Treatments for Stimulant Use Disorder: Evaluation of the Evidence

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October 4, 2021
The following individual has a relevant financial relationships to disclose:

Steven Shoptaw, PhD        Receipt of clinical supplies for research        Alkermes, Inc.

• All others involved in the planning and presentation of this activity have no relevant financial relationships.

• All speakers have been advised that any recommendations involving clinical medicine must be based on evidence that is accepted within the profession of medicine as adequate justification for their indications and contraindications in the care of patients. All scientific research referred to, reported, or used in the presentation must conform to the generally accepted standards of experimental design, data collection, and analysis.
Target Audience

• The overarching goal of PCSS is to train healthcare professionals in evidence-based practices for the prevention and treatment of opioid use disorders, particularly in prescribing medications, as well for the prevention and treatment of substance use disorders.
Educational Objectives

At the conclusion of this activity participants should be able to:

1. Demonstrate an understanding of the definition and epidemiology of stimulant use disorder, globally and in endemic areas
   – Key cultural factors and comorbidities.

2. Describe the neurobiology in development and maintenance of stimulant use disorder and how this relates to treatment outcomes
   – Withdrawal symptoms and their management

3. Review evidence for advancements in pharmacotherapies and behavioral therapies that can be brought into practice
   – A road map that offers hope for the near future
Definitions of a Spectrum: Stimulant Use to Stimulant Use Disorder: Mild to Moderate to Severe

No use or use that does not cause problems

Occasional use causes problems occasionally to frequently

Mild to Moderate SUD

Severe SUD (Addiction)

Fun

Fun with Problems

Problems
DSM-5 Definition: Stimulant Use Disorder

Maladaptive pattern of use, *clinically significant impairment or distress* and 2+ of the following in the same 12-months:

1. Tolerance
2. Withdrawal
3. Used for longer periods than intended
4. Can’t cut down or quit
5. Time spent getting, using or recovering
6. Give up social, work or fun activities
7. Craving or a strong desire or urge to use a substance
8. Continued use despite knowledge of negative consequences
9. Failure to fulfill major role obligations
10. Use in physically hazardous situations
11. Continued use despite social and interpersonal problems

Mild = 2-3 criteria;
Moderate = 4-5 criteria;
Severe = 6+ criteria

Estimated Prevalence of Methamphetamines

Methamphetamine Prevalence Estimates U.S.

- General population estimates remain low (0.7%)
- Dramatic rises in meth use among people who report using heroin and LSD

Heroin use cannot be measured adequately with a general population survey

Peter Reuter1,2, Jonathan P. Caulkins3,4 & Greg Midgette1,4

Palamar JJ. Drug Alc Dep. 2020 Jun 3;213:108089
Prevalence of Cocaine Use Globally, 2021

FIG. 19 Use of cocaine, by region and selected subregions, 2018

Source: UNODC, responses to the annual report questionnaire.

Number of Cocaine Users, Worldwide

Cocaine Use: NSDUH 2019

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

+ Difference between this estimate and the 2019 estimate is statistically significant at the .05 level.
Psychostimulant Overdose Deaths 2009-2019

Hedegaard et al., *NCHS Data Brief*, 406, April 2021
Increase in Prevalence of Acute Heart Failure by Stimulant Use; National Inpatient Sample

Shetty et al. 2021 *Int J Cardiology.* 331: 158-163
Culture and Comorbidities
Methamphetamine: Effects and Function

- Shift Workers
- Women
- Gay Men
- Bikers - Gangs
- Rural
- Youth

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<td>Loneliness</td>
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<td>Reaction Time</td>
<td>Timidity</td>
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Methamphetamine Use, HIV Incidence in MSM: Attributable Fraction

EXPLORE1

MACS2

1 Project EXPLORE; Koblin et al., 2006, AIDS, 20: 731-739
2 Multisite AIDS Cohort Study; Ostrow et al., 2009, JAIDS, 51: 349-355
Cocaine Use and Concurrent Psychiatric Symptoms

Fig. 2. Prevalence of Past-Year Mental Health Characteristics Among Adults Reporting Past-Year Cocaine Use, United States, 2018–2019 *Serious psychological distress is defined as a score of 13 or higher from the six items on the K6 Distress Scale, used by NSDUH for worst month in past year (CBHSQ, 2020; Kessler et al., 2005). Unweighted Sample Size = 85,765 Error bars represent 95% Confidence Interval. Source: National Surveys on Drug Use and Health, 2018–2019 (SAMHSA CBH, 2020).

