GETTING UP TO SPEED: PHARMACOLOGIC TREATMENT OF ADHD IN PATIENTS WITH COMORBID SUBSTANCE USE DISORDERS

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DISCLOSURE INFORMATION

- **Disclosure of Relevant Financial Relationships**

  I have no financial relationships to disclose.

- **Disclosure of Off-Label and/or Investigative Uses**

  I will discuss the following off-label use and/or investigational use in my presentation:

  Dextroamphetamine SR, methylphenidate SR, modafinil, armodafinil

OBJECTIVES

- Describe pharmacologic treatment options for ADHD in patients with substance use disorder
- Evaluate evidence for the pharmacologic treatment of ADHD in patients with stimulant use disorder and consider implications for clinical practice

ADHD

- Treatment should be preceded by assessment and diagnosis
- Assess for presence or history of substance use disorder or co-occurring disorders
- For adults with ADHD, first-line treatment is medication rather than CBT
  - For stimulant use disorder, first-line treatment is CBT rather than medication
- Determine level of impairment due to ADHD
- If there is a co-morbid SUD, it is optimal to treat the SUD first
  - But what if the SUD is treatment refractory?

ADHD AND SUBSTANCE USE DISORDERS

- 45% of people who use cocaine or methamphetamine had ADHD symptoms[1]

Hypotheses
Poor executive function leads to a lack of self-restraint
Reward system of the brain may be impaired
Substance use may be an attempt to self-treat symptoms
Symptoms of ADHD may lead to demoralization and failure

PREVALENCE AND RISK

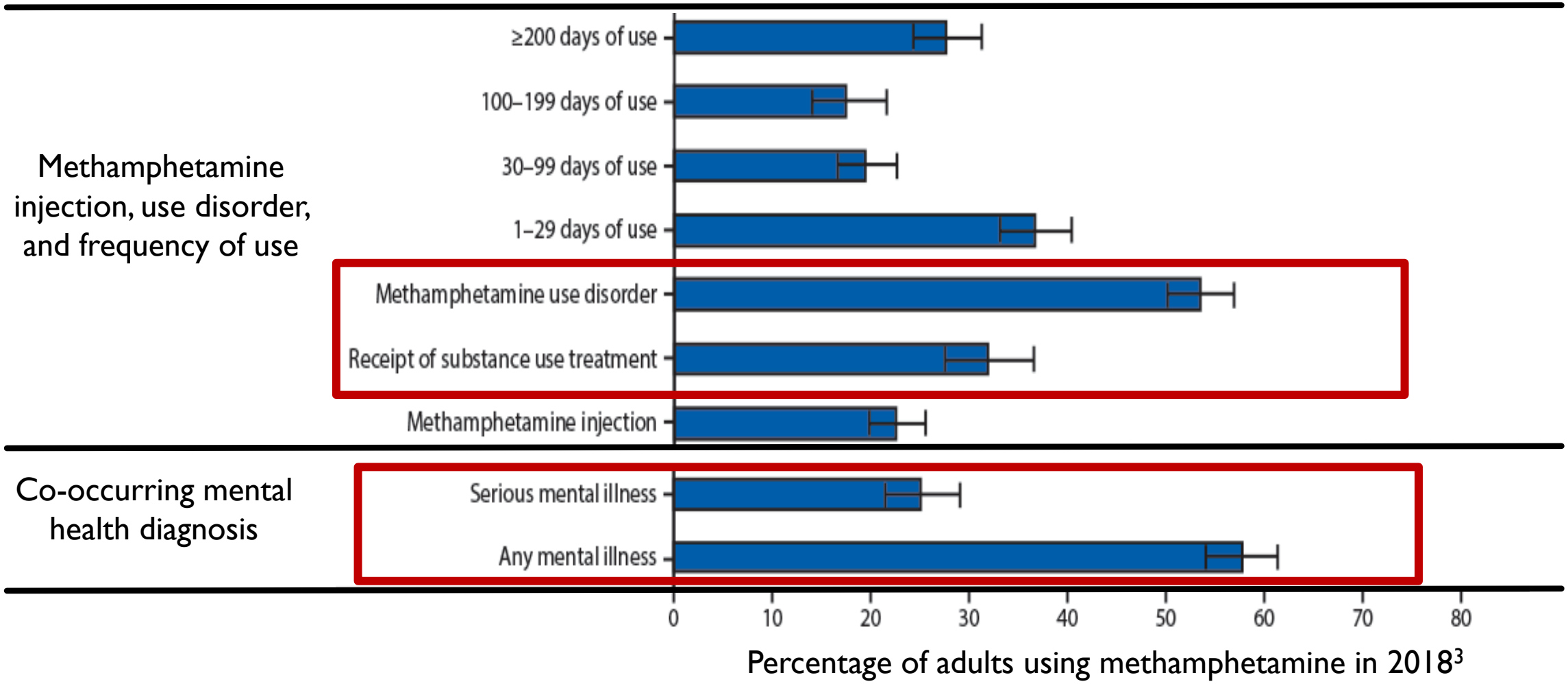
In 2018, an estimated 1.1 million people were diagnosed with methamphetamine use disorder and 1 million with cocaine use disorder[2]

From 2008 to 2015, amphetamine-related hospitalizations increased more than 270%[3]

Risk factors for stimulant use[2]:

- Men
- Age 18-25
- Lower educational attainment
- Annual household income <$50,000
- Living in nonmetro counties
- Co-occurring psychiatric condition

