PHARMACOLOGIC TREATMENTS FOR STIMULANT USE DISORDERS: WHAT DOES THE TREATMENT LITERATURE TELL US?

NYSAM ANNUAL VIRTUAL MEETING
FRIDAY, FEBRUARY 6TH

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ASAM American Society of Addiction Medicine

Disclosure Information

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Consultant: Major League Baseball
Unpaid Scientific Advisory Board Member: Novartis, Alkermes, Indivior

Keep this in Mind

- Everything I talk about is Off-Label Use
- No medication has been FDA-approved for the Treatment of Stimulant Use Disorder

People Aged 12 or Older with a Past Year Substance Use Disorder (SUD): 2018

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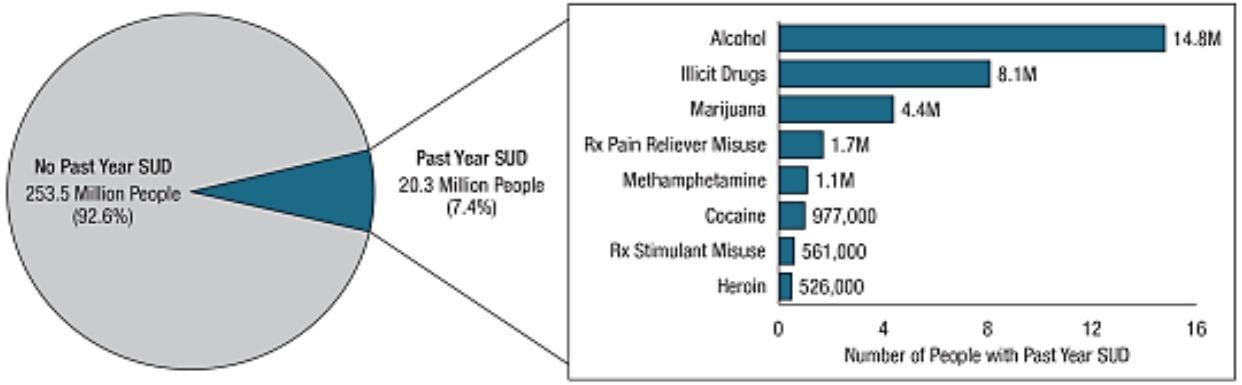
People Aged 12 or Older with a Past Year Substance Use Disorder (SUD): 2018



Rx = prescription.

Note: The estimated numbers of people with substance use disorders are not mutually exclusive because people could have use disorders for more than one substance.

SAMHSA
Substance Abuse and Mental Health Services Administration

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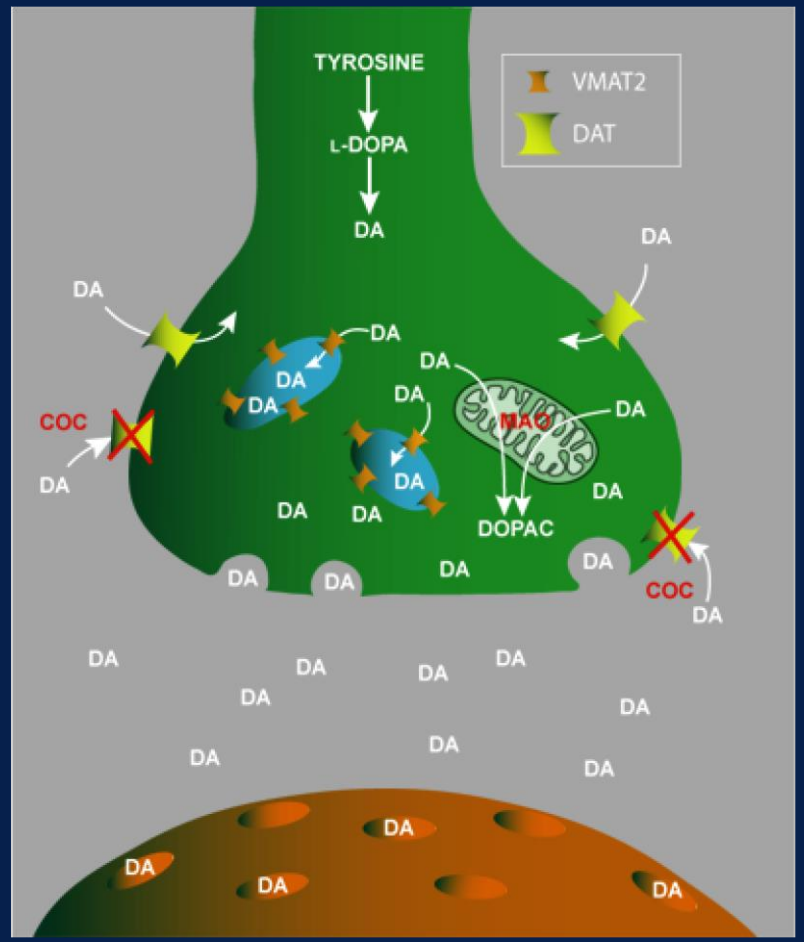
Treatment Literature

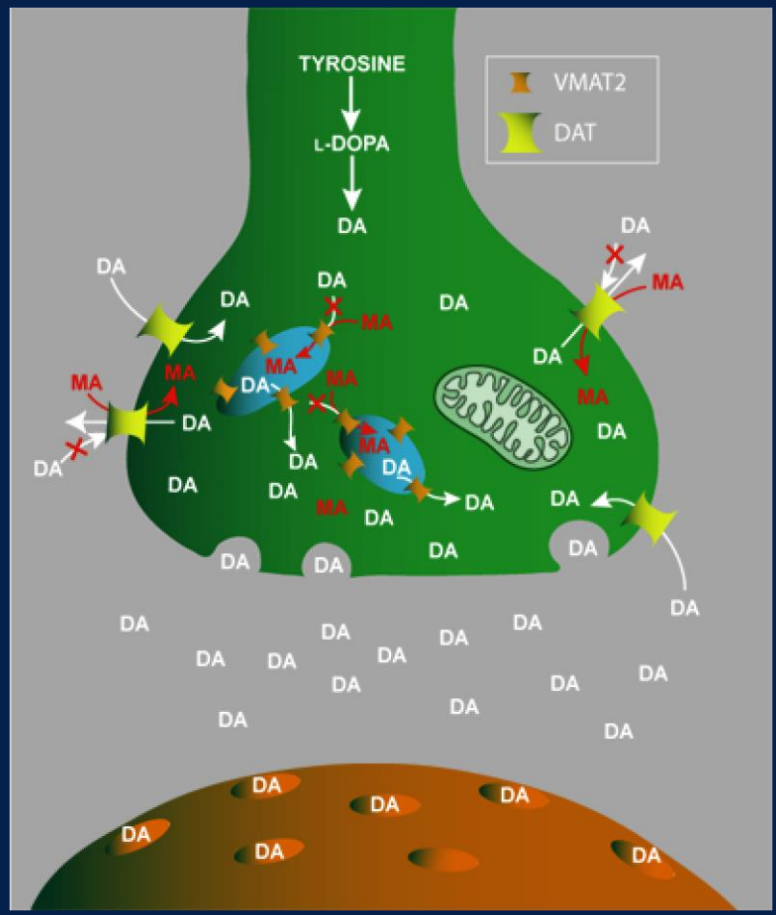
- Psychosocial Treatments
  - Systematic reviews of cognitive and behavioral treatments conclude that good clinical outcomes are achieved with
    - Cognitive-Behavioral Treatment (CBT; with and without Motivational Interviewing [MI]
    - Contingency Management (CM) therapies involving the use of reinforcement (Lee and Rawson, 2008).
  - There are questions regarding the durability of treatment effects (especially with respect to CM)
  - Furthermore, the effectiveness of psychosocial interventions is compromised by:
    - Poor rates of treatment induction and retention (Shearer, 2007),
    - Cognitive deficits in executive functioning, particularly those related to inhibitory control, have been hypothesized to potentially render heavily cognitive-based treatments less or ineffective (Baicy and London, 2007 Aharonovich 2008).

Pharmacology of Stimulants

COCAINE



METHAMPHETAMINE



Pharmacotherapy for Cocaine Use Disorder— A Systematic Review and Meta-analysis; 48 trials, 68 medications or combinations (Chan et al. 2019)

Table 1 Brief Summary of Findings

	Abstinence	Use	Lapse	Relapse	Retention	Harms
All Antidepressants: Bupropion, Desipramine, Fluoxetine, Mirtazapine, Nefazodone, Paroxetine, Sertraline, Venlafaxine	★★	★★	★	★	★★★	★★
Aminoketone: Bupropion	★	★	NA	NA	★★	Ø
SSRIs: Fluoxetine, Paroxetine, and Sertraline	NA	NA	Ø	Ø	★★	★
SSRI in patients abstinent at Baseline: Sertraline	NA	NA	★	★	★	Ø
All Antipsychotics: Aripiprazole, Haloperidol, Lamotrigine, Olanzapine, Quetiapine, Risperidone, Reserpine	★	★	Ø	Ø	★★	Ø
Psychostimulants: Dexamphetamine, Lisdexamfetamine, Mazindol, Methamphetamine, Methylphenidate, Mixed Amphetamine Salts, Modafinil, Selegiline	★	★	NA	NA	★★	★★
Cognitive Enhancing Drugs: Memantine, Atomoxetine	Ø	Ø	NA	Ø	Ø	Ø
Anxiolytic: Buspirone	Ø	NA	Ø	Ø	Ø	Ø
Anticonvulsants/Muscle Relaxants: Baclofen, Carbamazepine, Gabapentin, Lamotrigine, Phenytoin, Tiagabine, Topiramate, Vigabatrin	NA	★★	NA	NA	★★	Ø
Anticonvulsant: Topiramate	★	Ø	NA	NA	★★	Ø
Drugs for other substance use disorders: Acamprosate, Buprenorphine, Buprenorphine + Naloxone, Disulfiram, Naltrexone, Methadone, Varenicline	★	Ø	Ø	Ø	Ø	Ø
Disulfiram	★	★	NA	NA	★★	★
Dopamine agonists: Amantadine, bromocriptine, L dopa/Carbidopa, pergolide, cabergoline hydergine, and pramipexole	★	NA	NA	NA	★★	NA

Shading represents the direction of effect:

(No color)	Unclear
Grey	No difference
Green	Evidence of benefit
Red	Favors placebo

Symbols represent the strength of the evidence:

NA	No evidence or not applicable
Ø	Insufficient
★	Low
★★	Moderate
★★★	High

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Systematic Review and Meta-analysis: Pharmacologic Treatment: 17 trials, 13 medications evaluated for Amphetamine Use Disorder

(Chan et al., 2019)

Table 3 Brief summary of findings.

	Abstinence	Use	Retention	Harms
All Antidepressants	★★	Ø	★★	★
Aminoketone: Bupropion	★	★	★★	Ø
Atypical Antidepressant: Mirtazapine	NA	Ø	Ø	Ø
SSRI: Sertraline	Ø	NA	Ø	NA
Atypical Antipsychotics: Aripiprazole	Ø	★	Ø	Ø
Psychostimulants and Other Medications for ADHD				
All Psychostimulants: Modafinil, Dexamphetamine, Methylphenidate	★	Ø	★	NA
Methylphenidate	NA	★	★	NA
Atomoxetine	NA	Ø	Ø	Ø
All Anticonvulsant and Muscle Relaxants: Baclofen, Gabapentin, Topiramate	Ø	Ø	Ø	Ø
Topiramate	NA	★	★	★
Medications used for other substance use disorders				
Naltrexone	Ø	★	★	★★
Varenicline	NA	Ø	Ø	Ø

Shading represents the direction of effect:

(No color)	Unclear
Grey	No difference
Green	Evidence of benefit
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Symbols represent the strength of the evidence:

NA	No evidence or not applicable
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★★	Moderate
★★★	High

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Newer Methamphetamine Pharmacologic Treatment Review: Concluded Could Not Do a Meta-analysis

(Siefried et al. CNS Drugs 2020)

- **43 randomized controlled trials, 4065 participants, 23 medications; 21 of the studies with 5 medications (Mitrazapine, MPH, Modafinil, Naltrexone, Bupropion)**
- Outcomes and measures varied widely, making it difficult to synthesize the data
- 55 Primary Outcome measures (most common ones chosen)
  - Abstinence was the most common measure but looked at in MANY ways
  - Reduction in Use
  - Craving
  - Withdrawal
- When meta-analyses done, often can only do it on a small subset of the studies that share the same outcome measure
- Adherence- measured by pill count, MEMS, 11 studies did not report adherence. Few studies reported plasma metabolite/study drug

Newer Methamphetamine Pharmacologic Treatment Review: Concluded Could Not Do a Meta-analysis

(Siefried et al. CNS Drugs 2020)

- No pharmacotherapy demonstrated convincing results; however some agents demonstrated promise, suggesting further, larger studies are required.
- Most consistently positive results with dexamphetamine* and methylphenidate, naltrexone and topiramate. Less consistent findings with bupropion and mirtazapine*
- Future studies should consider the heterogeneity of those with amphetamine/methamphetamine dependence and the role of psychosocial intervention.

Treatment Literature

- **Overarching Categories:**
  - Agonists
  - Antagonists
  - Novel Mechanisms
  - Combined Pharmacotherapy
  - Psychiatric Comorbidity

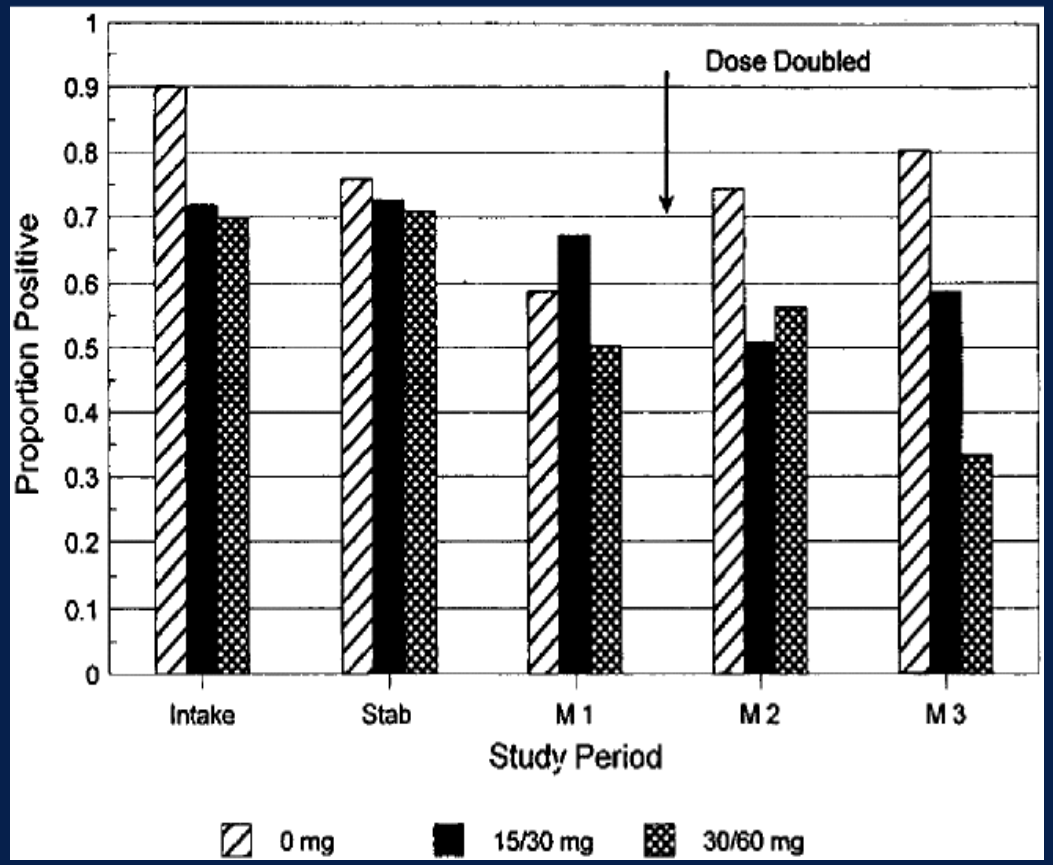
AGONIST Approach

- **Both cocaine and amphetamines given acutely increase synaptic levels of monoamines (DA/NA/5HT)**
- **However, chronic heavy users have reduced monoaminergic functioning (low baseline DA, blunted DA release, low D2/D3 receptor availability)**
  - anergia/anhedonia in early abstinence
  - impaired cognition/decision making, ↑impulsivity, cue-reactivity
  - deficit in DA signaling may drive continuing use/relapse
- **Possible mechanisms of therapeutic effects with agonists**
  - may restore monoaminergic functioning and reverse deficits contributing to ongoing use (e.g. normalizing ACC activity)
- **Decrease craving during early abstinence**

AGONISTS: Safety

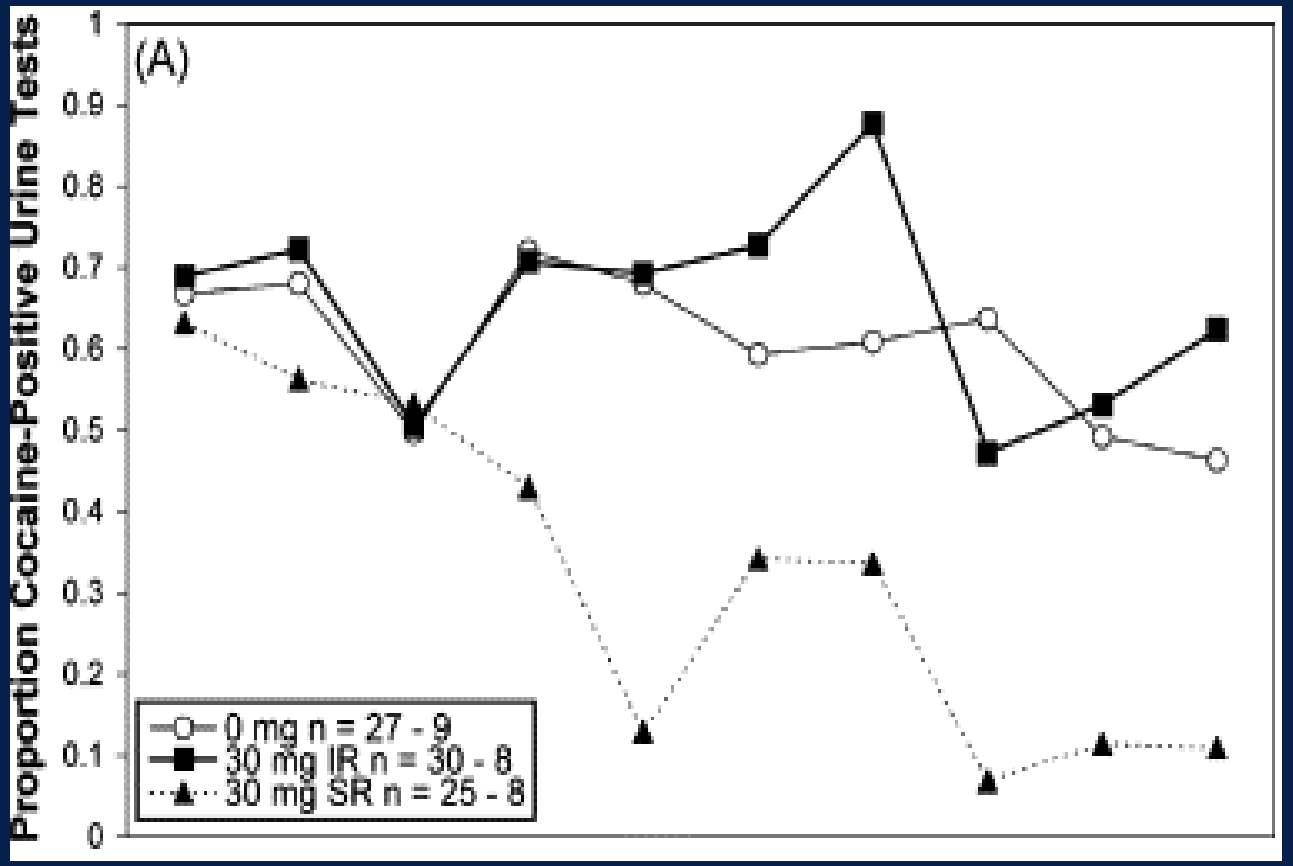
- There are concerns about abuse, diversion, and induction of craving BUT clinical evidence to date doesn't support increased craving. Abuse/diversion low among treatment seekers and can be managed
- Potential for adverse cardiovascular effects: need to screen out individuals with CV disease
- Good patient acceptance: familiarity with the drug
- However, my experience, often do not want highest dose- increased anxiety, insomnia

