

# Medication Options for Treatment of Stimulant Use Disorder: Optimistic Update and New Research

Marc Fishman MD

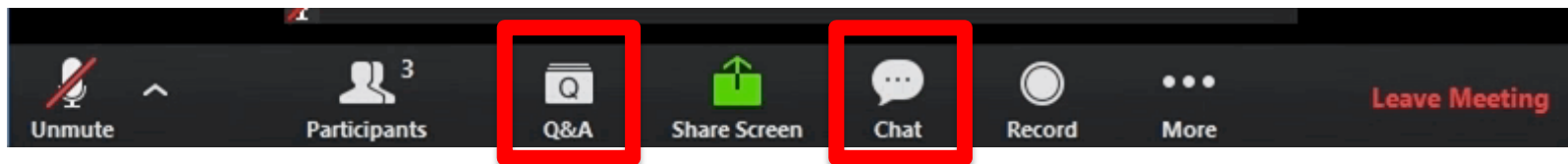
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# How to Ask a Question



Type in the chat box or use the Q&A function. Both are located at the bottom of your screen. You can choose who to send a chat or question to.

**We'll answer as many questions as we can at the end of the presentation.**

# Disclosures

- Alkermes – consultant, research funding
- Drug Delivery LLC – consultant
- Danya /ATTC – consultant
- NIDA – research funding
- ASAM – consultant
- National Assn Drug Court Professionals -- consultant

# Outline

- Background – scope of the problem
- Select research highlights
- Psychiatric comorbidity
- Summary recommendations
- Q&A



# Polling Question

- Are you familiar with some of the research on medication treatment for stimulant use disorder?
  - Yes
  - No

# Medications for Stimulant Use Disorder

- Enormous need
- Many attempts to find efficacy
- No home runs, nothing FDA-approved
- But some promising, and well worth trying

# Polling Question

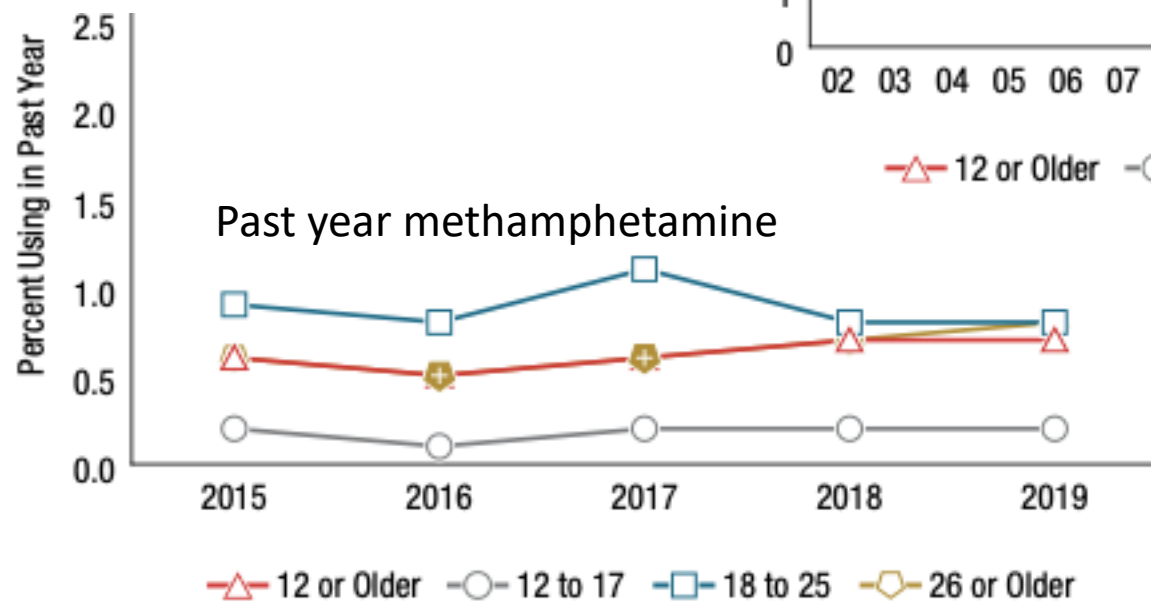
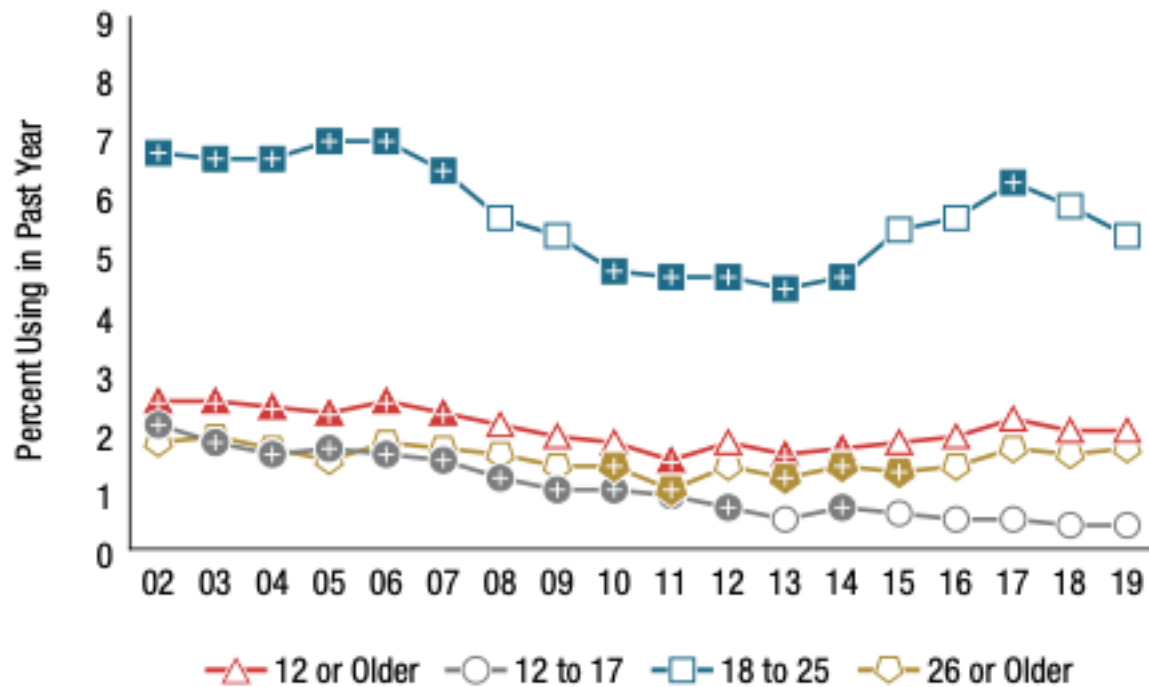
- Have you been clinically involved in medication treatment for any of these substances:
  - Opioids
  - Alcohol
  - Tobacco
  - Cocaine
  - Methamphetamine
  - Cannabis