CO-OCCURRING PSYCHIATRIC CONDITIONS



STIMULANT USE HARMS

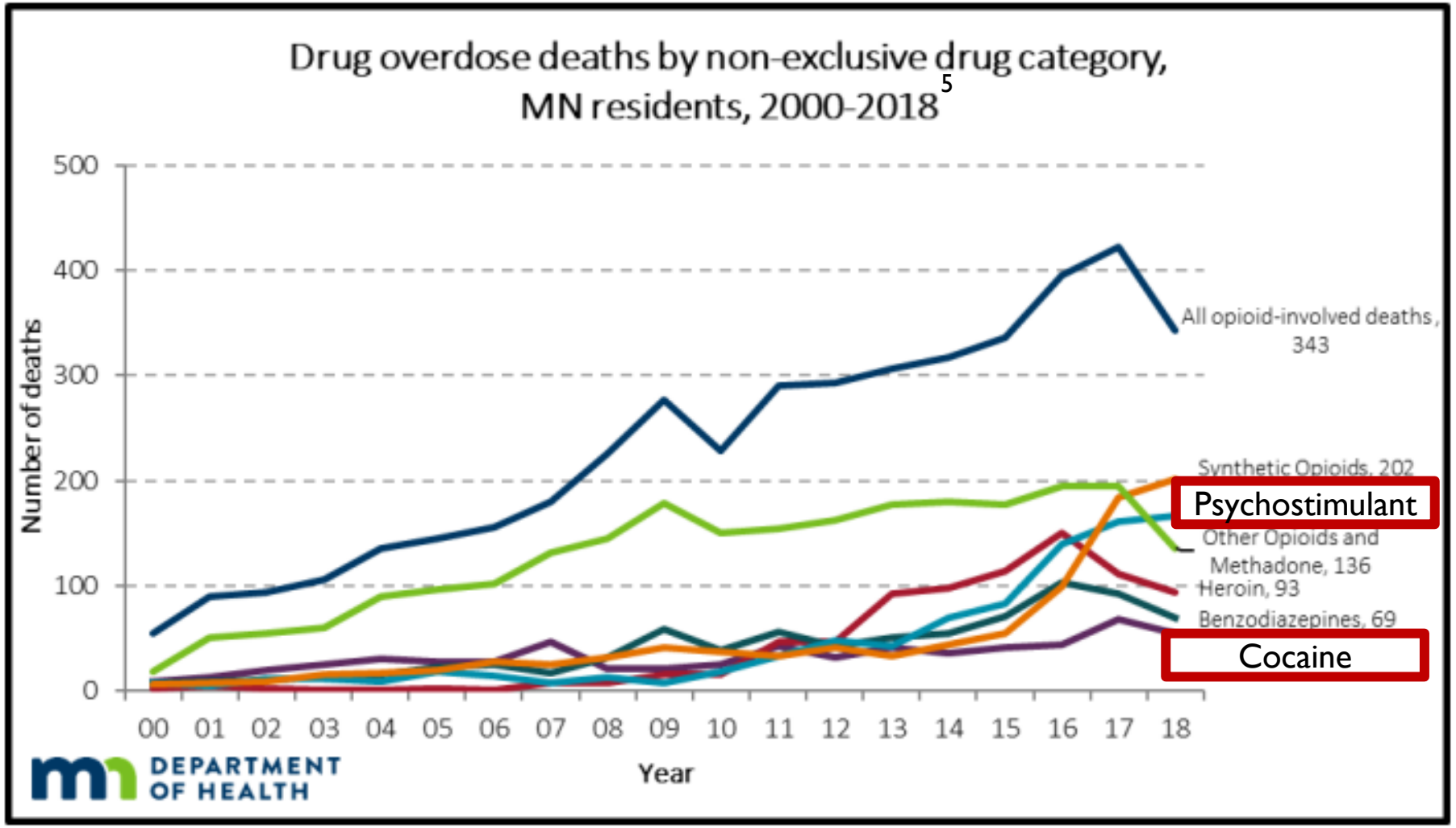
Elevated mortality

Increased incidence of infectious diseases

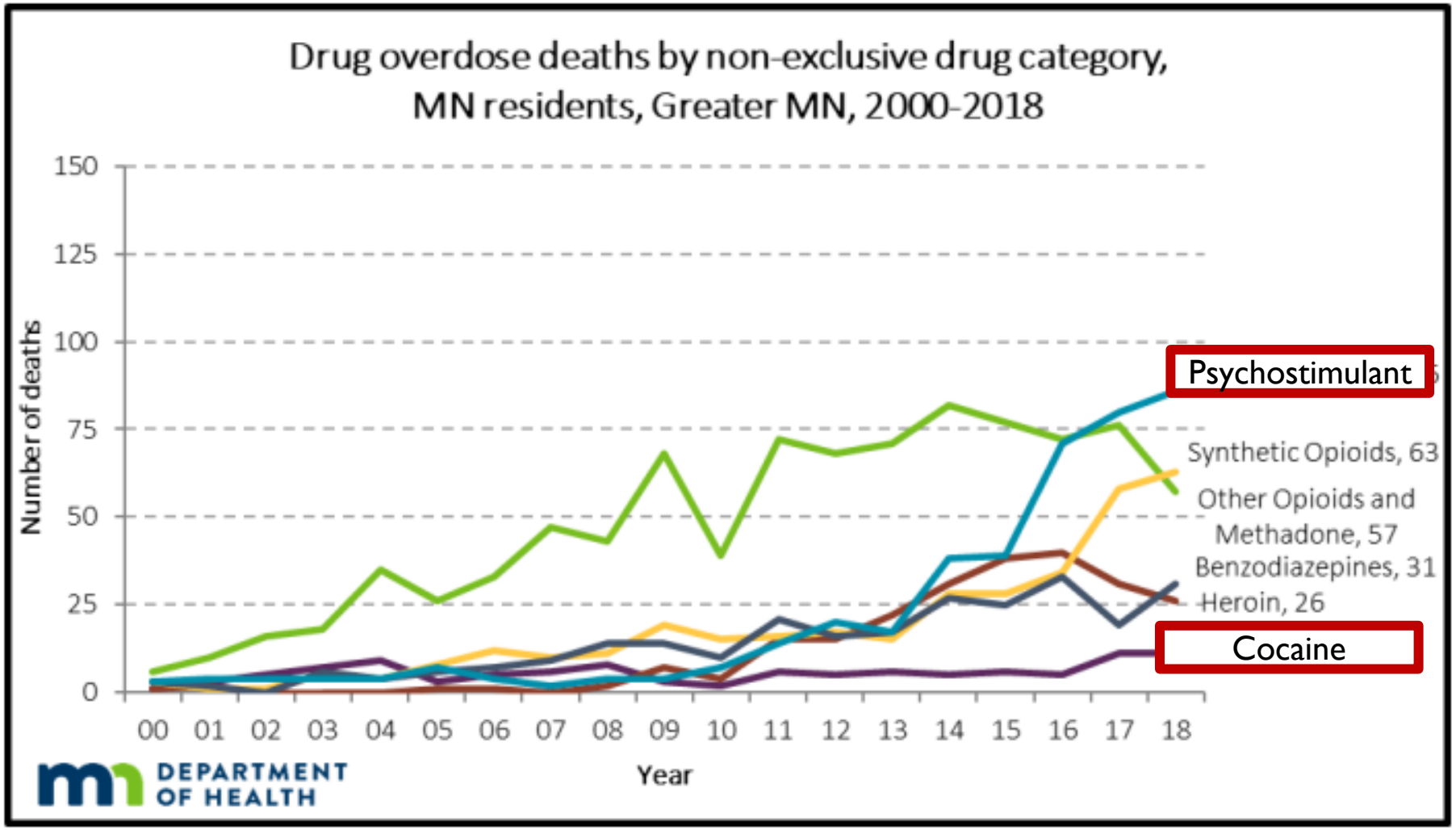
Poorly controlled mental health conditions

