Stimulant Use Disorder: Pharmacotherapy Review

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Learning Objectives

- Review primary literature pharmacologic agents studied for use in methamphetamine (MA) use disorder
- Analyze the strengths and limitations of the available primary literature related to these pharmacologic agents
- Utilize the provided literature to guide clinical decision making for medication use in MA use disorder

ESKENAZI HEALTH

- Stimulants
- Bupropion + Naltrexone
- Bupropion Monotherapy
- Naltrexone Monotherapy
- Antipsychotics
- Antidepressants
- Modafinil
- “Other” Agents

Disclaimer

- While pharmacologic agents have been evaluated, behavioral therapies are most effective
- Many studies involving pharmacotherapy also include required or optional behavioral therapy

NIDA. 2020, https://www.drugabuse.gov/publications/research-reports/methamphetamine/what-treatments-are-effective-people-who-misuse-methamphetamine Accessed 23 Feb. 2021.

Methamphetamine Use Disorder

Gasper J and Puzantian T. College of Psychiatric and Neurologic Pharmacists. Available at: https://cpnp.org/guideline/methamphetamine. Accessed on February 23, 2021.

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SR Dextroamphetamine (d-AMP) with Psychotherapy

Galloway GP, et al. *Clin Pharmacol Ther 2011*; 89:276-82.

- Received SR d-AMP 60 mg/day or placebo
- 8 week duration
- Weekly motivational enhancement therapy sessions
- Twice weekly UDS
- Returned medication bottle weekly
- 60 participants (30 in each group)
  - MA-Positive UDS, primary (p=0.894):
    - SR d-AMP: 2.9 ± 4.3 MA-negative results
    - Placebo: 3.2 ± 5.0
  - Self-reported abstinent days out of 56 days (p=0.842)
    - SR d-AMP: 27.2 ± 17.3 days
    - Placebo: 27.5 ± 16.8 days
  - MA withdrawal (p=0.018)- no scores provided
- Cravings (p=0.016)- no scores provided
  - Moderate adherence

SR=Sustained Release

SR d-AMP with Optional Psychotherapy

Longo M, et al. *Addiction* 2010;105:146-54.

- Received 20-110 mg/day of SR d-AMP or placebo
- Offered up to 4 psychotherapy sessions
- 12 week duration followed by 4 week reduction
- 49 participants
- Pharmacist-supervised administration
- Results:
  - Retention, primary (p=0.014):
    - SR d-AMP: 86.3 days ± 52.2 days
    - Placebo: 48.6 days ± 45.4 days
- Self-reported use MA use, primary (p=0.086):
  - Biggest reduction in the first month from start
  - No difference between groups from month to month during 3 month treatment period
- Objective MA use via hair concentration, primary (p-value not reported):
  - No difference between groups
- Dependence via LDQ, primary (p=0.046):
  - Mean score difference: SR d-AMP 11.5 vs placebo 15.5

LDQ= Leeds Dependence Questionnaire

d-AMP with Optional Psychotherapy Pilot Trial

Shearer J, et al. *Addiction* 2001; 96:1289-96.

- Compared 20-60 mg d-AMP to placebo
  - Goal was to determine feasibility of a randomized trial, not efficacy of d-AMP
- 41 participants
- Results:
  - MA-Positive UDS:
    - No difference at 6 weeks (x^2=0.6, p=0.4) or 12 weeks (x^2=0.8, p=0.4)
  - Self-reported use (t=-0.58, p=0.56):
    - No difference in use per day for d-AMP (1.8 [SD 1.1] to 1.4 [SD 2.5]) vs. placebo (2.8 [SD 2.9] to 1.9 [SD 2.6])
  - Therapy session attendance (x^2=4.5, p=0.03)
    - d-AMP mean 2.6 sessions vs. placebo mean 1.4 sessions
  - SDS scores (p=0.06):
    - Significant difference for BOTH groups from start to end, but no difference between groups at follow-up (d-AMP 10.3 to 5.3, placebo 10.7 to 7.8)
  - High dropout rate

SDS= Severity of Dependence Scale

Methylphenidate (MPH) Use With Matrix Model

Aryan N, et al. *Subst Abuse Treat Prev Policy* 2020; 15:72.

- RCT looking at therapeutic effects of MPH with Matrix Model treatment
- 12 week duration
- 85 participants
- Results:
  - Negative MA UDS in last week **(P<0.001):**
    - Matrix Model: 2 out of 40 (20%); OR 2.59 (95% CI 0.87-7.75)
    - MPH: 9 out of 22 (40.9%); OR 4.95 (95% CI 1.79-13.68)
    - Matrix-MPH: 13 out of 21 (61.9%); OR 7.63 (95% CI 2.82-20.67)
    - Control: 1 out of 22 (5.0%)
  - Secondary outcomes: reduction in MA cravings, addiction severity, mental health

SR MPH for MA Use Disorder (Trial 1)

Rezaei F, et al. *Daru* 2015; 23:2.