# Scope of the Problem



**Figure 13. Past Year Cocaine Use among People Aged 12 or Older: 2002-2019**

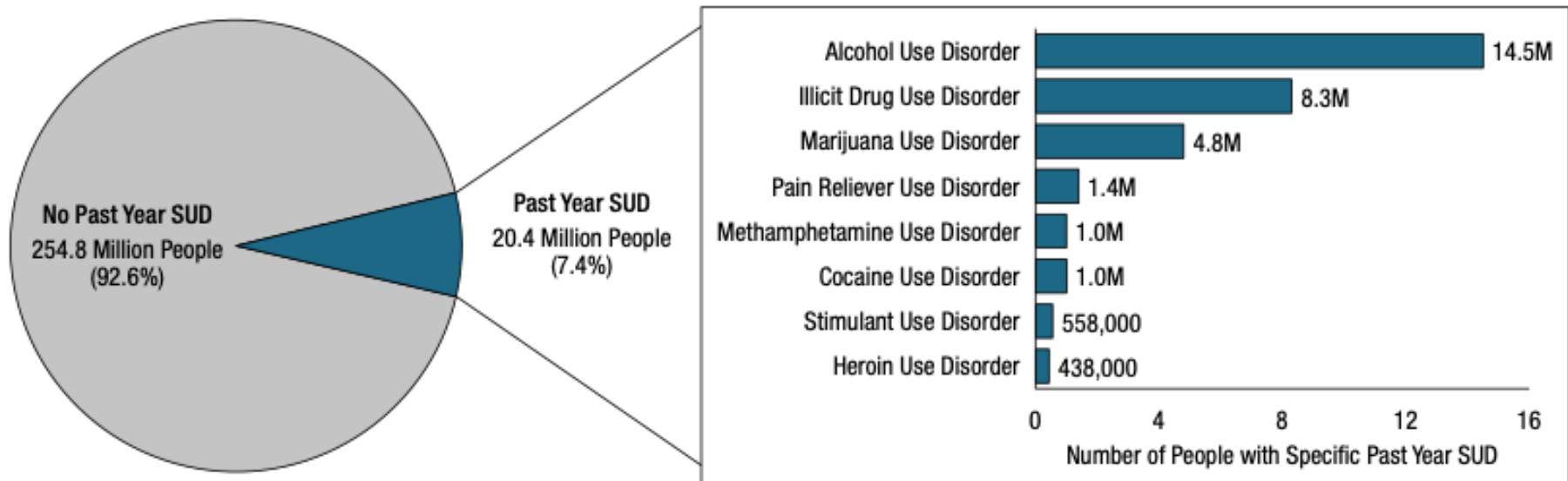
## Use Prevalence



Source: NHSDUH

# Disorder Prevalence

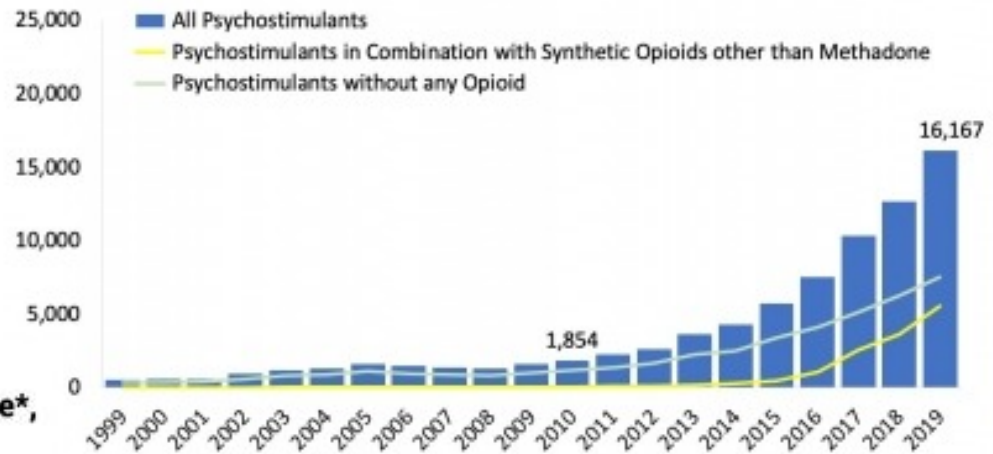
**Figure 46. People Aged 12 or Older with a Past Year Substance Use Disorder (SUD): 2019**



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.

