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Treatment for Stimulant Use Disorder: Maximizing Evidence Based Practices

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Clinical Challenges for Individuals with Methamphetamine Use Disorder

Overdose death

Limited understanding of stimulant addiction

Ambivalence about need to stop use

Impulsivity/Poor judgement

Cognitive impairment and poor memory

Paranoia

Clinical Challenges with Individuals with Methamphetamine Use Disorder

Anhedonia

Hypersexuality/Hyposexuality

Violence and psychosis

Powerful Pavlovian trigger-craving response

Very poor retention in outpatient treatment

Special Treatment Consideration Should Be Made for the Following Groups

People who inject methamphetamine.
People who use methamphetamine daily.
Women (high rates of physical/sexual abuse).
Homeless, chronically mentally ill and/or individuals with high levels of psychiatric symptoms at admission.
Men who have sex with men (MSM).
People who use stimulants who are under the age of 21.
Individuals in medication treatment for OUD.

Interest in Reducing Methamphetamine and Opioid Use among Syringe Services Program Participants in Washington State McMahan et al, 2020 Drug and Alcohol Dependence

- In a sample of 583 participants at a Washington State syringe exchange program (443 opioids; 140 methamphetamine), survey data were collected on their attitudes about stopping drug use.
- 82% of the individuals who reported opioids as their main drug expressed an interest in reducing/stopping opioid use
- 46% of individuals who reported methamphetamine as their main drug expressed an interest in reducing/stopping their meth use.

Treatment for Individuals with Stimulant Use Disorder

Lappan SN, Brown AW, Hendricks PS. Dropout rates of in-person psychosocial substance use disorder treatments: a systematic review and meta-analysis. Addiction. 2020 Feb;115(2):201-217. doi: 10.1111/add.14793.

Dropout rates of in-person psychosocial substance abuse treatment: a systematic review and meta-analysis (Lappan et al., Addiction, 2020)

- Meta-analysis of in-person psychosocial SUD treatment.
- Drop out rates in first 90 days of treatment
- 151 studies, with 26,243 participants.
- Results yielded overall average dropout rates, and predictors of dropout.

Substance Targeted and Dropout

Treatment Target	Dropout Rate
Heroin	25.1
Tobacco	25.5%
Alcohol	26.1%
Cocaine	48.7%
Methamphetamine	53.5%

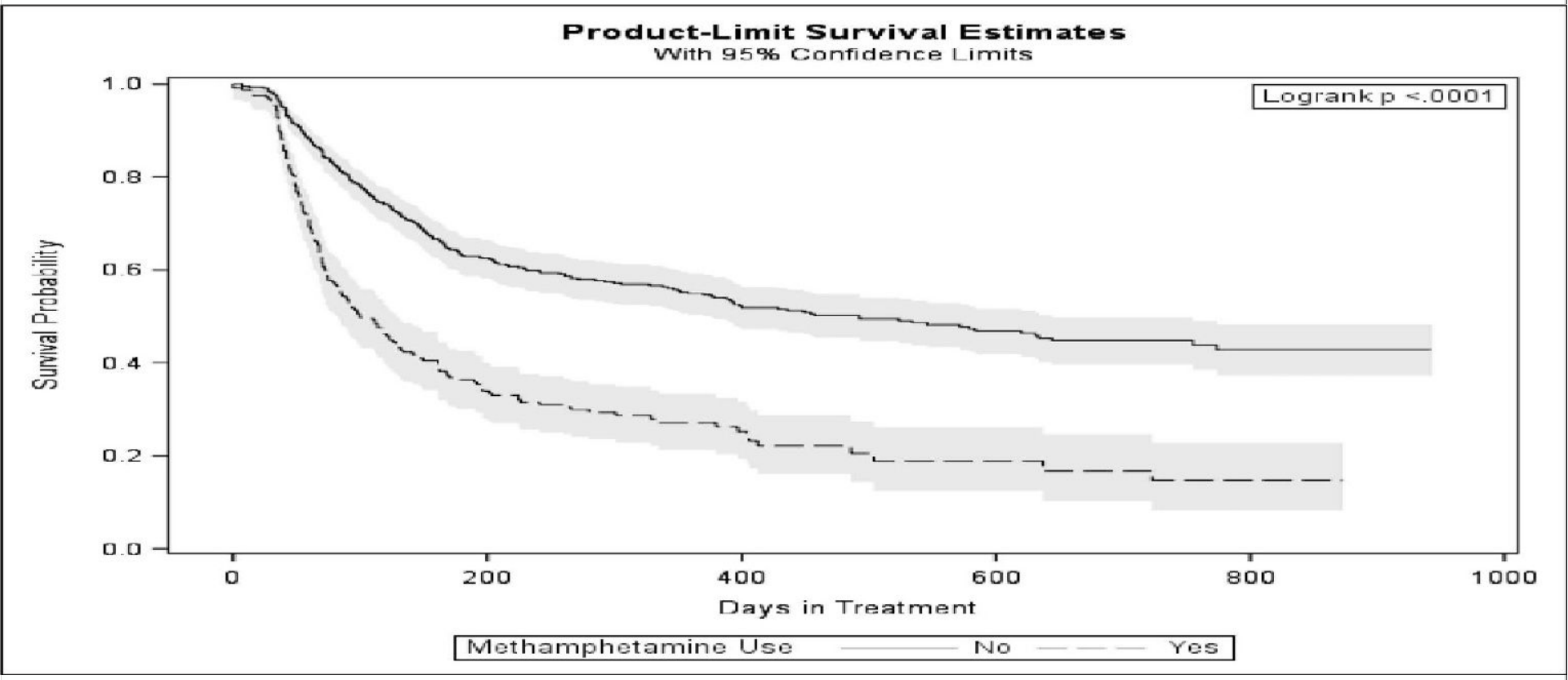
Judith I. Tsui, et al (2020) Association between methamphetamine use and retention among patients with opioid use disorders treated with buprenorphine. Journal of Substance Abuse Treatment 109:80–85