Increased risk of cardiovascular events

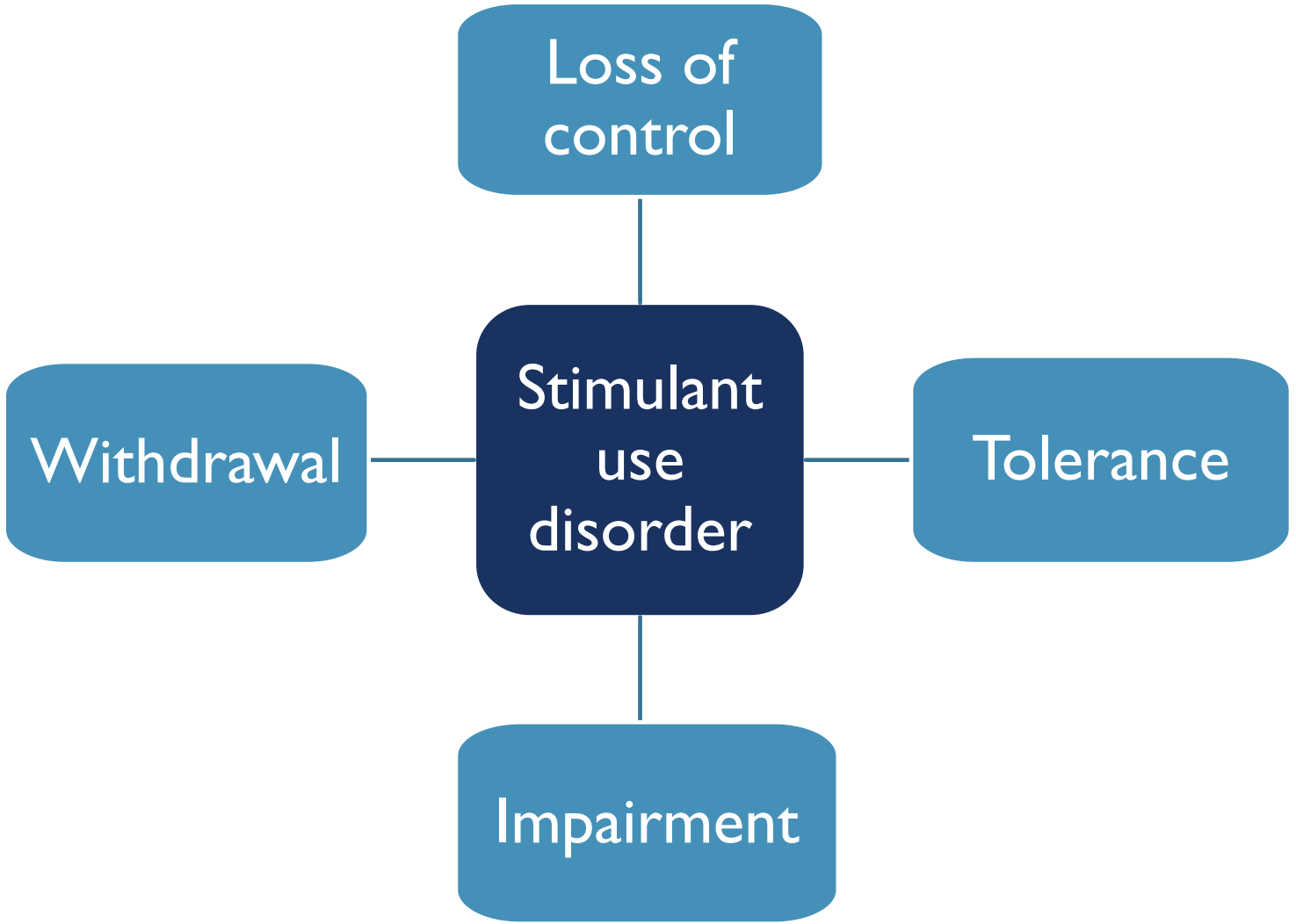
STATEWIDE DRUG OVERDOSES



STATEWIDE DRUG OVERDOSES



STIMULANT USE DISORDER



MEDICATIONS FOR STIMULANT USE DISORDER

- Psychostimulants
  - Amphetamines (Adderall, Vyvanse)
  - Methylphenidate (Ritalin, Concerta)
  - Modafinil (Provigil)
  - Armodafinil (Nuvigil)
- Bupropion
- Mirtazapine
- Topiramate
- Naltrexone
- Disulfiram

No FDA-approved treatment options[7]

MEDICATIONS FOR ADHD

- Psychostimulants
  - Amphetamines (Adderall, Vyvanse)
  - Methylphenidate (Ritalin, Concerta)
  - Modafinil (Provigil)
  - Armodafinil (Nuvigil)
- Bupropion (Wellbutrin)
- Atomoxetine (Strattera)
- SSRI/SNRI
- TCA
- Guanfacine, clonidine** Small trials show these are not efficacious for ADHD in adults

MODAFINIL / ARMODAFINIL

- Mechanism of action:
  - Binds to dopamine transporter and inhibits dopamine reuptake
- FDA approved indications:
  - Narcolepsy, shift work sleep disorder
- Therapeutic doses: modafinil 200-400 mg/day, armodafinil 150-300mg/day
- Monitoring:
  - Blood pressure, heart rate
- Safety feature: the effects cannot be intensified through high-dose IV use due to its insolubility in water and instability at high temperatures
- Schedule IV = refills allowed

