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

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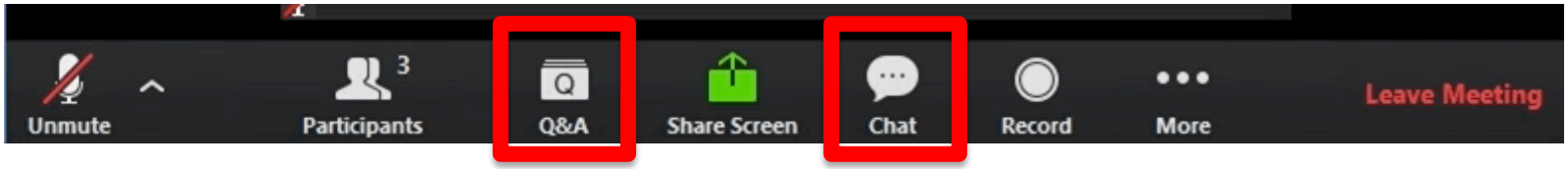
How to Ask a Question



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

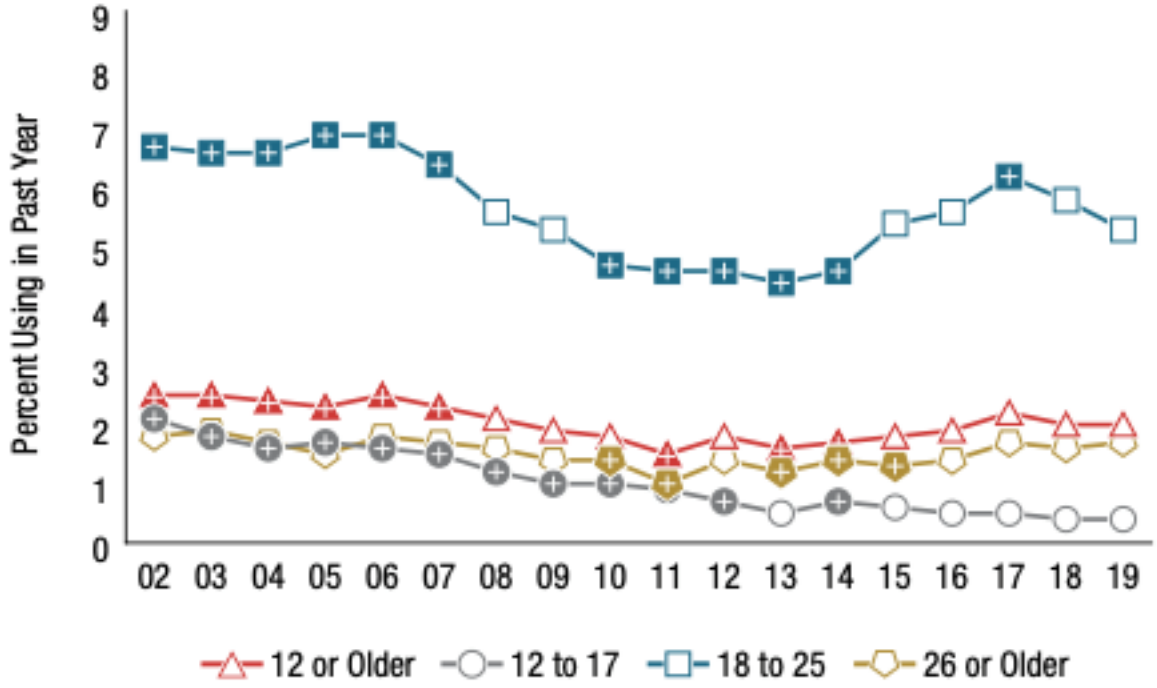
Polling Question

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

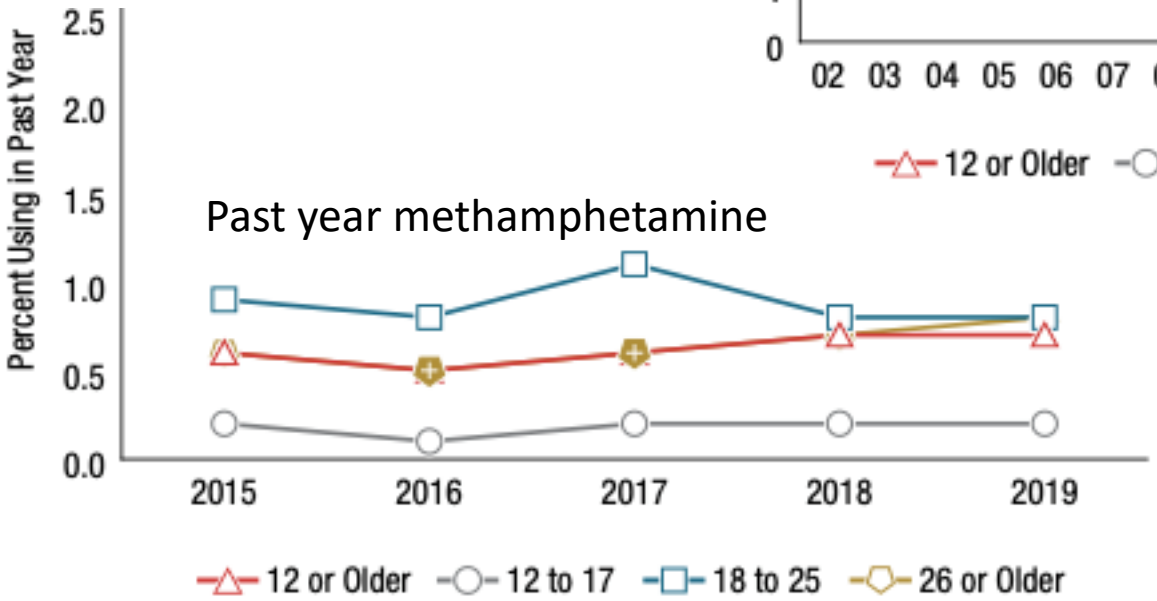
Scope of the Problem

Use Prevalence

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