Mustaquim D et al. Addict Behav. 2021 Sep;120:106950.
All behavior is brain – including “motivated” behaviors like stimulant use.

Cocaine and methamphetamine have direct effects on neurons in stimulating and sustaining dopamine release.

Behavioral and potential medication therapies affect neurotransmission, which in turn corresponds with behavior.
Dopamine Dysfunction in Stimulant Use Disorder

**COCAIN**E: Primarily blocks DA transporters

**AMPH/METH:** Inhibits DA reuptake AND increases reverse transport of DA into cleft

**AMPH/METH Effects Dose Dependent**
- Low doses block DA transport
- High doses also reverse DA transport

Both effect 5-HT and NE transporters

Low Dose Methamphetamine can be Therapeutic; High Dose Causes Damage to Nerve Cells

Dose

The Case of James

James is a 42 year old Black/African American gay man who is seeing you because his partner, John, is saying he needs help. John is complaining that James’ “weekend warrior” use of methamphetamine is interfering with their life together. He tells you this is impossible as he is in long-term recovery from addiction to crack cocaine in his early 20s and he knows how to control his meth use. James became HIV-positive a few months ago and has started HIV treatment and currently is virally suppressed suppression (good response to HIV management). James smokes cigarettes 1-1.5 packs per day.

In developing the treatment plan for James, which of the following best captures your thoughts about James’ primary behavioral goal?

a. Stop/reduce methamphetamine use
b. Stop/reduce cigarette smoking
c. Consultation with James’ infectious disease physician
d. A and B
e. All of the above
Pharmacotherapies
If there were an effective pharmacotherapy for cocaine use disorder, what would it do?
Pharmacotherapy for Stimulant Use in MSM: Mirtazapine 30 mg/day


Coffin et al., *JAMA Psychiatry*. 2020. 77(3):24-255

Both trials in San Francisco among MSM and Trans Women
Broadly Effective Medication for Meth Use Disorder

A Responses

Percentage of Participants with a Response

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<th>Percentage</th>
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<td>2</td>
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<td>Weighted average</td>
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Difference, 11.1 percentage points

NNT 12 Wks = 9

B Methamphetamine-Negative Urine Samples

Percentage of Negative Urine Samples

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<tr>
<td>Wk 16</td>
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Secondary Outcomes

In comorbid group of people with ADHD plus Cocaine Use Disorder, amphetamine salts extended release shows dose-response association on cocaine use.
Replication and Extension: Mixed Amphetamine Salts-Extended Release + Topiramate


Fig. 3. Model-estimated (adjusted by sex, alcohol use disorder, and site) probabilities (in percentages) and 1 standard error of positive urine toxicology, weeks 2-13. Observed proportions are displayed as separate markers.
Summary Pharmacotherapies

After 25 years, there are some signals for efficacy, though there still is no FDA approved treatment for methamphetamine addiction:

- Mirtazapine effects in MSM are impressive, particularly replication
  - Effect is reduction in use, not abstinence (like naltrexone for alcohol)
  - So far only tested in San Francisco and in MSM
- Large trial, strong signal for XR-NTX+Bupropion over placebo for reducing methamphetamine use

Mixed Amphetamine Salts shows consistent signal for cocaine addiction

- Dose-dependent effects observed for people with ADHD
- Combination MAS-ER plus topiramate shows two replications
Behavioral Therapies
Meta-analysis of Behavioral Therapies for Stimulant Use Disorder

- CM +/- either community reinforcement approach or CBT had superior efficacy and acceptability compared to TAU at 12 weeks and at end of treatment.

Contingency Management and Substance Use Disorders

• Operant conditioning (Skinner, 1938)
• Initial concepts derived from work with delinquent boys (Yates, 1970)
• Early work in MMT clinics to encourage opioid abstinence (Stitzer et al, 1977)
• Application to cocaine dependence by Higgins’ group (1993, 1994)
• Original voucher-based CM now has alternative “fishbowl method” (Petry 2000)
Fishbowl

- Urine results determine number of draws
- First negative = 3 draws with increases by 1 for each consecutive negative sample to a cap
- Prizes are:
  - 50 “good job”
  - 30 “low prize” ($1-2)
  - 17 “medium prize” ($5-10)
  - 3 “big prize” ($50)