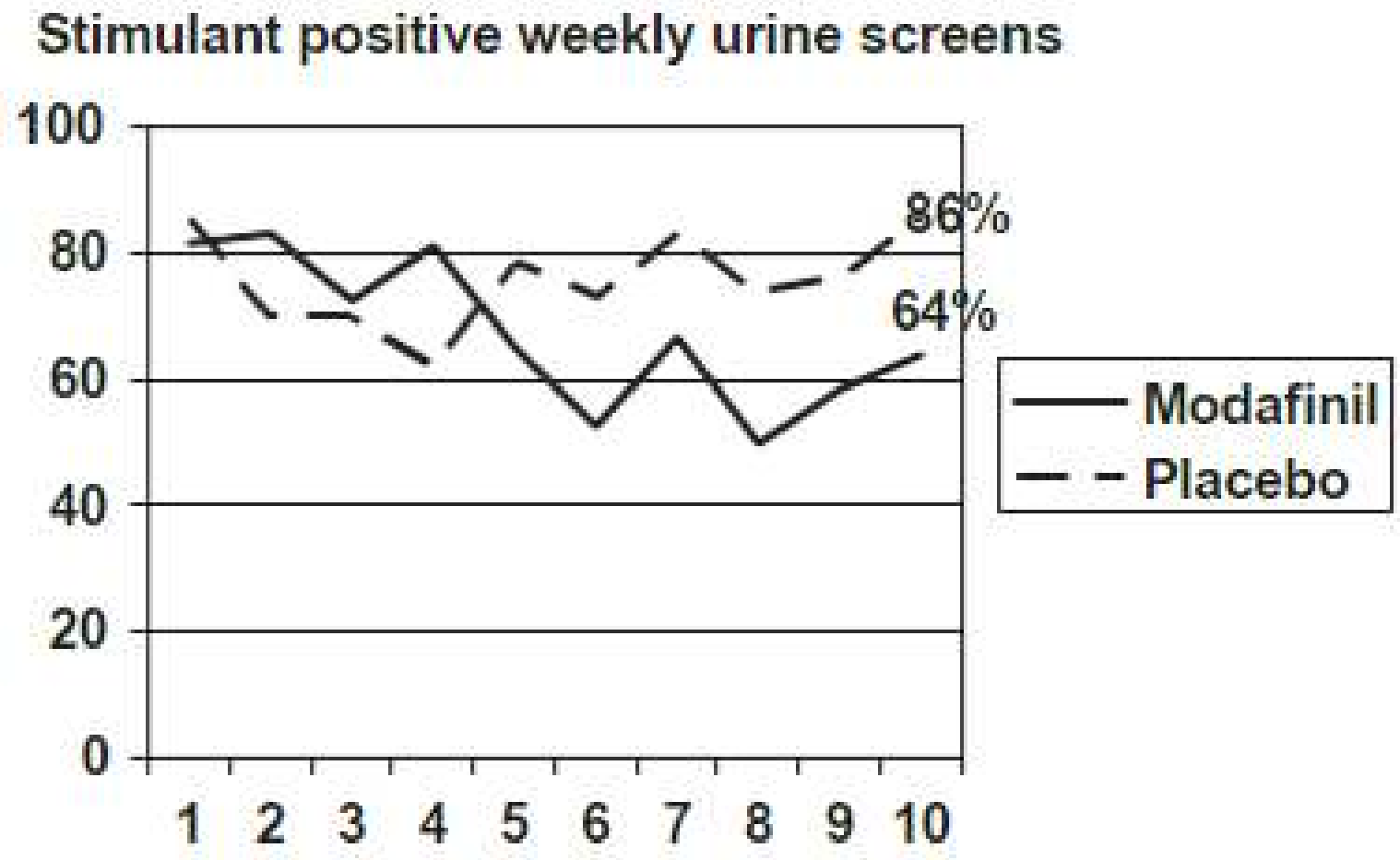
A DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF MODAFINIL (200 MG/DAY) FOR METHAMPHETAMINE DEPENDENCE

Study	• 10-week randomized double-blind placebo-controlled trial
Population	• 80 individuals with methamphetamine dependence
Study Groups/Design	• Randomly assigned to placebo or modafinil 200 mg/day • Offered cognitive behavioral intervention • Primary outcome: negative urine samples • Other outcome: health and psychosocial data
Results	• 29% in the modafinil group and 36% in the placebo group completed the study • Reduction in systolic blood pressure in modafinil group (24% with hypertension at baseline vs 15% at follow-up) • 18% of modafinil vs 53% of placebo experienced weight loss • More negative urine samples in medication-compliant individuals

Shearer et al, 2009

MODAFINIL RESULTS CONTINUED

- No significant difference in urine drug screens or cravings



Modafinil for Treatment of Stimulant Use Disorder: A Case Series

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U.S. Department of Veterans Affairs

University of Minnesota Medical School
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Background

- Stimulant use is a serious public health concern in the United States. Unfortunately, there are currently no Food and Drug Administration (FDA) approved medications for the treatment of cocaine, methamphetamine, or other stimulant use disorders.
- Modafinil, a wakefulness promoting agent approved for the treatment of narcolepsy, obstructive sleep apnea, and shift work sleep disorder, has been utilized off-label for patients with stimulant use disorders.
- Modafinil antagonizes dopamine transporters to increase dopamine availability in the brain, although to a lower extent than amphetamines; as such, it has a lower potential for abuse or misuse compared to traditional prescription stimulants. Modafinil has also been shown to have effects on norepinephrine, orexin, and histamine. Through these mechanisms, it is believed that modafinil may be beneficial in the treatment of cocaine and methamphetamine dependence.
- While a number of clinical trials have evaluated this potential indication, results have been mixed overall. Therefore, our analysis aims to understand the role of modafinil in a real-world setting.

Disclosures

None

Methods

- This is a prospective case series performed at the Minneapolis Veterans Affairs Health Care System. Patients seen in the Addiction Recovery Services clinic who carried a Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) diagnosis of stimulant use disorder were offered treatment with off-label modafinil titrated based on efficacy and tolerability.
- All care, including psychotherapy and other psychotropic medications, was continued as usual.
- Due to nature of study (i.e. prospective), stimulant use was evaluated using patient self-report or UDS as routinely collected.
- The primary outcome was change in self-reported stimulant use (i.e. reduction, abstinence, or no change).
- Secondary outcomes included participation in recovery groups and adverse events reported.