Association Between Methamphetamine Use and Retention Among Patients With Opioid Use Disorders Treated With Buprenorphine

- The study utilized data on adult patients receiving buprenorphine from Washington State Medication Assisted Treatment-Prescription Drug and Opioid Addiction program clinics between November 1, 2015, and April 31, 2018 (N=799). Past 30-day substance use data were collected at baseline, 6-months, and date of program discharge.

- 30% (n=237) of individuals reported meth use at admission. Baseline methamphetamine use was associated with more than twice the relative hazards for discharge in adjusted models (aHR=2.39; 95% CI: 1.94–2.93).

Association Between Methamphetamine Use and Retention Among Patients With Opioid Use Disorders Treated With Buprenorphine



Do Individuals who use methamphetamine respond differently to behavioral treatments than individuals who use cocaine?

In published research studies where treatment response to behavioral treatments have been compared with individuals who use cocaine vs individuals who use methamphetamine,there is:

No evidence of differential treatment response .

Systematic Reviews and Meta-analyses

PLOS | MEDICINE

RESEARCH ARTICLE

Comparative efficacy and acceptability of psychosocial interventions for individuals with cocaine and amphetamine addiction: A systematic review and network meta-analysis

Franco De Crescenzo[1,2,3], Marco Ciabattini[4], Gian Loreto D'Alò[4], Riccardo De Giorgi[1,2], Cinzia Del Giovane[5], Carolina Cassar[6], Luigi Janiri[3], Nicolas Clark[7], Michael Joshua Ostacher[8,9], Andrea Cipriani[1,2]*

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Check for updates

PLOS Medicine | December 26, 2018

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Meta-analysis findings DeCrescenso, et al, 2018.

Network meta-analysis was used to analyze 50 clinical studies (6,943 participants) on 12 different psychosocial interventions for cocaine and/or amphetamine addiction.

The combination of contingency management and community reinforcement approach, was the most efficacious and most acceptable treatment both in the short and long term.

Psychosocial Interventions for Cocaine and Psychostimulant Amphetamines Related Disorders. *Werner Paulo Knapp, Bernardo Soares, Michael Farrell, Maurício Silva deLima. (2009) The Cochrane Collaboration.*

Twenty-seven randomized controlled studies (3663 participants) fulfilled inclusion criteria and had data that could be used for at least one of the main comparisons.

- The comparisons between different type of behavioral interventions showed results in favor of treatments with <u>some form of contingency management in respect to both reducing dropouts and lowering cocaine use</u>.

Responding to global stimulant use: Challenges and opportunities Lancet (Farrell et al, 2019)

Psychosocial interventions other than contingency management have weak and non-specific effects on stimulant problems and there are no effective pharmacotherapies. Substantial research investment is needed to develop more effective, innovative, and impactful prevention and treatment.

Non-pharmacological interventions for methamphetamine use disorder: a systematic review AshaRani, PV, et al. Drug and Alcohol Dependence, 2020

- 44 Studies reviewed.
- Conclusions: While Contingency Management (CM) interventions showed the strongest evidence favoring the outcomes assessed, tailored CBT alone or with CM was also effective in the target population.

Ronsley C, Nolan S, Knight R, Hayashi K, Klimas J, Walley A, et al. (2020) Treatment of stimulant use disorder: A systematic review of reviews. PLoS ONE 15(6): e0234809. https://doi.org/10.1371/journal.pone.0234809

Treatment of stimulant use disorder: A systematic review of reviews

Ronsley et al., 2020

- Synthesize available evidence on psychosocial and pharmacologic interventions for the treatment of stimulant use disorder.
- Identify the most effective treatments.
- Highlight gaps for future study.