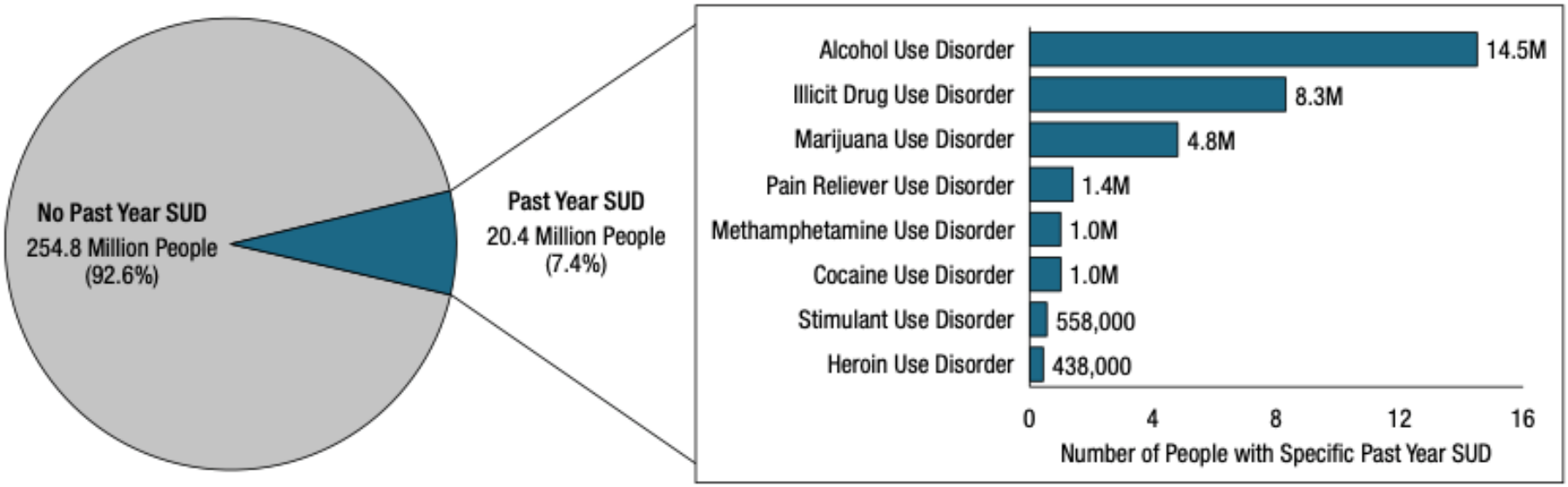
Past year methamphetamine



Source: NHSDUH

Disorder Prevalence

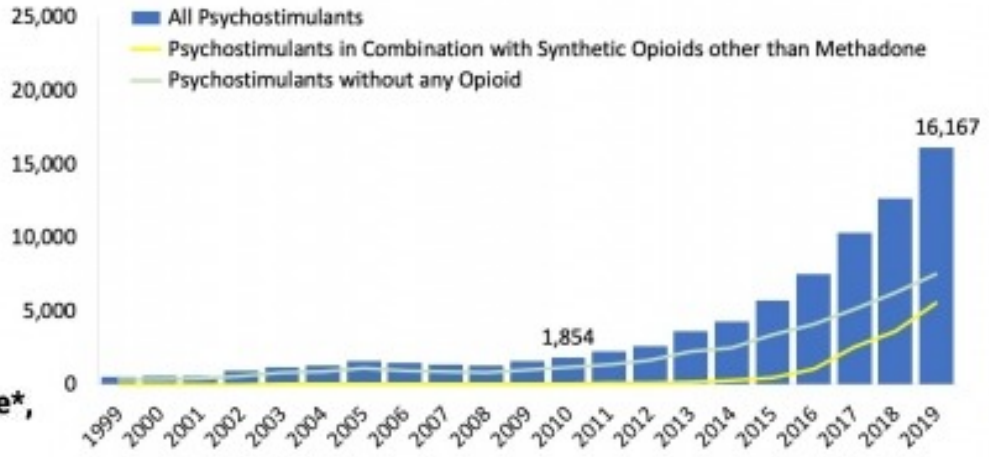
Figure 46. People Aged 12 or Older with a Past Year Substance Use Disorder (SUD): 2019



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.

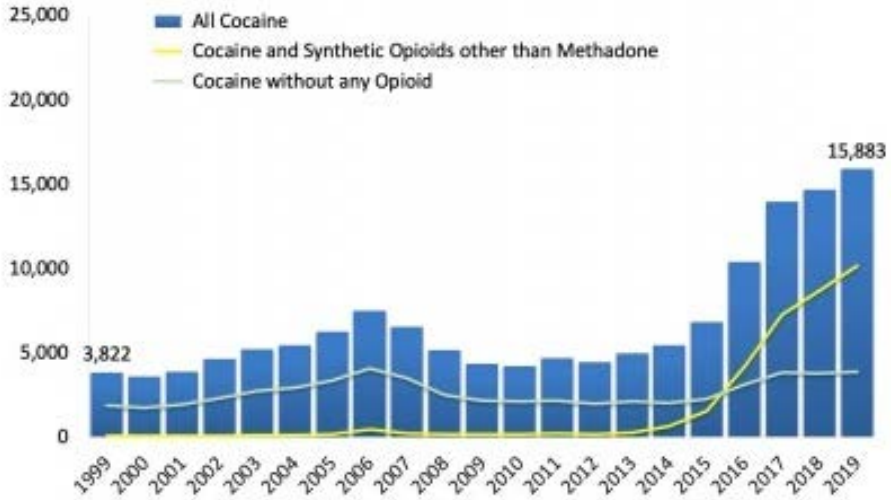
Overdose Deaths

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



g deaths with drug overdose as the underlying cause, the psychostimulants with abuse potential (primarily