Data

Patient	Gender	Race	Stimulant Use Disorder	Modafinil Maximum Dose	Modafinil Duration	Stimulant Use	Reason for Discontinuation	Weekly Recovery Activity
1	Male	African American	Cocaine	400mg - 600mg**	3 months	Unchanged	Overuse, Ineffective	No
2	Male	Caucasian	Cocaine	400mg	3 months	Unchanged	Ineffective	No
3	Male	African American	Cocaine	400mg	3 months*	Abstinent	-	Yes
4	Male	African American	Cocaine	400mg	6 months*	Reduced	-	Yes
5	Transgender Female	Caucasian	Methamphetamine	400mg	3 months*	Reduced	-	Yes
6	Male	Caucasian	Methamphetamine	200mg	9 months*	Abstinent	-	Yes
7	Male	Caucasian	Methamphetamine	400mg	6 months*	Reduced	-	Yes
8	Male	African American	Cocaine	400mg – 600mg**	12 months*	Abstinent	-	Yes
9	Male	Caucasian	Methamphetamine	400mg	3 months	Reduced	Worsen psychosis	Yes
10	Male	Caucasian	Methamphetamine	200mg	6 months*	Abstinent	-	Yes
11	Male	Caucasian	Methamphetamine	200mg	3 months*	Unchanged	-	Yes
12	Male	Caucasian	Methamphetamine	200mg	3 months	Unchanged	Insomnia	Yes
13	Male	Caucasian	Methamphetamine	400mg	1 month	Unchanged	Ineffective	Yes
14	Male	Caucasian	Methamphetamine	200mg	5 months*	Abstinent	-	Yes
15	Female	Caucasian	Methamphetamine	200mg	1 month*	Abstinent	-	Yes

* Denotes ongoing modafinil use (beyond data collection time) ** Patient used higher modafinil dose than prescribed

Results

Between July 2017 and September 2018, a total of 15 patients were initiated on modafinil for stimulant use disorder at our facility. Five patients were diagnosed with cocaine use disorder and ten patients were diagnosed with methamphetamine use disorder. The majority of patients had co-morbid mental health disorders (mood disorders, PTSD, schizophrenia) and/or comorbid substance use disorders. No patients were prescribed atomoxetine, bupropion, naltrexone, stimulants, or topiramate, though one patient was prescribed mirtazapine for insomnia. At the time of data collection (November 2018), the average prescribed dose of modafinil was 320mg daily (range 200-400mg). Self-reported stimulant use was reduced or eliminated in ten patients (67%). More specifically, six patients (40%) reported abstinence, four patients (27%) reported reduced use, and five patients (33%) reported no change in use pattern. Urine drug screens confirmed self-reported use patterns. Two patients (13%) overused their prescribed modafinil. In all but two cases, modafinil was well tolerated with no side effects reported.

Discussion

The majority of patients prescribed modafinil reduced or ceased stimulant use. Modafinil was well tolerated overall, with the most common reason for discontinuation being perceived lack of efficacy. While one could argue that the reduction of stimulant use could be attributed to recovery group participation, patients who were prescribed modafinil qualitatively reported improved engagement in recovery groups as compared to patients not prescribed modafinil.

Conclusions

- Modafinil is a well-tolerated medication treatment option for patients with stimulant use disorders.
- Use of modafinil in patients with stimulant use disorders may improve engagement in psychotherapeutic recovery groups.
- This data, along with previously published research, may be used to support addition of modafinil to the VA formulary for use in patients with stimulant use disorders.

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DEXTROAMPHETAMINE AND METHYLPHENIDATE

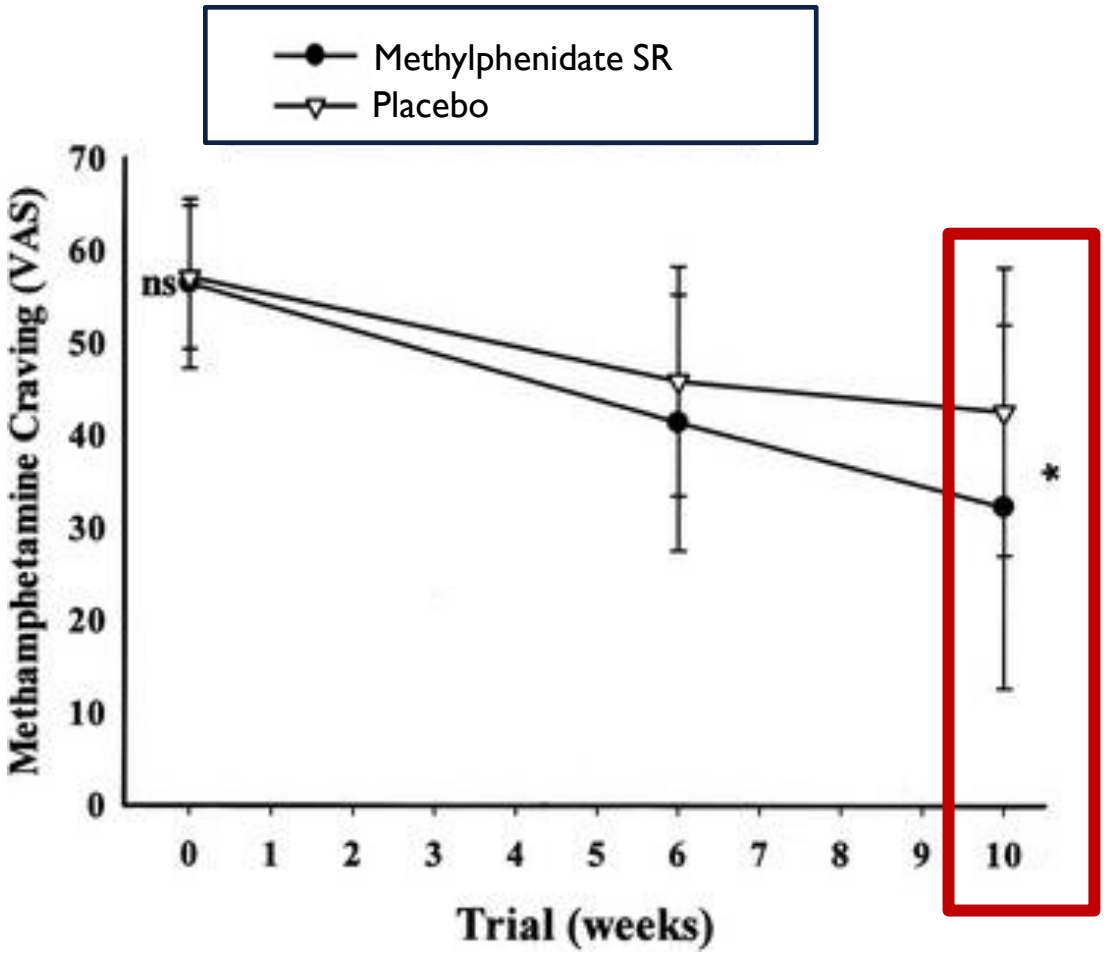
- Mechanism of action:
  - Increases dopamine and norepinephrine in the synapse
- FDA approved indications:
  - ADHD, narcolepsy
- Dose studied:
  - Dextroamphetamine Sustained Release (SR): 15-60 mg/day
  - Methylphenidate SR: 18-54 mg/day (Real world: max 72mg/day)
- Monitoring:
  - Blood pressure, heart rate, EKG
  - Weight loss
  - PDMP