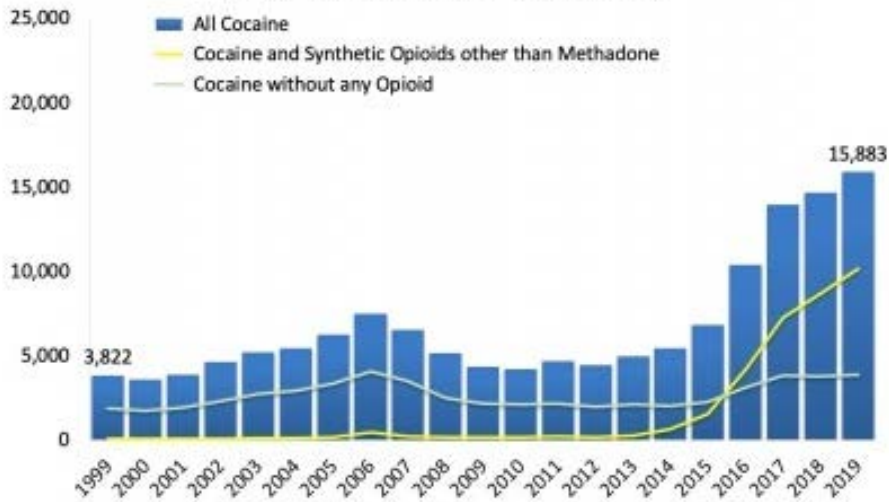
# Overdose Deaths

**Figure 6. National Drug Overdose Deaths Involving Psychostimulants with Abuse Potential (Primarily Methamphetamine)\*, by Opioid Involvement Number Among All Ages, 1999-2019**



\*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. Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2019 on CDC WONDER Online Database, released 12/2020.

**Figure 7. National Drug Overdose Deaths Involving Cocaine\*, by Opioid Involvement, Number Among All Ages, 1999-2019**



\*Among deaths with drug overdose as the underlying cause, the cocaine category was determined by the T40.5 ICD-10 multiple cause-of-death code. Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2019 on CDC WONDER Online Database, released 12/2020.

# Stimulants

## Methamphetamine vs Cocaine

- Both very high potency stimulants
- Overlapping clinical profiles and biology
- Regional and cultural differences in use patterns
- More similar than not
- More studies targeting cocaine than methamphetamine, some expectation of dual coverage for medication treatments

# Research Highlights

# Polling Question

- If you have been involved in medication treatment for stimulant use disorder, which of the following medications has that included:
  - Prescription stimulants
  - Bupropion
  - Topiramate
  - Naltrexone
  - Disulfiram
  - Mirtazapine
  - Others

# Medications for Stimulant Use Disorder

## Agents that Show Promise

- Agonists
  - Mixed amphetamine salts (MAS), dextroamphetamine, methylphenidate, modafinil
- Topiramate
- Naltrexone
- Bupropion
- Disulfiram
- Mirtazapine
- Buprenorphine
- Doxazosin

# Cocaine



# Review of Rx for Cocaine

- Most promising
  - Prescription stimulants
  - Topiramate
  - Disulfiram
- Maybe promising
  - Galantamine
  - Combos: MAS+TPM, NTX+Disulfiram, NTX+Bup
- In the works:
  - Ketamine, vaccine

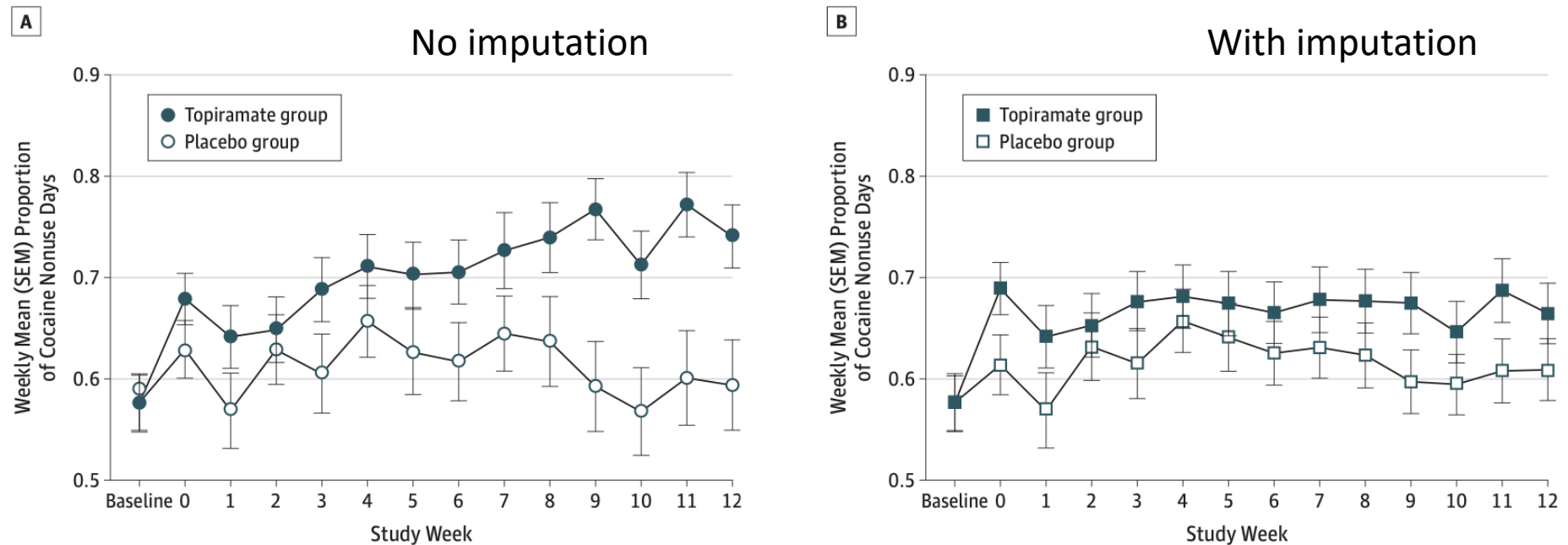
Kampman. The treatment of cocaine use disorder. *Science advances*. 2019.

Brandt et al. Pharmacotherapeutic strategies for treating cocaine use disorder—what do we have to offer? *Addiction*. 2020.

# Topiramate for Cocaine

- Topiramate 300mg/d vs placebo increased non-use days, non-use weeks (17% vs 6%)

Figure 2. Weekly Mean Proportion of Cocaine Nonuse Days From Baseline Through Study Week 12



Johnson et al. Topiramate for the Treatment of Cocaine Addiction  
A Randomized Clinical Trial. *JAMA Psychiatry*. 2013.