Dextroamphetamine; Methamphetamine (Desoxyn) for Cocaine Use Disorder



(Grabowski et al., 2001; J Clinical Psychopharmacology)

DOSING MATTERS



(Mooney et al., 2009; Drug and Alcohol Dependence)

FORMULATION MATTERS

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Sustained-release dexamfetamine in the treatment of chronic cocaine-dependent patients on heroin-assisted treatment: a randomised, double-blind, placebo-controlled trial

(Nuijten et al. 2016; Lancet)

	Sustained-release dexamfetamine group (n=38)	Placebo group (n=35)	Exp(B) (95% CI)	Wald χ^2 (df=1)	p value	Effect size
Primary outcome						
Days of cocaine use during 12-week study	44·9 (29·4)	60·6 (24·3)	1·67 (1·05–2·67)	4·66	0·031	d=0·58
Secondary cocaine use-related outcomes						
Longest period of consecutive cocaine abstinence (days)	17·9 (24·9)	6·7 (11·7)	2·69 (1·66–4·36)	16·17	<0·0001	d=0·58
Consecutive cocaine abstinence for ≥21 days	11 (29%)	2 (6%)	6·72 (1·37–32·97)	5·52	0·019	NNT=4·3
Days of cocaine abstinence in final 4 weeks	15·2 (10·8)	7·5 (9·1)	2·04 (1·26–3·31)	8·45	0·004	d=0·77
Proportion cocaine-negative urine samples in final 4 weeks	10·6 (25·1)	3·9 (17·9)	2·60 (1·14–5·94)	5·11	0·024	d=0·31

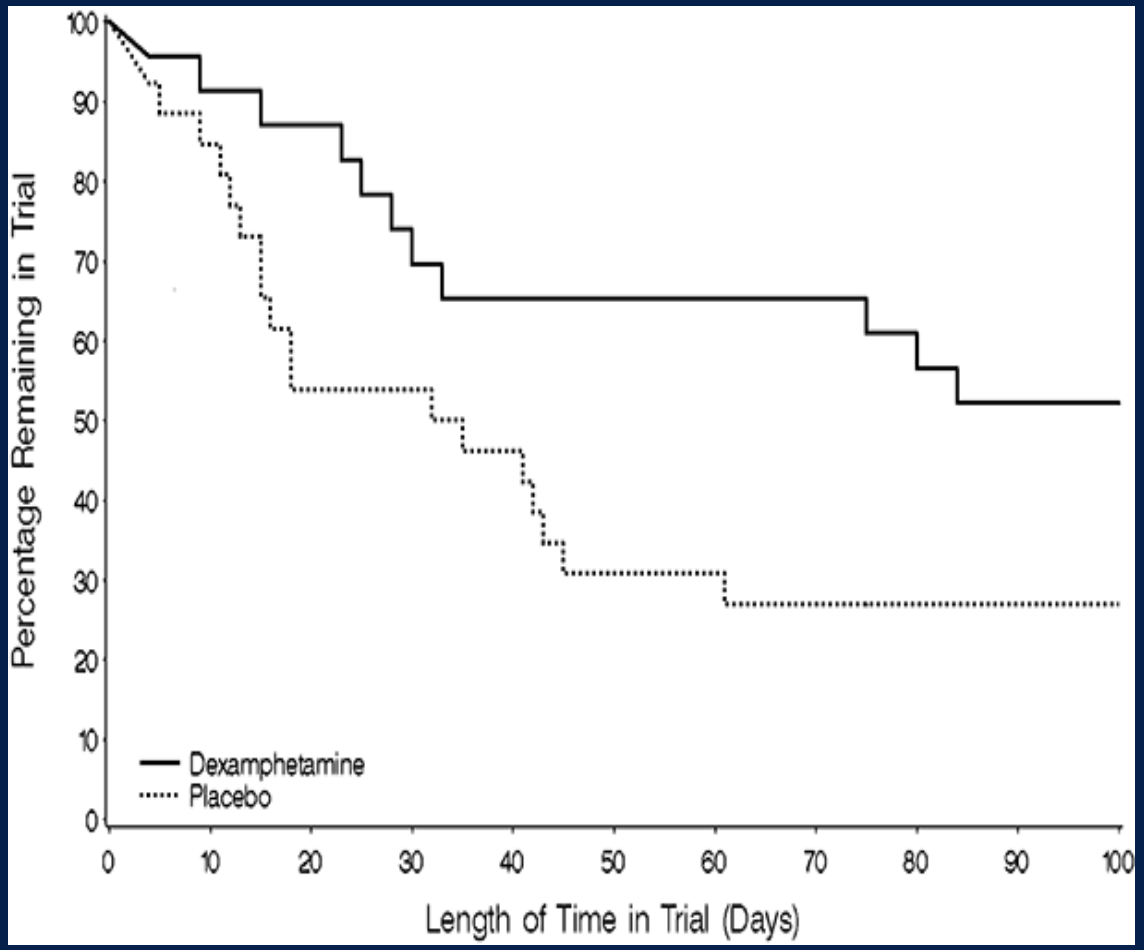
Data are mean (SD) or n (%), unless otherwise specified. Exp(B)=exponentiated value of regression coefficient B; odds ratio. df=degrees of freedom. d=Cohen's d, which is a standardised effect size. NNT=number needed to treat.

Table 2: Primary and secondary cocaine use-related outcomes

AGONIST: dextroamphetamine sustained release for stimulant use disorder (methamphetamine)

(Longo et al, 2010)

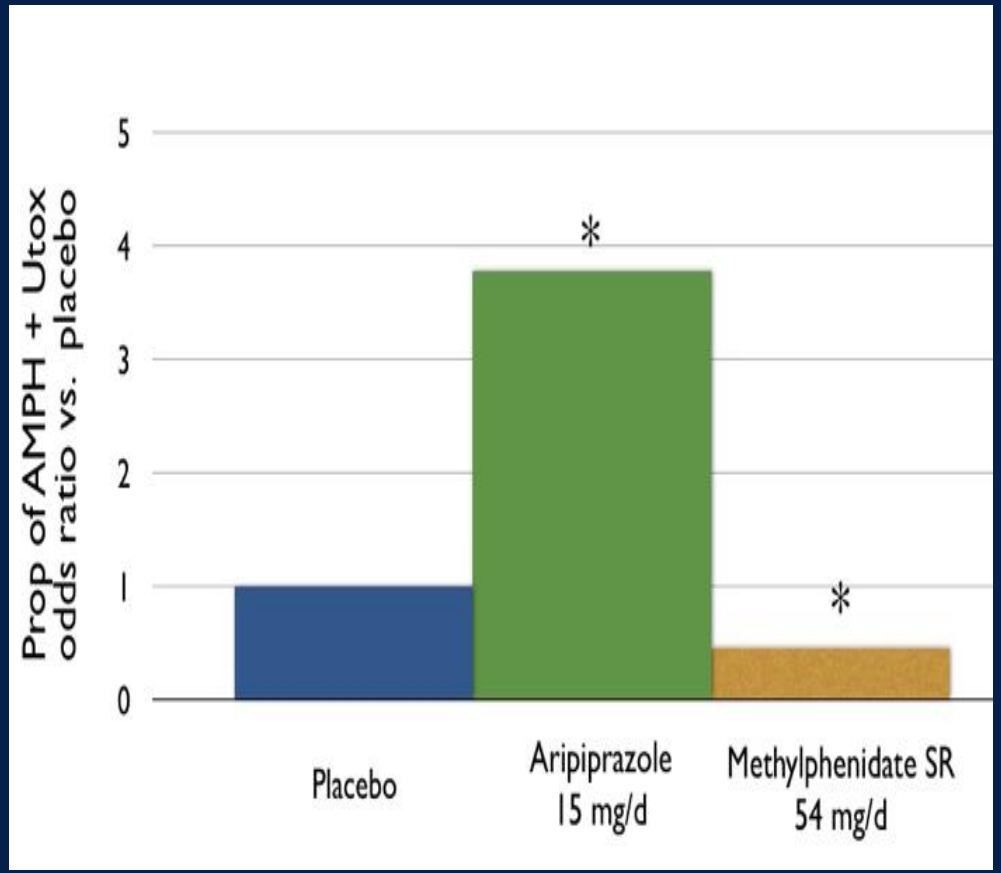
- Heavy, IV MA users (N=49)
- d-AMPH SR 110 mg/d (avg 80 mg/d)
- Significantly better tx retention, improvement in withdrawal symptoms and disease severity
- Dexamphetamine remained in treatment 86.3 days compared with 48.6 days for those receiving placebo (P = 0.014).
- Significant reductions in self-reported methamphetamine use between baseline and follow-up within each group (P < 0.0001), with a trend to a greater reduction among the dexamphetamine group (P = 0.086). Small sample size and approx. 50% drop-out
- Hair analysis, there was a significant decrease in methamphetamine concentration for both groups (P < 0.0001).



AGONIST: Methylphenidate OROS (MPH-SR) for Stimulant Use Disorder (Methamphetamine)

(Tiihonen et al, AJP 2007)

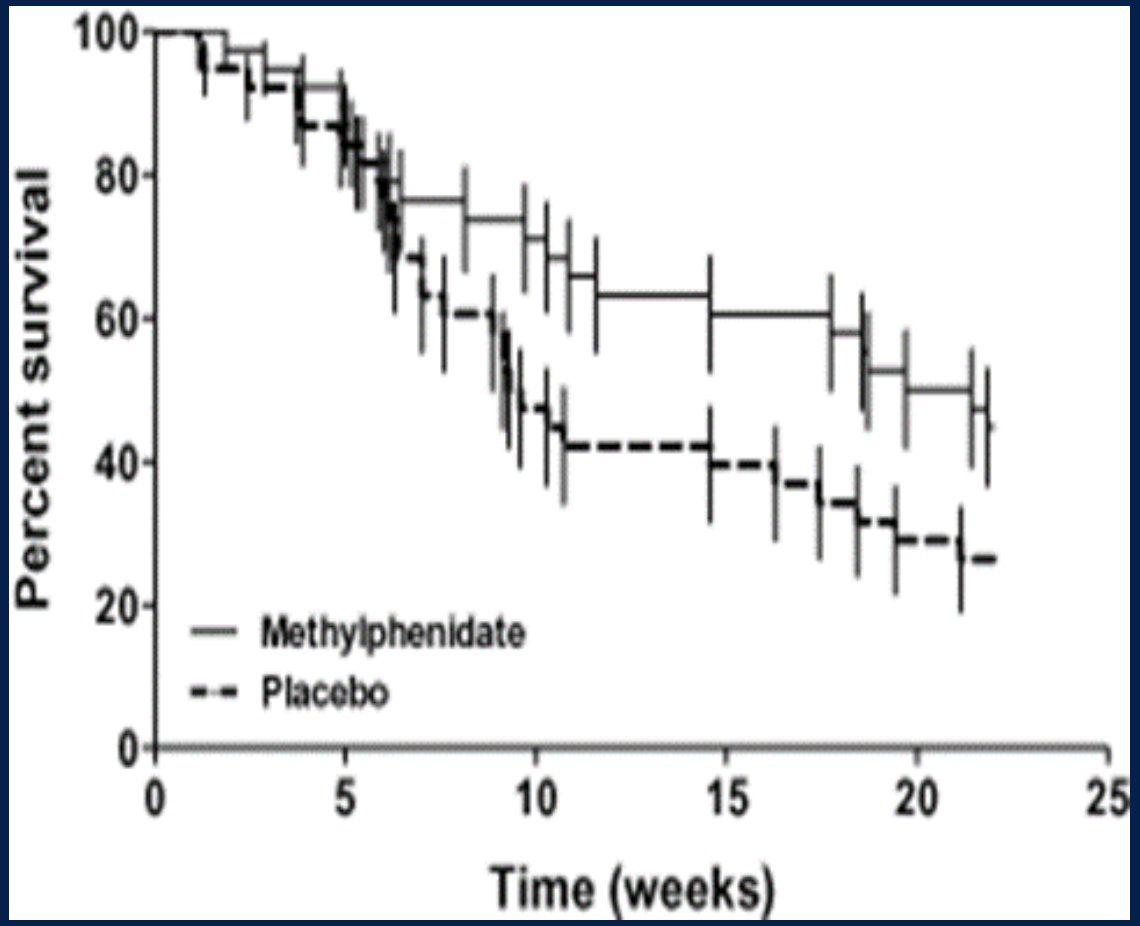
- Abstinence-induction, 20 wk trial in severe intravenous AMPH abusers (100% positive AMPH urines at baseline and >8 mean sx of dependence)
- MPH-SR 54 mg/d (lower equipotent dose than trials using amphetamine formulations)
- Primary Outcome: Proportion of Amph-positive urines
- Had planned to run 70 in each treatment arm but study was stopped due to positive results of interim-analysis (first 53 pts); methylphenidate >> placebo
- MPH group had sig more negative urines than placebo (OR= 0.46)



AGONIST: Methylphenidate OROS (MPH-SR) for Stimulant Use Disorder (Methamphetamine)

(Miles et al., 2013)

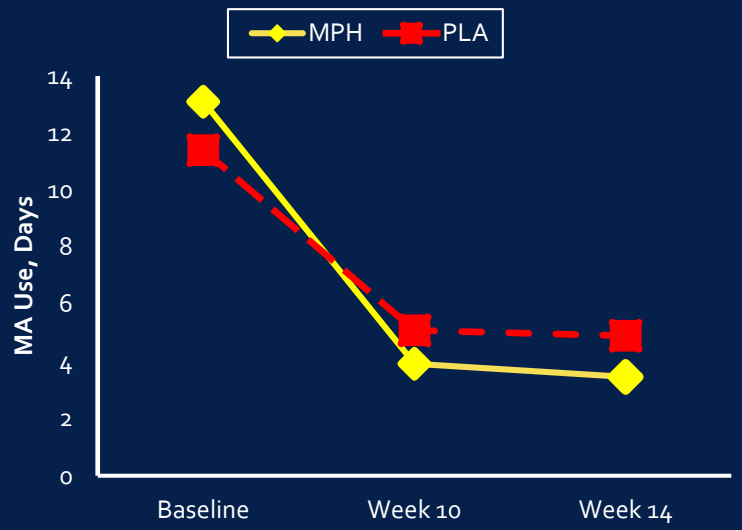
- Abstinence-induction study, 22 weeks
- Severe MA users (N=78)
- MPH-SR 54 mg/d (this is a fairly low dose, approx. 40-50 mg immediate release MPH)
- Significantly better treatment retention on MPH, but overall low retention and no effect on use (80-90% +urine)

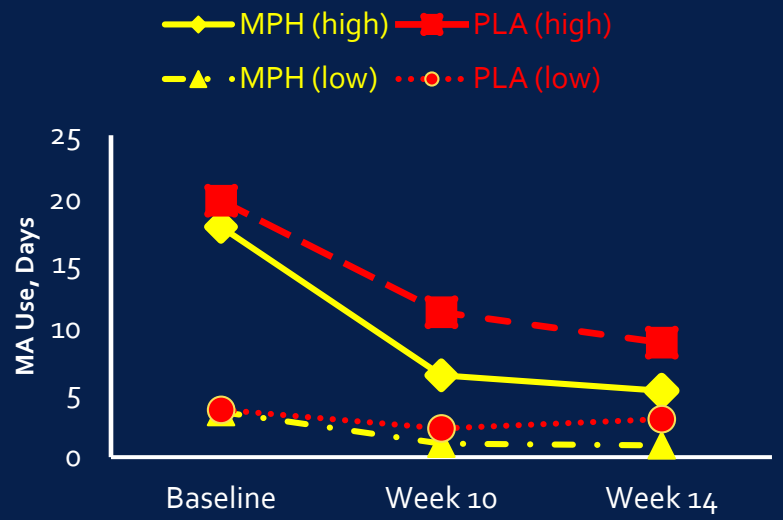


Frequency of Use at Baseline May Matter: (OROS-MPH targeting Methamphetamine Use Disorder)

(Ling et al. 2015)