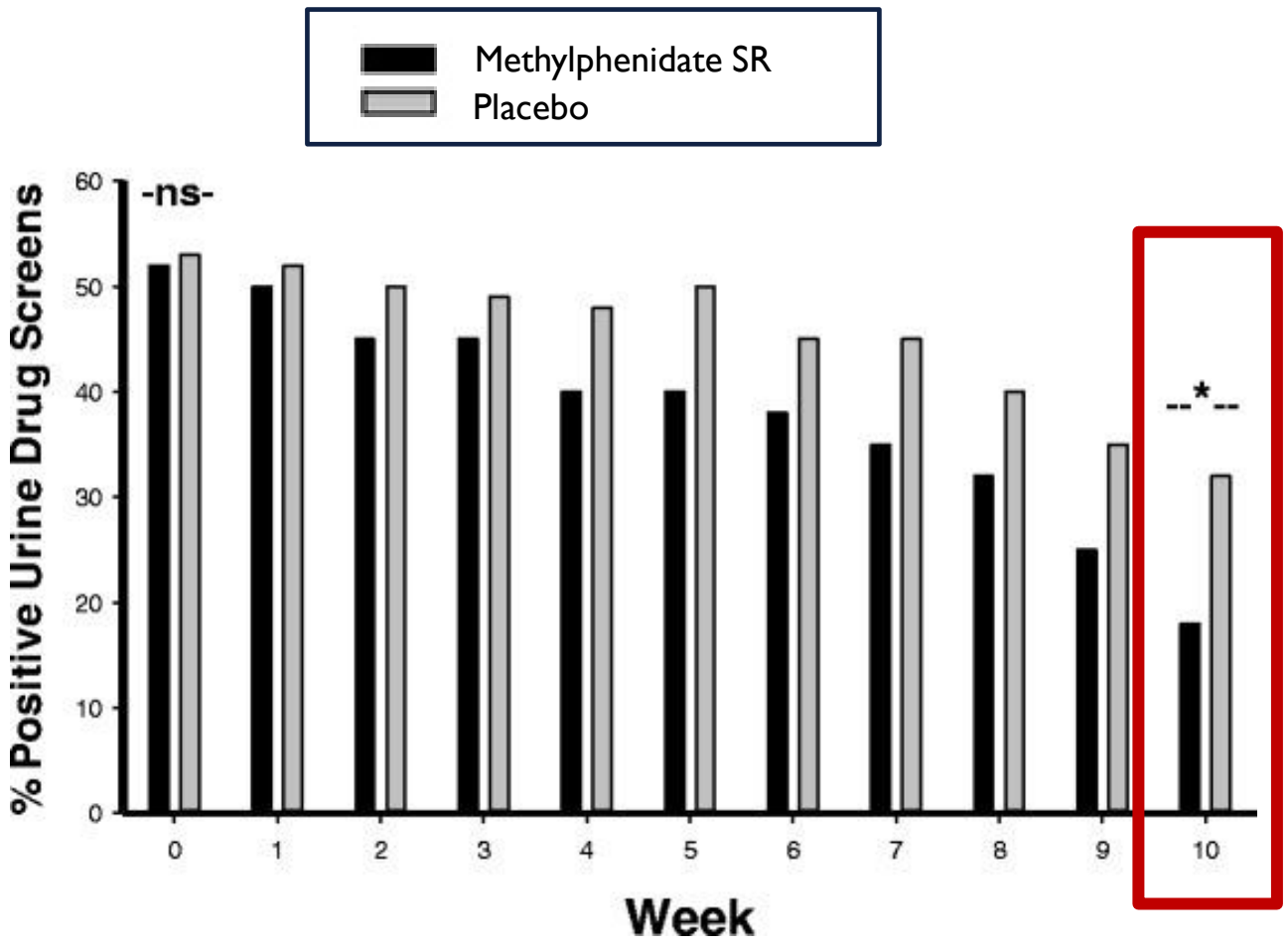
SUSTAINED-RELEASE METHYLPHENIDATE IN METHAMPHETAMINE DEPENDENCE TREATMENT: A DOUBLE-BLIND AND PLACEBO-CONTROLLED TRIAL

Study	• 10-week randomized double-blind placebo-controlled trial
Population	• 56 individuals with methamphetamine dependence • Excluded individuals with ADHD
Study Groups/Design	• Randomly assigned to methylphenidate SR 54 mg or placebo • Medication administered daily under staff supervision • Primary outcome: methamphetamine cravings • Other outcome: weekly urine drug screens
Results	• Trial completion: 64% of treatment group 57% of placebo group • No significant difference in adverse effects

Rezaei et al, 2015

METHYLPHENIDATE SR RESULTS CONTINUED





EXTENDED-RELEASE MIXED AMPHETAMINE SALTS VS PLACEBO FOR COMORBID ADULT ATTENTION-DEFICIT HYPERACTIVITY DISORDER AND COCAINE USE DISORDER: A RANDOMIZED CLINICAL TRIAL

Study	• 13 week randomized double-blind placebo-controlled trial
Population	• 126 adults with comorbid ADHD and cocaine use disorder
Study Groups/Design	• Randomly assigned to placebo or mixed ER amphetamine salts 60 or 80 mg • Weekly cognitive behavioral therapy (CBT) sessions • Primary outcomes: ADHD symptom severity, negative urine drug screens • Other outcome: percentage of patients achieving abstinence for the last 3 weeks
Results	• 74% of individuals completed the study • Dry mouth was the only adverse event that occurred significantly more in the amphetamine group

Levin et al, 2015

MIXED AMPHETAMINES RESULTS CONTINUED

Outcome	60 mg vs. Placebo	80 mg vs. Placebo
Reduction in ADHD symptom severity	75% vs 40% (*P* < 0.001)	58% vs 40% (*P* = 0.07)
Cocaine abstinence	OR = 2.92 (95% CI, 1.15–7.42; *P* = 0.02)	OR = 5.46 (95% CI, 2.25–13.27; *P* < 0.001)
Proportion of cocaine abstinence in the last 3 weeks	17.5% vs 7% OR = 5.85 (95% CI, 1.04–33.04; *P* = 0.04)	30.2% vs 7% OR = 11.87 (95% CI, 2.25–62.62; *P* = 0.004)

Abstinence in the last 3 weeks was no different between the 80 mg and 60 mg groups (OR = 0.49; 95% CI, 0.16–1.53; *P* = 0.22)

AMPHETAMINES VS. METHYLPHENIDATE

- 2018 network meta-analysis of clinical trials of ADHD drugs concluded that amphetamines were moderately more efficacious in reducing core ADHD symptoms compared with methylphenidate
- Amphetamines are associated with higher risk of adverse events
- There do not appear to be differences in efficacy between short versus long-acting stimulants
- Methylphenidate does not show up on standard urine drug screen; amphetamines do show up, making it difficult to differentiate between recreational (meth) use and prescribed (Adderall) use.
  - If someone is prescribed an amphetamine and uses recreational meth, UDS confirmation testing is needed.

