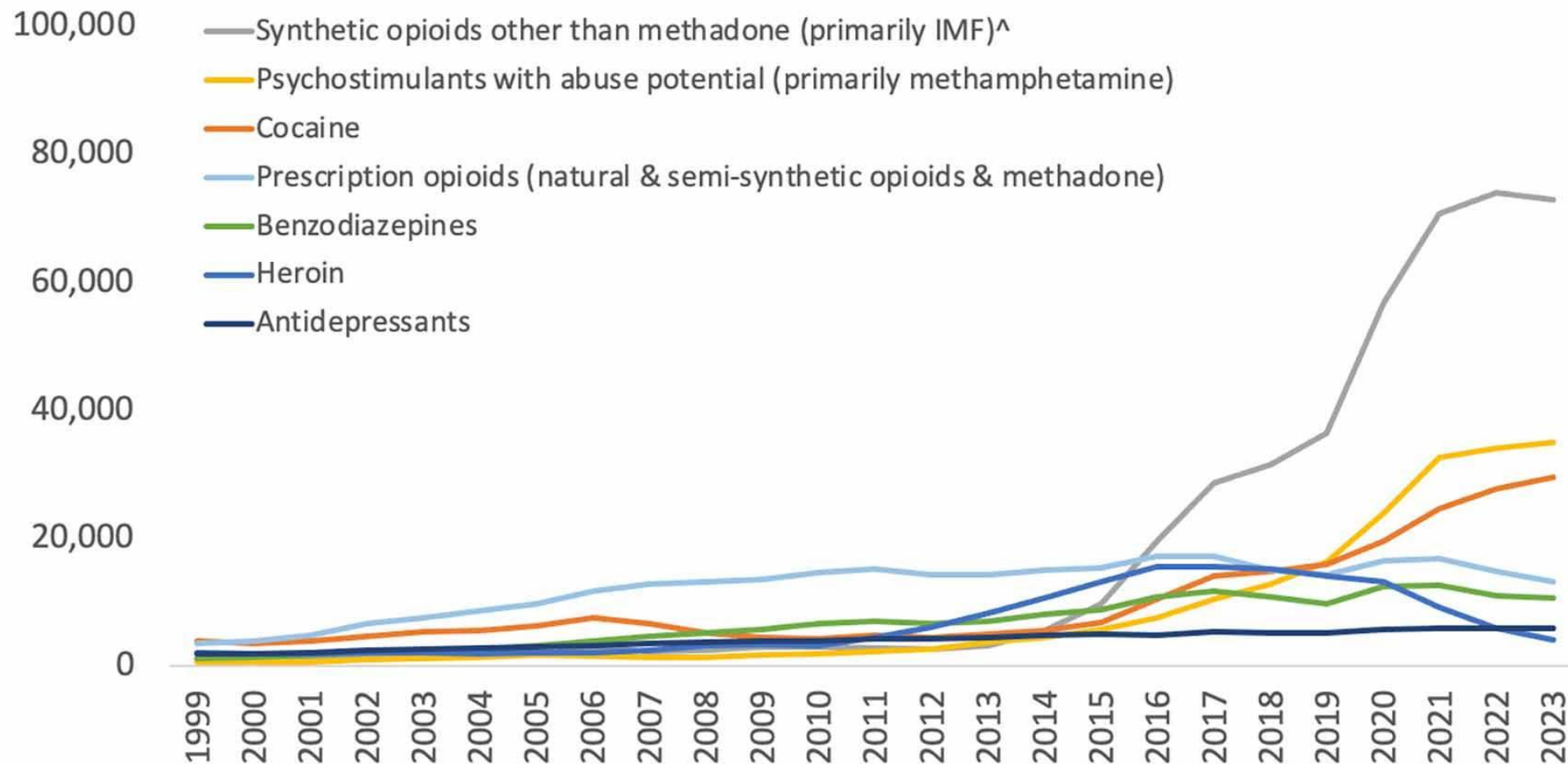


Stimulant use disorders: a review of the evidence behind treatment options

Presented by Dr. Katherine Krieger
February 4, 2026

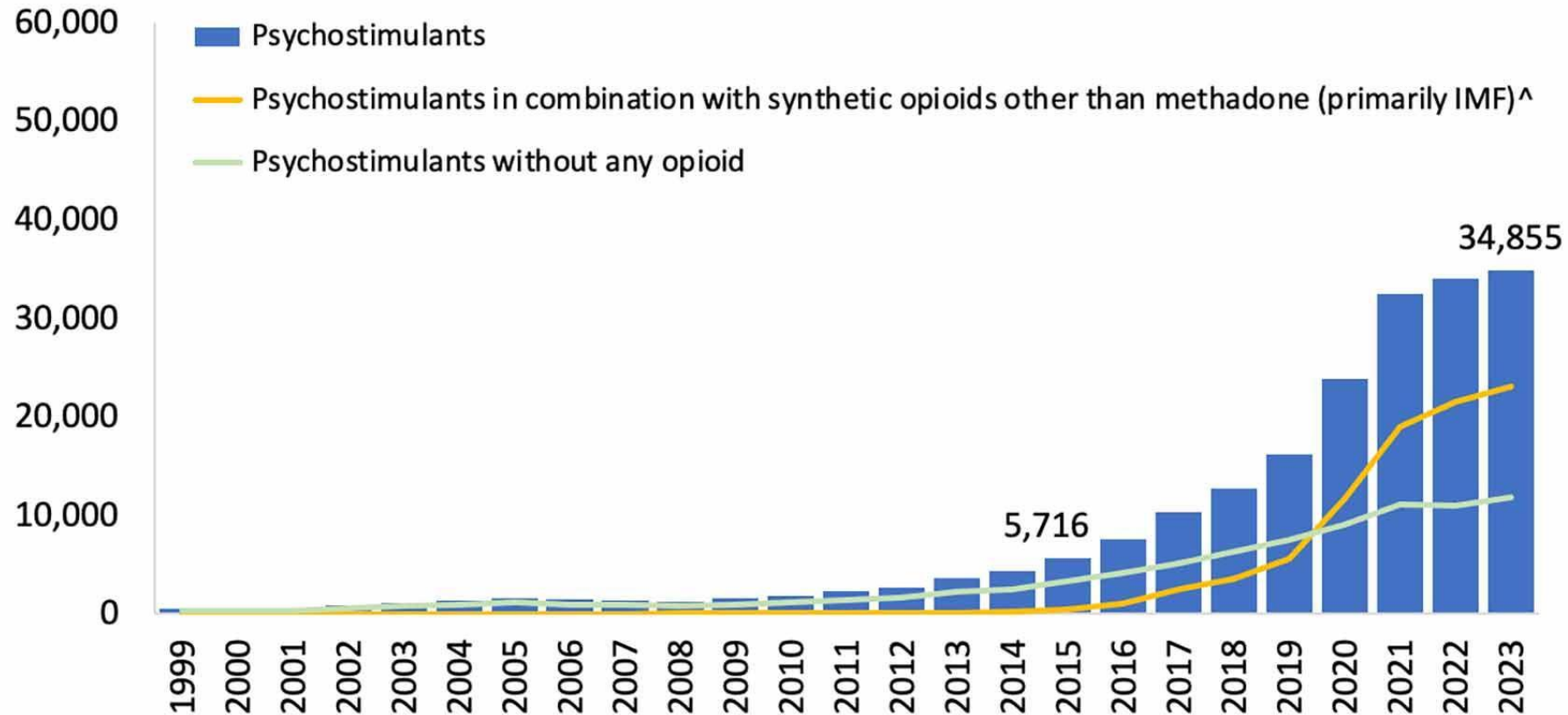
- Stimulant drugs are second only to cannabis as the most widely used class of illicit drug globally [8]
- In the past 10 years
 - Overdose death rates for cocaine have increased 3 fold
 - Overdose death rates for other stimulants (methamphetamine, amphetamines, prescription) have increased 12 fold [11]
- Beyond mortality risk, StUD has significant long term health consequences
 - Cardiac
 - Pulmonary
 - Cognitive
 - Dental
 - Infectious complications

Figure 2. U.S. Overdose Deaths*, Select Drugs or Drug Categories, 1999-2023



*Includes deaths with underlying causes of unintentional drug poisoning (X40–X44), suicide drug poisoning (X60–X64), homicide drug poisoning (X85), or drug poisoning of undetermined intent (Y10–Y14), as coded in the International Classification of Diseases, 10th Revision. ^Illicitly manufactured fentanyl. Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2023 on CDC WONDER Online Database. released 1/2025.