methamphetamine) ry was determined by the T43.6 ICD-10 multiple cause-of-death code. Abbreviated to *psychostimulants* in the bar chart above. : Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2019 on CDC IER 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

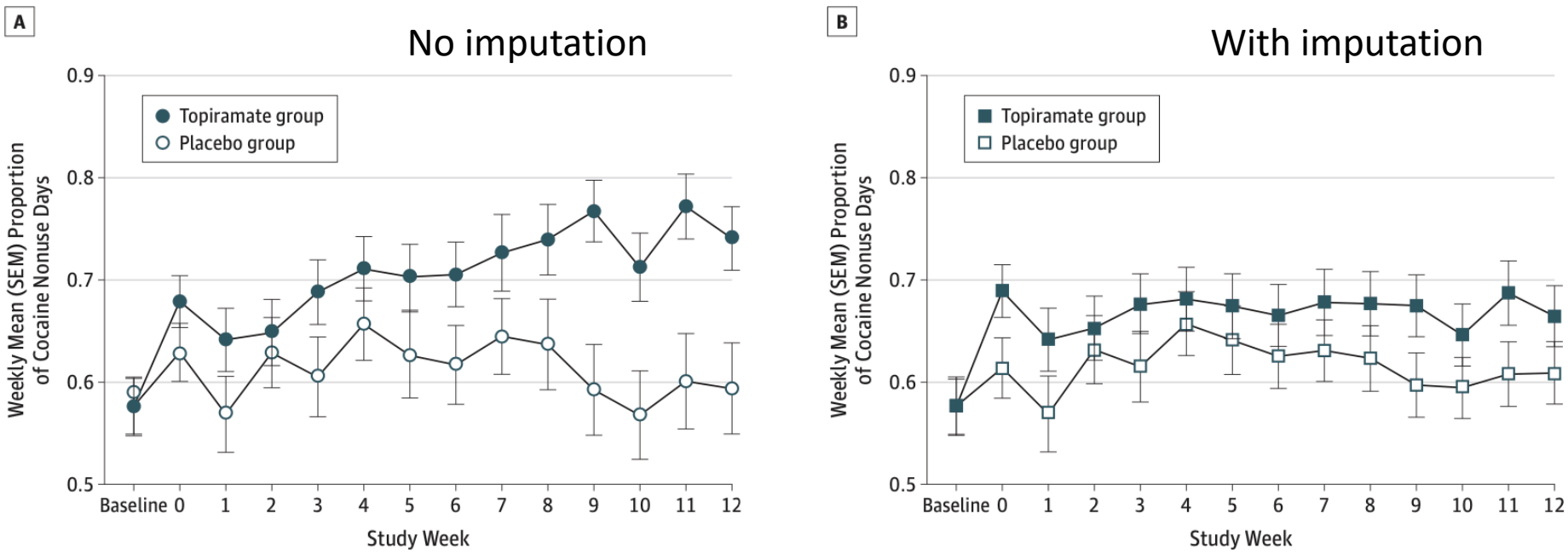
- Most promising
  - Prescription stimulants
  - Topiramate
  - Disulfiram
- Maybe promising
  - Galantamine
  - Combos: MAS+TPM, NTX+Disulfiram, NTX+Bup
- In the works:
  - Ketamine, vaccine

