this patient in the following settings:
- - Hospital
- - Residential level of care 3.5-3.7
- - Outpatient Clinic

- What options are there to utilize?
- - Benzodiazepines?
- - Second generation antipsychotics?
- - How about the blood pressure and heart rate?

After a few days

- Patient underwent safe taper to withdraw benzodiazepines
- Patient is endorsing hypoactivity and anhedonia now endorses that is craving methamphetamines.
- After explaining benefits and risks is decided to be started with off label use of Bupropion and Long Acting Naltrexone
- What diagnoses are these medications approved for?
- How can we obtain these medications for our patients?
- How does coordination to receive Vivitrol occurs

Are there any other options pursuing off label use of these medications

- Can I get approval every 3 weeks?
- What do I do if I can't get Vivitrol, would oral Naltrexone work?
- Can I supplement that 4th week with oral Naltrexone
- My patient is having insomnia due to the Extended Release Bupropion, can I use Sustained Release or Immediate Release?
- How frequently is it required to perform liver function tests?

Case #2

- 42 yo patient PMH of cannabis use disorder moderate, stimulant use, tobacco use ½ ppd, hypertension comes today because use of methamphetamines has progressed. Now injecting daily and smoking daily about 1 gram of meth, which has led to to financial problems, admissions to the hospital due to infections, and anxiety as life is "spiraling down."
  - *"I can't sleep, I keep on thinking how to reduce my use but I can't, and I want to be clear with you doc, I do not want to stop because I know that if I use only a couple of times per week I will enjoy it again."*
- Also reports concerns about heart beating fast, even when not using. Blood pressure has risen even while on medication. Not smoking tobacco. Denied other substances.

Height: 5'4", Weight 115 lbs, BMI 19.7

Vitals: BP: 142/87 HR: 88 RR: 16 T: 96.8

Therapeutic options and questions to ask ourselves

- - Patient opted to trial mirtazapine

- - Are there areas to explore in primary care for this patient population?
  - ASCVD Risk Estimator + (acc.org)
  - Cholesterol 154 HDL: 45 LDL 78
- - Aspirin?
- - Statins?
- - ACEI, ARB?
- - Echocardiogram?