# Topiramate + MAS for Cocaine

Drug and Alcohol Dependence 206 (2020) 107700



ELSEVIER

Contents lists available at ScienceDirect

## Drug and Alcohol Dependence

journal homepage: [www.elsevier.com/locate/drugalcdep](http://www.elsevier.com/locate/drugalcdep)



Full length article

### Extended release mixed amphetamine salts and topiramate for cocaine dependence: A randomized clinical replication trial with frequent users

Frances R. Levin<sup>a,b,\*</sup>, John J. Mariani<sup>a,b</sup>, Martina Pavlicova<sup>c</sup>, C. Jean Choi<sup>d</sup>, Amy L. Mahony<sup>a</sup>, Daniel J. Brooks<sup>a</sup>, Adam Bisaga<sup>a,b</sup>, Elias Dakwar<sup>a,b</sup>, Kenneth M. Carpenter<sup>a,b</sup>, Nasir Naqvi<sup>a,b</sup>, Edward V. Nunes<sup>a,b</sup>, Kyle Kampman<sup>e</sup>

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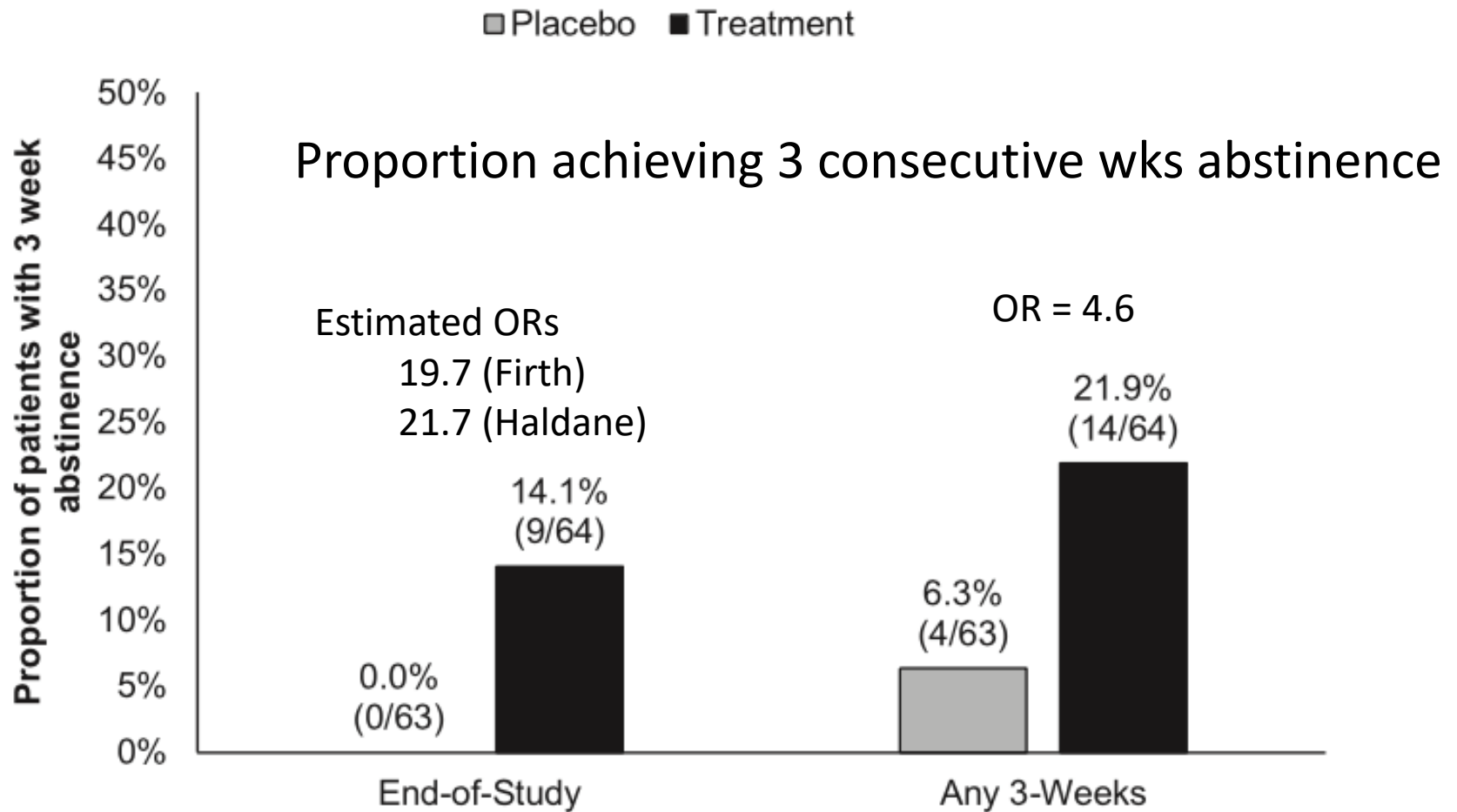
Kampman et al. Extended release mixed amphetamine salts and topiramate for cocaine dependence: A randomized clinical replication trial with frequent users. *Drug and Alcohol Dependence* 206 (2020)



# Topiramate + MAS for Cocaine Methods

- 12 wk treatment for CUD with  $\geq 9$ d use /mo
- N= 127 randomized to either:
  - MAS-ER + Topiramate , or
  - Double placebo
- 1 wk placebo lead-in, placebo-responders and study non-adherents excluded (25%)
- Titrations
  - MAS over 2 wks 10→60
  - Topiramate over 6 wks 25/d → 100 bid
- Background counseling: medical management
- 2 sites: Columbia and U Penn
- 3 uds per wk, missing imputed as positive
- Outcomes: 3 consecutive wks abstinence, % pos UDS