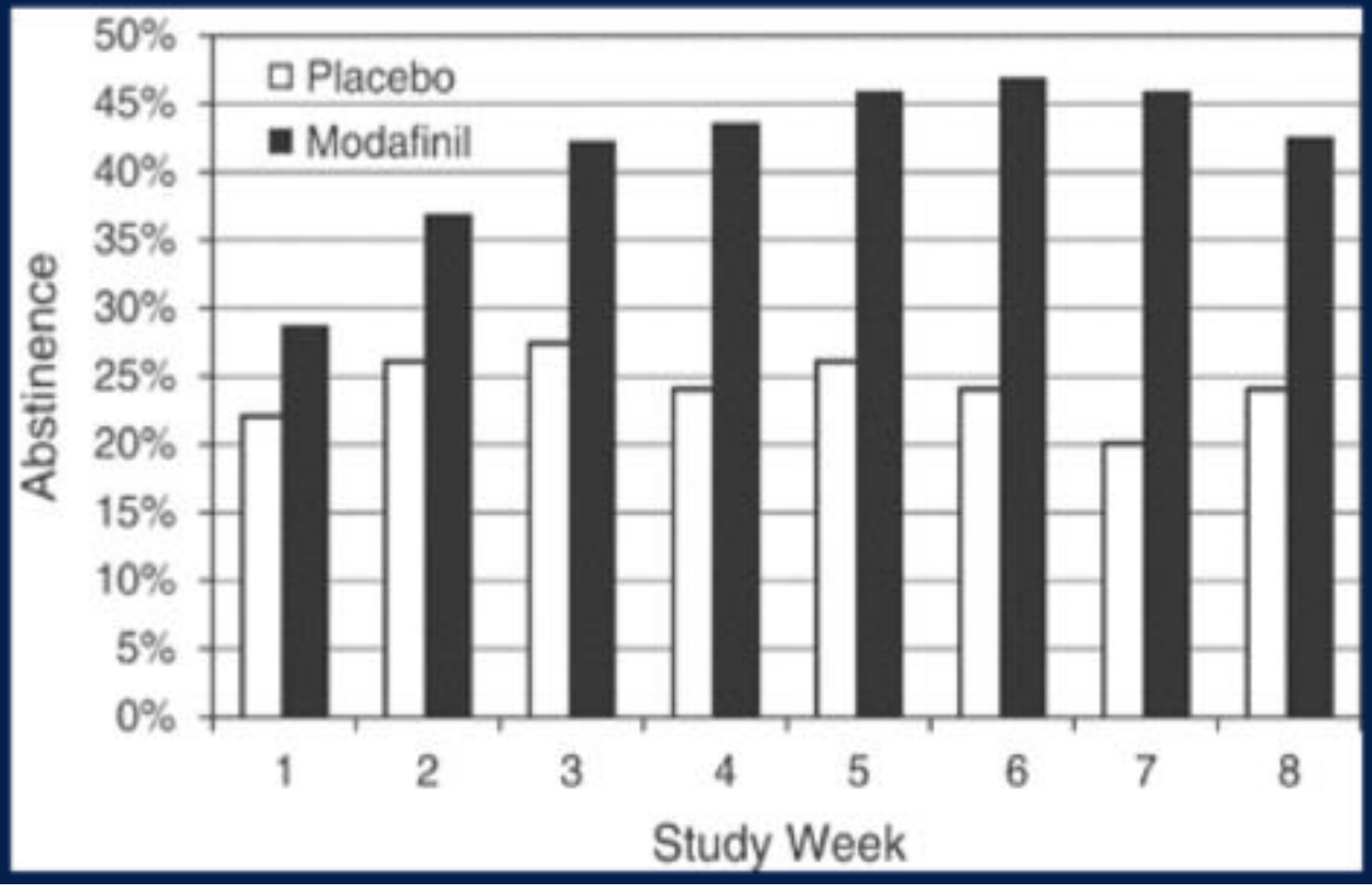
- Abstinence-induction, 14 wk trial
- Pbo vs. MPH-SR 54 mg/d (N=110)
- Medication during weeks 1-10
- Outcome: No medication effect on a primary outcome (days of use in prev. 30d)
- Positive effect of MPH was seen during active phase, most evident in moderate-severe users (> 10 days/30 days at baseline), and in completers
- MPH also decreased craving



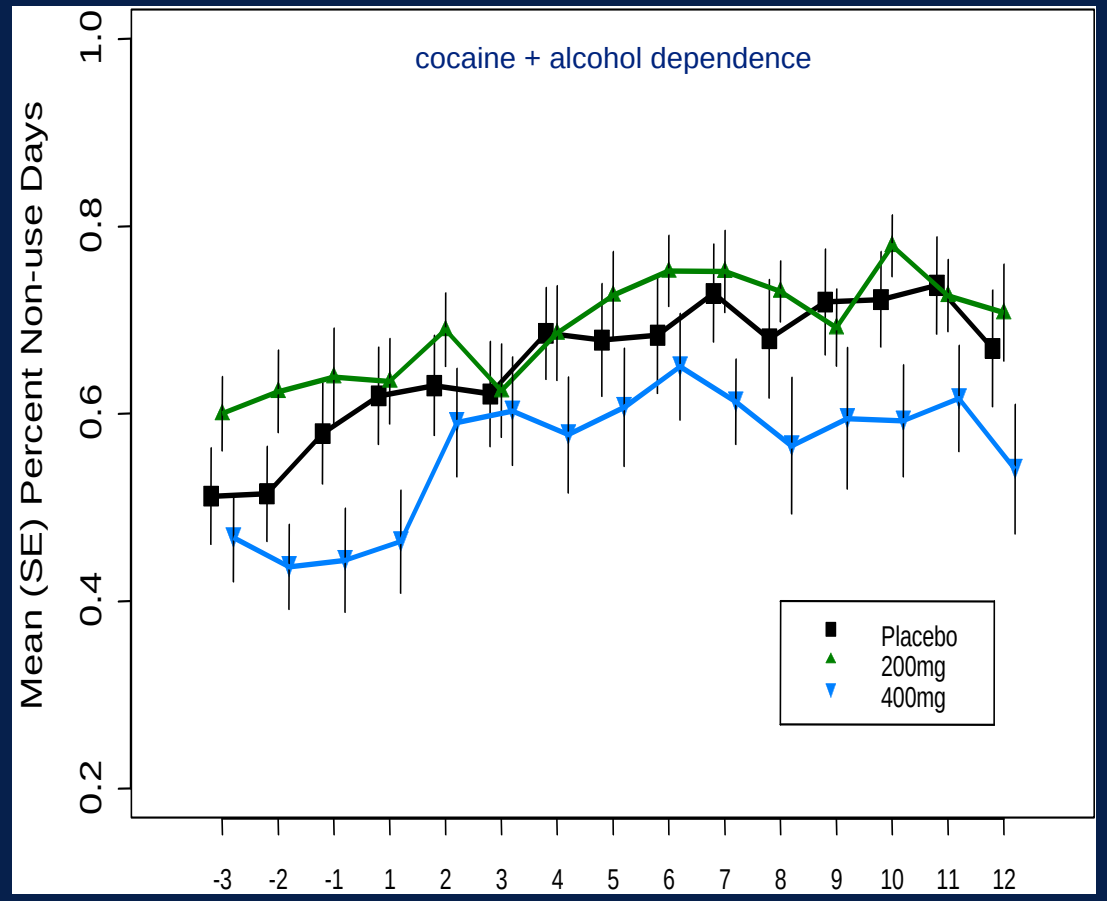


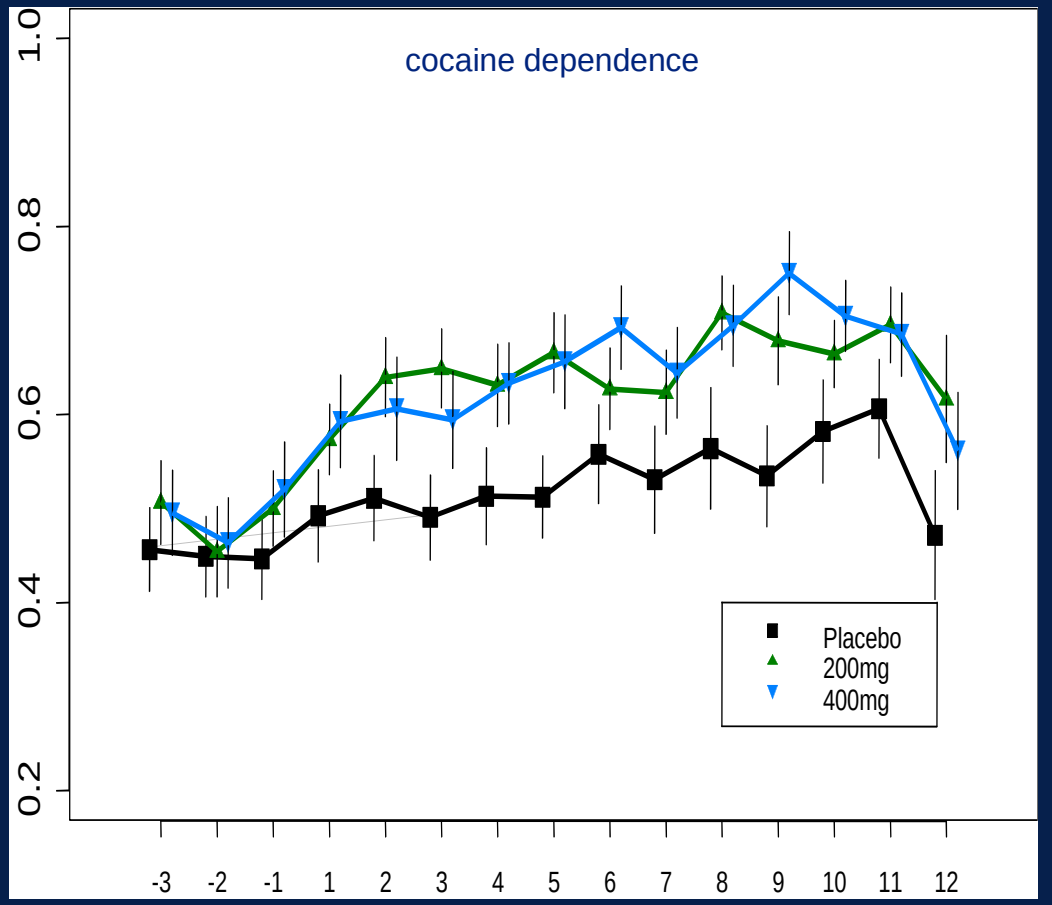
AGONIST: Modafinil for Cocaine Use Disorder

(Dackis et al, 2005)



AGONIST: Modafinil





(Anderson et al, 2009; Drug and Alcohol Dependence; n =210)

Modafinil for treatment of cocaine dependence without co-morbid alcohol dependence

(Kampman et al. 2015)

- 94 CUD patients, 8 week double-blind trial; Contingency management for adherence to study procedures
- Received 300 mg or placebo. Primary outcome self-reported cocaine use confirmed with urine benzoylecgonine test.
- Why prior trials negative with CUD without AUD?
  - Dackis et al 2012; large sample 210 patients; poorer retention than Kampman trial (61% vs. 80% and poorer medication adherence. Gender difference, treatment response in men at higher dose (400 mg)
  - Schmitz et al. One study (2014), only 18 patients on active med and 6 discontinued treatment;

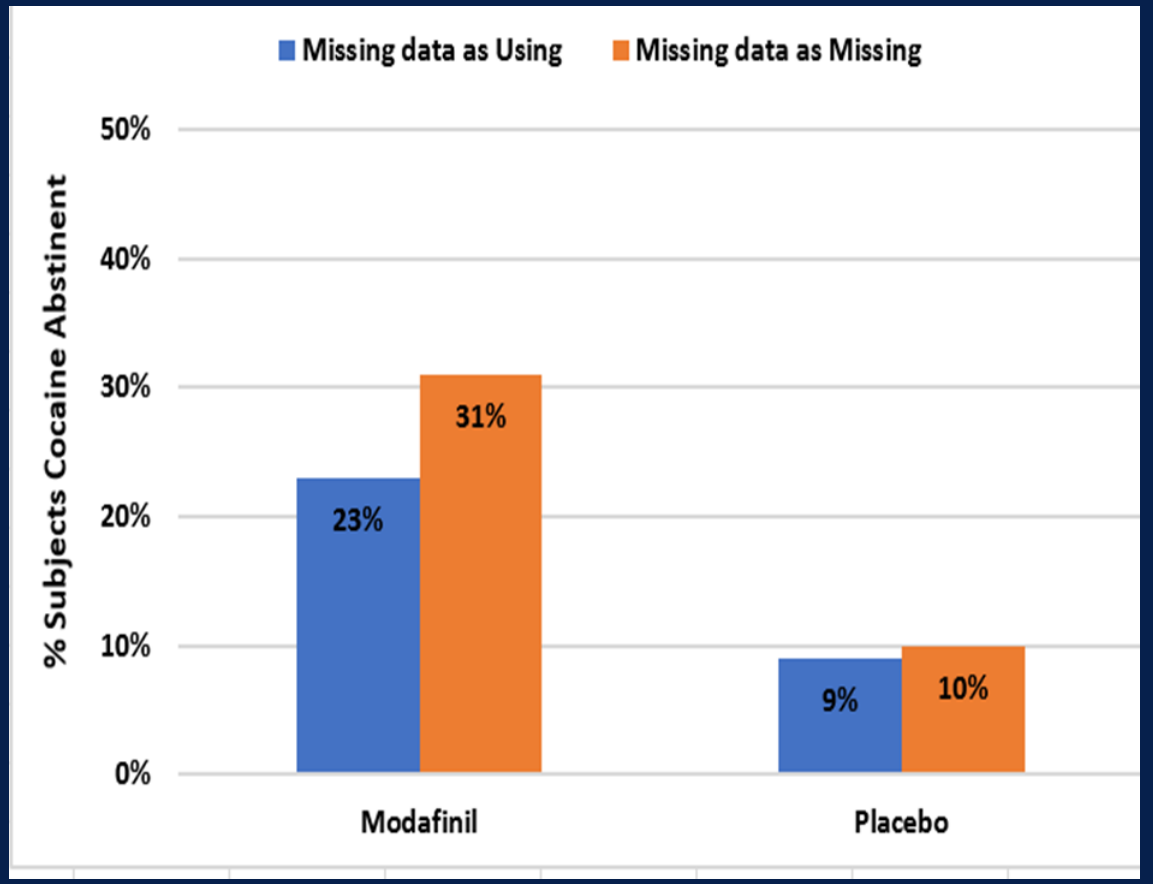


Fig. 3. Percent of subjects abstinent from cocaine during weeks 6–8.

Psychopharmacology (2020) 237:2233–2255
https://doi.org/10.1007/s00213-020-05563-3

REVIEW

Prescription psychostimulants for the treatment of stimulant use disorder: a systematic review and meta-analysis

Vitor S. Tardelli[1] · Adam Bisaga[2] · Felipe B. Arcadepani[1] · Gilberto Gerra[3] · Frances R. Levin[2] · Thiago M. Fidalgo[1]

Received: 8 February 2020 / Accepted: 18 May 2020 / Published online: 29 June 2020

- Meta-analysis of RCTs using agonist treatment for cocaine/amphetamine UD
- Medications: Modafinil, methylphenidate, amphetamine formulations
- n = 2,889 (38 trials) from 8-26 weeks (majority of trials targeting cocaine use disorder
- outcomes: retention and abstinence

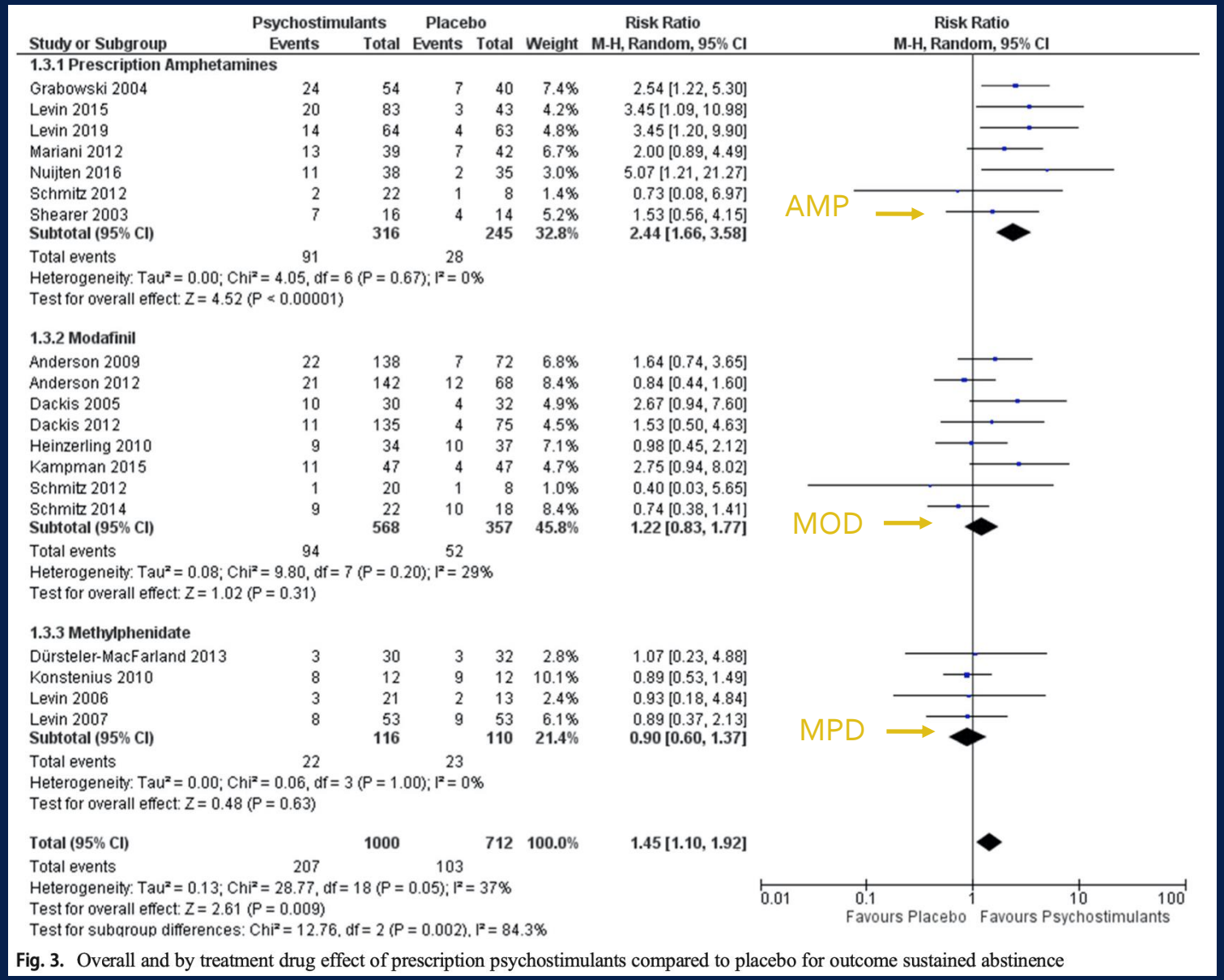


Fig. 3. Overall and by treatment drug effect of prescription psychostimulants compared to placebo for outcome sustained abstinence