Interventions reviewed

- 29 reviews resulted.
- 11 interventions were examined:
  - Contingency management
  - Cognitive behavioral treatment
  - Acupuncture
  - Antidepressants (e.g., fluoxetine, bupropion)
  - Dopamine agonists (e.g., levodopa)
  - Antipsychotics (e.g., aripiprazole)
  - Anticonvulsants (e.g., topiramate)
  - Disulfiram
  - Opioid agonists (e.g., buprenorphine, methadone)
  - N-acetylcysteine (for acetaminophen overdose)
  - Psychostimulants (e.g., modafinil, methylphenidate)

Conclusions

- The strongest body of evidence was for contingency management.
- Of pharmacologic treatments, psychostimulants appear to be the most promising, but data are insufficient to support clinical use and further research is necessary.
- Some positive results for opioid agonist treatment, n-acetylcysteine, disulfiram, and antidepressants.
- All other interventions found predominantly negative results.

Contingency Management (also known as Motivational Incentives)

Contingency Management

A technique employing the systematic delivery of positive reinforcement for desired behaviors. In the treatment of methamphetamine dependence, vouchers or prizes can be "earned" for submission of methamphetamine-free urine samples or for attendance at treatment sessions.

The 3 Essential Elements

1. Target behaviors must be readily detected
2. Tangible reinforcers are provided whenever the targeted behavior is demonstrated
3. When the target behavior does not occur, the reinforcers are withheld

Founding Principles

1. Identify Target Behavior
2. Choice of Target Population
3. Choice of Reinforcer
4. Incentive Magnitude
5. Frequency of Incentive Distribution
6. Timing of Incentive
7. Duration of Intervention

FOUNDING PRINCIPLES

1. Identify Target Behavior

A target behavior should be:

- Problematic and in need of change
- Observable
- Measurable
- Relatively easy for the patient to accomplish (at least initially)

2. Choice of Target Population

EXAMPLES:

- Patients not responding to treatment
- Newly enrolled patients
- Users of a specific substance (e.g., patients enrolled in a methadone program and continuing to use cocaine)
- Vulnerable population (e.g., pregnant women)

3. Choice of Reinforcer

- May be different from what *you* want or like to do—and it is not what *you* think is good for the patient
- Critical to view from patients' perspectives, or you will compromise effectiveness

3. Choice of Reinforcer continued

Three major types of incentive programs

- **Access to clinic privileges**
  Example: Take-home dose of methadone
- **On-site prize distribution**
  Example: A prize cabinet contains many small prizes, some large prizes and a few jumbo prizes
- **Vouchers or other token economy systems**
  Example: Points or vouchers are accumulated in an account and redeemed for retail goods or services

4. Incentive Magnitude

- Will determine the degree to which the intervention is effective
- Should be able to compete with reinforcement derived from the behavior targeted for change
- Increases as the desired behavior is repeated

The Fishbowl Method gives patients the opportunity to win prizes of varying magnitude.

NANCY PETRY, PH.D.

5. Frequency of Incentive Distribution

- Can the targeted behavior be reinforced frequently?
- What method will be used to distribute incentives?
- How often will the incentive be distributed?

6. Timing of Incentive

- Immediacy is important
- Poor timing can undermine the most well-planned intervention

7. Duration of Intervention

How long?

Until the patient...

- Internalizes the recovery process
- Develops naturally-occurring reinforcers that support recovery

Course Content

- Why Use Motivational Incentives?
- Definitions
- History & Research
- Founding Principles
- **Low Cost Incentives**
- Perspectives

Managing the Cost

- **MIEDAR** studies focused on managing the cost and efficacy of incentives
- **Fishbowl Method** – patients select a slip of paper (or ticket) from a Fishbowl
- Behavior is reinforced immediately
- Patient draws from the Fishbowl immediately after a drug-free urine screen
- Patient exchanges prize slip for a selected prize from the cabinet

NANCY PETRY, PH.D.

Fishbowl Method

Fishbowl Ticket Ratios

To manage cost, ticket ratios are as follows:

TICKET	COST	CHANCE
Good Job	$0	50.0%
Small	$1	41.8%
Large	$20	8.0%
Jumbo	$80–$100	0.2%

Fishbowl Method

Patients select an increasing number of draws each time they display a targeted behavior.

- Get one draw for the first drug-free urine sample, two draws for the second drug-free urine sample, and so on
- Lose the opportunity to draw a prize with a positive urine screen, but are encouraged and supported
- When patients test drug-free again, they start with one draw

Challenges

Isn't this just rewarding patients for what they should be doing anyway?

That's a common concern. But sometimes the problem is that patients are not doing the things that are good for them and need a motivational boost!

Contingency Management for the Treatment of Methamphetamine Use Disorder: A Systematic Review

Brown and DeFulio, 2020

- A review of 27 studies.
- All included a contingency management intervention for methamphetamine users.
- Outcomes:
  - Drug abstinence
  - Retention in treatment
  - Attendance/treatment engagement
  - Sexual risk behavior
  - Mood/affect
  - Treatment response predictors

Results of CM Treatments

- Reduced methamphetamine use in 26 of 27 studies.
- Longer retention in treatment.
- More therapy sessions attended; higher use of other services and medical services.
- Reductions in risky sexual behavior.
- Increases in positive affect and decreases in negative affect.