BUPROPION

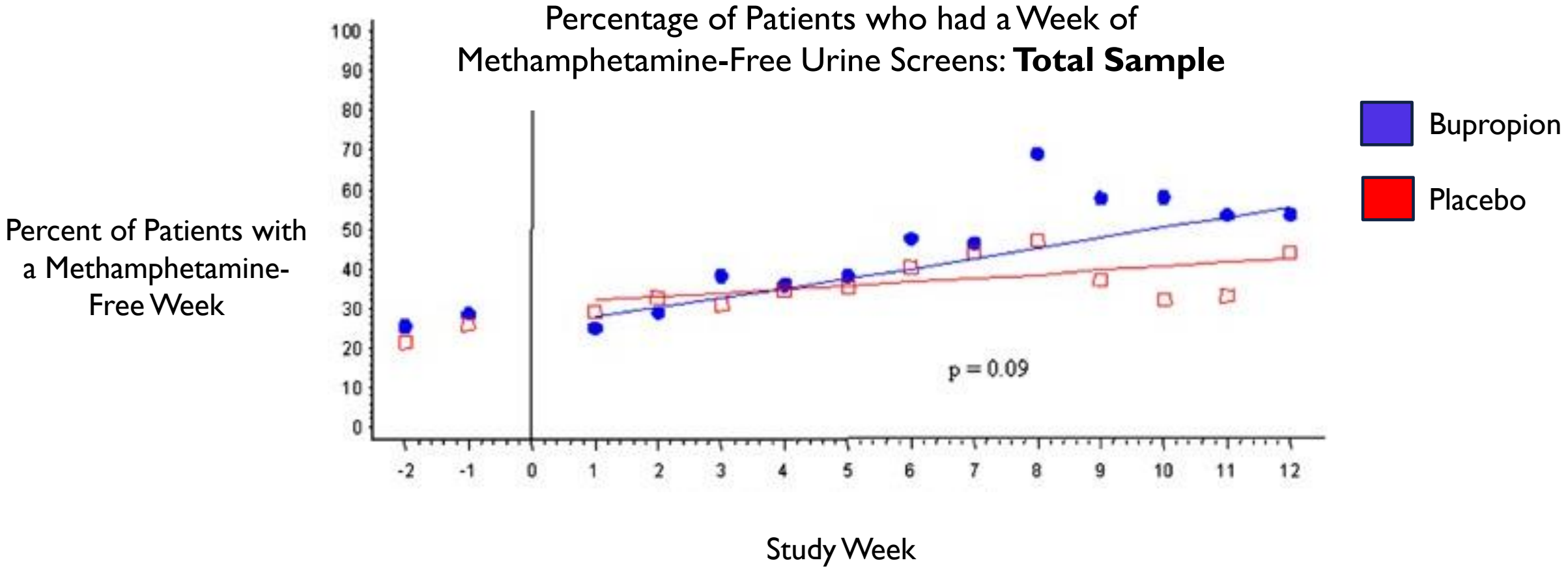
- Mechanism of action:
  - Blocks reuptake of dopamine and norepinephrine
- FDA approved indications:
  - Major depressive disorder, seasonal affective disorder, tobacco cessation
- Dose studied:
  - Bupropion SR 150 mg twice a day (Real world: bupropion XL up to 450mg qam)
- Monitoring:
  - Blood pressure, heart rate
  - Weight loss
- FYI- can cause false positive for stimulants on UDS, consider confirmation testing

BUPROPION FOR THE TREATMENT OF METHAMPHETAMINE DEPENDENCE

Study	• 12-week randomized double-blind placebo-controlled study
Population	• 151 participants with a diagnosis of methamphetamine dependence
Study Groups/Design	• Randomly assigned to placebo or bupropion SR 150 mg twice daily • Individuals had clinic visits 3 times a week for assessments, urine drug screens, and 90-minute group psychotherapy • Primary outcome: methamphetamine-free week • Secondary outcomes: cravings
Results	• 52.8% of the placebo group and 51.9% of the bupropion group completed the study • No difference in weekly craving scores