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

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: 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[a,b,*], John J. Mariani[a,b], Martina Pavlicova[c], C. Jean Choi[d], Amy L. Mahony[a], Daniel J. Brooks[a], Adam Bisaga[a,b], Elias Dakwar[a,b], Kenneth M. Carpenter[a,b], Nasir Naqvi[a,b], Edward V. Nunes[a,b], Kyle Kampman[e]

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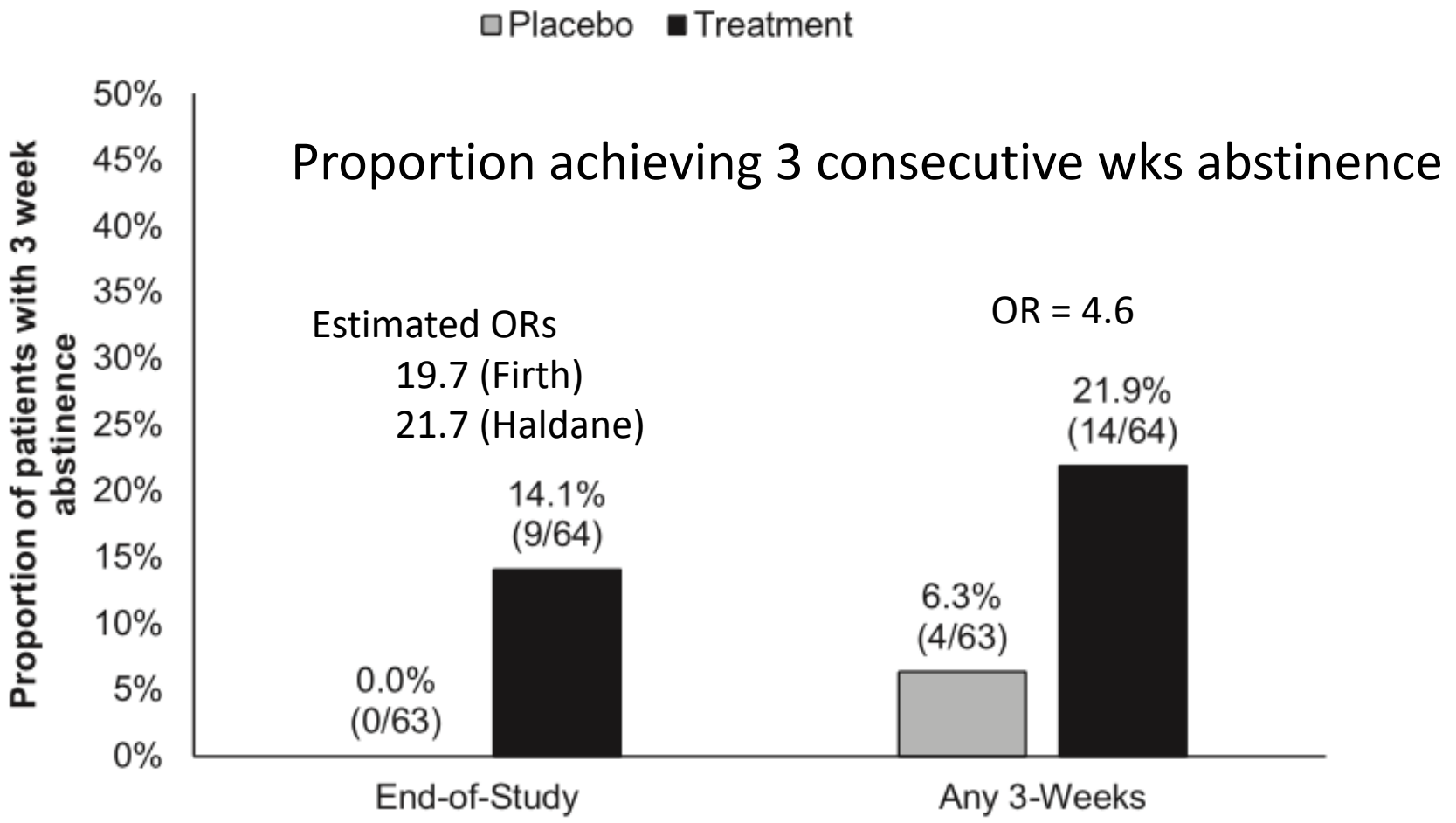
Kampman et al. Extended release mixed amphetamine salts and topiramate for cocaine dependence: A randomized clinical replication trial with frequent users. *Drug and Alcohol Dependence 206 (2020)*