- sustained abstinence: AMP

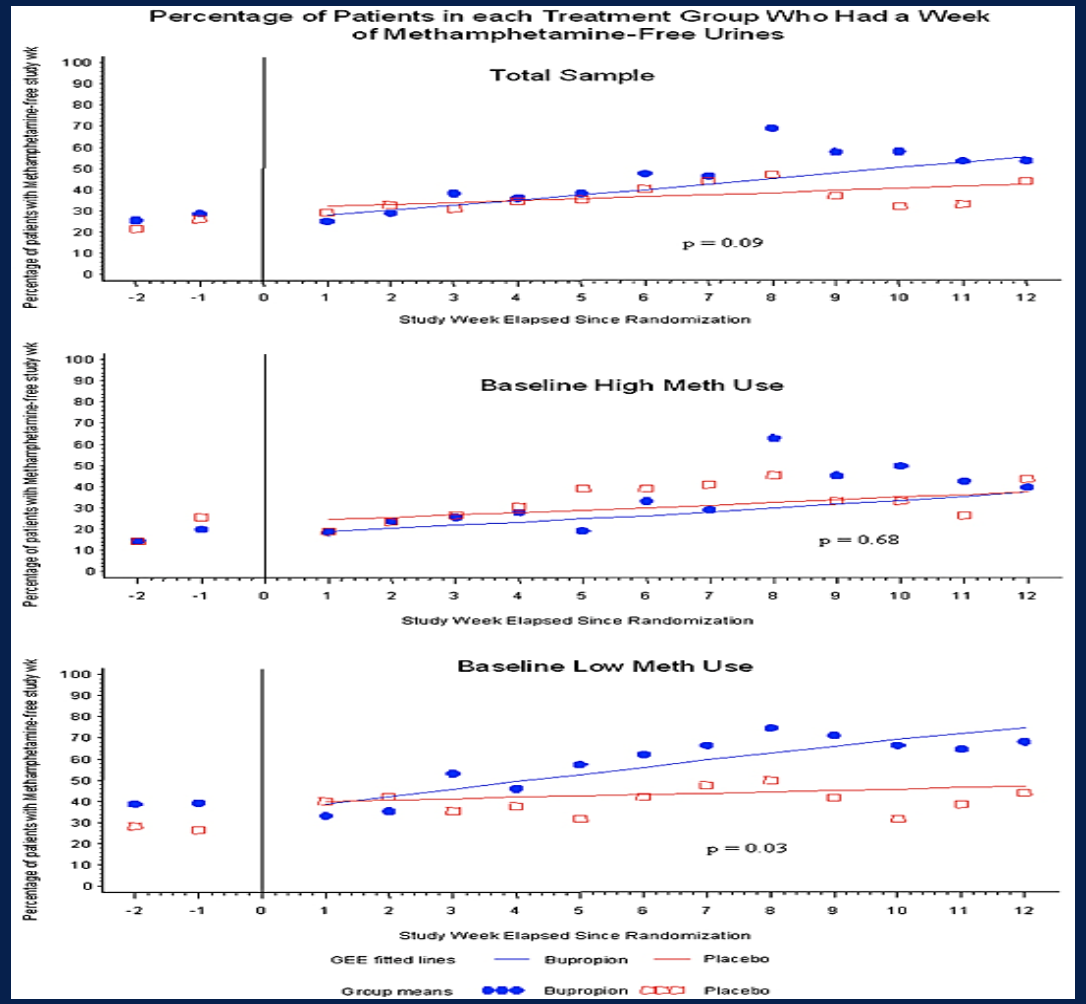
(Tardellli et al. 2020)

BUPROPION STUDIES FOR COCAINE DEPENDENCE

STUDY NAME	DESIGN	SAMPLE SIZE	RETENTION	FINDINGS
Margolin et al. 1995	*Double-blind trials, 12 weeks CBT once a week*	*149 methadone-maintenance patients with CUD*	*84% completed trials*	*Negative trial, percent positive urines high in both groups*
Poling et al. 2006	*Double-blind, trial, 60 months- 4 arms: CM/VC and Bupropion/Placebo*	*106 methadone-maintenance patients with CUD*	*56-63% completers*	*CM plus Bup outperformed all other treatment arms in terms of weeks of continuous cocaine abstinence*
Shoptaw et al. 2008	*Double-blind, placebo-controlled,16 week, thrice weekly CBT*	*70 cocaine abuse/dependence*	*Less than 20% completers*	*Negative trial, Both groups had over 60% negative urines; neg trial*

Indirect Agonist: Bupropion for Methamphetamine Dependence

- DA/NA reuptake inhibitor, ↓ subjective effects and craving in human lab
- 151 MET Dependent treatment seekers enrolled.
- Primary Outcome: Change in Proportion of METH-free weeks
- A subgroup of patients with low-level male METH use had + response.
  - (≤ 18 days/month, bup treatment increased weekly periods of abstinence compared to placebo (GEE, p=0.03)
- McCann et al. (2016) Secondary analysis, end of study abstinence, buprop> Pbo



(Elkashef et al., 2008)

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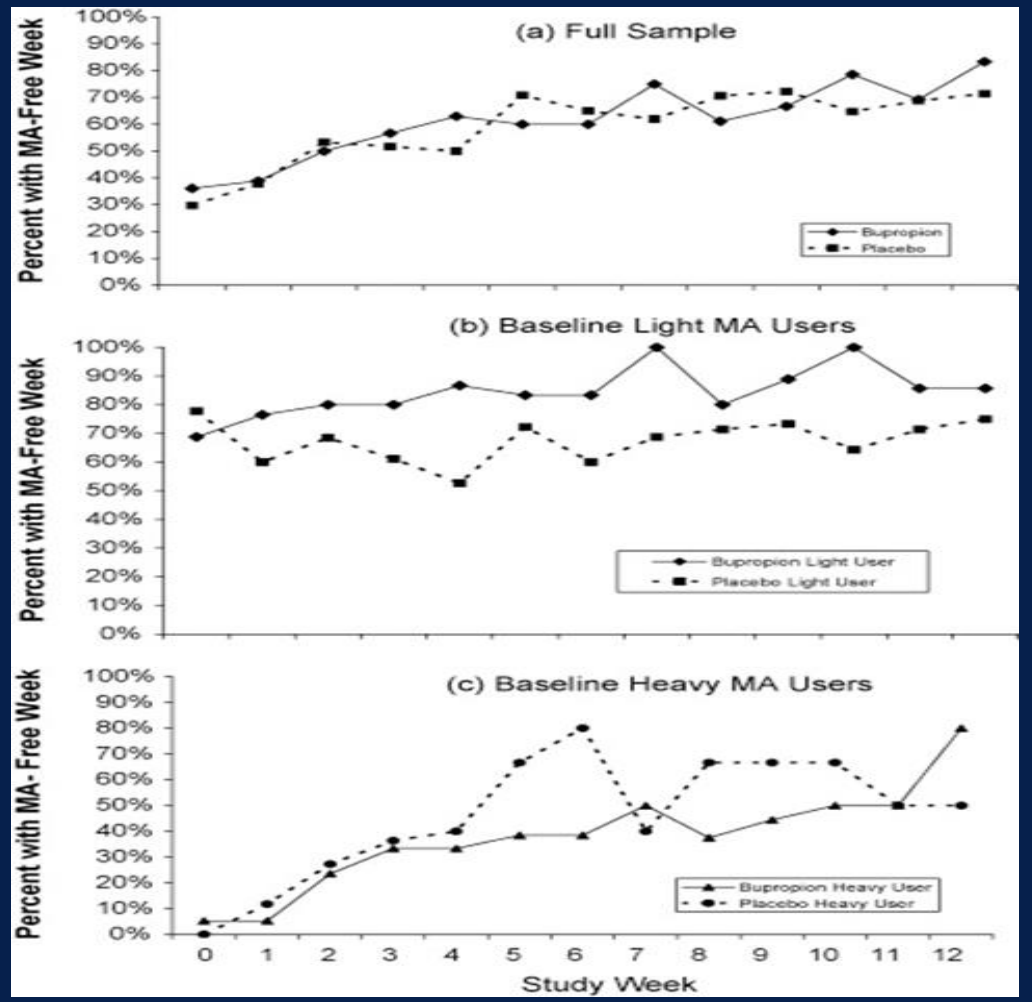
AGONIST: Bupropion for Methamphetamine Dependence

- 73 MET dependent treatment seekers enrolled and randomized to 150 mg 2x/day BUP-SR
- Primary Outcome: Change in Proportion of METH-free weeks
- Received CBT and Contingency Management
- No difference in urine drug screens or retention for the 2 treatment arms
- Post-hoc analysis: Lighter users at baseline (0-2 MA-positive urines out of 6 collected) had a greater reduction of use on BUP compared to placebo (OR=2.81, p< 0.001)



(Shoptaw et al., 2008)

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ANTAGONIST Approach

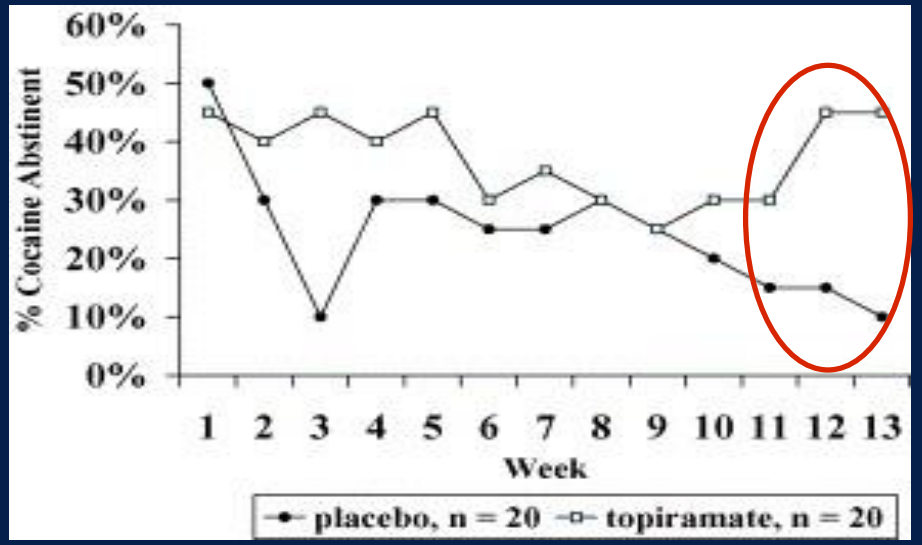
- **Proposed mechanism of action:**
  - Blocks euphoric effects and facilitates the decrease in use through extinction
  - May prevent relapse by blocking initial use (lapse)
- **Antagonist/blocker approach is generally less effective than agonist in the treatment of addictions as it requires high-level of motivation**
- **SAFETY**
  - if blockade is incomplete participants may take more drug to compensate for the lack of effects
  - potentially aversive (DA blockers) → poor adherence

ANTAGONIST Approaches Used for Cocaine and/or Amphetamine Use Disorders

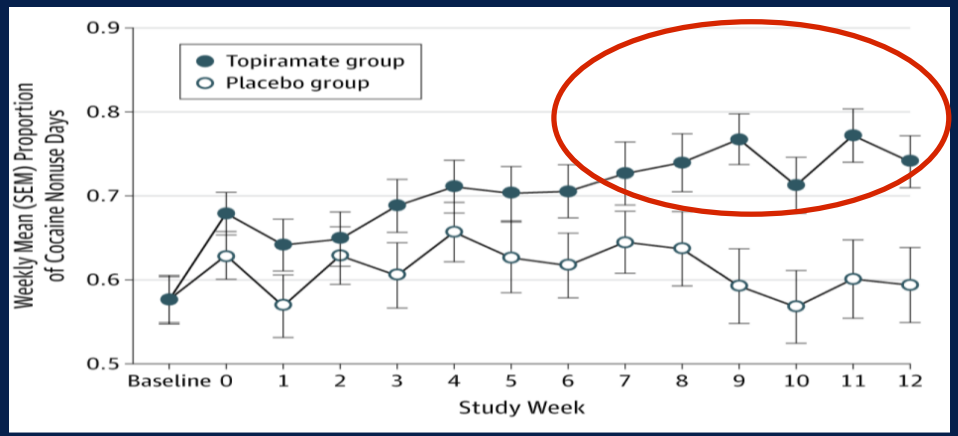
- **Peripheral Blockers**
  - Vaccine
- **Indirect antagonists**
  - (↑GABA) topiramate, tiagabine, gabapentin, vigabatrin, baclofen
  - (↓opiate) naltrexone
  - (↓NA) doxazosin (block α1)
- **Presynaptic DA depletion**
  - reserpine
- **DA receptor blockers/partial D agonists**
  - olanzapine, buspirone (5 HT-1A agonist; D3/D4 antagonists)

Topiramate for Cocaine Use Disorder

- Decreases DA effects of stimulants via ↑GABA potentiation and (↓glutamate) activity
- Slow titration needed to achieve target dose (200-300 mg/d)
- For those who were abstinent at baseline, abstinent in last 2 weeks of trial; Kampmann et al. 2004
- For those using at baseline (n=142); Days abstinent/week during trial; Johnson et al. 2013



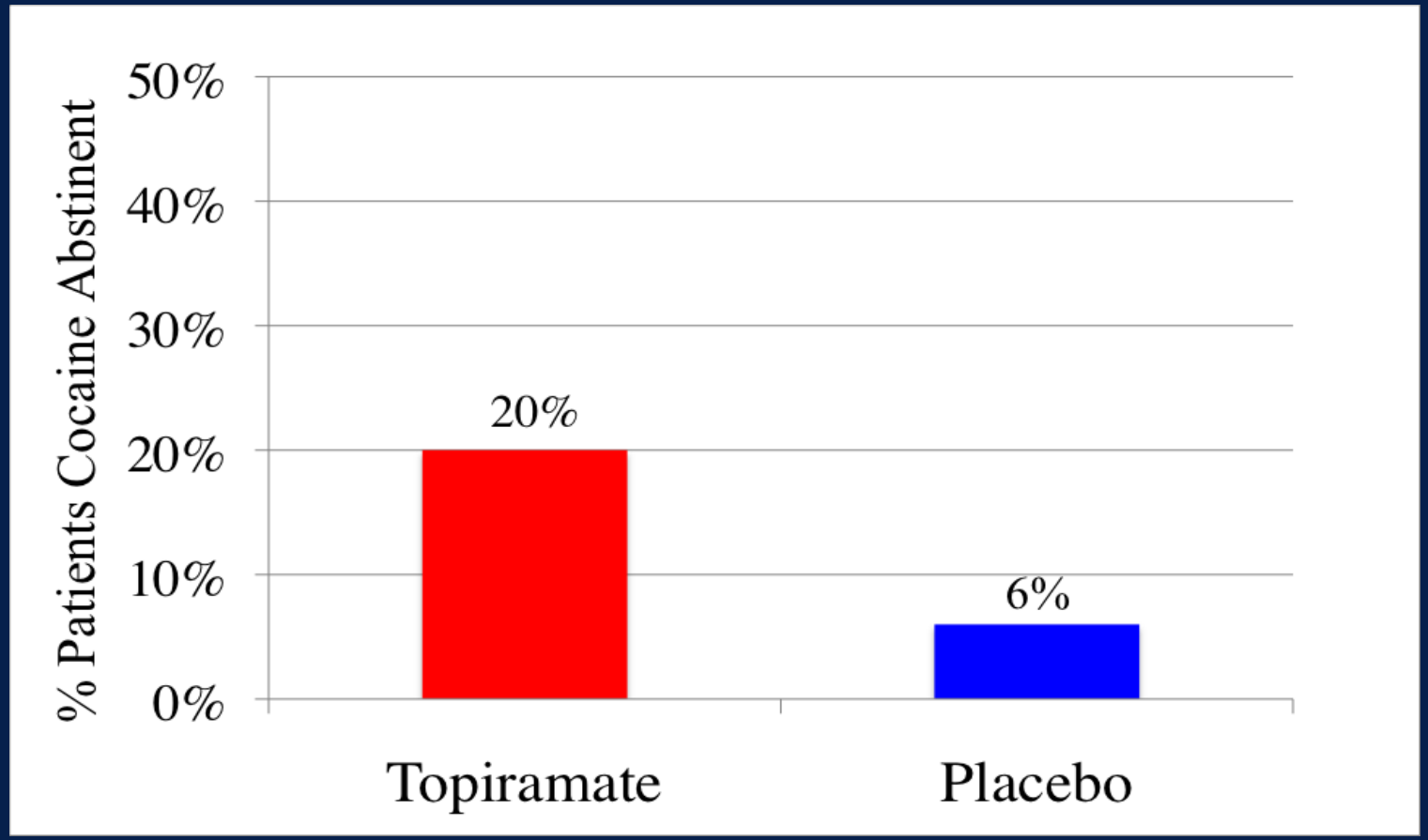
(Kampman et al., 2004)



(Johnson et al., 2013; JAMA Psychiatry)

Topiramate for Cocaine Use Disorder and Comorbid Alcohol Use Disorder: Percent Abstinent weeks 12-14

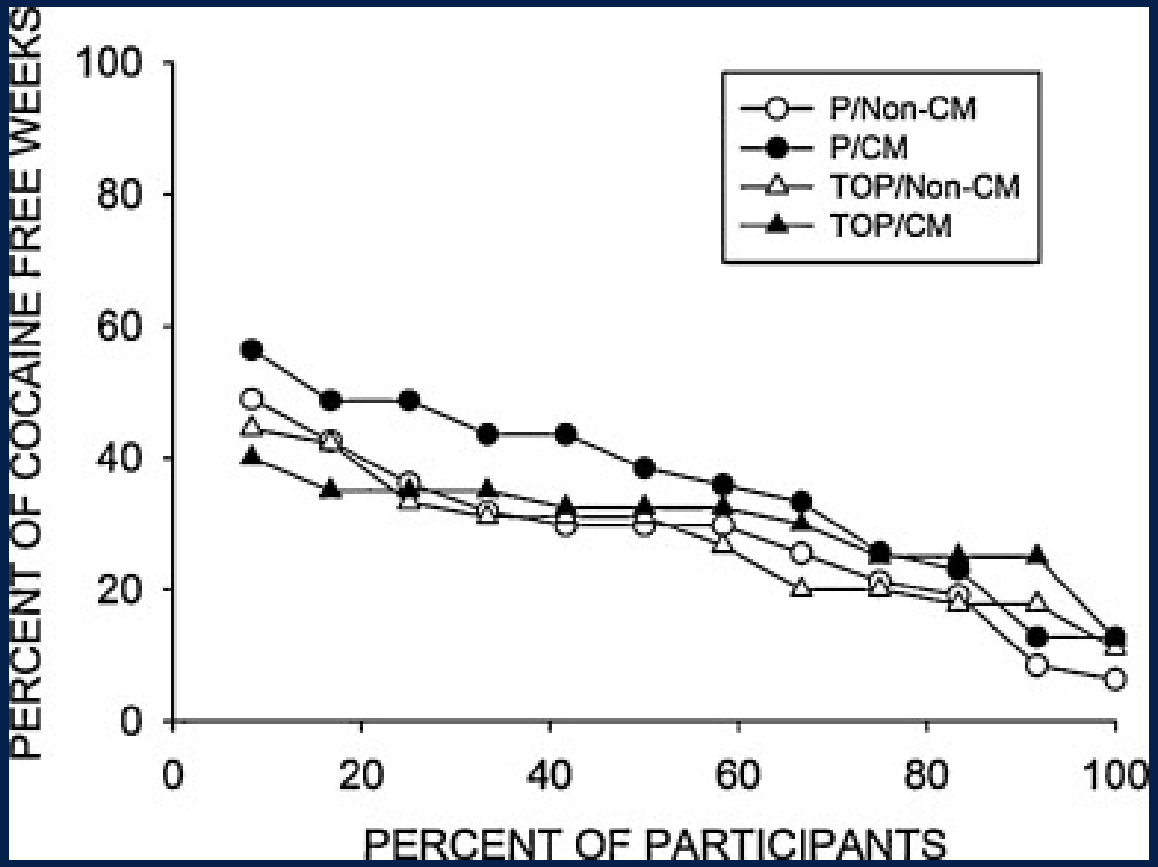
(Kampman et al. 2013; n=170)