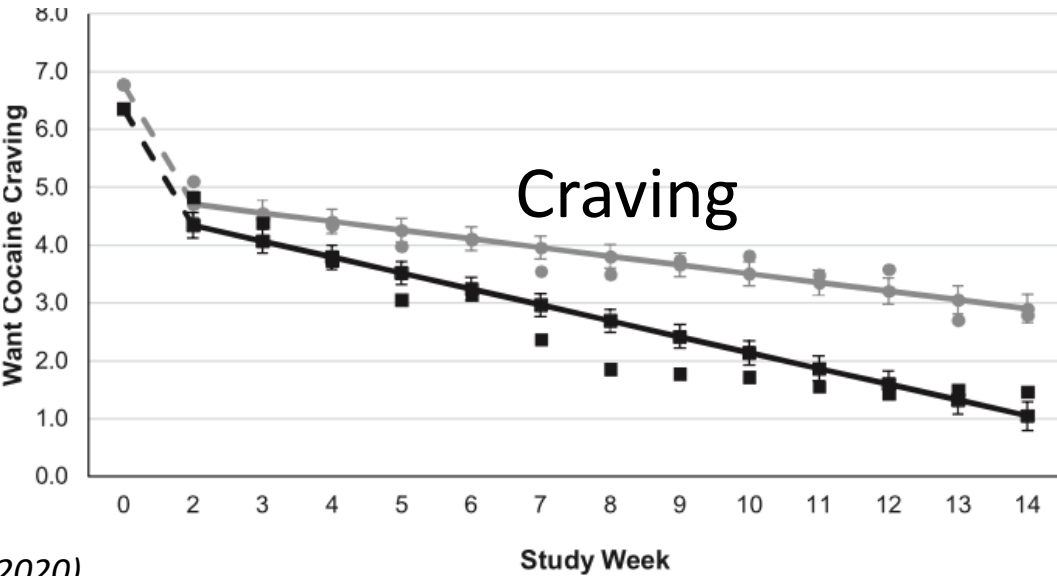
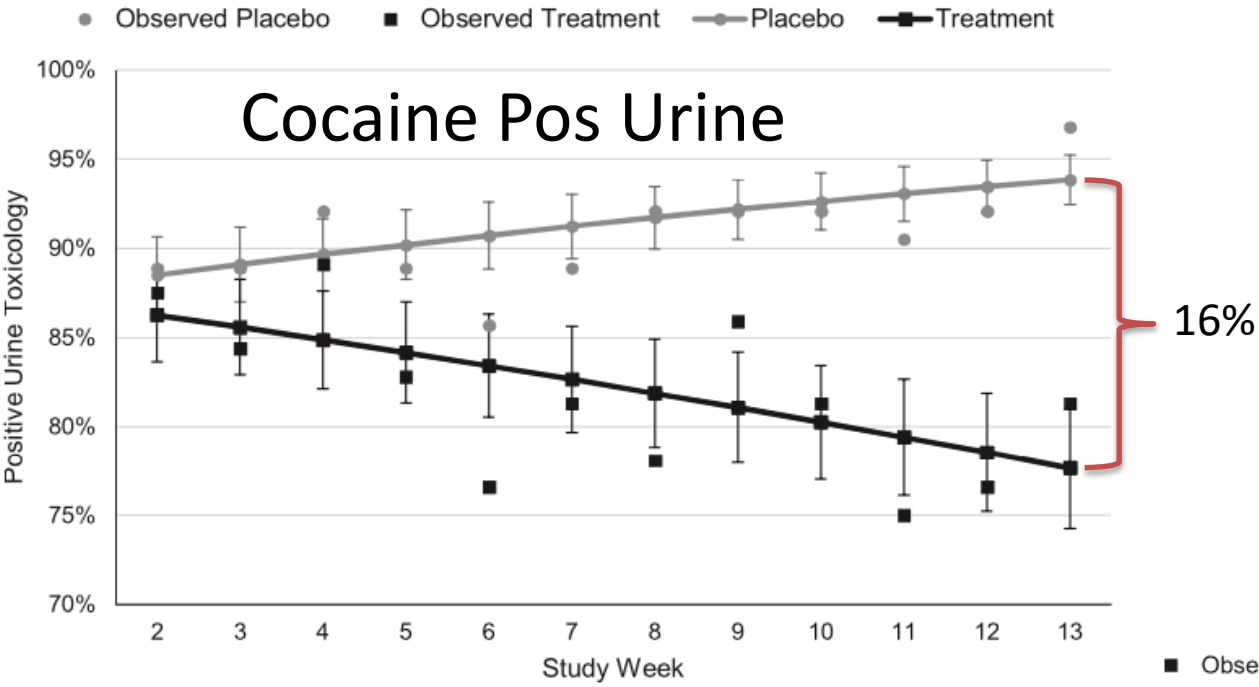
# Topiramate + MAS for Cocaine Results



Kampman et al.. *Drug and Alcohol Dependence* 206 (2020)

# Results

## Cocaine Pos Urine



Kampman et al.. *Drug and Alcohol Dependence* 206 (2020)

# Topiramate + MAS for Cocaine Implementation Considerations

- Frequent med discontinuation (MAS 20%, TPM 25%) and dose reduction (MAS 31%, TPM 19%)
  - (most common reason HR/BP)
- Medication adherence (riboflavin): 60-70%
- Diversion not noted



# Topiramate + MAS for Cocaine Conclusions

- Combination topiramate + MAS-ER improves outcomes for cocaine addiction
- Overall effect modest, but NNT=7, not too shabby
- Potential barriers to broad adoption
- Previous support for both individually, better with both, possible serial addition strategy?