Topiramate + MAS for Cocaine Methods

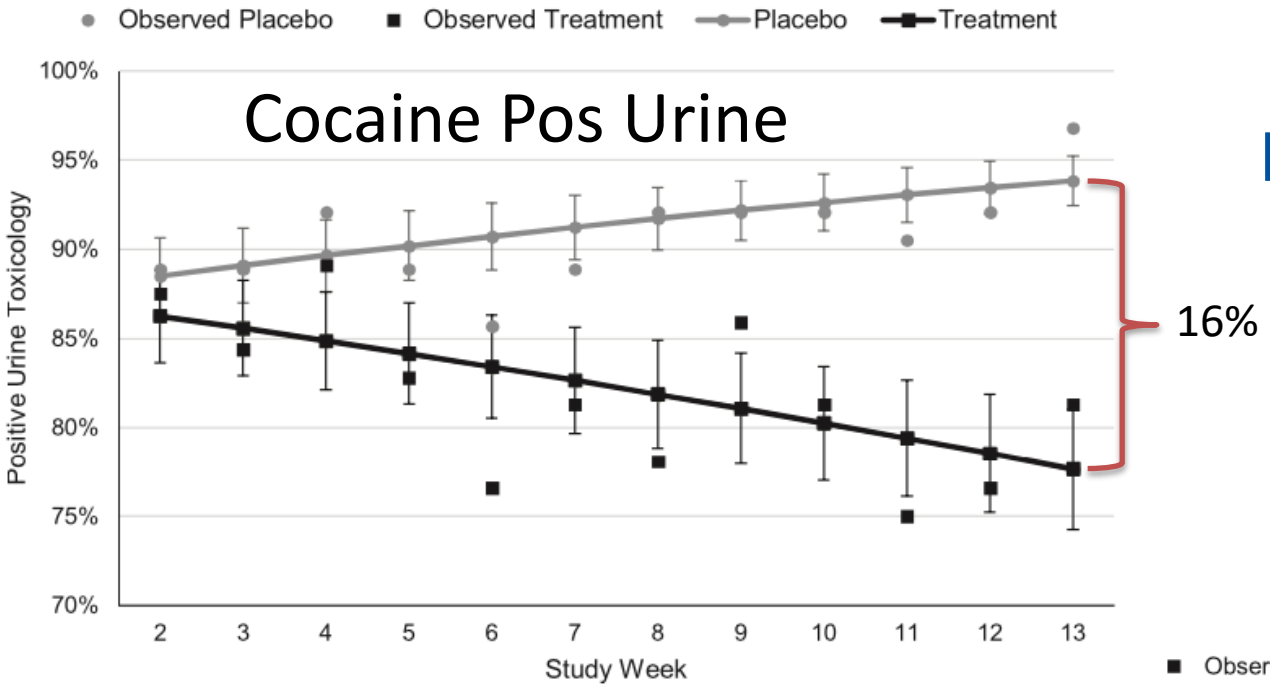
- 12 wk treatment for CUD with ≥9d use /mo
- N= 127 randomized to either:
  - MAS-ER + Topiramate , or
  - Double placebo
- 1 wk placebo lead-in, placebo-responders and study non-adherents excluded (25%)
- Titrations
  - MAS over 2 wks 10→60
  - Topiramate over 6 wks 25/d → 100 bid
- Background counseling: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