Figure 7. U.S. Overdose Deaths Involving Psychostimulants with Abuse Potential*, 1999-2023



*Among deaths with drug overdose as the underlying cause, the psychostimulants with abuse potential (primarily methamphetamine) category was determined by the T43.6 ICD-10 multiple cause-of-death code. Abbreviated to *psychostimulants* in the bar chart above.
^Illicitly manufactured fentanyl. Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2023 on CDC WONDER Online Database, released 4/2024.

ASAM guidelines for StUD

• Non pharmacologic treatments

- 1. **Contingency management** (**high certainty, strong recommendation**)
 - Incentives given such as vouchers to reinforce positive behavior
 - 2. **Community reinforcement approach** (**low certainty**)
 - Psychosocial intervention focused on helping individuals meet social/emotional needs in healthier ways than substance use
 - 3. **CBT** (**low certainty**)
 - Help individuals challenge unhelpful beliefs and develop coping skills to manage triggers and cravings.
 - 4. **The Matrix Model** (**moderate certainty**)
 - 16 weeks program utilizing various therapeutic interventions: CBT, family therapy, relapse prevention tools
-
- “Contingency management (CM) has demonstrated the best effectiveness in the treatment of StUDs compared to any other intervention studied and represents the current standard of care.”
 - <10% of addiction treatment programs utilize CM. Barriers include regulations, financial costs, program resources

ASAM guidelines: pharmacological treatments for StUD

- Unlike opioids and alcohol, no pharmacotherapies have been approved by the US Food and Drug Administration for the use of StUD
 - Existing evidence for treating StUD with medications is low quality
 - Pharmacotherapy use is currently off label

ASAM guidelines: pharmacologic treatments C-StUD

- **Non-Psychostimulant**

- Bupropion (**Low Certainty**, conditional recommendation)
 - Co-occurring TUD, depressive disorder
- Topiramate (**Low Certainty**, conditional recommendation)
 - Co-occurring AUD

- **Psychostimulant**

- Modafinil (**Low Certainty**)
- ER mixed amphetamine salts +Topiramate – (**Moderate Evidence**)
 - consideration for co-occurring ADHD, AUD
- ER mixed amphetamine salts alone (**Low Certainty**)

ASAM guidelines: pharmacologic treatment for ATSUD

- **No pharmacotherapy is FDA approved**
- **Non-Psychostimulant**
 - Bupropion (**Low certainty**)
 - Co-occurring TUD, depressive disorder
 - Bupropion IM + Naltrexone (**Moderate Certainty**)
 - Co-occurring AUD, depressive disorder, TUD
 - Topiramate (**Low Certainty**)
 - Mirtazapine (**Low Certainty**)
- **Psychostimulant**
 - Methylphenidate (**Low Certainty**)
 - Amphetamine salts (eg Adderall) +Topiramate (**Low Certainty**)
 - Co-occurring ADHD, AUD