Topiramate for Cocaine Use Disorder

- Methadone patients (N=171)
- Randomized to topiramate 300 mg/d or PBO
- No difference in coc-abstinence
- With other studies, put the "nail in the coffin"

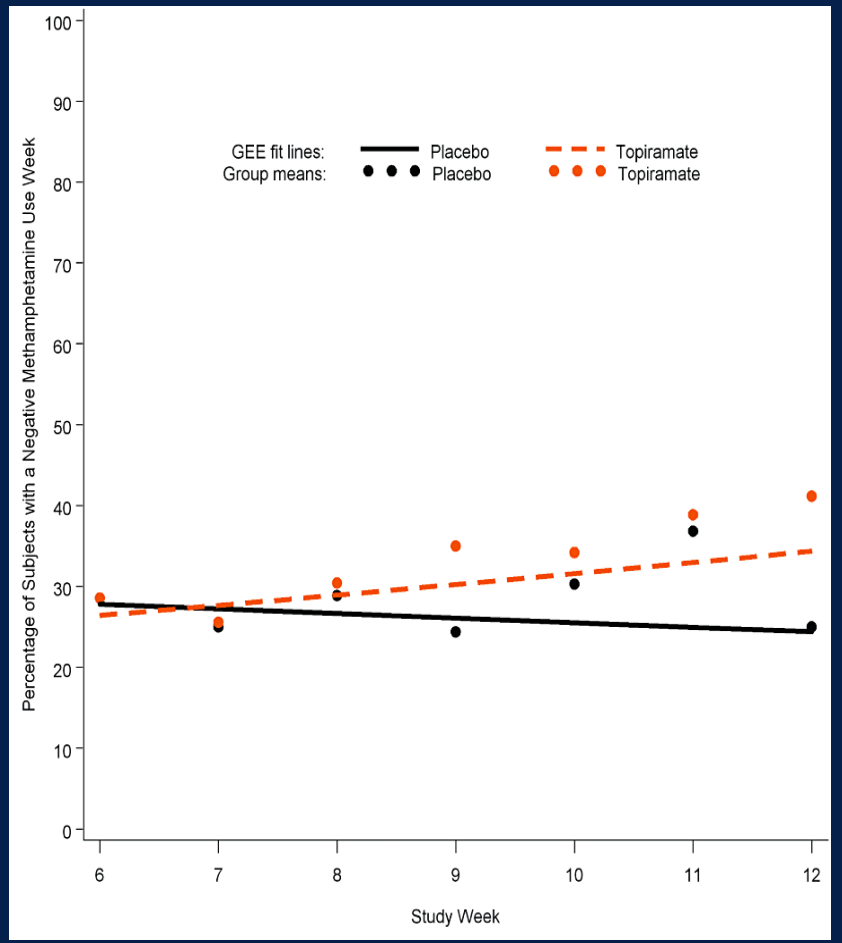
(Umbricht et al. DAD 2014)

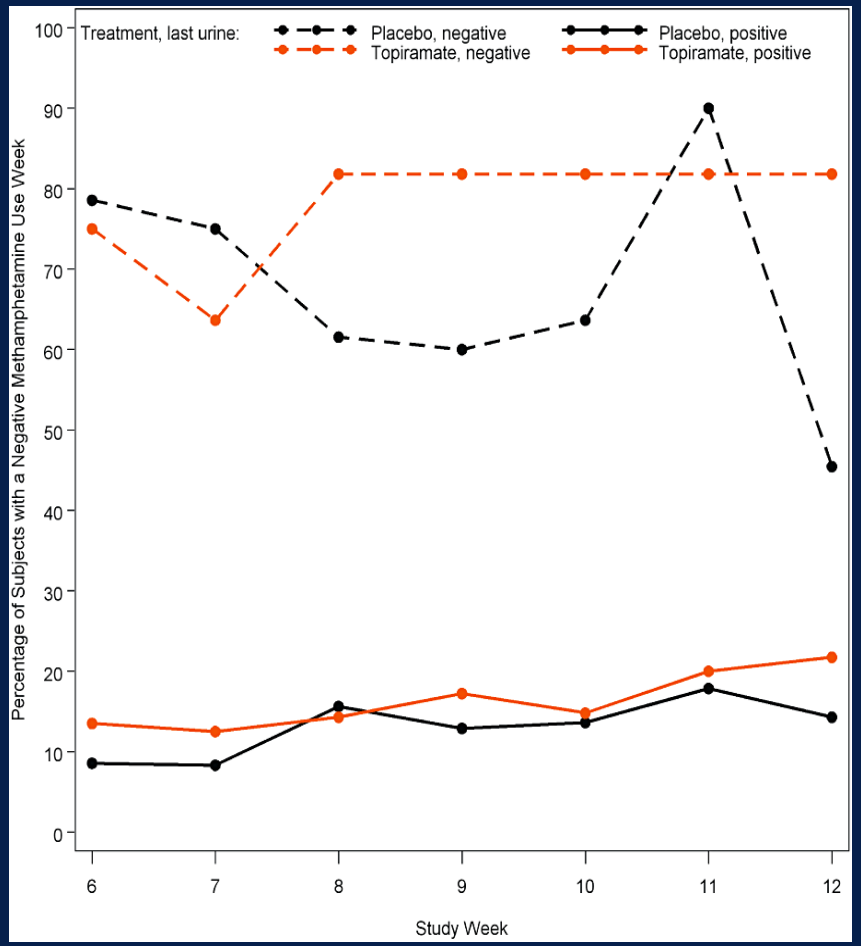


ANTAGONIST: Topiramate for Methamphetamine Use Disorder

(Elkashef et al., 2012)

- 140 randomized to Topiramate 200 mg/d (wks 6-12) Combined with brief compliance therapy
- Primary outcome: Abstinence wks 6-12
- No topiramate effect on METH abstinence for entire sample
- However, treatment effect seen on secondary measures (CGI severity, meth levels)
- Negative weeks of methamphetamine use (p=0.02) more likely found among those who had negative urine at randomization





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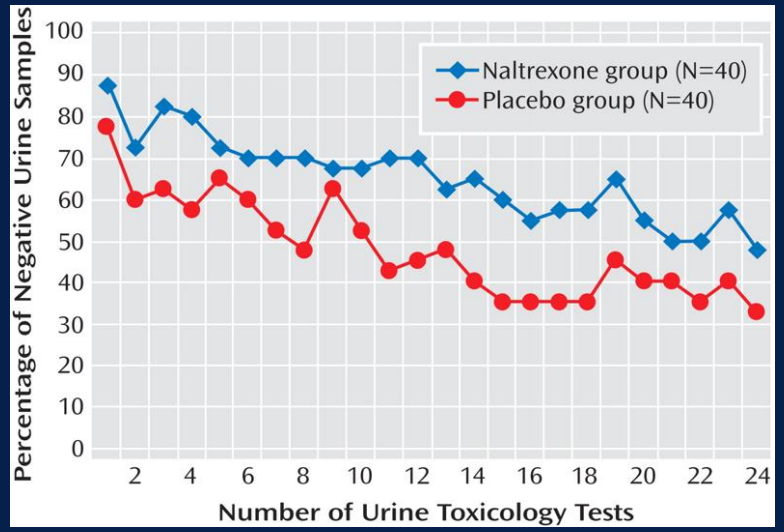
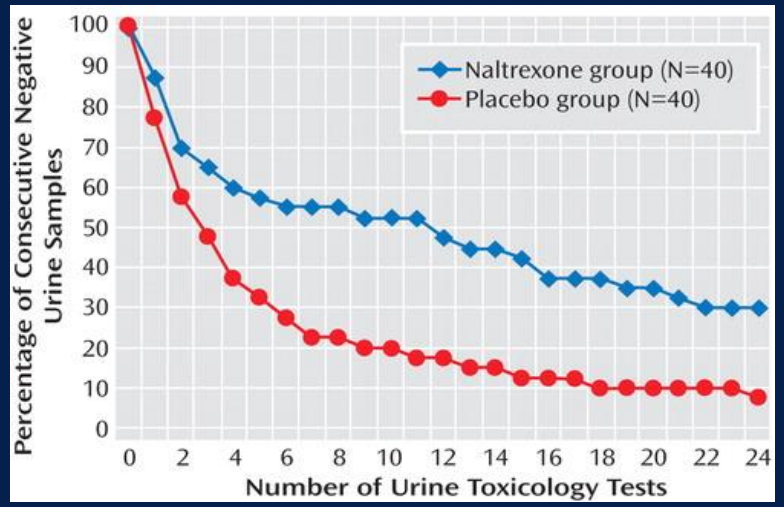
ANTAGONIST: Oral Naltrexone for Amphetamine Use Disorder

(Jayaram-Lindstrom et al.,2008)

- Decreases DA effects of stimulants via ↓opioidergic activity.
- Prior laboratory study found that naltrexone lessened subjective effects of dexamphetamine and craving.
- Double-blind 12 weeks study. Oral naltrexone 50 mg/day and relapse prevention therapy.
- Individuals had to have negative urines for 2 weeks prior to randomization. Rationale: Inclusion of patients who not only expressed "verbal motivation" and commitment to treatment but also displayed supporting behavioral evidence (approx. 1/3 of patients couldn't do this).
- Primary outcome: Abstinence from amphetamine use, totally number of neg amph urine samples during 12 weeks of treatment.
- Naltrexone group had greater number of amph-negative urines ($p < 0.05$) and length of continuous abstinence ($p<0.05$)





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Extended-Release Naltrexone for Methamphetamine Dependence among Men Who Have Sex with Men: A Randomized Placebo-Controlled Trial

(Coffin et al., 2018; Addiction; n=100)

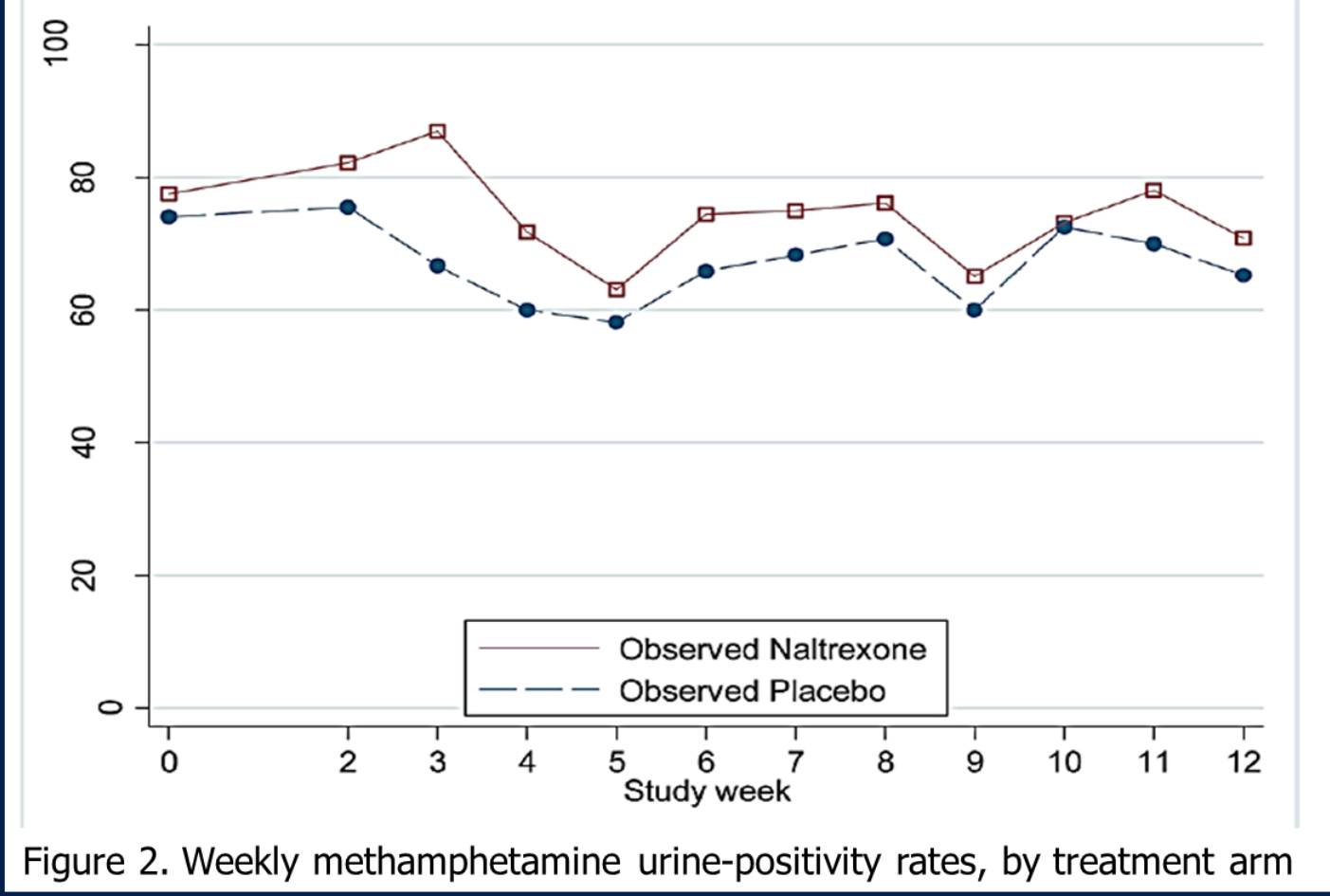
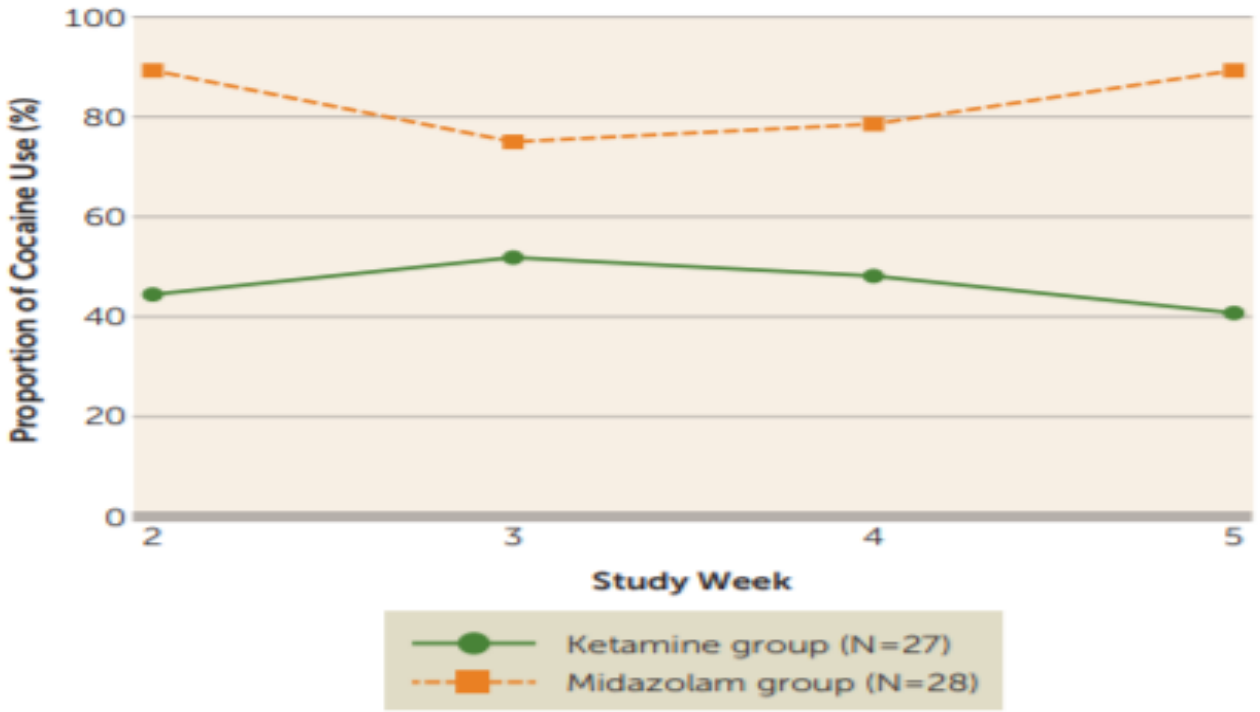


Figure 2. Weekly methamphetamine urine-positivity rates, by treatment arm

Single Ketamine Infusion Combined With Mindfulness-to Treat Cocaine Dependence: A Randomized Clinical Trial

(Dakwar, Nunes, Hart, Foltin, Mathew, Carpenter, Choi, Basaraba, Pavlicova, Levin; Am J Psychiatry 2019)

FIGURE 3. Observed proportion of cocaine use over time, by treatment group, in a randomized controlled trial of ketamine and a mindfulness-based behavioral modification for cocaine dependence



The proportion of participants in the ketamine group with urine-test-confirmed abstinence over the last 2 weeks of the trial was 48.2% (13/27), compared with 10.7% (3/28) in the midazolam group. The odds of end-of-study abstinence in the ketamine group was 6 times that in the midazolam group (odds ratio=5.7, 95% CI=1.3, 25.1; X^2 =5.34, df=1, p=0.02)