Three Major Challenges to using CM

- Medicaid regulations that restrict the amount of incentives that can be given to patients to $75 per patient per year.
- Where does the funding for incentives come from?
- Staff resistance to the idea of incentives
  - Patients should not have to be “paid” or “bribed”; recovery is the reward
  - Motivation needs to come from within, etc……

Current status of Treatment Approaches for Methamphetamine Use Disorder

- Contingency management unanimously (5 systematic reviews and meta-analyses) found to have best evidence of effectiveness.
- Other approaches with less but clear evidence of support: Cognitive Behavioral Therapy (CBT) and Community Reinforcement Approach (CRA).
- Approach with evidence for treatment of a broad variety of SUD: Motivational Interviewing (MI).
- Approach with recent studies showing benefit to methamphetamine users: Physical Exercise (PE) (e.g., Rawson et al., 2015).

Community Reinforcement Approach (CRA)

Community Reinforcement Approach

Community Reinforcement Approach (CRA) is a combination of behavioral strategies that address the role of environmental contingencies in encouraging or discouraging drug use, and attempts to rearrange these contingencies so that a non-drug using lifestyle is more rewarding than a using one.

Components of CRA

- Behavioral skills training
- Social and recreational counseling
- Marital therapy
- Motivational enhancement
- Job counseling
- Relapse prevention

A sample of CRA Topics

- Functional Analysis
- Drug Refusal Skills
- Social Skills/Assertiveness Training
- Social Recreational Counselling
- Employment Preparation Skills
- Relationship Happiness Scale
- Positive Interactions

Cognitive Behavioral Therapy

- CBT is a form of “talk therapy” based on principles of social learning theory.
  - Used to teach, encourage and support individuals in reducing or stopping their harmful drug use
  - Provides skills aimed at sustaining abstinence
  - Addresses negative thought patterns and helps to develop coping strategies to prevent relapse

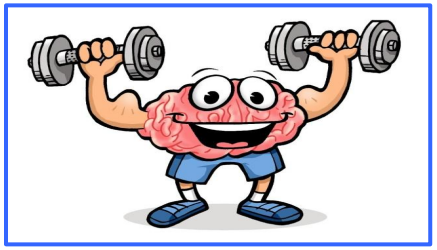
Motivational Interviewing

- MI aims to help individuals resolve their ambivalence and initiate change positive change in their lives.
- In a recent randomized clinical trial, MI demonstrated positive benefit with decreased MA use and lower cravings in participants receiving MI regardless of intensity.

Exercise as a Treatment Intervention for Methamphetamine Dependence

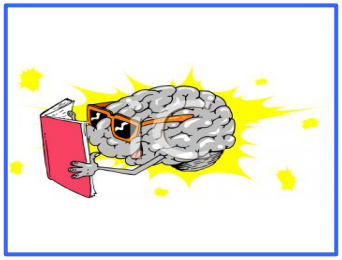
Impact of Exercise on Methamphetamine Use Outcomes N=135

Exercise Group:
1h, 3 days/wk



N=69

Health Education Group:
1h, 3 days/wk



N=66

Exercise Summary

- For individuals in the first 100 days of meth recovery, exercise:
  - Improves physical conditioning
  - Reduces weight gain
  - Improves cardiovascular functioning (increases heart rate variability)
  - Reduces symptoms of anxiety and depression
  - Reduces craving for methamphetamine
  - Enhances recovery of dopamine system
  - Reduces relapse to methamphetamine post discharge (except in very heavy users)

Medications

Medications for Cocaine Use Disorder

Medications with positive studies and under consideration.

topiramate*
modafinil*
bupropion*
amphetamine salts
disulfiram (mixed, worse retention)
propranolol (WD)
buprenorphine+naltrexone

Medications for Methamphetamine Use Disorder

Medications with positive studies and under consideration

Bupropion/naltrexone
mirtazapine

bupropion
naltrexone
methylphenidate
d-amphetamine
topiramate

Medications for MUD with Mostly Negative Results: A small subset

- Imipramine
- Desipramine
- Tyrosine
- Ondansetron
- Fluoxetine
- Sertraline,
- Paroxetine
- Aripiprazole
- Gabapentin
- N-acetylcysteine
- Varenicline

Colfax GN, Santos GM, Das M, Santos DM, Matheson T, Gasper J, Shoptaw S, Vittinghoff E. Mirtazapine to reduce methamphetamine use: a randomized controlled trial. Arch Gen Psychiatry. 2011 Nov;68(11):1168-75. doi: 10.1001/archgenpsychiatry.2011.124. PMID: 22065532; PMCID: PMC3437988.

Background

- Mirtazapine is an FDA-approved antidepressant.
- It is a mixed monoamine agonist/antagonist which facilitates the release of norepinephrine, serotonin, and dopamine.
- Methamphetamine users have depressed neurotransmitter activity in the absence of MA.
- MA-seeking may be partly reinforced by the increase in monoamine levels.
- Mirtazapine may alleviate MA craving and withdrawal symptoms by increasing monoamine levels and reduce MA use.