Topiramate

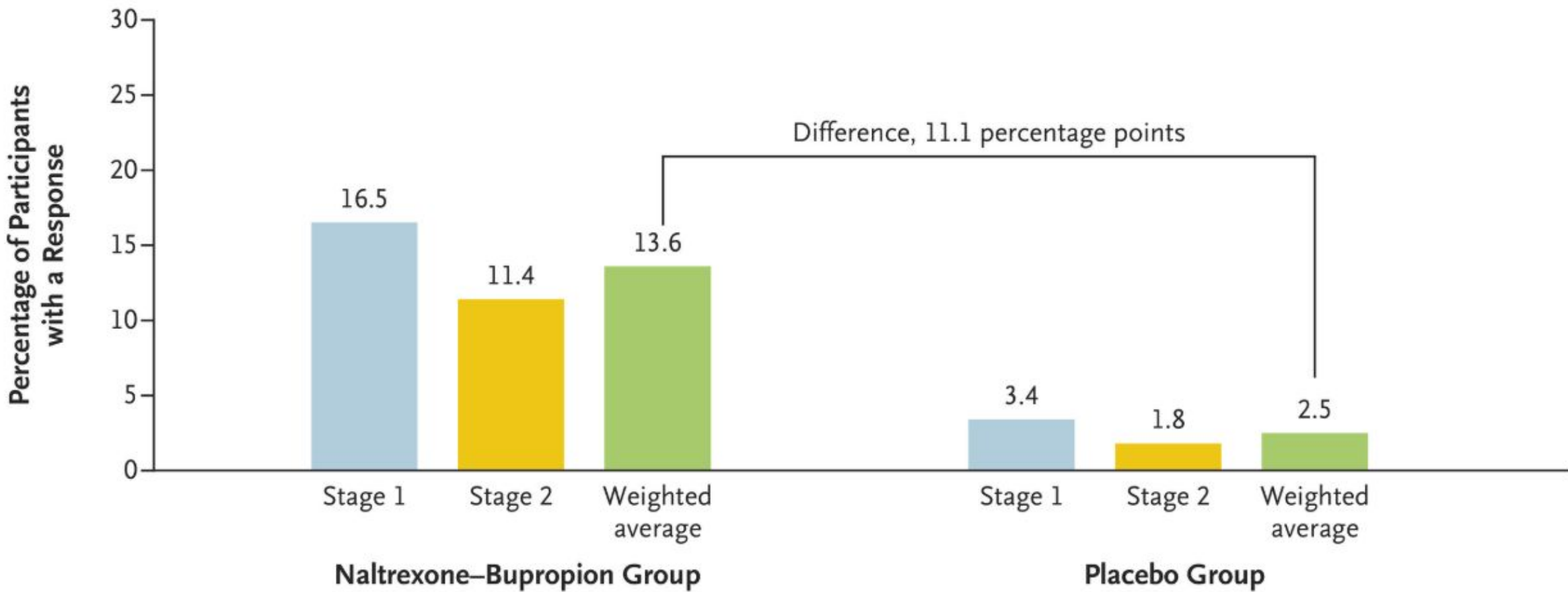
- In a 12-week double blind RCT, 142 patients with C-StUD treated with CBT + topiramate in escalating doses to 300 mg v placebo.
 - Topiramate group had greater proportion of cocaine nonuse days (13.3 versus 5.3 percent) [2].
- In a 13 week RCT, 40 patients with cocaine use were assigned to topiramate (200 mg daily) or placebo. Topiramate group was more likely to achieve 3 weeks of sobriety and more likely to be abstinent during last 5 weeks of the trial [3].
- ASAM clinical guideline committee “judged that the evidence only somewhat favors topiramate, they concluded that topiramate might be considered for patients with cocaine use”

A pilot trial of topiramate for the treatment of cocaine dependence. Kampman KM, Pettinati H, Lynch KG, Dackis C, Sparkman T, Weigley C, O'Brien CP. Drug Alcohol Depend. 2004;75(3):233.