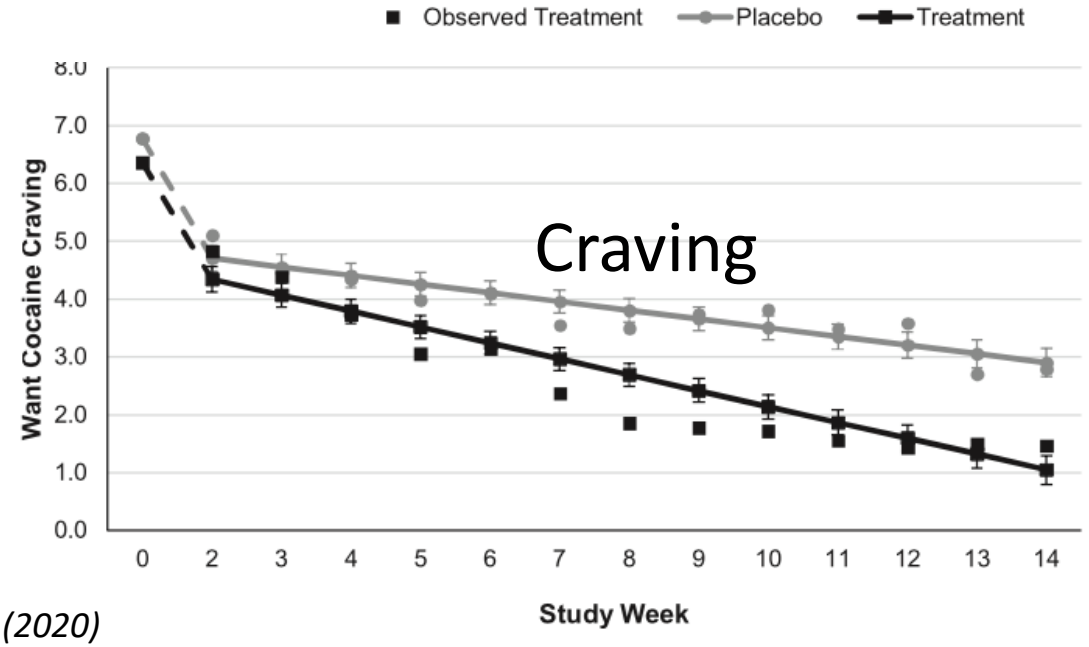
Topiramate + MAS for Cocaine Results



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

Results





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

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

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

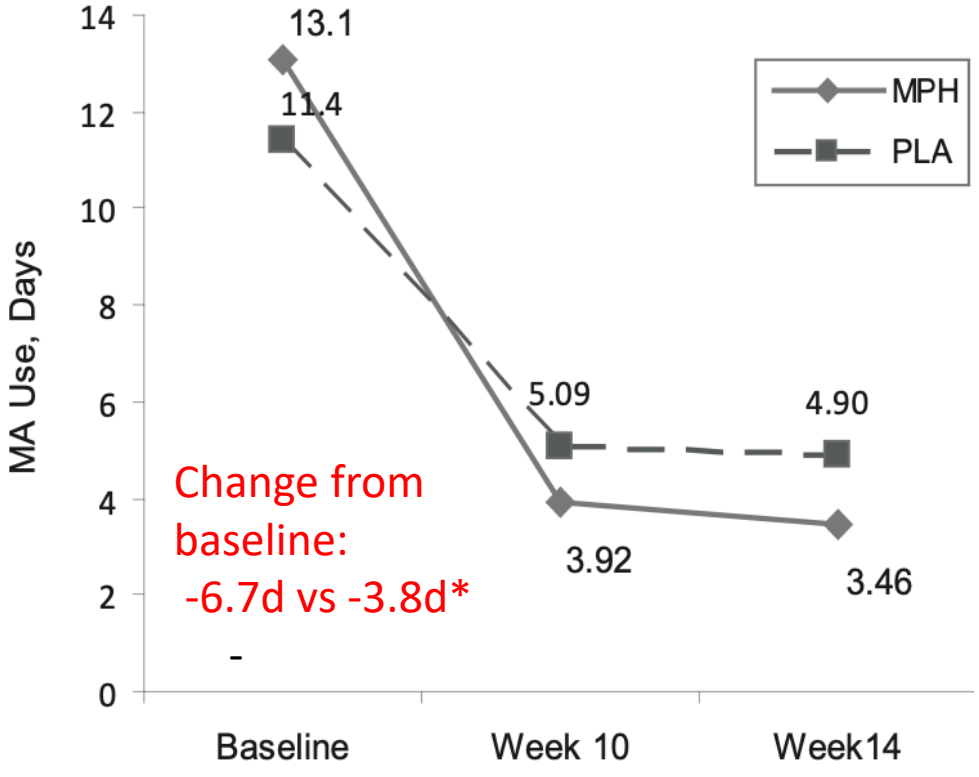
Siefried et al. Pharmacological Treatment of Methamphetamine/Amphetamine Dependence: A Systematic Review. CNS Drugs (2020) 34:337–365