- Received 18 to 64 mg/day of SR MPH or placebo
- 10 week duration
- 54 participants
- Results:
  - MA craving scores (primary): Significantly less in SR MPH (MD -10.28, [95% CI 0.88-19.18], p=0.03)
- MA positive UDS: Only significant difference at 10 weeks
- Depressive symptoms: Significantly less in SR MPH group by end of 10 weeks (MD 2.03, [95% CI 0.31-3.75], p=0.02)

SR MPH Use for MA Use Disorder (Trial 2)

Ling W, et al. *Addiction* 2014; 109:1489-500.

- Compared SR MPH 18 to 54 mg/day to placebo in a two phase trial
  - 10 weeks assigned either treatment or placebo followed by 4 weeks placebo
- 110 participants
- Included weekly CBT and incentives for MA-negative UDS
- Participants compensated for time/travel
- Results:
  - Self-reported MA use in the last 30 days of the 10 weeks (primary): No difference (p=0.22)
  - MA use difference from baseline to 10 weeks: 6.56 days (SR MPH) vs. 3.82 days (placebo) (p=0.03)
  - High dropout rate

Extended-Release (ER) MPH for MA Use Disorder

Miles SW, et al. *Addiction* 2013; 108:1279-86.

- Compared ER MPH 18-54 mg/day to placebo
- 22 week duration
- Clinic supervised them taking the ER MPH
  - Excluded anyone who missed >6 doses in a row
- Twice weekly UDS and weekly cravings assessment
- Intent to treat
- 78 participants (39 in each group)
- Results:
  - Positive UDS (p=0.89):
    - ER MPH: Mean 89% (SD 19 [95% CI: 82,95])
    - Placebo: Mean 90% (SD 14 [95% CI: 86,95])
  - Cravings assessment (p=0.9):
    - ER MPH: Mean -21.2 (SD 40 [95% CI: -41.1,-1.3])
    - Placebo: Mean -13.3 (SD 30.4 [95% CI: -30.8,4.3])
  - Poor adherence (based on study definition)

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Bupropion + Naltrexone (NTX)

Trivedi MH, et al. *N Engl Med* 2021; 384:140-53.	
Objective	• To assess the efficacy of utilizing these two agents in the treatment of MUD
Design	• Multisite (8 sites), double-blind, two-stage, placebo-controlled trial
Methods	• Sequential parallel comparison design to evaluate efficacy and safety of long-acting injectable NTX (380 mg every 3 weeks) plus ER Bupropion (450 mg daily) in adults with moderate or severe MA use disorder • 12 week duration- 6 weeks per stage • Stage 2 was for participants in the placebo group who did not have a response in stage 1 would be randomized to stage 2 • Went to clinic twice a week for urine drug screens (UDS) • Recruited patients with use of advertisements and direct referrals • Participants were compensated • Intent to treat population

Endpoints	• Primary:
	  • Response (meaning at least 3 methamphetamine-negative urine samples out of 4 samples obtained at the end of stage 1 or stage 2)
	  • If they had two or more missing UDS or self-discontinued the trial, then recorded as not having a response
	• Secondary:
	  • Percentage of meth-negative UDS
	  • Most severe meth craving in the last week (via VAS)
	  • Depressive symptoms (weekly via PHQ-9)
	  • Results of the treatment effectiveness assessment at week 6 and week 12

Bupropion + NTX Results

Trivedi MH, et al. *N Engl Med* 2021; 384:140-53.	

Patient Population	• 403 randomized in stage 1
	  • 109 (27%) in treatment group and 294 (73%) in placebo
	• 225 in placebo group did not respond in stage 1 and randomized in stage 2
	  • 114 (50.7%) in treatment group and 111 (49.3%) in placebo
	• Overall characteristics:
	  • Average age 41 years, 68.7% were male, 71.2% were White, and 38.7% were employed. On average, participants used MA on 27 of the 30 days before consent was provided
	  • Average adherence in Stage 1: 75.1% treatment vs. 83.5% placebo
	  • Average adherence in Stage 2: 77.4% treatment vs. 82.0% placebo

Primary Result	• Response:
	  • Overall weighted response: 13.6% treatment vs. 2.5% placebo
	  • Treatment effect: 11.1 ± percentage points (z-test: 4.53, $p<0.001$)
	  • NNT to have a response: 9

Secondary Results	• Percentage of meth-negative UDS: 95% CI: 3.5 to 10.1 • Most severe meth craving in the last week (via VAS): 95% CI: -13.8 to -5.6 • Depressive symptoms (weekly via PHQ-9): 95% CI: -1.9 to -0.2 • Results of the treatment effectiveness assessment at week 6 and week 12: 2.3 to 5.7
Conclusions	• Authors concluded that while the response to buprenorphine + NTX was low, there was a greater response compared to placebo.