Kampman et al.. *Drug and Alcohol Dependence* 206 (2020)



# Methamphetamine

# Review of Rx for methamphetamine

- Most promising
  - Prescription stimulants
  - Naltrexone
  - Topiramate
- Maybe promising
  - Bupropion
  - Mirtazapine
- In the works:
  - Riluzole, N-acetyl cysteine, monoclonal antibody

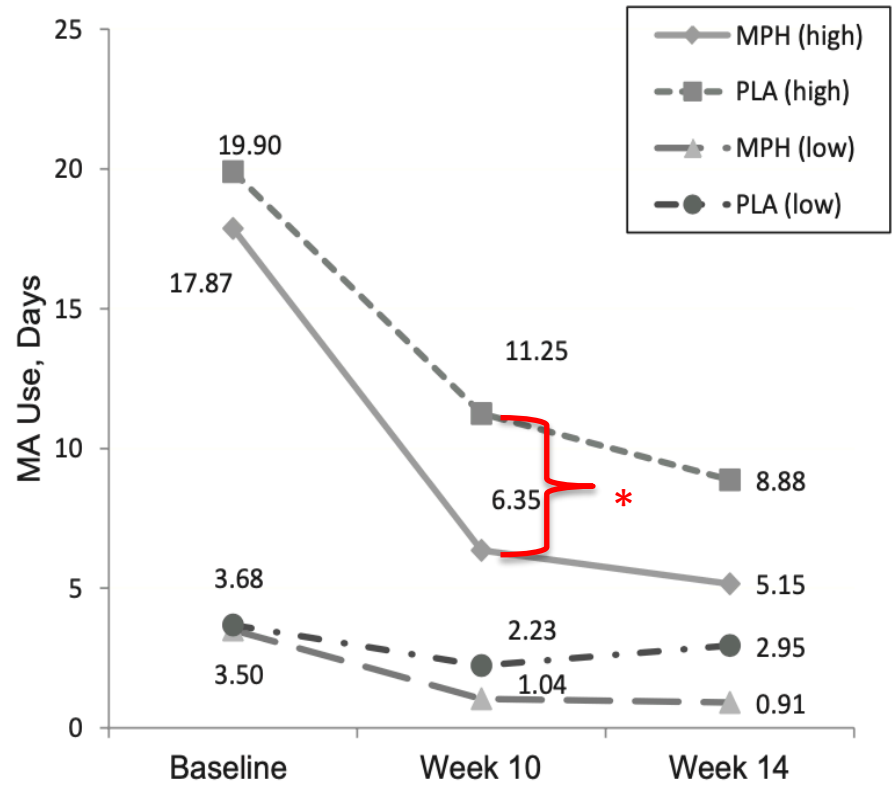
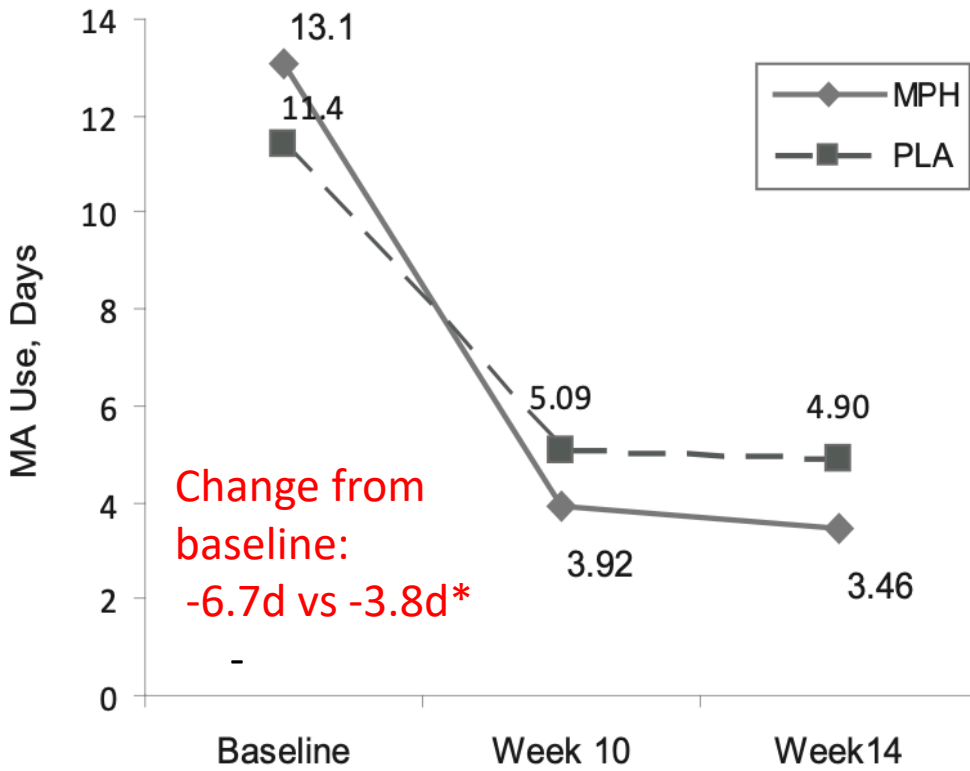
Siefried et al. Pharmacological Treatment of Methamphetamine/Amphetamine Dependence: A Systematic Review. *CNS Drugs* (2020) 34:337–365

# MPH for Methamphetamine

Ling et al. *Addiction*, **109**, 1489–1500.2014

- MPH 56mg x 10wk + CM + weekly CBT
- MPH reduced MA use > placebo, in some secondary outcomes
- Effect greater for higher severity (<10d/30)

Wk 14 MA+ UDS: 16% vs 34%\*



# XR-NTX + Bupropion for Methamphetamine

*The NEW ENGLAND JOURNAL of MEDICINE*

ORIGINAL ARTICLE

## Bupropion and Naltrexone in Methamphetamine Use Disorder

M.H. Trivedi, R. Walker, W. Ling, A. dela Cruz, G. Sharma, T. Carmody, U.E. Ghitza, A. Wahle, M. Kim, K. Shores-Wilson, S. Sparenborg, P. Coffin, J. Schmitz, K. Wiest, G. Bart, S.C. Sonne, S. Wakhlu, A.J. Rush, E.V. Nunes, and S. Shoptaw

Trivedi et al. Bupropion and Naltrexone in Methamphetamine Use Disorder  
N Engl J Med 2021;384:140-53.

# XR-NTX + Bupropion for Methamphetamine Methods

- N= 403 (+ a subset of 225) randomized to:
  - XR-NTX q3wks + bupropion 450 mg/d vs
  - double placebo
- Mod-severe MUD, use 18d/mo and 2 UDS+ in screening
- 8 sites, NIDA CTN
- 2 stages of 6 wk treatment
- UDS 2x/wk
- Weekly background counseling (similar to MM)

Trivedi et al. N Engl J Med 2021;384:140-53.