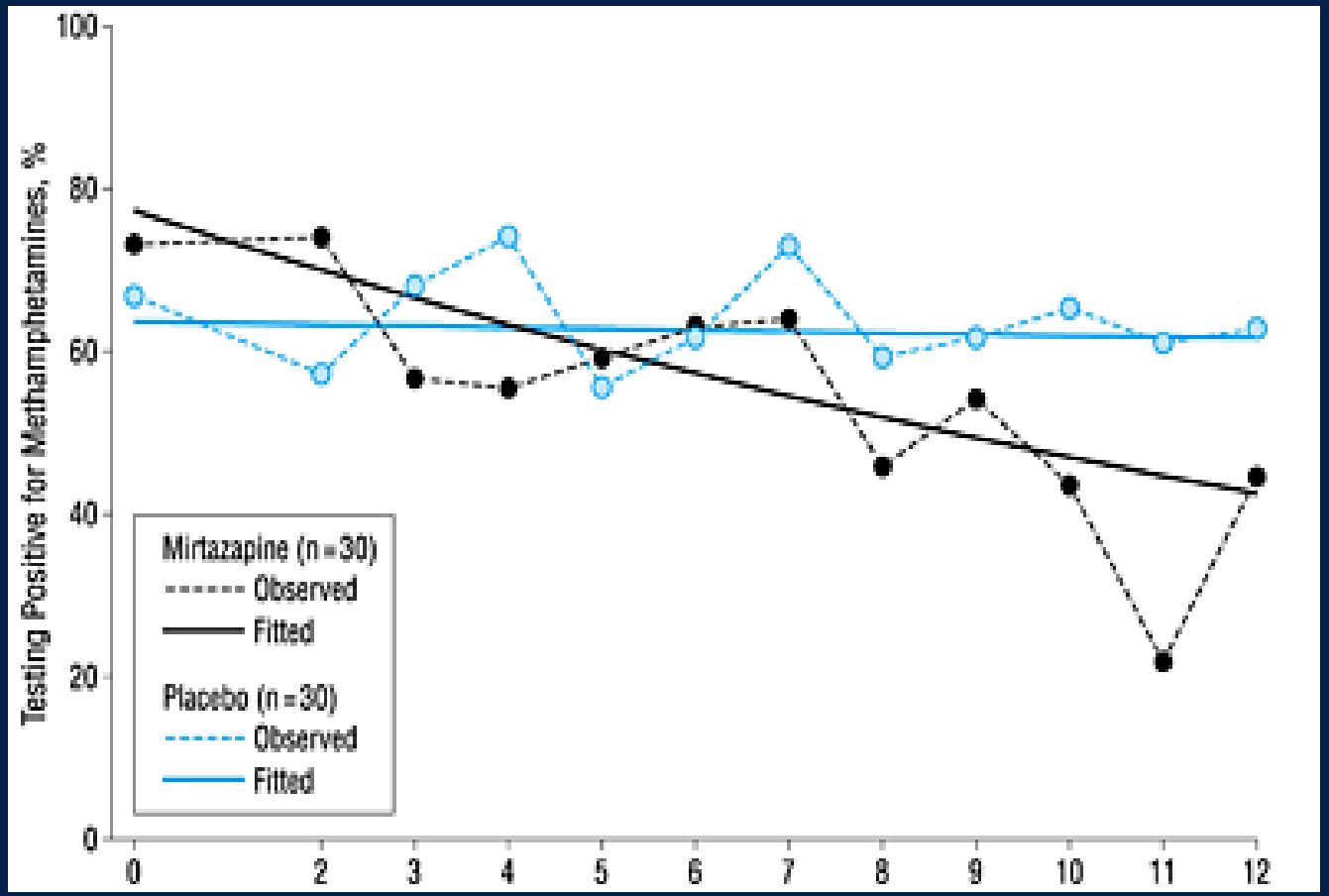
Mitrazapine for Methamphetamine Use Disorder

- Enhances release of DA/NA/5HT (5HT1A agonist and α2 antagonist)
- 60 MSM (93% completed 12- week trial), med compliance approximately 50%
- Mirtazapine group had fewer methamphetamine-positive urine test results compared with participants assigned to the placebo group (relative risk, 0.57; 95% CI, 0.35-0.93, P = .02).

- Urine positivity
  - Placebo: 67% (20 of 30 participants) to 63% (17 of 27)
  - Mitrazapine: 73% (22 of 30) to 44% (12 of 27)

- The number needed to treat to achieve a negative weekly urine test result was 3.1.

(Colfax et al., 2011)



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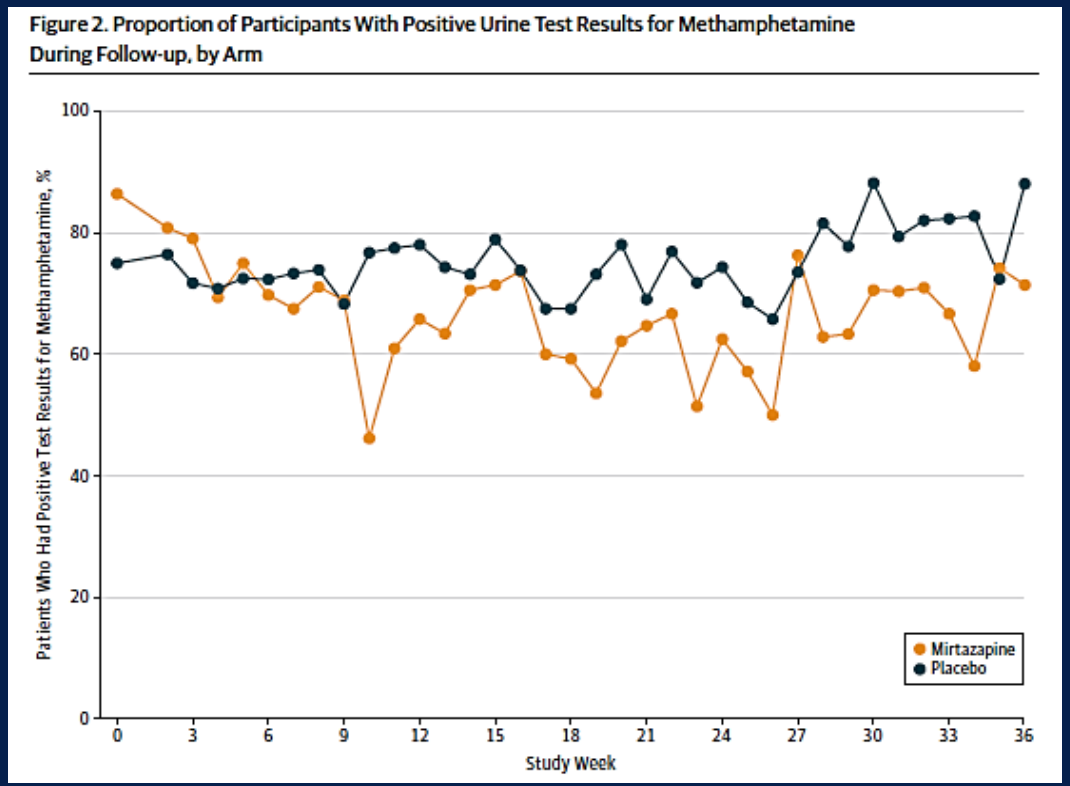
Effects of Mirtazapine for Methamphetamine Use Disorder Among Cisgender Men and Transgender Women Who Have Sex With Men A Placebo-Controlled Randomized Clinical Trial

(Coffin et al. 2019; JAMA)

- Double-blind, placebo-controlled trial, 120 were enrolled. Mitrazapine 30 mg/day or placebo- once daily for 24 weeks
  - The rate of methamphetamine-positive urine test results significantly declined among participants randomized to mirtazapine vs placebo
    - At 12 weeks: (risk ratio[RR], 0.67 [95% CI, 0.51-0.87]).
    - At 24 weeks (RR, 0.75 [95% CI, 0.56-1.00])
    - At 36 weeks (RR, 0.73 [95% CI,0.57-0.96]) vs placebo.
  - Mean (SD) medication adherence by WisePill dispenser over 2 to 12 weeks:
    - 38.5%(27.0%) in the mirtazapine group
    - 39.5% (26.2%) in the placebo group (P = .77)
  - Mean (SD) medication adherence by WisePill dispenser over 13 to 24 weeks:
    - 28.1% (23.4%) in the mitrazapine
    - 38.5% (27.0%) in the placebo group (P = .59)

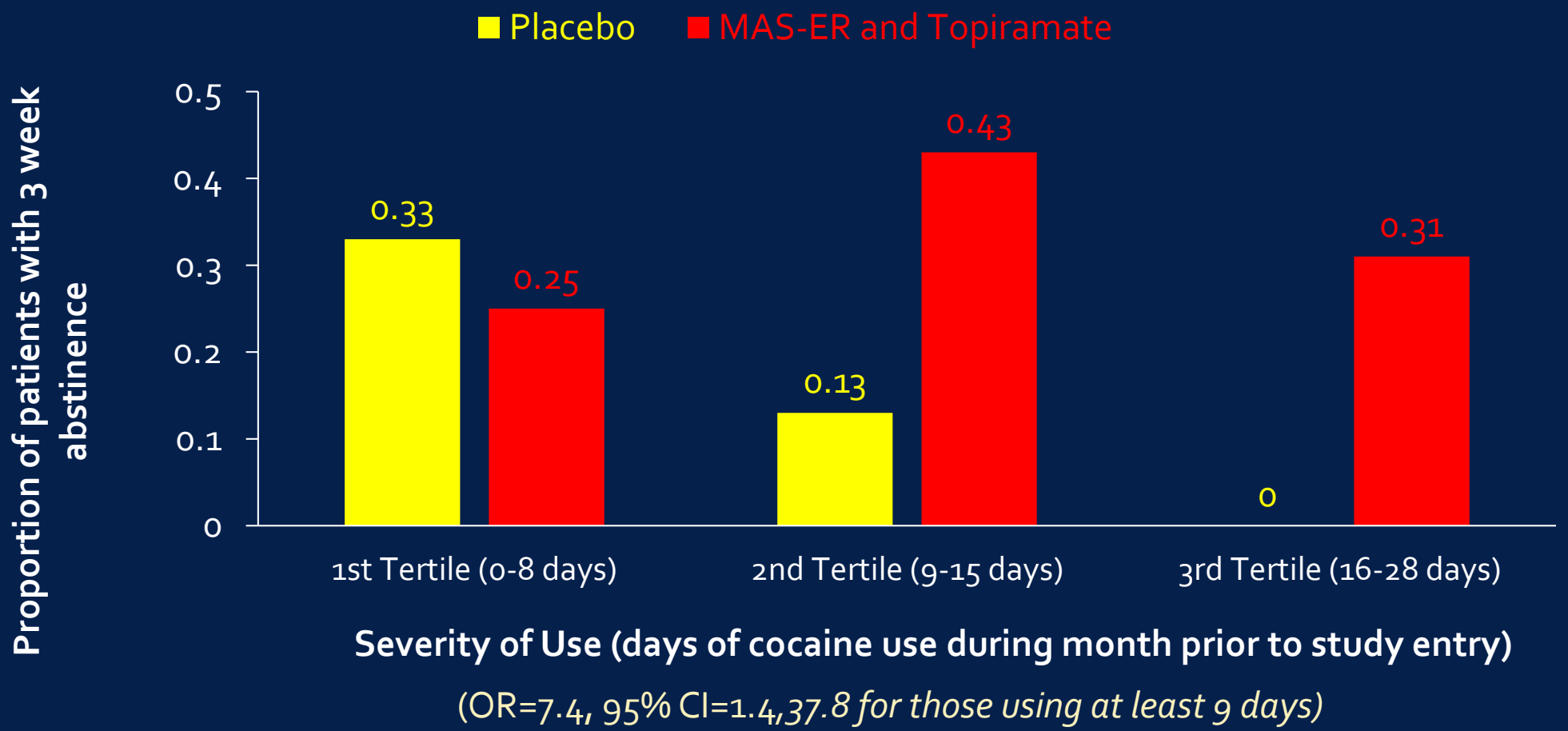


Combination Pharmacotherapies for Stimulant Use Disorder

(Stoops & Rush, 2014; Expert Rev Clin Pharmacol)

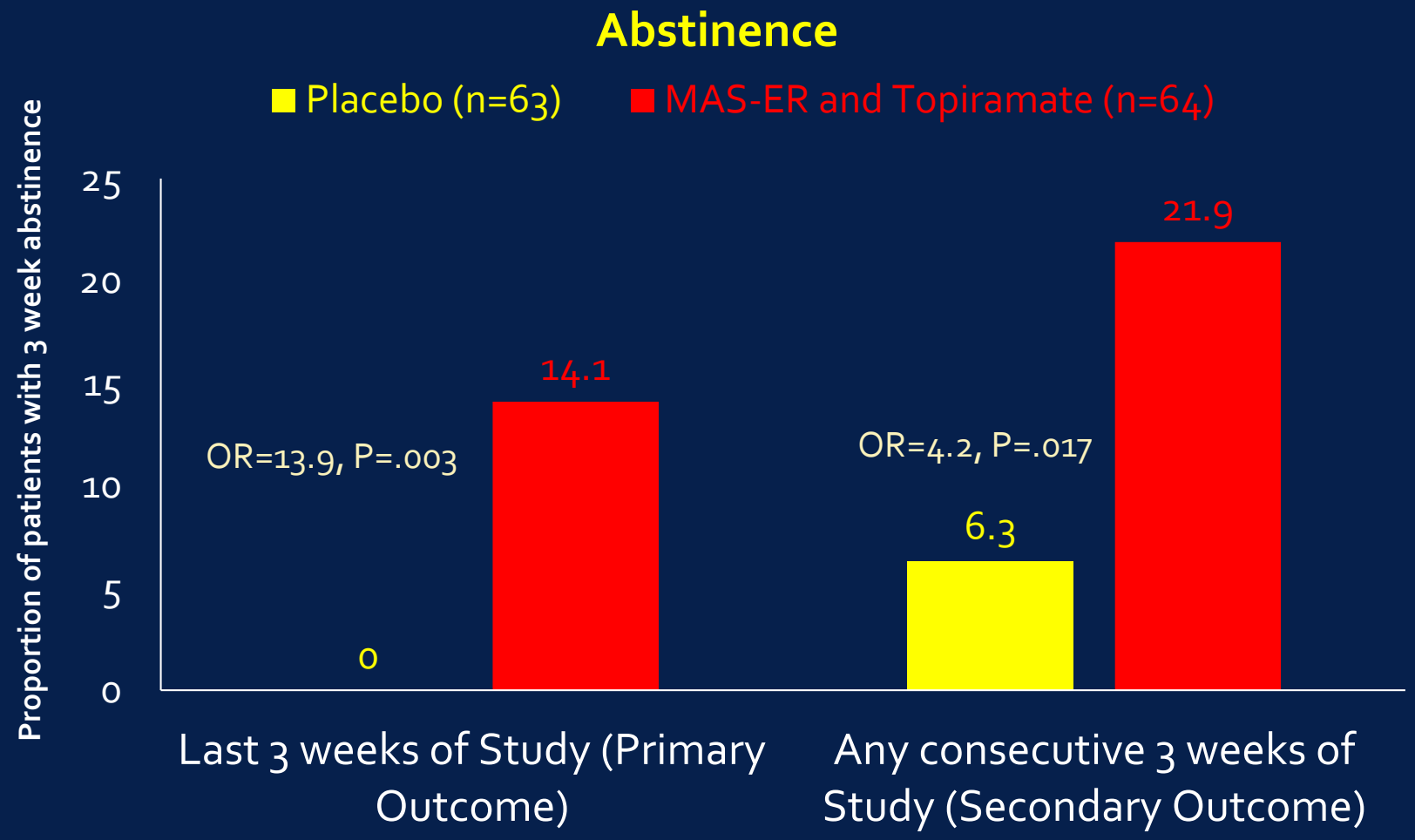
- Key Issues:
  - Effective pharmacotherapies for stimulant use disorders remain to be identified.
  - Use of innovative strategies, like combination treatment, is necessary to develop successful medications to manage cocaine or amphetamine use disorder.
  - Combination treatment is a viable strategy for a number of reasons:
    - Use of lower doses of individual constituents to minimize side effects
    - Possibility of achieving additive or synergistic effects with combinations
    - Targeting the diverse neurotransmitter systems impacted by stimulant drugs.

Cocaine Outcome-Single Site Trial



Mariani, J. J., Pavlicova, M., Bisaga, A., Nunes, E. V., Brooks, D. J., & Levin, F. R. (2012).
Extended Release Mixed Amphetamine Salts and Topiramate for Cocaine Dependence: A Randomized Controlled Trial. Biol Psychiatry

Extended Release Mixed Amphetamine Salts and Topiramate for CUD: A Replication Study with High Frequency Users (Levin et al. 2020, DAD)



Note: Results adjusted for baseline cocaine use and site. Both not significantly associated with primary outcome.

Bupropion and Naltrexone in Methamphetamine Use Disorder

(Trivedi et al., 2021; N Engl J Med)

- Multisite, double-blind, two-stage, placebo-controlled trial with the use of a sequential parallel comparison design to evaluate the efficacy and safety of:
  - Extended-release injectable naltrexone (380 mg every 3 weeks) plus oral extended-release bupropion (450 mg per day)
- Adults with moderate or severe methamphetamine use disorder (frequent users at least 18 days/month).
- In the first stage of the trial, participants were randomly assigned to receive naltrexone–bupropion or matching injectable and oral placebo for 6 weeks. (0.26:0.74 ratio)

Bupropion and Naltrexone in Methamphetamine Use Disorder

(Trivedi et al., 2021; N Engl J Med)

- Those in the placebo group- no response in stage 1 underwent rerandomization in stage 2 and were assigned in a 1:1 ratio to receive naltrexone–bupropion or placebo for an additional 6 weeks.
- Urine samples were obtained from participants twice weekly.
- The primary outcome was a response, defined as at least three methamphetamine-negative urine samples out of four samples obtained at the end of stage 1 or stage 2, and the weighted average of the responses in the two stages is reported.

- Smartphone-based application to track tablet ingestion but not observed.