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Bupropion Monotherapy for MA Use Disorder

- Five RCTs available (4 summarized here)
- Duration of each RCT: 12 weeks
- Dosing utilized most commonly: SR 150 mg PO BID
- Included required psychotherapy
- Small sample sizes
- Overall Findings:
  - One study found no significant difference in MA use (2 trials) or abstinence (2 trials)
  - No significant difference in depressive symptoms
  - Three studies found that when stratified by amount used at baseline, more benefit in participants who reported a lower use at baseline
  - Low adherence rates (anywhere from 32-54% for the confirmed adherence evaluations)

Anderson AL, et al. *Drug Alcohol Depend* 2015; 150:170-4.
Elkashef AM, et al. *Neuropsychopharmacology* 2008; 33:1162-70.
Heinzerling KG, et al. *Addiction* 2014; 109:1878-86.
Shoptaw S, et al. *Drug Alcohol Depend* 2008; 222-32.

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NTX Monotherapy for MA Use Disorder

- Systematic review of the 4 RCTs for either MA or amphetamine
  - Two long-acting injections (LAI) and two oral (PO)
- Trial duration:
  - Two trials= ~12 weeks
  - One trial= 6 months
  - One trial= two 5 day inpatient stays
- Naltrexone dosing:
  - LAI: 380 mg every 4 weeks
  - PO: 50 mg daily
- Required therapy sessions
- Results:
  - The two PO NTX studies found a significant difference in cravings
  - One PO NTX study found a significant difference in abstinence (only 3 evaluated this)
  - Low adherence aside from the 6 month LAI NTX trial

Lam L, et al. *Clin Toxicol* 2019; 57:225-33.

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Antipsychotics for MA Use Disorder

- Aripiprazole (3 RCTs)
  - Aripiprazole dosing: 10 mg, 15 mg, or 20 mg
  - Two studies (vs. placebo) found no difference in cravings
  - One study looked at aripiprazole vs. methylphenidate vs. placebo and found aripiprazole was associated with statistically significant increase in MA-POSITIVE UDS compared to placebo
- Risperidone (1 RCT)
  - Risperidone vs. Methylphenidate
    - Risperidone dosing: 2 mg
    - Both had a statistically significant decrease in cravings per week over 4 weeks
    - Numerically greater reduction with risperidone vs. methylphenidate (6.31±8.31 vs. 19.6±12.45)

Tiihonen J, et al. *Am J Psychiatry* 2007; 164:160-2.
Coffin PO, et al. *Drug Alcohol Dependence* 2014; 140:e36.
Sulaiman AH, et al. *Int J Psychiatry Clin Pract* 2013; 17:131-8.
Solhi H, et al. *Saudi Pharm J* 2014; 22:191-4.

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Antidepressants in MA Use Disorder

Fluoxetine

- 40 mg daily
- Study was from 1999
- Results:
  - Did not reduce MA use

Mirtazapine

- 30 mg daily
- 3 RCTs
- One large sample size
- One required therapy
- Results:
  - In two of the trials:
    - Reduction in MA use
    - Reduction in sexual risk behaviors
  - No difference in depressive symptoms

Sertraline

- 50 mg twice daily
- Compared without and with Matrix Model treatment
- Large sample size (229 participants)
- Results:
  - When sertraline monotherapy was compared to placebo: significantly greater MA-positive UDS
  - Did not affect cravings, depressive symptoms

Karila L, et al. *Br J Clin Pharmacol* 2010; 69:578-92.
Coffin PO, et al. *JAMA Psychiatry* 2020; 77:246-55.
Colfax GN, et al. *Arch Gen Psychiatry* 2011; 68:1168-75.
Cruickshank C, et al. *Drug Alcohol Revs* 2008; 27:326-33.
Shoptaw S, et al. Drug Alcohol Dependence 2006; 85:12-18.

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Modafanil in MA Use Disorder

- Four RCTs
- 200-400 mg daily
- Therapy required in one trial but optional in two trials
  - One trial did not evaluate therapy
- Results:
  - No difference in MA use, retention in treatment, or cravings
  - Low adherence rates

Anderson AL, et al. *Drug Alcohol Dependence* 2012; 120:135-41.
Heinzerling KG, et al. *Drug Alcohol Dependence* 2010; 109:20-9.
Lee N, et al. *Drug Alcohol Rev* 2013; 32:88-95.
Shearer J, et al. *Addiction* 2009; 104:224-33.

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“Other” Agents in MA Use Disorder

- Other agents that have been studied with minimal studies available:
  - Atomoxetine
  - Buprenorphine
  - Gabapentin
  - N-acetylcysteine
  - Topiramate

Gasper J and Puzantian T. College of Psychiatric and Neurologic Pharmacists. Available at: https://cpnp.org/guideline/methamphetamine. Accessed on February 23, 2021.

Conclusions

- No pharmacologic agent has demonstrated consistent results across trials
- Limited number of RCTs are available
- Use of behavioral interventions and/or psychotherapy can cloud the effect of the medication
- Common limitations include:
  - Small sample size
  - More male participants
  - High drop out rates
  - Low adherence
  - Limited generalizability to practice

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Questions?

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