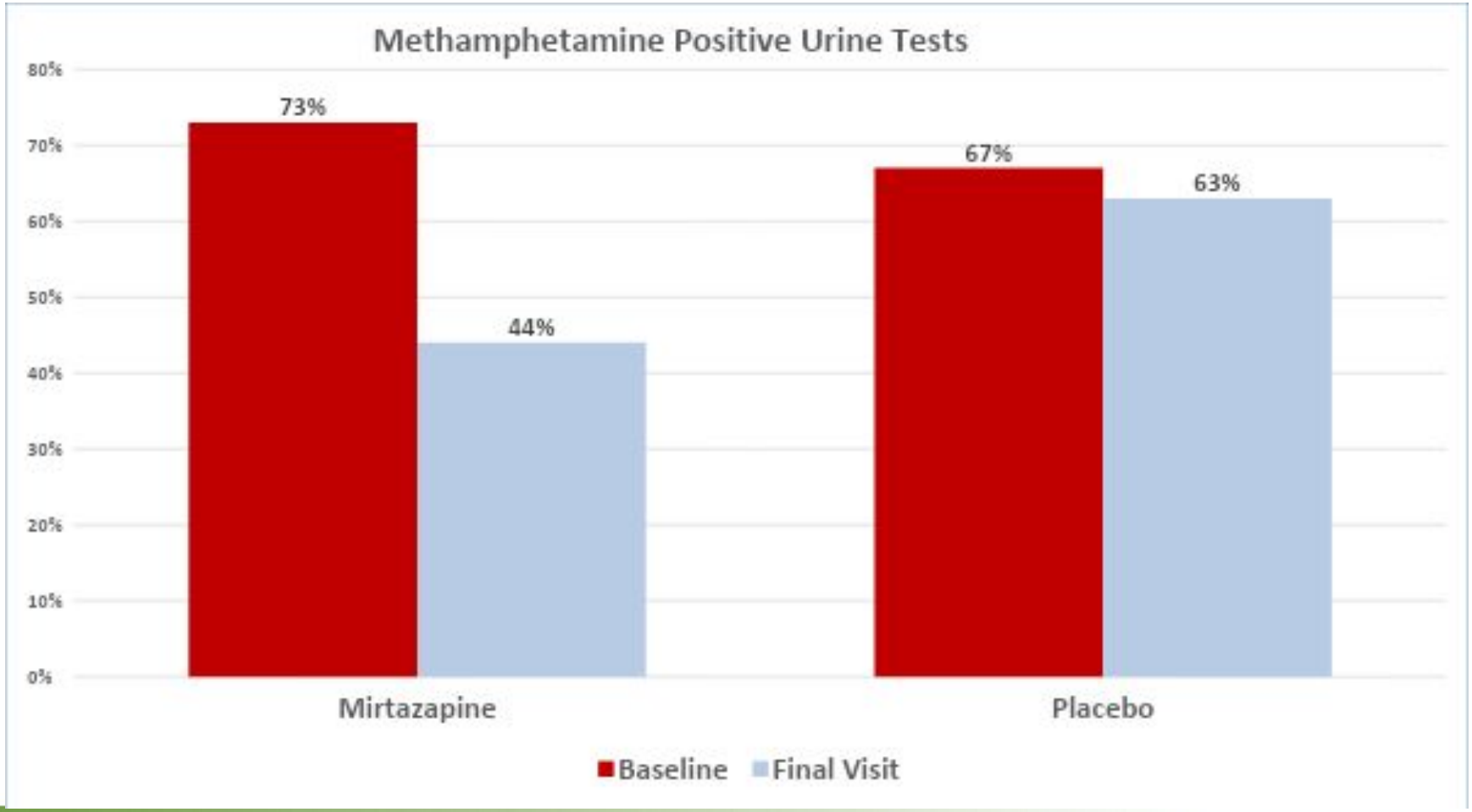
Methods

- Participants were 60 methamphetamine dependent, sexually active MSM, interested in ceasing or reducing MA use.
- Randomized, double-blind design with assignment to once daily placebo or 30 mg mirtazapine. Medication adherence was tracked by MEMS cap and self-report.
- 12-week study period; weekly data visits; weekly 30-minute, manual-driven, cognitive/behavioral, substance use counseling.

Results

Fewer methamphetamine positive urine tests in the mirtazapine group compared to the placebo group.