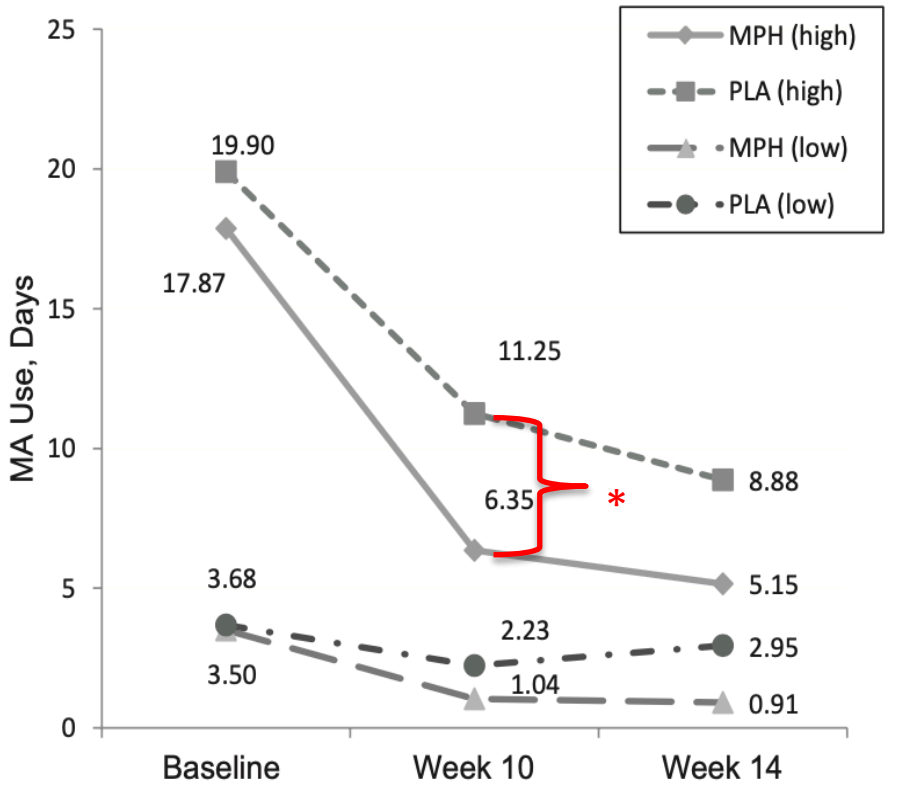
MPH for Methamphetamine

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

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

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





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)

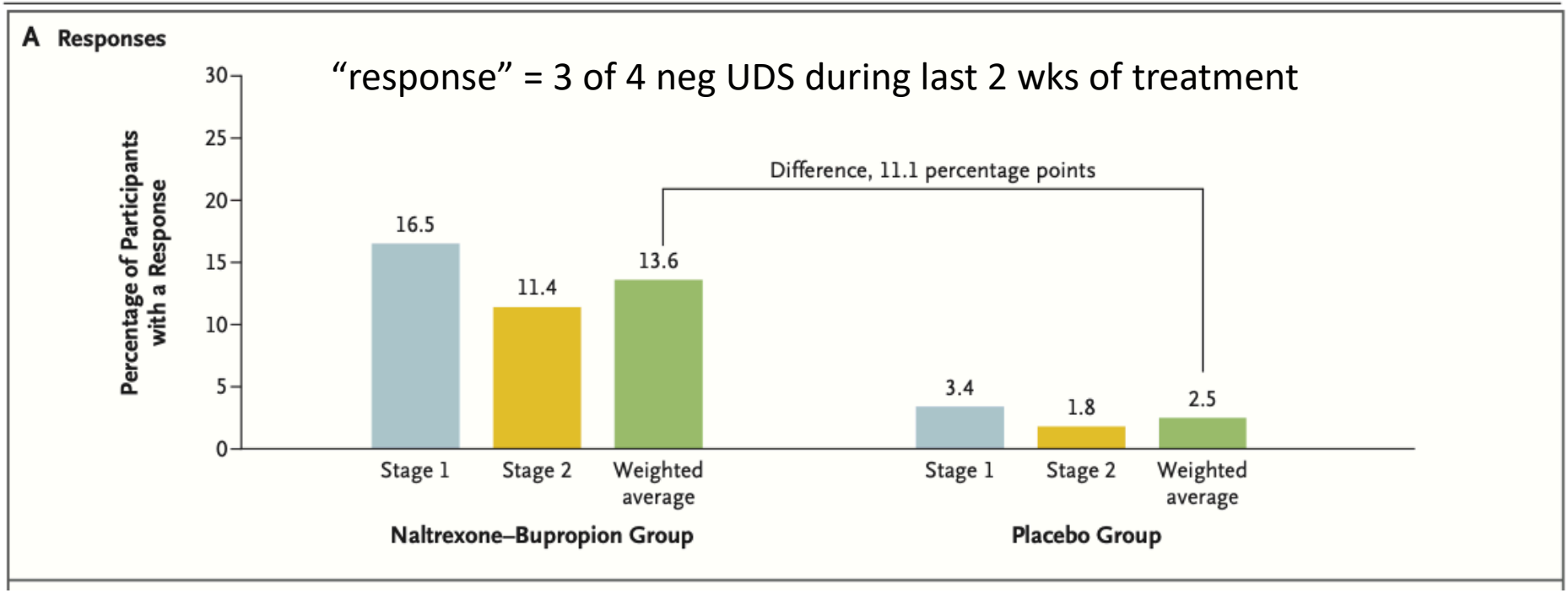
Trivedi et al. N Engl J Med 2021;384:140-53.