Bupropion and Naltrexone in Methamphetamine Use Disorder

(Trivedi et al., 2021; N Engl J Med n=403)

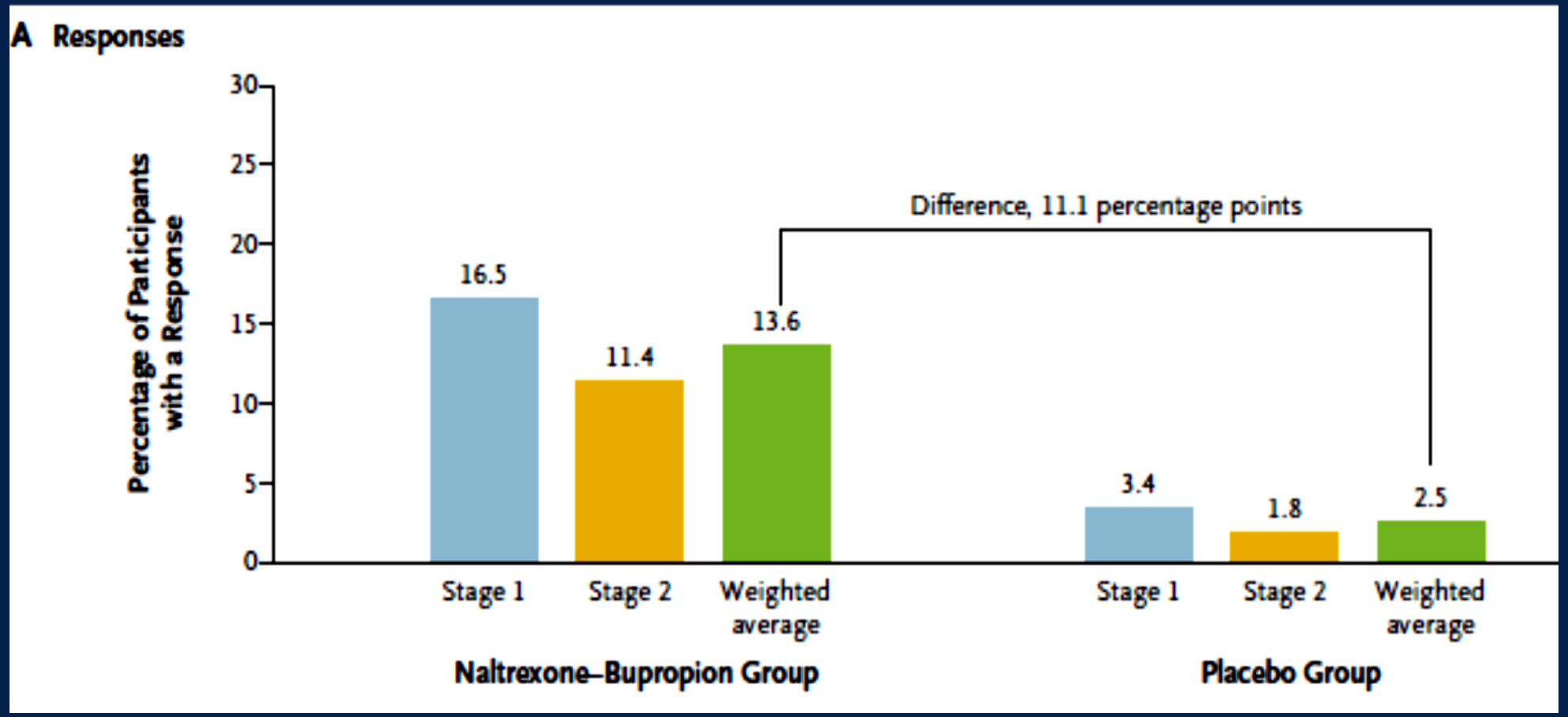
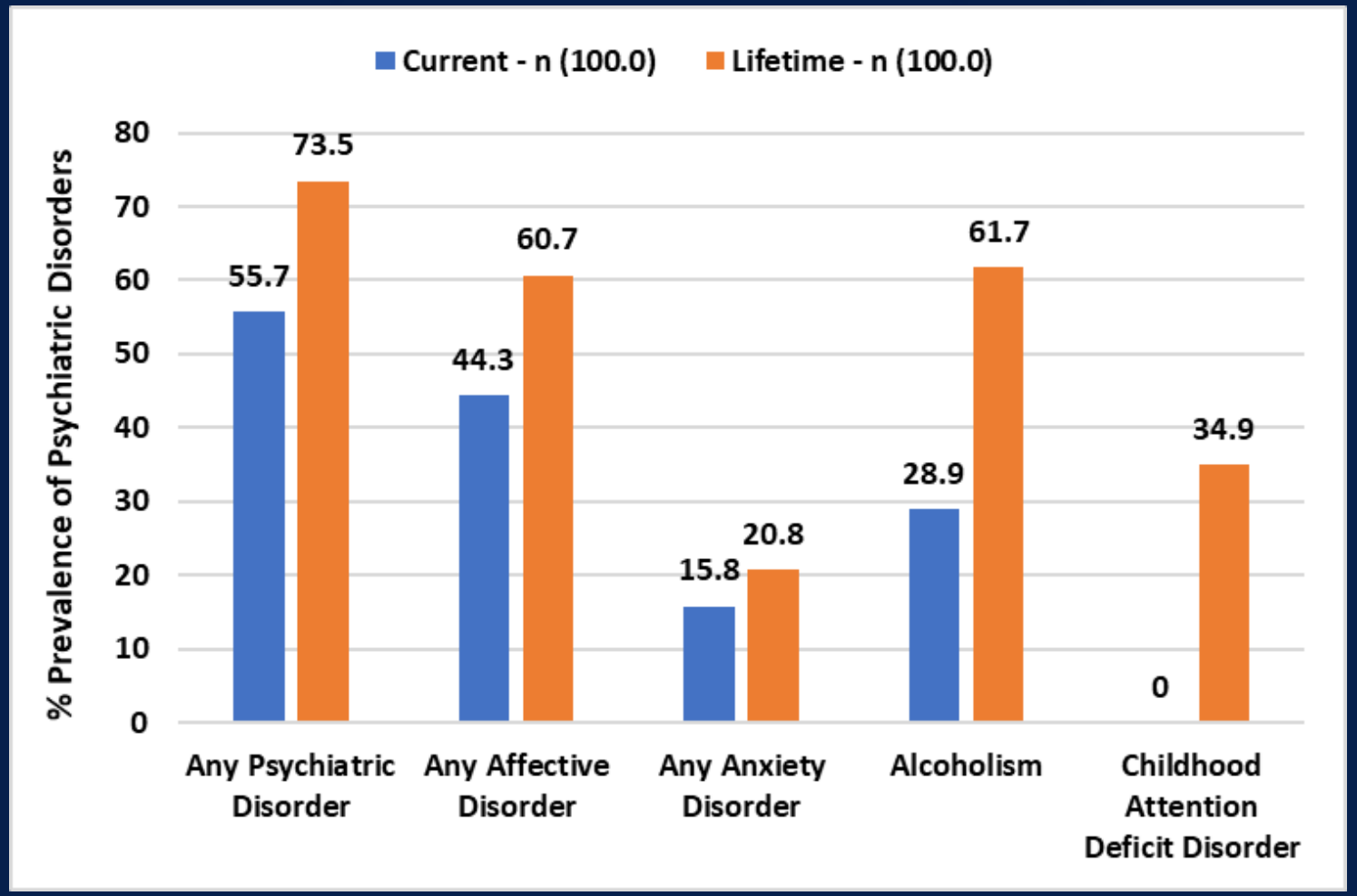


Figure 2. The primary outcome was a response, defined as at least three methamphetamine-negative urine samples out of four samples obtained at the end of stage 1 or stage 2

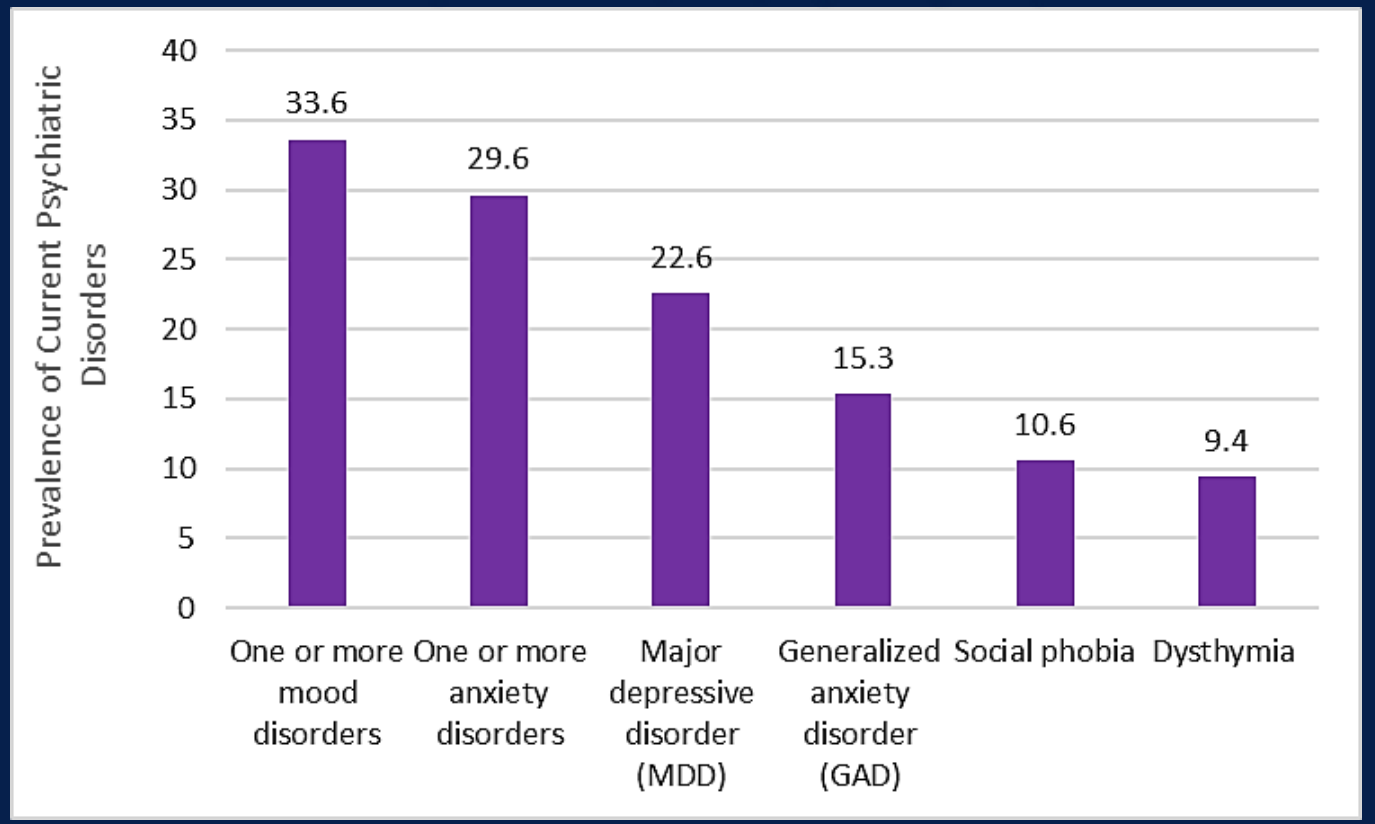
Psychiatric Diagnoses of Treatment-Seeking Cocaine Abusers

(Rounsaville et al. 1991, Arch Gen Psychiatry)



Demographic and clinical characteristics of current comorbid psychiatric disorders in a randomized clinical trial for adults with stimulant use disorders

(Warden et al., 2016; Psychiatry Res.)



- Residential settings (N=302)
- Participants enrolled in Stimulant Reduction Intervention using Dosed Exercise (STRIDE),

13 Double-Blind, Placebo Controlled-Trials for Those with Affective Disorders and Stimulant Use Disorders

Study	Sample Size and Group	Drug	RX Use/Results
Nunes et al. 1995	N =113; 60% Depressed	Cocaine	Imipramine: Depression +/ Cocaine - Cocaine + intranasal users
Schmitz et al. 2001	N=68, Major Depression	Cocaine	Fluoxetine: Depression -/ Cocaine - *RDR
Brady et al. 2002	N= 67 Affective illness (subsample)	Cocaine	Carbamazepine: Depres +/ Cocaine - (trend)
Ciraulo et al., 2005	N = 69 Major Depression	Cocaine	Nefazadone: Depression -/ Cocaine - *RDR
McDowell et al. 2005	N =111; Major Depression or Dysthymia	Cocaine	Desipramine: Depress +/ Cocaine -
Brown et al. 2007	N= 44, Bipolar, depression or mixed	Cocaine	Citocoline: Affective sxs -/ Cocaine + at exit, (No use 1-12 wks prior to entry, Relapse approach)
Brown et al. 2010	N=12, Bipolar I and II	Cocaine	Quetiapine: Depression – (but large effect size)/ Cocaine -
Brown et al. 2012	N= 120; Bipolar, depressed or mixed	Cocaine	Lamotrigine: Depression -/ Cocaine – (but less dollars use +) *VHDO
Brown et al. 2012	N=48; Bipolar depression or Major Depression	Methamph	Citicoline: Depression +/Methamph -; Better retention
Oliveto et al. 2012	N=89; inpatient to n=59 outpt; Depressed sxs	Cocaine	Sertraline: Depression -/Cocaine Time to lapse/relapse +; End abstinence – (reports if had slightly larger sample would be +) *RDR
Afshar et al 2012	N= 24; Major Depression; Dysthymia, SI-Depression	Cocaine	Mirtazapine: Depression -/ Cocaine - *RDR
Raby et al. 2014	N= 130; Major Depression of Dysthymia	Cocaine	Venlafaxine: Depression -/Cocaine - *HPRD
Brown et al. 2015	N=122 Bipolar depression or mixed	Cocaine	Citocoline: Affective illness -/ Cocaine + early on (no difference as study progresses)

Sertraline Delays Relapse in Recently Abstinent Cocaine- Dependent Patients with Depressive Symptoms

(Oliveto et al, 2012; Addiction)

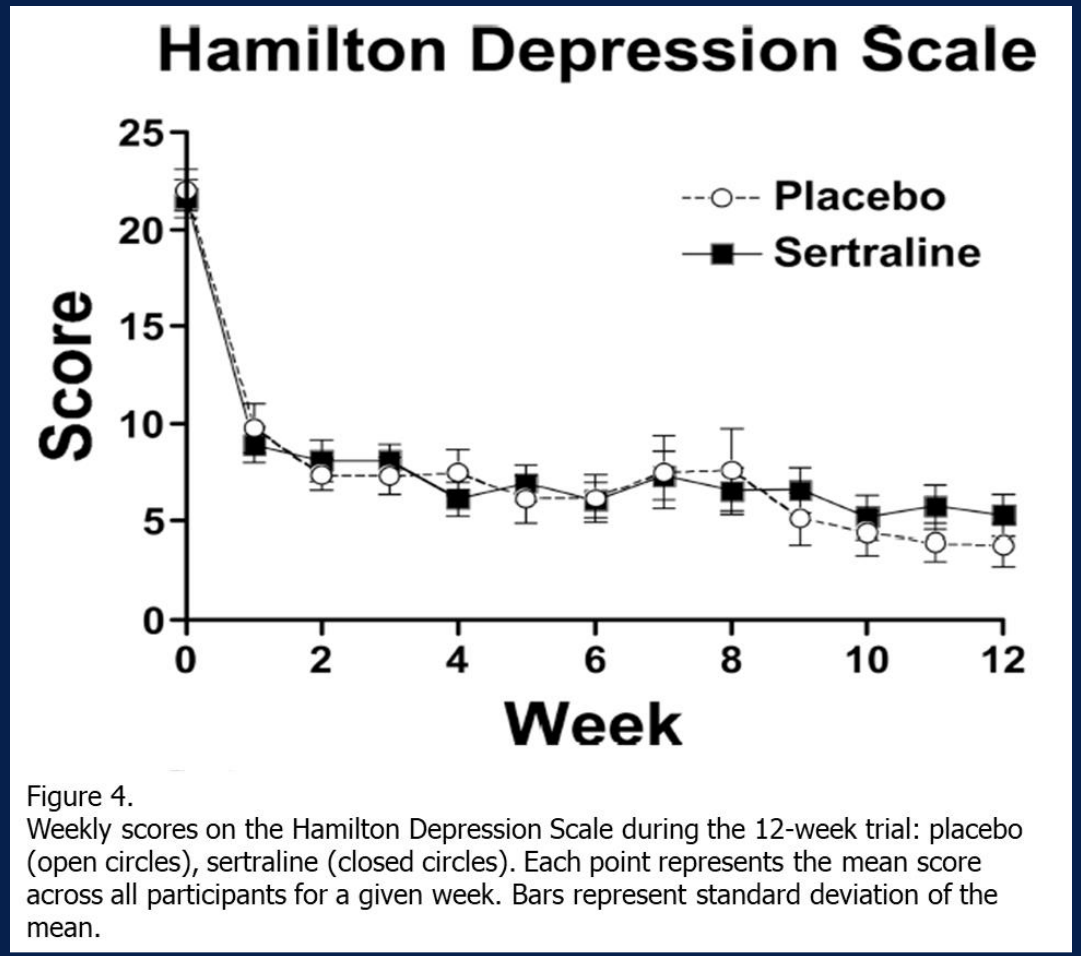


Figure 4.
Weekly scores on the Hamilton Depression Scale during the 12-week trial: placebo (open circles), sertraline (closed circles). Each point represents the mean score across all participants for a given week. Bars represent standard deviation of the mean.

Sertraline Delays Relapse in Recently Abstinent Cocaine- Dependent Patients with Depressive Symptoms

(Oliveto et al. 2012)

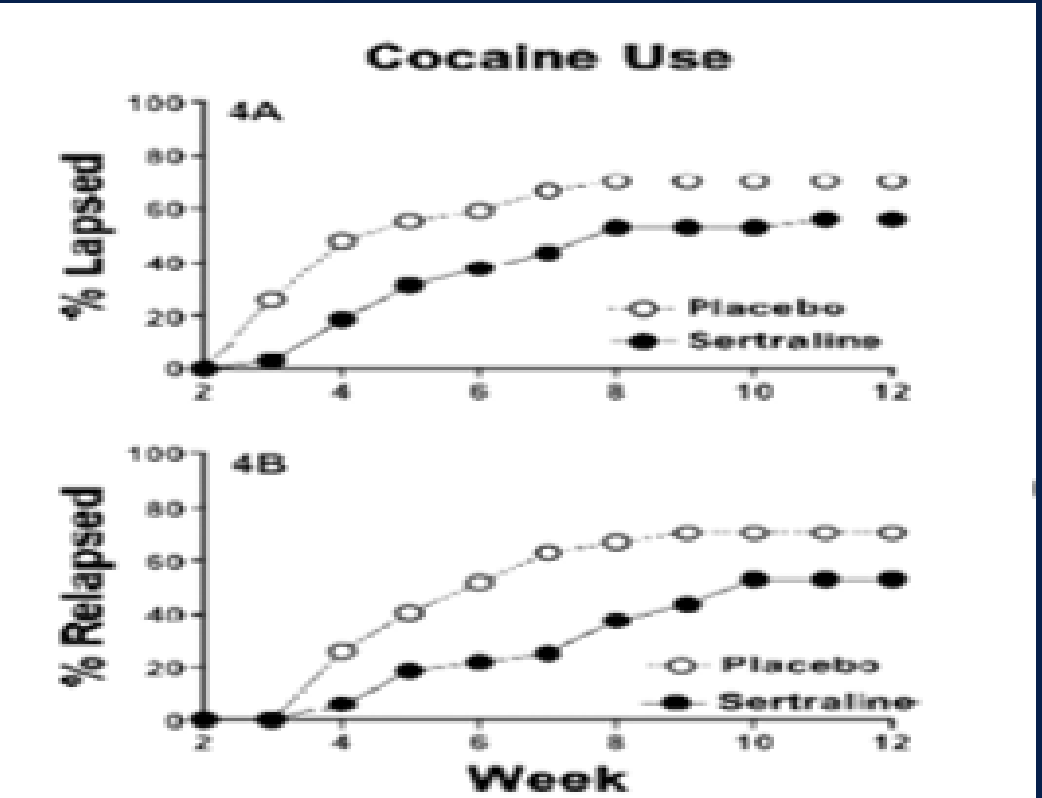


Figure 3.
The percentage of participants who lapsed (i.e., first urine sample positive for cocaine; top panel) or relapsed (i.e., first two consecutive urine samples positive for cocaine; bottom panel) each week across the outpatient portion of the 12-week trial: placebo (open circles), sertraline (closed circles).