Mirtazapine :Results



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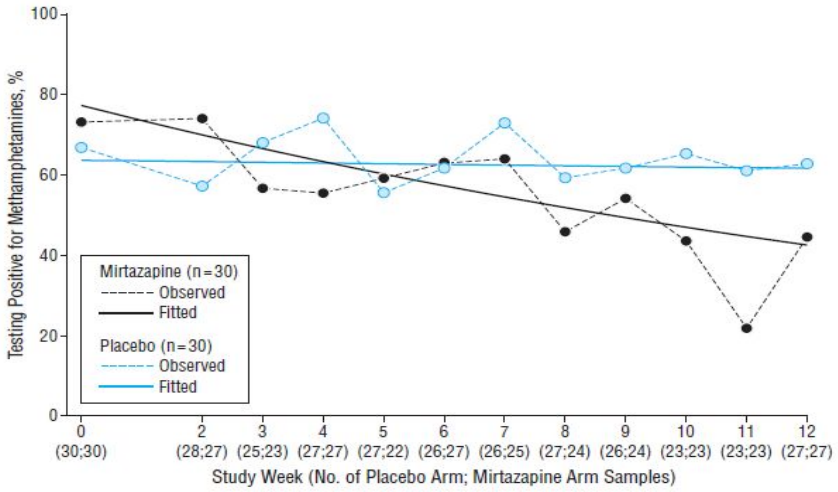
Results

Observed and fitted weekly urinalysis results, according to treatment arm.



Discussion

- The addition of mirtazapine to substance use counseling decreased methamphetamine use.
- Mirtazapine was associated with decreases in sexual risk behaviors.
- These effects were despite low to moderate medication adherence (48.5% by MEMS cap; 74.7% by self-report).

Coffin PO, Santos GM, Hern J, Vittinghoff E, Walker JE, Matheson T, Santos D, Colfax G, Batki SL. Effects of Mirtazapine for Methamphetamine Use Disorder Among Cisgender Men and Transgender Women Who Have Sex With Men: A Placebo-Controlled Randomized Clinical Trial. JAMA Psychiatry. 2020 Mar 1;77(3):246-255. doi: 10.1001/jamapsychiatry.2019.3655. PMID: 31825466; PMCID: PMC6990973.

Background

- An expanded replication of the Colfax trial.