Bupropion and Naltrexone in Methamphetamine Use Disorder

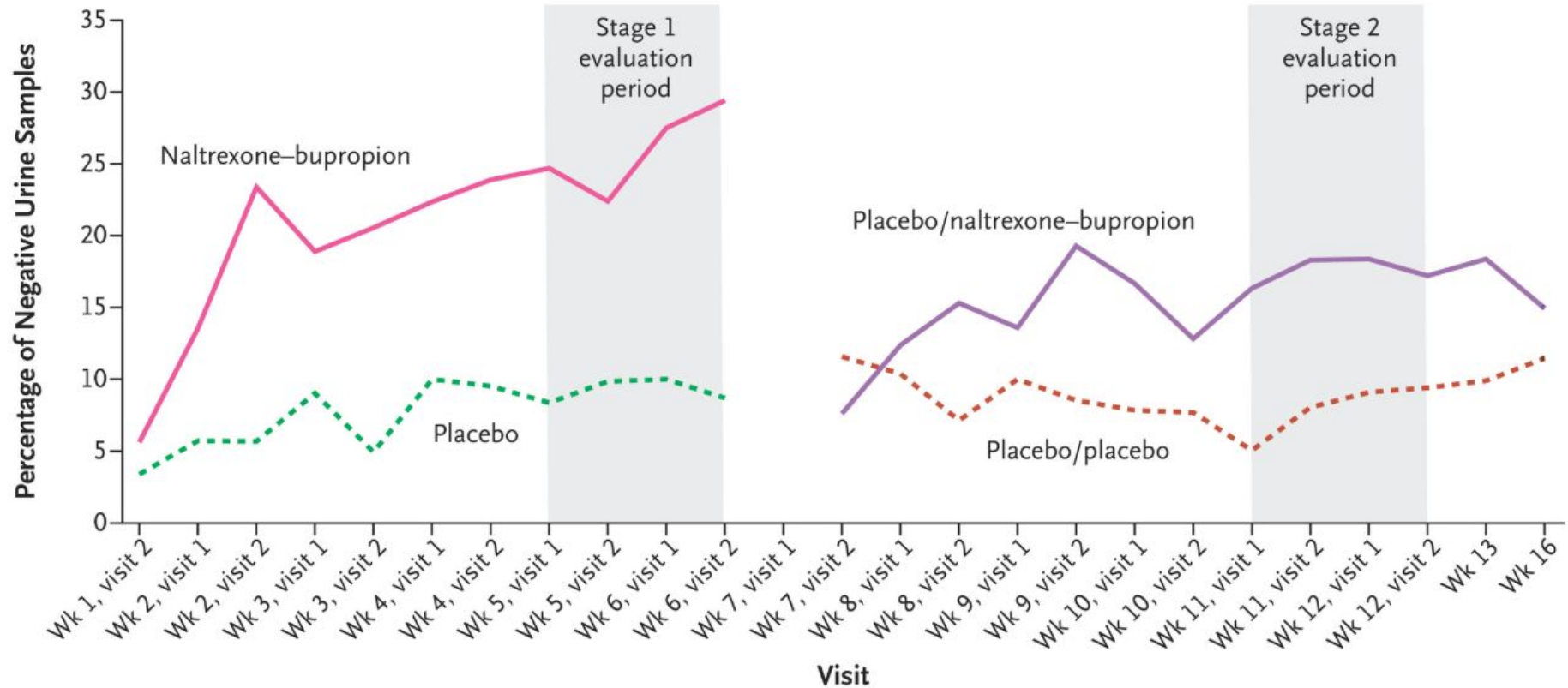
- Multisite, double-blind, two-stage, placebo-controlled trial at 8 sites around the US
- **Naltrexone 380 mg IM q 3 weeks and bupropion 450 mg daily in adults** with moderate or severe methamphetamine use disorder
 - 1st stage of the trial: participants randomly assigned to naltrexone-bupropion or placebo x 6 weeks.
 - 2nd stage: Those in placebo group w/o a response in stage 1 underwent rerandomization x an additional 6 weeks.
- Twice weekly UA's obtained. Primary outcome: ≥ 3 out of 4 negative UA's.
- Response stage 1: **16.5% in med v 3.4% placebo.**
- Response stage 2: **11.4% in med v 1.8% placebo**
- Authors Conclusions: The response over 12 weeks among participants who received (meds) was low but was higher than that among participants who received placebo. [7]

A Responses



Percentage of participants with a response (at least 3 out of 4 neg urine samples) at the end of stage 1 (weeks 5-6)

B Methamphetamine-Negative Urine Samples



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

Percentage of negative urine samples by week

Efficacy and Safety of Modafinil for Treatment of Amphetamine-Type Stimulant Use Disorder: A Systematic Review and Meta-Analysis of Randomized Placebo-Controlled Trials

- 5 randomized, placebo controlled studies were included
- Authors noted this study was unique in that it looked at a wider range of outcomes (9 total including cravings, significant adverse events , retention in treatment), did not pool data with data of other psychostimulants and looked specifically at ATSUD. **Prior meta analysis did not find modafinil helped with increasing abstinence.**
- **Modafinil did not significantly impact ATS use, retention in treatment or treatment discontinuation**
- Results were consistent across subgroup analysis when looking at 200 and 400 mg daily.
- Author's conclusions: **"There is currently no evidence suggesting that modafinil has a statistically significant effect on efficacy outcomes in populations with ATSUD"**

Mirtazapine for the treatment of amphetamine and methamphetamine use disorder: A systematic review and meta-analysis

- **2 placebo controlled, RCT included**
- **Study population:** cis-gender men and transgender women
- Mirtazapine increases dopamine, norepinephrine, and serotonin levels in the *mesocorticolimbic system*
- **Hypothesis:** increased monoamine levels may alleviate MA/A cravings and withdrawals

Mirtazapine for the treatment of amphetamine and methamphetamine use disorder: A systematic review and meta-analysis

- **Continued MA/A use:** mirtazapine likely results in small reduction in continued MA use compared to placebo after 12 weeks. Moderate certainty evidence due to imprecision
- **Retention in treatment:** likely has no impact
- **High risk sexual behaviors:** Unclear
- **Depression symptom severity:** little to no difference
- **Cravings:** insufficient data

Pharmacological Treatment of Methamphetamine/Amphetamine Dependence: A Systematic Review. 2020