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

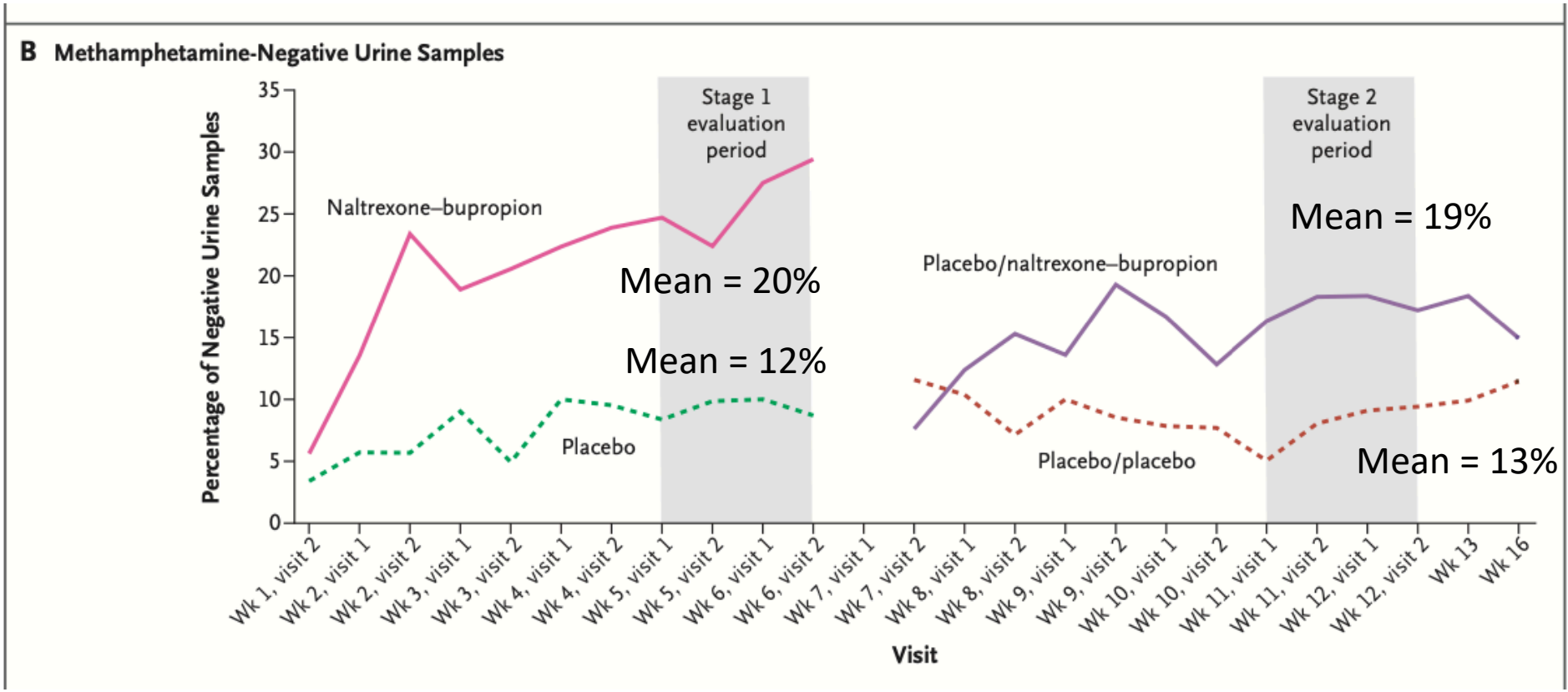
Trivedi et al. N Engl J Med 2021;384:140-53.

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 sxs
- 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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