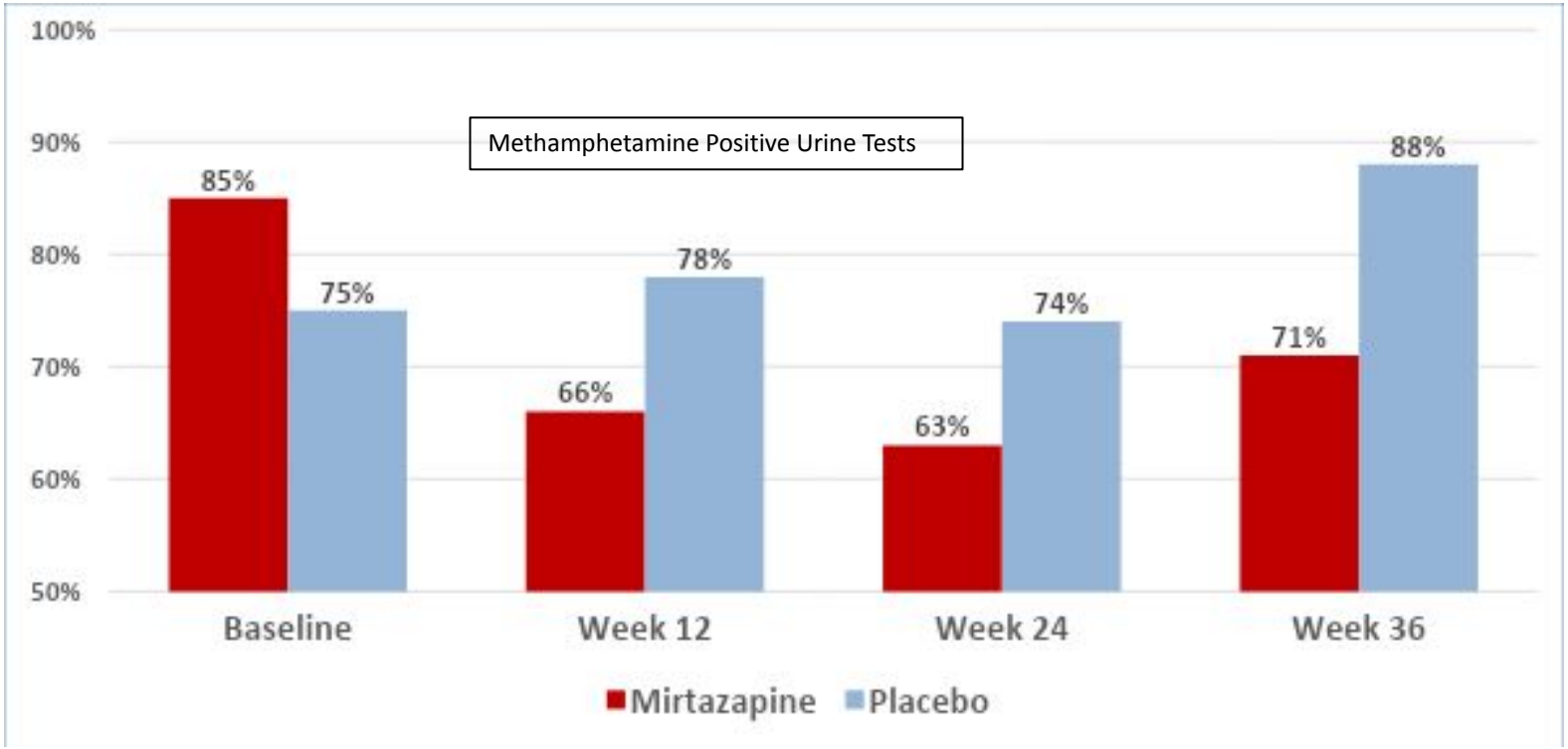
Methods

- Participants were 120 methamphetamine dependent, sexually active cisgender men (115) and transgender women (5) who have sex with men, and interested in ceasing or reducing MA use.
- Randomized, double-blind design with assignment to once daily placebo or 30 mg mirtazapine. Medication adherence was tracked by WisePill dispenser and self-report.
- 24-week study period and 12-weeks of follow-up; weekly data visits; weekly 30-minute, manual-driven, cognitive/behavioral substance use counseling.

Results

- Significantly fewer methamphetamine positive urine tests by week 12 in the mirtazapine group compared to the placebo group.
- Mirtazapine group had significant reductions in MA positive urine test results at weeks 24 and 36 vs placebo.
- Mirtazapine group had fewer sexual partners, fewer episodes of condomless anal sex and receptive anal sex with partners who were serodiscordant.

Fewer methamphetamine positive urine tests in the mirtazapine group compared to the placebo group.



Discussion

- In this expanded replication, the addition of mirtazapine to substance use counseling reduced methamphetamine use and some HIV risk behaviors.
- These effects were despite low to moderate medication adherence:
  - Mirtazapine (WisePill): Week 12, 38.5%; week 24, 28.1%
  - Placebo (WisePill): Week 12, 39.5%; week 24, 38.5%
  - Mirtazapine (Self-report): Week 12, 44.3%; week 24, 38.8%
  - Placebo (Self-report): Week 12, 46.1%; week 24, 37.5%

Trivedi MH, Walker R, Ling W, Dela Cruz A, Sharma G, Carmody T, Ghitza UE, Wahle A, Kim M, Shores-Wilson K, Sparenborg S, Coffin P, Schmitz J, Wiest K, Bart G, Sonne SC, Wakhlu S, Rush AJ, Nunes EV, Shoptaw S. Bupropion and Naltrexone in Methamphetamine Use Disorder. N Engl J Med. 2021 Jan 14;384(2):140-153. doi: 10.1056/NEJMoa2020214. PMID: 33497547.

Background

- Bupropion is an FDA-approved antidepressant.
- It is a stimulant-like antidepressant that acts through the norepinephrine and dopamine systems and might ameliorate methamphetamine withdrawal dysphoria.
- Previous research with bupropion for methamphetamine dependence has been encouraging.
- Naltrexone is an opioid receptor antagonist which is effective with opioids and moderately so with alcohol.
- It may attenuate the reinforcing effects of other substances.
- A small open-label study pilot trial suggested naltrexone plus bupropion may be effective with methamphetamine use disorder.

Methods

- A multi-site, two-stage, placebo-controlled, trial.
- 403 participants with moderate to severe MA use disorder were enrolled in stage 1; 225 were enrolled in stage 2.
- Participants stated a desire to quit or reduce MA use and reported use on at least 18 of the 30 days before consent.
- Treatments: extended release injectable naltrexone (380mg every 3 weeks); oral extended release bupropion (450mg daily).
- Stage 1 randomization was in a 0.26:0.74 ratio (naltrexone-bupropion to placebo injection and oral tablet).

Methods

- Stage 2 participants were from the Stage 1 placebo group who did not have a response in Stage 1.
- Stage 2 randomization to the 2 groups was in 1:1 ratio.
- Stage 1 was 6 weeks; Stage 2 was 6 weeks.
- Urine samples were collected twice each week.
- **Primary outcome was a response defined as at least 3 methamphetamine-negative urine samples out of 4 obtained at the end of Stage 1 or Stage 2.**
- The weighted average of the responses in the 2 stages is reported.