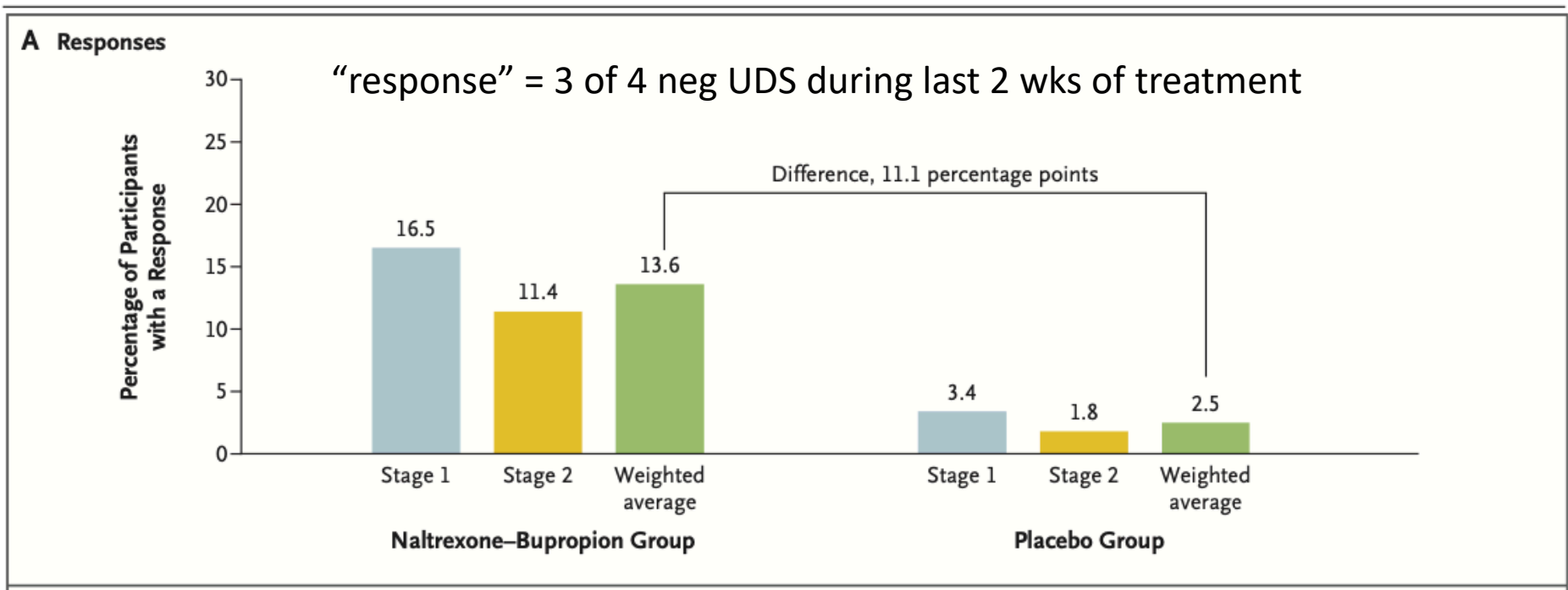
# XR-NTX + Bupropion for Methamphetamine

## Methods

- Sequential parallel design trial
  - Initial randomization for stage 1
  - Re-randomization for placebo non-responders for stage 2
- Outcomes: “response” = 3 of 4 neg UDS last 2 wks of treatment, % neg UDS

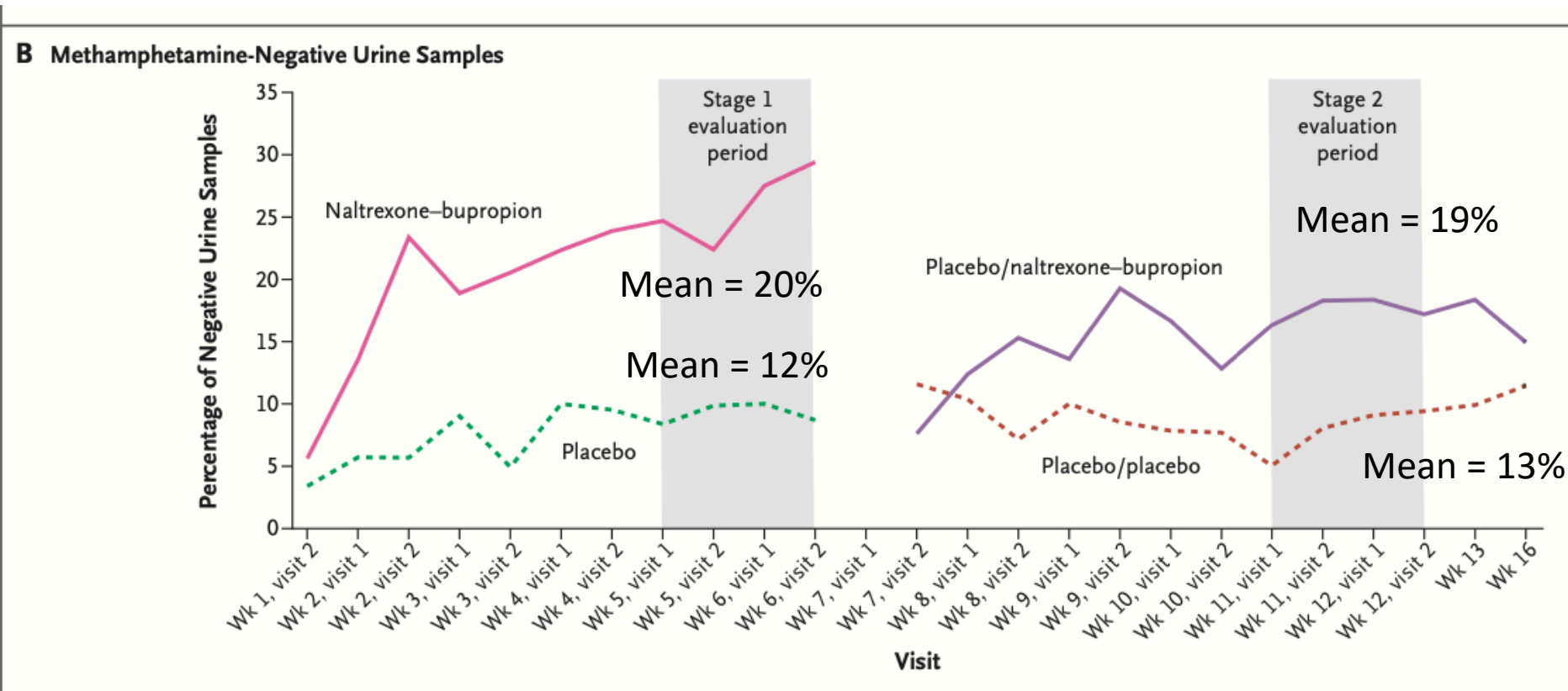
Trivedi et al. N Engl J Med 2021;384:140-53.