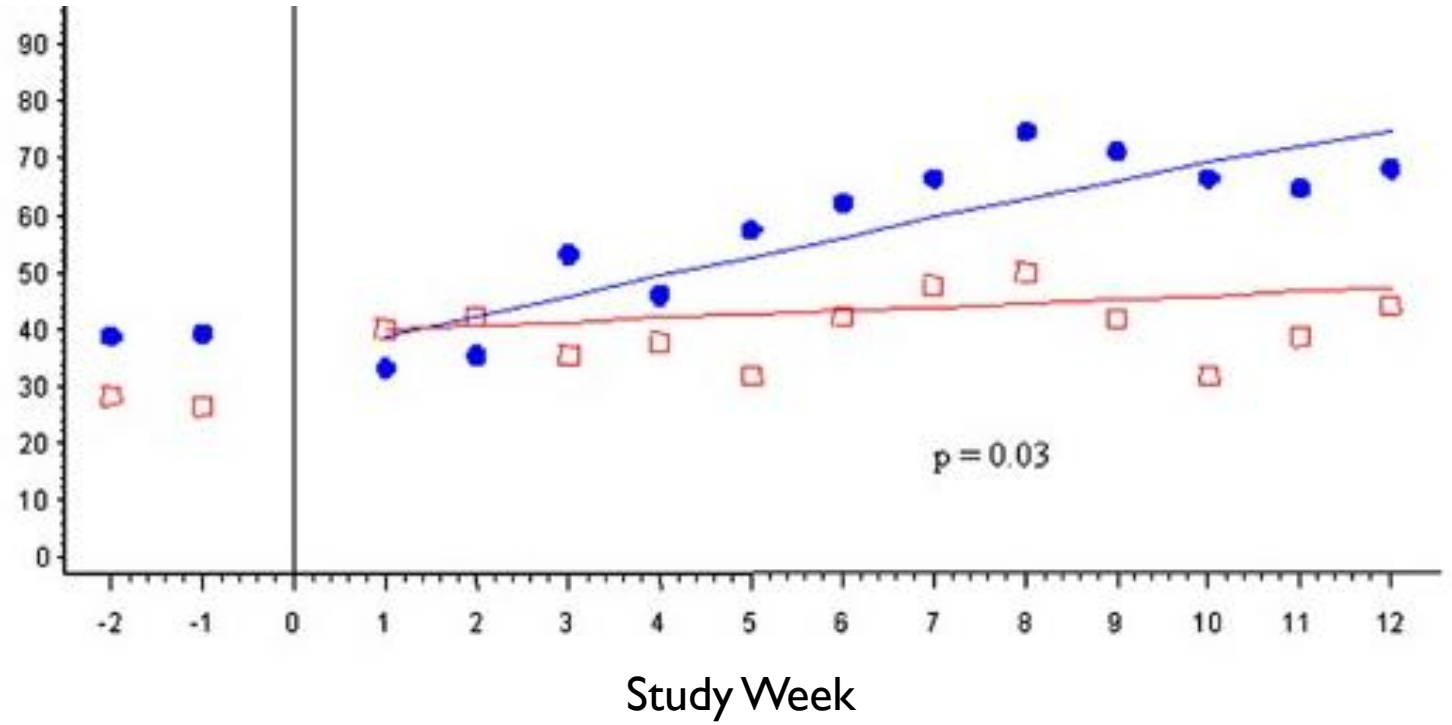
Elkashef et al 2008

BUPROPION RESULTS CONTINUED



BUPROPION RESULTS CONTINUED

Percentage of Patients who had a Week of Methamphetamine-Free Urine Screens: **Baseline Low Use**

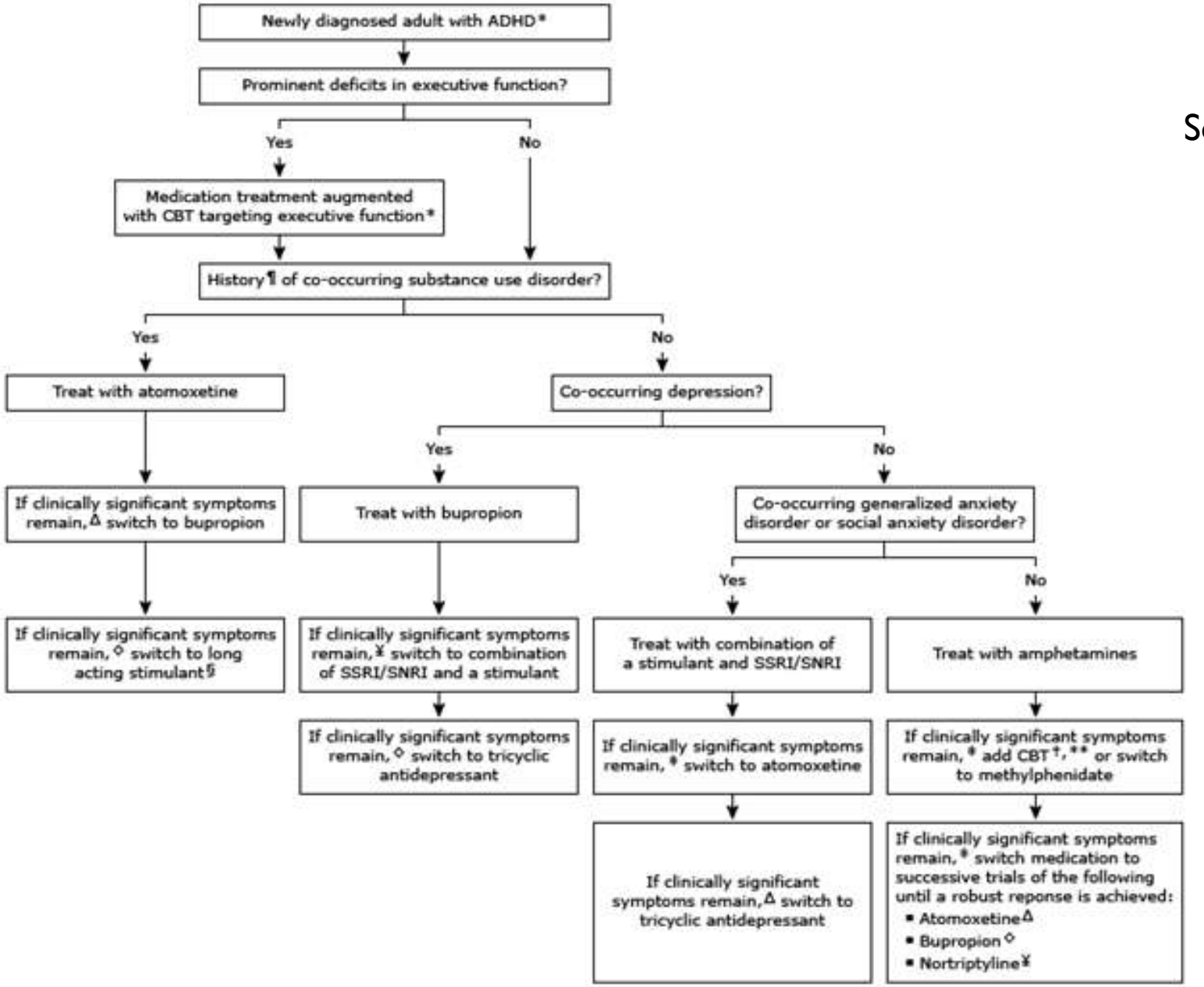


Baseline low use: Less than 18 days in the last 30

Bupropion

Placebo

Approach to treating ADHD in adults



Source: UpToDate

KEY TAKEAWAYS

- Goals of treatment are patient-specific
- There are no FDA-approved pharmacologic treatment options for stimulant use disorder
- Extended-release amphetamines, methylphenidate, armodafinil, modafinil, and bupropion are tools for treating comorbid ADHD and stimulant use disorder
- Benefit of pharmacologic treatment is likely greater than the risk of not offering treatment

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QUESTIONS?