Results

Stage 1		
Had a response		
Treatment	16.5%	18/109
Placebo	3.4%	10/294

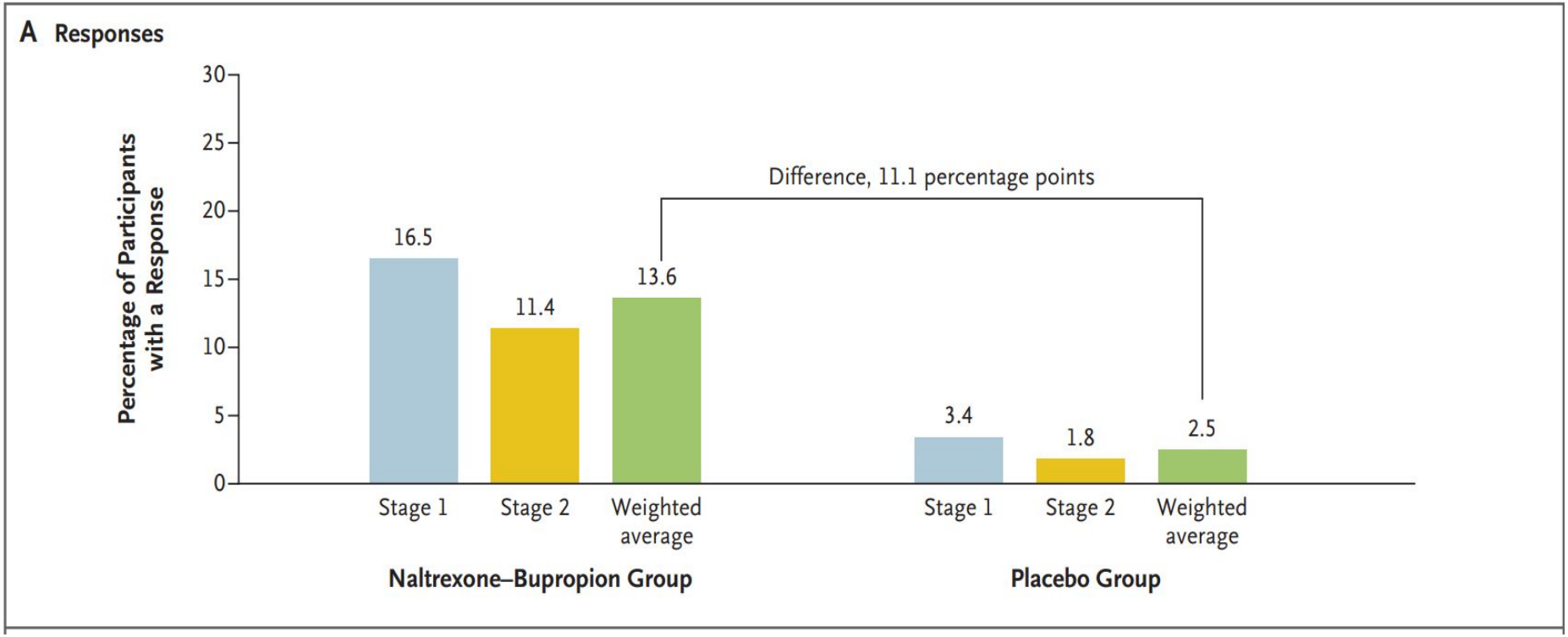
Stage 2		
Had a response		
Treatment	11.4%	12/114
Placebo	1.8%	2/111

Weighted average response across both stages:

13.6% naltrexone-bupropion

2.5% Placebo

Percentage of Participants with a Response



Discussion

- The response over a period of 12 weeks by the naltrexone-bupropion group was low, but higher than that among participants receiving placebo.

Chan B, Freeman M, Ayers C, Korthuis PT, Paynter R, Kondo K, Kansagara D. A systematic review and meta-analysis of medications for stimulant use disorders in patients with co-occurring opioid use disorders. Drug Alcohol Depend. 2020 Nov 1;216:108193. doi: 10.1016/j.drugalcdep.2020.108193. Epub 2020 Aug 1. PMID: 32861136.

Background

- The use of stimulants by people with opioid use disorder has increased greatly.
- Untreated stimulant use disorders are associated with poorer outcomes for OUD.
- This was a review of the evidence for medications for stimulant use disorder specifically for people with co-occurring OUD.

Discussion

- An examination of multiple classes of medications used for the treatment of cocaine and methamphetamine use disorders in people with OUD found no strong evidence that any was effective in increasing abstinence, reducing use, or improving retention.
- There is almost no evidence regarding treatment of methamphetamine use disorder in people with OUD.
- Antidepressants and disulfiram may worsen treatment outcomes when used for treatment of cocaine use disorders in patients with OUD.

TRUST: Treatment of Individuals who Use Stimulants: TRUST

An Integrated Behavioral Model

TRUST: The Components

TRUST is an integrated, evidence-based, multi-component program for the treatment of individuals with stimulant use disorders. The contents include:

1. Motivational incentives (based on contingency management research),
2. Elements of cognitive behavioral therapy
3. Elements of community reinforcement approach,
4. Motivational interviewing skills,
5. Physical exercise

Participation in recovery support programs encouraged (eg. 12-Step; Moderation management).

Appendix includes other EBPs to augment the core program at the discretion of each organization.

TRUST: The Priorities

- 1. Establish a positive, compassionate, non-judgemental relationship with individuals who use stimulants to promote their engagement and retention in treatment
- 2. Provide incentives to promote participation (retention) in treatment. Retention is the single most important measure of treatment benefit.
- 3. Provide respectful evidence-based guidance/information/support to individuals who uise stimulants that can help them make changes in their lives to promote a reduction/discontinuation of methamphetamine/cocaine use.

TRUST Training Program

- Eight 2 hour zoom training sessions
- Bi-monthly coaching/mentoring zoom sessions beginning two weeks after the last training session for 3 months, followed by a monthly mentoring session for an additional 7 months.
- A minimal amount of data on number of patients, retention in treatment and UA data (If possible) collected and submitted weekly

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