# XR-NTX + Bupropion for Methamphetamine Results – Treatment Response



Trivedi et al. N Engl J Med 2021;384:140-53.

# XR-NTX + bupropion for methamphetamine Results – Neg UDS



Means are per person across 6 wks

Trivedi et al. N Engl J Med 2021;384:140-53.



# XR-NTX + bupropion for methamphetamine

## Conclusions

- Combination XR-NTX + bupropion improves outcomes for methamphetamine addiction
- Overall effect modest, but NNT=9, not bad
- Methods notes
  - 6 wks short duration, probably underestimates effect
  - High adherence, low attrition may not generalize?
  - What about the other groups? – stage 1 active treatment responders and non-responders, stage 1 placebo responders (very few)
  - Sequential trial design didn't achieve desired enrichment

Trivedi et al. N Engl J Med 2021;384:140-53.

# Polling Question

- In the treatment setting you are involved with, do you think incorporating medications as part of routine treatment for stimulant use disorder would be feasible?
  - Yes
  - No

# Prescription Stimulants for Stimulant Use Disorder

## Possible Implementation Issues

- Attitudes
- Diversion and misuse
- Side effect profile and monitoring (mood, insomnia, BP)
- Duration of supply
- Medical staffing
- Direct administration (OTP-style?)

# XR-Naltrexone for Stimulant Use Disorder

## Possible Implementation Issues

- Insurance coverage
- Q3 wk dosing
- Concern about co-use of opioids
- Medical staffing
- Patient acceptability
- What about adding bupropion?
- What about adding buprenorphine?

## Polling Question

- In the treatment setting you are involved with, do you think incorporating prescription stimulants (eg methylphenidate or mixed amphetamine salts) as medication for stimulant use disorder would be feasible?
  - Yes
  - No

# Psychiatric Co-Morbidity

# Psychiatric Co-Morbidity

- Depression and psychosis both very common with both cocaine and MA
- Presents questions for treatment
  - Acute presentation
  - Longer term
- Management of acute intoxication/withdrawal
  - Agitation
  - Psychosis
  - Sleep disturbance

# Stimulants and Psychosis

- Common presentation in acute intoxication
- >50% develop psychotic sx's
- 80% resolution with 30d abstinence, but 10-15% persistence
- Common vulnerability: schizophrenia incidence 5x greater in relatives of those with meth-induced psychosis



# Co-Occurring Disorders Diagnostic Approaches: Sensitivity vs Specificity Take a Stance

- Wait for the possibility of spontaneous resolution
  - Better diagnostic precision
  - Less possibility of unnecessary treatment
  - Less opportunity for early and effective treatment
- Move ahead with a presumptive diagnosis
  - Less diagnostic precision
  - Possibility of over-aggressive treatment
  - Better opportunity for earlier and more effective treatment

# Approaches to Treatment Co-Occurring Psychiatric Disorders

- History of rapid spontaneous sx resolution probably predictive
- But lingering sxs productive target for treatment
- Psychiatric Rx can be an engagement tool
- Insomnia low hanging fruit for relief
- Are mirtazapine or bupropion preferred antidepressants?
- Persistent psychosis and depression poor prognosis

# Conclusions

# Stimulant Use Disorder Medications

## Summary Conclusions

- Maybe not home runs, but very solid doubles, esp in the absence of anything better
- Are these ready for prime time? YES
- Does effect for one stimulant generalize to the other? Probable overlap
- What about real-world conditions
  - Patients, logistics, attrition, adherence, monitoring and support, insurance coverage

# Overall

## Conclusions, Questions and Next Steps

- Very exciting to see our tool chest expanding! (although we can anticipate adoption will lag)
- Shouldn't we aspire to a in standard which every patient offered full menu of options including these? What will it take?
- What about possible augmentation effects of more intensive counseling? CM?
- What about patient selection and treatment matching strategies? Sequencing?
- More shall be revealed – stay tuned for further research and real-world experience

## Case

- 48 M longstanding smoked cocaine, injection heroin, multiple treatment dropouts
- Stabilized on buprenorphine with opioid abstinence, but continues cocaine
- Topiramate titration to 300 mg/d, subjective reduction in craving, use reduced but persistent
- Side effects leading to topiramate dose reduction
- Addition of MAS-ER, titration to 50 mg/d, gradual improvement, best retention to date, intermittent HTN



## Case

- 36 M chronic methamphetamine, hospitalized following suicidal depression with paranoid delusions, treated with SSRI and aripiprazole
- Intermittent relapse to MA but retained in OP treatment
- Switch SSRI to bupropion, switch to more sedating antipsychotic and titrate with waxing/waning psychosis and insomnia
- Add naltrexone, add topiramate

# Take Home Messages

- Try any and all of these
  - Increasing treatment effectiveness even a little would be worthwhile. Any engagement in treatment for longer retention would be worthwhile.
  - Prescription stimulants maybe most promising (but potential adoption barriers)
  - Naltrexone (+/- bupropion), topiramate, disulfiram
  - If able to retain, consider combos and serial trials
- 
- **Therapeutic optimism remains our best tool!**



**There will not be a quiz!  
(...but maybe Q&A)**

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