- Reviewed 43 studies that collectively enrolled 4065 participants. 23 individual pharmacotherapies, alone or in combination were reviewed – **Not all are listed below but medications included:**
 - 5 antidepressants which included SSRI, mirtazapine, bupropion
 - Tricyclic antidepressant
 - Topiramate
 - Antipsychotic
 - Methylphenidate
 - Dexamphetamine
 - Gabapentin
 - Naltrexone
 - Buprenorphine
 - NAC
 - Benzodiazepine
- Meta analysis was not possible due to different outcomes/measures
- Overall 70.3% participants were male, 69.8% dependent on MA only

Pharmacological Treatment of Methamphetamine/Amphetamine Dependence: A Systematic Review. 2020

- CM demonstrated significant reduction in use +/- CBT but effects often not sustained after cessation
- Residential rehab decreased use at 3 months v no treatment but effect not maintained at 3 years
- “No pharmacotherapy yielded convincing results for the treatment of AMPH/MA dependence; mostly studies were underpowered and had low treatment completion rates”

Pharmacological Treatment of Methamphetamine/Amphetamine Dependence: A Systematic Review. 2020

- 79% of studies excluded participants with comorbid mental health diagnoses or on medications prescribed for mental health diagnoses.
- Research suggests that transient psychotic symptoms are observed in up to 40% of MA-using populations, possibly more among treatment seekers.
- 42% of people who had used MA in the past year also reported concurrent mental illness—**3x as high as the non-illicit drug-using population**
- “The exclusion of relatively common comorbidities such as polydrug dependence and mental health comorbidities limits the generalisability of many of the studies”

Psychostimulants for StUD

- Another off label medication being investigated.
- Arguments in support of use include that similar to how opioid agonists like buprenorphine and methadone are used in the treatment of OUD, prescription stimulants may provide similar agonism to relieve withdrawal symptoms and prevent or reduce StUD.

Psychostimulant drugs for cocaine dependence [1]

- 26 studies involving 2366 participants
- Studies assessed nine drugs: bupropion, dexamphetamine, lisdexamfetamine, methylphenidate, modafinil, mazindol, methamphetamine, mixed amphetamine salts and selegiline.
- Found **very low quality evidence that psychostimulants improved sustained cocaine abstinence**, but **did not reduce cocaine use among participants who continued to use it.**
- Found moderate quality evidence that **psychostimulants did not improve retention in treatment**

Prescription psychostimulants for the treatment of amphetamine-type stimulant use disorder: A systematic review and meta-analysis of randomized placebo-controlled trials. 2023

- 10 RCT included in the meta analysis
- Trials studied methylphenidate 54- 180 mg and dextroamphetamine 60 -110 mg for 2 – 24 weeks (max ADHD dose 108 and 50 mg respectively)

Prescription psychostimulants for the treatment of amphetamine-type stimulant use disorder: A systematic review and meta-analysis of randomized placebo-controlled trials. 2023

- Stimulants ↓ end point cravings but did not reach significance for ATS use measured with UA's.
- No effect observed for self reported ATS use, retention in treatment, early stage craving, withdrawal or depressive symptoms.
- In a sensitivity analysis, treatment was associated with a statistically significant reduction in UA positive for ATS after removing studies with high risk of bias
- In subgroup analysis, methylphenidate and high doses of PP were negatively associated with ATS use by UA
 - Greater benefit found with high dose PP however only one study with > 162 mg methylphenidate. Moderate RR for ATS use. Such difference in treatment effect was not present at lower doses

Extended-Release Mixed Amphetamine Salts vs Placebo for Comorbid Adult Attention-Deficit/Hyperactivity Disorder and Cocaine Use Disorder: A Randomized Clinical Trial

- 13 week placebo controlled RCT trial, 126 participants with ADHD + cocaine use
- Participants received ER mixed amphetamine salts (60 or 80 mg) or placebo daily + CBT
- More patients achieved at least 30% ↓ in ADHD symptoms in med group
- Rates of continuous abstinence in last 3 weeks were greater for medication groups than placebo:
 - 30.2% for 80 mg
 - 17.5% for 60 mg
 - 7.0 % for placebo
- Author conclusion: Extended-release mixed amphetamine salts in robust doses along with CBT are effective for treatment of co-occurring ADHD and C-StUD, both improving ADHD symptoms and reducing cocaine use.
- Per UpToDate: Adderall XR: >40 mg/day rarely necessary, 60 mg/day max dose for ADHD
- Rate of ADHD 2.5 -4 % in general population, 10-24% of those seeking treatment for SUD

Association of Pharmacological Treatments and Hospitalization and Death in Individuals With Amphetamine Use Disorders in a Swedish Nationwide Cohort of 13 965 Patients