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<td>Totals</td>
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Meta Analyses of Contingency Management

- $d=0.46$ (Benishek et al., 2014, *109*:1426-1436) – Prize based only
- $d=0.58$ (Dutra et al., 2008, *Am J Psychiatry* 165:179-187)
- $d=0.52$ (Griffith et al., 2000, *Drug Alc Dep* 58:55-66)
- $d=0.40$ (Prendergast et al., 2006, *Addiction* 101:1546-1560)

If Contingency Management were a medication it would be standard of care
Dopamine D2-D3 Availability Predicts Outcomes for Contingency Management of Cocaine Use Disorder

Cognitive Behavioral Therapy

- Teaches skills to instill abstinence
- Early recovery skills, especially use of structure to schedule activities
- Teaches skills to interrupt craving (trigger, thought, craving, use) – thought stopping
- Teaches skills to return to abstinence following lapse or relapse

Motivational Interviewing: Basic Assumptions

- People change thinking and behavior along a series of stages
- Individuals may enter treatment at different “stages of change”
- The natural change process can be changed using MI techniques
- MI engages individuals in longer term treatment and promotes specific behavior changes
- Confrontation of “denial” is counterproductive and may be harmful
Summary on Behavioral Therapies

• Treatment works for who it works for – Costs and chronicity when recommending treatments
• Contingency Management – highly efficacious with consistent signal
• Motivational Interviewing – brief sessions
• Cognitive Behavioral Therapy – “teachy” with meetings with therapist over weeks/months
• 12-Steps is an ubiquitous social fellowship
The Case of James, Continued

James returns to see you the week after the intake. He tells you that he is not interested in working with you to do things he already knows how to do in establishing some kind of recovery. In his early 20s, he was a member of cocaine anonymous (12-steps) for years and has no interest in returning to that program. James’ medical insurance policy is comprehensive in coverage. He is not opposed to medications, but would really like to be part of a contingency management program (not currently available at your clinic). He doesn’t want “behavior change school,” but he likes talking to you.

What are your first recommendations for James’ treatment plan?

a. Cognitive behavioral therapy
b. Motivational interviewing (4 sessions)
c. Smoking cessation medications
d. Extended release naltrexone + bupropion
e. HIV medication counseling
Translation to Practice

Prerequisites to translate these findings to clinical practice settings include the following:

1. Perhaps the most important - an energetic champion to implement evidence-based treatments into practice. This includes emphasis on science/evidence in translation of programs to clinic
   a. Advocate for investments in training staff and changing workflows within the clinic to address “whole person”
   b. Quality improvement processes, clinical supervision, team “huddles,” staff training.

2. Multiple disciplines within and also linked to the treatment team: medical clinicians, behavioral specialists, recovery navigators with all working at “top of license”

3. Infrastructure support to manage private insurance, Medicare, Medicaid
Closing Points

• Stimulant use, misuse and disorder are linked with neural adaptation that corresponds with development of addiction and targets for treatments

• There is no broadly effective, FDA approved medication for stimulant use disorder
  ▪ Medications with some promise for methamphetamine (mirtazapine, XR-NTX+Bup)
  ▪ Cocaine (MAS-ER, MAS-ER+Topiramate)

• Raises question whether it is time for stimulant addiction treatment to start with medication foundation?

• Contingency management is most efficacious behavioral therapy, though MI and CBT used more

• Integrated treatments provide help to patients that can include biology, behavior and culture – all elements important to helping people reach and maintain their goals regarding stimulant use


References (cont’d)

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• Shetty et al. 2021 Int J Cardiology. 331: 158-163
Thank You!

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PCSS Mentoring Program

- PCSS Mentor Program is designed to offer general information to clinicians about evidence-based clinical practices in prescribing medications for opioid use disorder.

- PCSS Mentors are a national network of providers with expertise in addictions, pain, evidence-based treatment including medications for opioid use disorder (MOUD).
  - 3-tiered approach allows every mentor/mentee relationship to be unique and catered to the specific needs of the mentee.
  - No cost.

For more information visit: https://pcssNOW.org/mentoring/
Have a clinical question?

Ask a Colleague

A simple and direct way to receive an answer related to medications for opioid use disorder. Designed to provide a prompt response to simple practice-related questions.

http://pcss.invisionzone.com/register
PCSS is a collaborative effort led by the American Academy of Addiction Psychiatry (AAAP) in partnership with:

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