Psychiatric comorbidity in treatment-seeking substance use disorder patients with and without attention deficit hyperactivity disorder: results of the IASP study

(van Emmerik-van Oortmerssen et al. 2014; Addiction)

Variable	ADHD⁻ N=1037	ADHD⁺ N=168	OR[abcd]	95% CI OR	o^2_u(SE)[e]
Primary substance of abuse (1033/165)[f]					
Opioids (%)	10.4	11.5	0.8	0.5-1.4	4.79 (1.60)
Stimulants (%)	12.6	30.3	3.1***	2.0-5.1	0.98 (0.47)
Cannabis (%)	9.7	17.0	1.7	1.0-2.9	2.02 (0.97)
Other drug (%)	8.6	6.1	0.7	0.3-1.3	0.28 (0.19)
Alcohol (%)	58.8	35.2	0.4***	0.3-0.6	2.97 (1.04)

[a] For all variables except 'age' multi-level logistic regression analysis with random intercept, independent variable ADHD (yes/no), comorbid condition as dependent variable and site as level two, σu2= level two variance of the intercept;
[b] for 'age' multi-level linear regression analysis with random intercept, independent variable ADHD (yes/no), age as dependent variable and site as level two, σu2= level two variance of the intercept, mean difference (SE) instead of odds ratio (OR);
[C] reference category: no ADHD

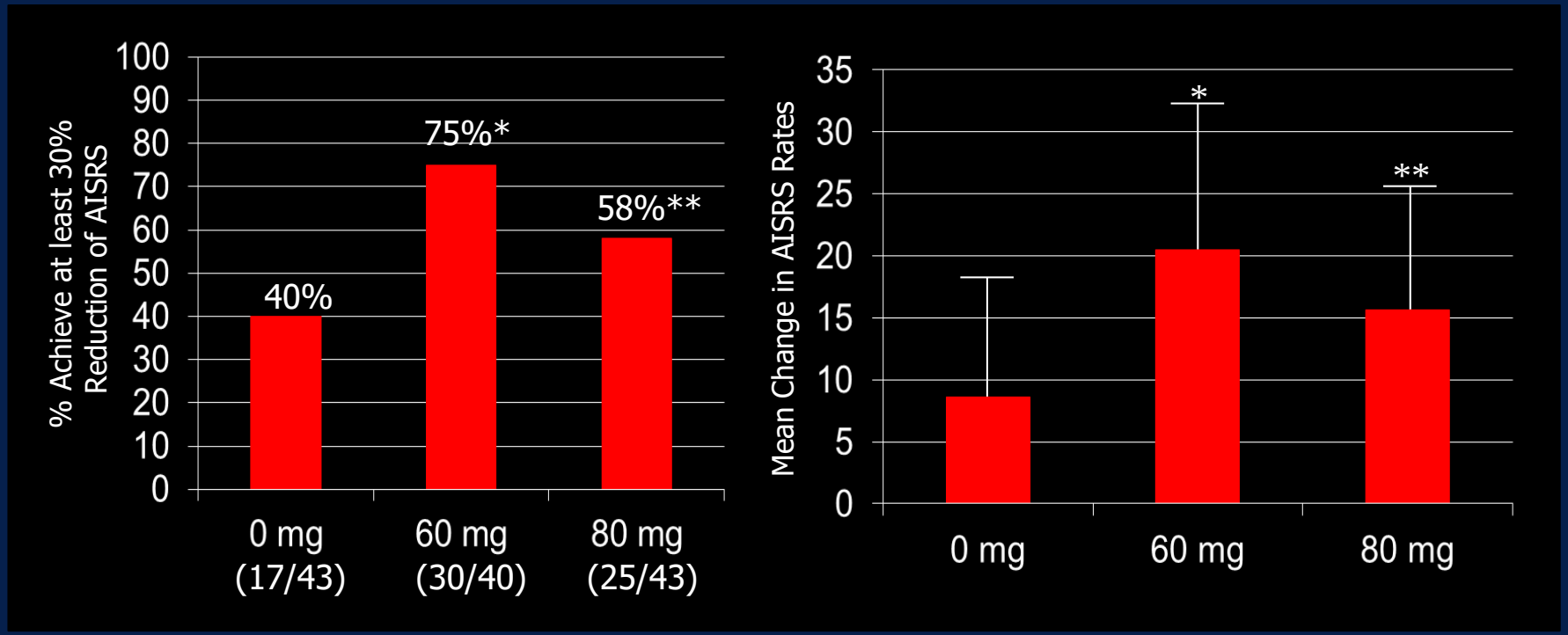
Extended-Release MAS-XR vs. Placebo for ADHD and Cocaine Use Disorder

(Levin et al., *JAMA Psychiatry*, 2015)

- Randomized, placebo-controlled 13-week trial conducted at 2 sites: Columbia University/NYSPI and University of Minnesota
- Three times a week visits
- MAS-XR 80 mg/day, and MAS-XR 60 mg/day vs placebo or maximum tolerated dose
- Weekly individual manualized psychotherapy using cognitive-behavioral therapy/relapse prevention treatment targeting cocaine use and ADHD
- Voucher incentives based on attendance and $10/week for return of medication bottles

Extended-Release MAS-XR vs. Placebo for ADHD and Cocaine Use Disorder Primary ADHD Outcomes

(Levin et al., *JAMA Psychiatry*, 2015)

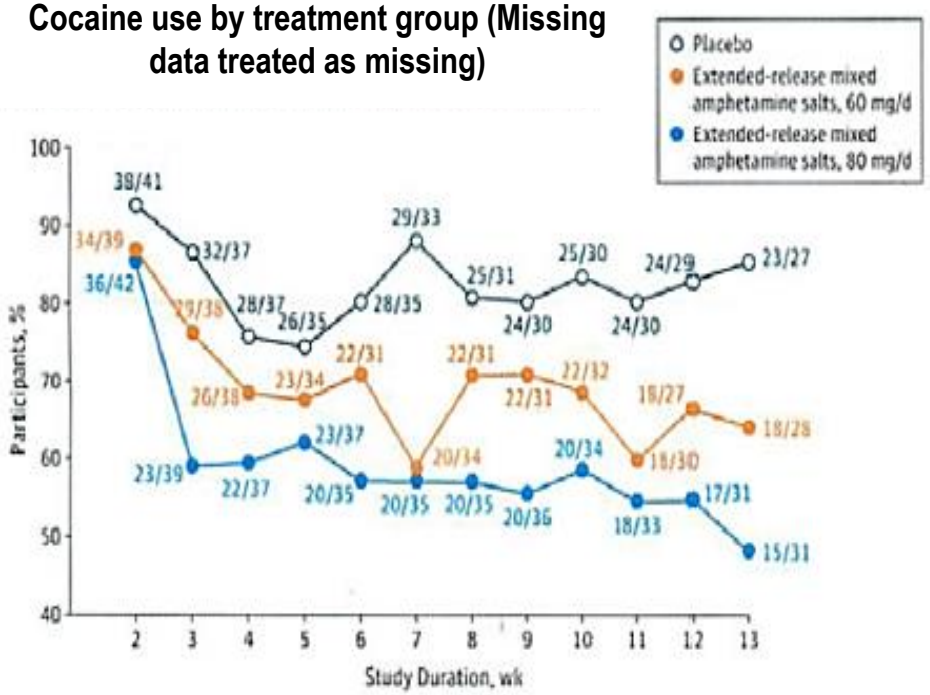


* p = 0.0009
** p = 0.069

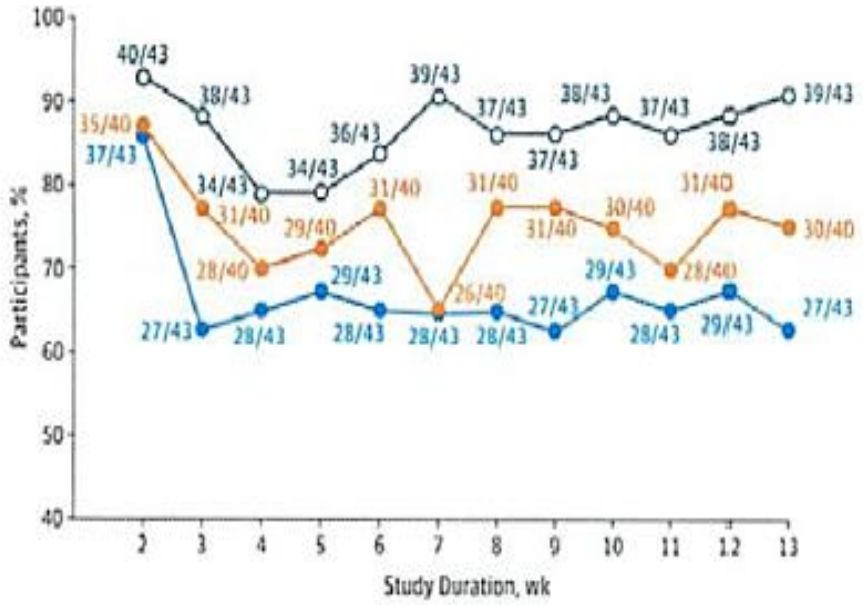
* p = <0.0001
** p = 0.014

Cocaine Use by Treatment Group (Self report confirmed by urine toxicology)

Cocaine use by treatment group (Missing data treated as missing)



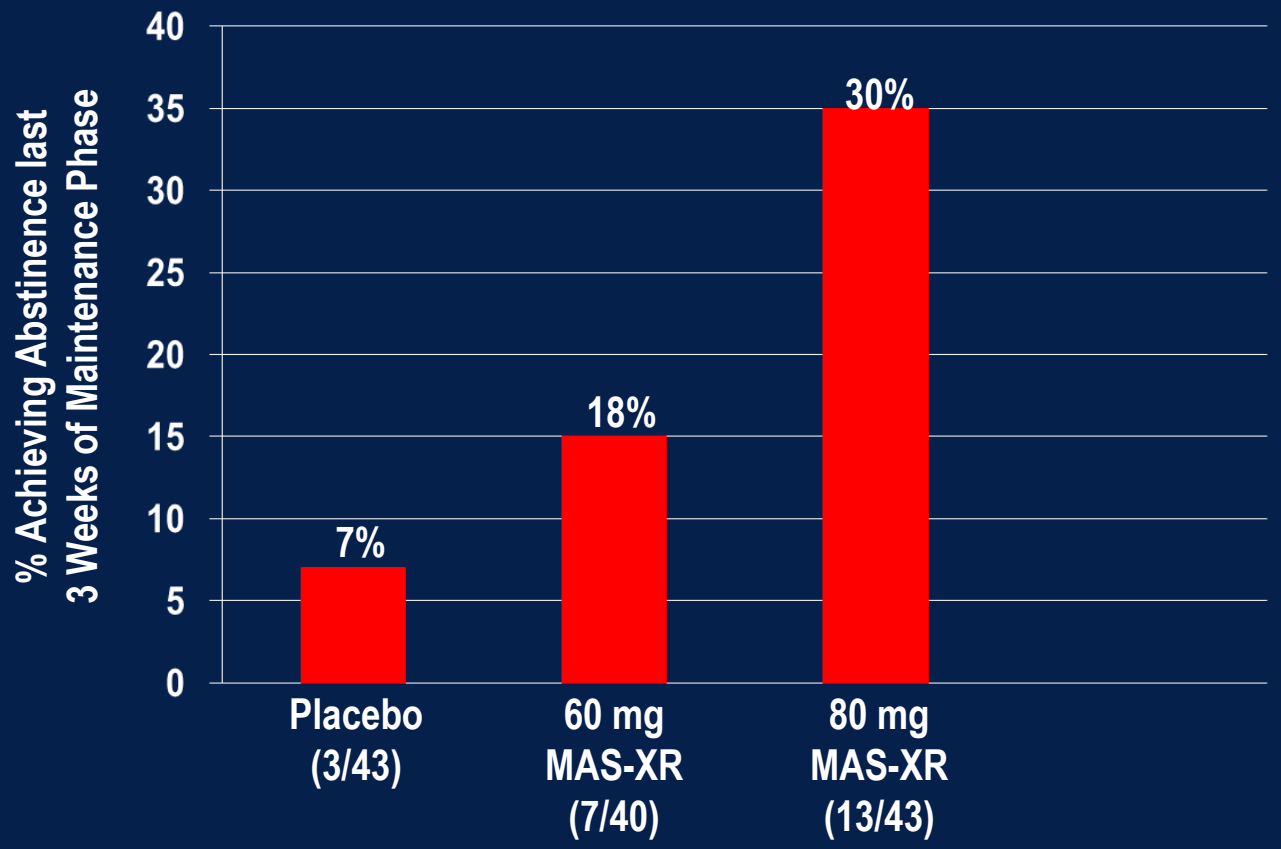
Cocaine use by treatment group (Missing data imputed as using)



There was a significant main effect of treatment, with higher abstinence in MAS-XR 80 mg than in PBO (p=0.0002, OR=5.46, CI: 2.25-13.27) and as well as higher abstinence in MAS-XR 60 mg over PBO (p=0.02, OR=2.92, CI: 1.15-7.425). There was also a main effect of study week (p=0.01)

Cocaine Use Outcome

(Levin et al., *JAMA Psychiatry*, 2015)

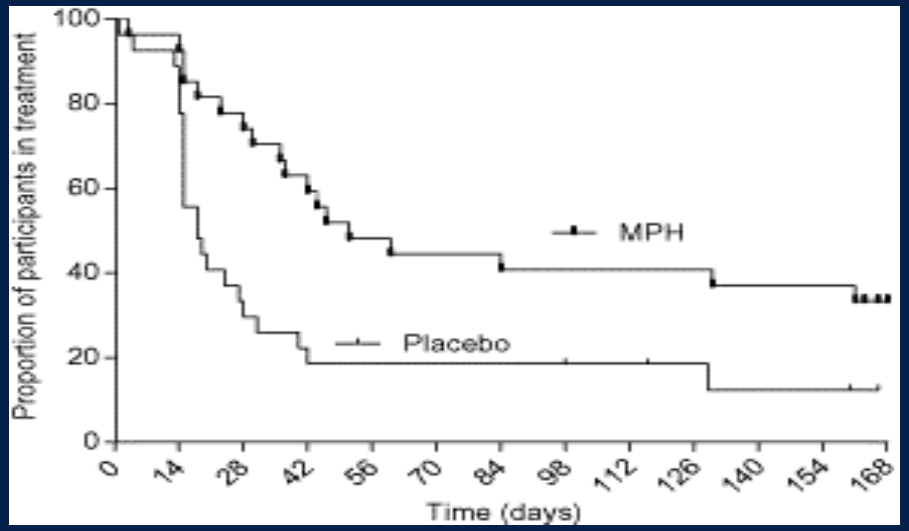


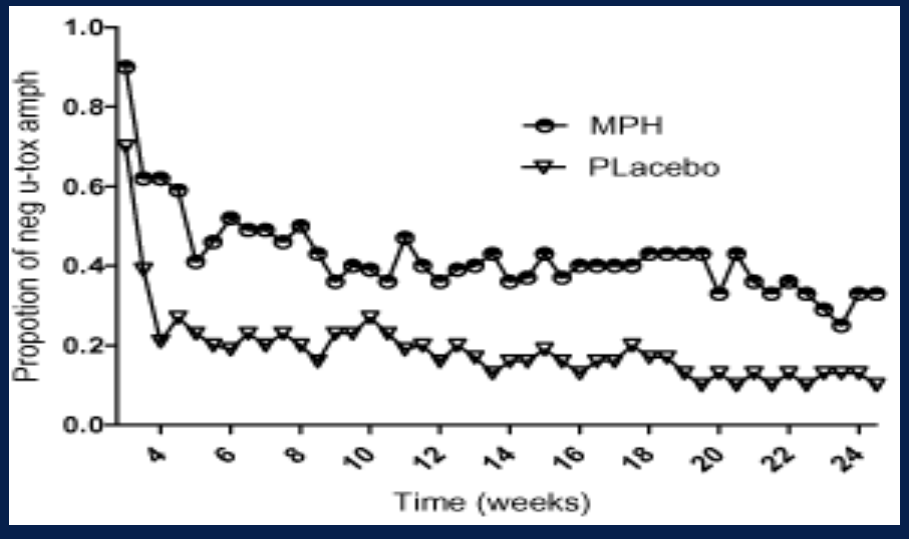
MAS-ER 60 mg vs. placebo (OR=5.85 [CI: 1.04-33.04]; p=0.045)
MAS-ER 80 mg vs. placebo (OR=11.87 [CI: 2.25-62.62]; p=0.004)

AGONIST: Methylphenidate SR (OROS: Concerta) for Amphetamine Use Disorder

(Konstenius et al, 2014)

- Relapse prevention trial, MA dependent adults with ADHD recruited from prison
- 90% intravenous users(N=54, all male)
- 2 wk on med before release, MPH-SR 180 mg/d (avg 148), no changes in BP (high dose)
- **Greater improvement in ADHD symptoms for those on MPH. Those that reduced their ADHD symptoms by at least 30%:**
  - **MPH group, 65%**
  - **Placebo group, 27%** **(p = 0.012)**
- **Proportion of negative amphetamine urines**
  - **MPH group, 23%**
  - **Placebo group, 14%** **(p= 0.019)**





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Why is the Literature So Confusing and What is Missing?

- Limiting Generalizability
  - Often women are excluded (almost 25% of the AMPH trials, or majority are men, over 70%)
  - Often comorbid mental health diagnoses or concomitant medications for comorbid health diagnoses excluded

- Difficulty Reaching Conclusion re: Efficacy
  - Methodologic choices:
    - Abstinence facilitation vs. Relapse (high vs. low users)
    - Psychotherapy platform
    - Assessment of adherence
    - Dosing choices
    - Including/Excluding Those with Opioid Use Disorder (Generally leads to greater negative results for stimulant use disorders)
  - Broad selection of outcomes and measures across studies
  - Need studies examining the efficacy of pharmacotherapy alone vs. combined medication and various forms of behavioral interventions

Conclusions: What shows promise

Cocaine

- MAS-XR (high dose if +ADHD)
- Dextroamphetamine
- Modafinil (if no alcohol use disorder)
- Topiramate (if go slowly, and titrate to side effects)
- Ketamine
- Combination of MAS-XR and Topiramate
- Dosoxysn

Amphetamine

- Methylphenidate (moderate to high dose in frequent users/those with ADHD).
- Dextroamphetamine
- Modafinil (compliant)
- Bupropion (low-level users)*
- Naltrexone (may need to use for relapse prevention and high enough doses)
- Topiramate (low-level users)
- Mirtazapine
- Combination of XR-Naltrexone and Bupropion

- Modified from Slide: Adam Bisaga; Trials in Yellow n >100;

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