- Swedish nationwide cohort study of 13 965 individuals from 2006-2018
- Ages 16 to 64 years living in Sweden with a first-time diagnosis of amphetamine or methamphetamine use disorder and without previous diagnoses of schizophrenia or bipolar disorder
- 69.3% male, mean age: 34.4
- Primary outcome: hospitalization due to SUD and any hospitalization or death
- Secondary outcome: all-cause mortality

Association of Pharmacological Treatments and Hospitalization and Death in Individuals With Amphetamine Use Disorders in a Swedish Nationwide Cohort of 13 965 Patients

- 54.0% were taking antidepressants, 43.7% benzodiazepines, 36.3% antipsychotics, 28.2% ADHD medications, 10.8% were taking lisdexamphetamine, 20.5% SUD medications, and 12.2% mood stabilizers.
- Study **did not** determine reason for stimulant prescriptions
- 74.0% hospitalized due to SUDs, 82.3% were hospitalized due to any cause or died, and 9.5% died of any cause.

Association of Pharmacological Treatments and Hospitalization and Death in Individuals With Amphetamine Use Disorders in a Swedish Nationwide Cohort of 13 965 Patients

- Oral **naltrexone** was not associated with a lower risk of hospitalizations or death
- **Buprenorphine** associated with a significantly lower risk of any hospitalization or death
- **Topiramate was** not associated with either increased or decreased risk of outcomes
- **Antidepressants** as a group were associated with a statistically significant increase in risk hospitalization or death, and **mirtazapine and bupropion** were not associated with any outcomes

Association of Pharmacological Treatments and Hospitalization and Death in Individuals With Amphetamine Use Disorders in a Swedish Nationwide Cohort of 13 965 Patients

- **Lisdexamphetamine** was the only med that had statistically significant decrease in risk of 3 outcomes: SUD hospitalization, any cause hospitalization or death
- **Benzodiazepines** had significantly increased risk in all 3 outcomes
- **Methylphenidate** use also was associated with lower all-cause mortality (not a primary outcome)
- **Combo of 2 or more SUD medications, lisdexamphetamine, and buprenorphine** were associated with lower risk of any hospitalization or death compared to periods when the same individual was not taking the meds

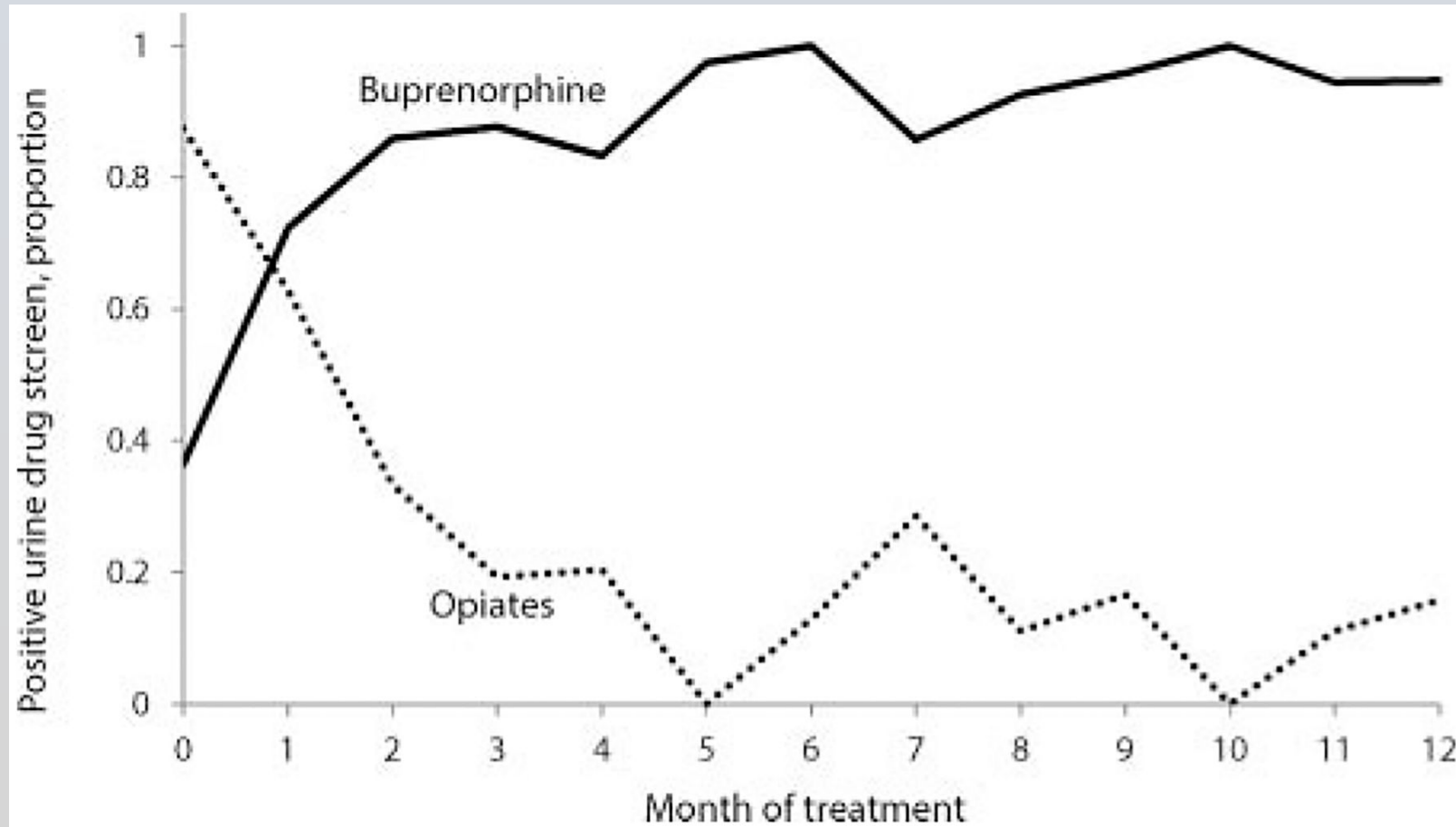
Table 2. Risk of Outcomes Associated With Use of Lisdexamphetamine Compared With Nonuse of Lisdexamphetamine in Within-Individual Model Stratified by Dose Categories in Defined Daily Doses (DDD)

	DDD/d	Events, No.	Individuals, No.	Person-years	aHR (95% CI)
Risk of hospitalization due to substance use disorder					
Lisdexamphetamine by dose categories					
<45 mg/d	<1.50	72	457	185	1.10 (0.80-1.52)
45 to <65 mg/d	1.50 to <2.17	86	425	308	0.70 (0.52-0.93)
65 to <85 mg/d	2.17 to <2.83	117	399	394	0.75 (0.57-0.99)
≥85 mg/d	≥2.83	197	525	546	0.83 (0.67-1.03)
Risk of hospitalization due to any cause or death					
Lisdexamphetamine by dose categories					
<45 mg/d	<1.50	124	455	185	1.02 (0.80-1.30)
45 to <65 mg/d	1.50 to <2.17	167	423	308	0.77 (0.62-0.95)
65 to <85 mg/d	2.17 to <2.83	246	398	392	0.79 (0.64-0.96)
≥85 mg/d	≥2.83	372	517	542	0.92 (0.78-1.07)

Abbreviation: aHR, adjusted hazard ratio.

- Lisdexamphetamine is licensed for doses of 30 to 70 mg for ADHD
- In this study, the most beneficial outcome was observed in 45 to 85 mg

Data from 2011- 2014. Outcomes in persons with OUD started on buprenorphine.



Bachhuber MA, Thompson C, Prybylowski A, Benitez J MSW, Mazzella S MA, Barclay D. Description and outcomes of a buprenorphine maintenance treatment program integrated within Prevention Point Philadelphia, an urban syringe exchange program. *Subst Abus.* 2018;39(2):167-172. doi: 10.1080/08897077.2018.1443541. Epub 2018 May 4. PMID: 29474119; PMCID: PMC9333078.

Misuse and diversion of stimulant medications prescribed for the treatment of ADHD: a systematic review [14]

- 2008 systematic review explored past year stimulant misuse in general populations
 - Misuse 5 – 9% in school aged young people, and 5 – 35% in young adults.
 - 11 – 29% had sold their prescribed stimulant medication,
 - 23% of young people prescribed stimulants for ADHD had been asked to sell, trade or give away medications.
- A 2012 systematic review
 - 44% misuse rate based on one adult study,
 - 3% from a study of young people aged 10-21
- 2020 review: 4-35% of individuals reported non-medical use of their own prescription stimulant
- Meta-analysis concluded misuse of prescription stimulants to be 22.6% and prevalence of diversion to be 18.2%.

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