Disclosures

Dr. Shoptaw has received clinical supplies for research from:

• Alkermes, Inc
• Indivior, Inc
• Gilead Sciences, Inc
Objectives

- Factors linked with culture, epidemiology and comorbidities for people with stimulant use disorders
- Best evidence for medications for methamphetamine and cocaine use disorders
- Factors important to treat the "Whole Person"
- Infrastructure "pain points" to provide culturally competent, whole-person care for individuals with stimulant use disorder
Culture, Epidemiology, Comorbidities
Your patient is a 37-year-old Caucasian woman, Joleen, who has been using fentanyl and cocaine for the past year. The fentanyl on the streets is so strong. For six days, Joleen was so high on fentanyl and cocaine she was unable to move, sat in her own waste outside a metro stop and developed open skin wounds with infections. When she lost all consciousness, her fiancé called 911 and Joleen was transported to the hospital where she was cleaned up and treated with IV antibiotics.

You’ve managed Jordan’s opioid use disorder with buprenorphine sufficiently that she has not eloped from hospital. During her week, you order an HIV test and guess what? She tests newly HIV positive. Her viral load is 1,200,000 copies. Infectious diseases started treatment for her new case of HIV infection.

As part of your comprehensive treatment, what is your preferred plan for addressing Joleen’s cocaine use disorder?

A. Do nothing
B. Refer Joleen to social work for dispo back to community
C. Start medication (Mixed Amphetamine Salts 60mg +/- Topiramate 200mg)
D. Get Joleen to drug-free rehab
## Methamphetamine Effects and Function Shape

### Treatment Goals

<table>
<thead>
<tr>
<th>Physical</th>
<th>Psychological</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Heart Rate</td>
<td>↑ Confidence</td>
</tr>
<tr>
<td>↑ Blood Pressure</td>
<td>↑ Alertness</td>
</tr>
<tr>
<td>↑ Pupil Size</td>
<td>↑ Mood</td>
</tr>
<tr>
<td>↑ Respiration</td>
<td>↑ Sex Drive</td>
</tr>
<tr>
<td>↑ Sensory Acuity</td>
<td>↑ Talkativeness</td>
</tr>
<tr>
<td>↑ Energy</td>
<td>↑ Energy</td>
</tr>
<tr>
<td>↓ Appetite</td>
<td>↓ Boredom</td>
</tr>
<tr>
<td>↓ Sleep</td>
<td>↓ Loneliness</td>
</tr>
<tr>
<td>↓ Reaction Time</td>
<td>↓ Timidity</td>
</tr>
</tbody>
</table>

- Gay Men
- Shift Workers
- Bikers – Gangs
- Women
- Rural
- Youth
- Homeless
In the United States, 3.6% (10.2M people) aged 12 and older misused CNS stimulants in the past year

- Multiracial (5.0%)
- White (3.9%)*
- Hispanic (3.6%)
- Black (2.6%)*
- Asian (1.5%)

*sig diff p<0.01

NSDUH, Methamphetamine 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 Reuter\textsuperscript{1,2} \textsuperscript{a}, Jonathan P. Caulkins\textsuperscript{3} \textsuperscript{a} & Greg Midgette\textsuperscript{1} \textsuperscript{a}
Syphilis, methamphetamine and HIV incidence in LA County - Syndemics

Figure 26: Molecular HIV cluster cases by zip code and priority level, LAC, 2018-2020

Note: Clusters are colored as low priority (blue: < 5 persons with new HIV diagnoses between 2018-2020), medium priority (green: ≥ 5 persons with new HIV diagnoses between 2018-2020), and high priority (orange/red: ≥ 5 cases diagnosed in 2020). Among 282 persons identified in high priority clusters, 195 (69%) were interviewed through Partner Services where additional behavioral and clinical information was collected.

Among persons in high priority clusters, 18% had a history of methamphetamine use, 11% had a history of being unhoused, 66% reported anonymous sex partners, and 49% had co-infection with syphilis.

The highest number of high priority clusters were in West Hollywood, Downtown, and South Los Angeles zip codes.

Overdose Crisis 4th Wave: Poly-Substance Use

Friedman J, Shover CL. Addiction. 2023 Sep 13. DOI: 10.1111/add.16318
Increase in Prevalence of Acute Heart Failure by Stimulant Use; National Inpatient Sample

ASAM/AAAP Stimulant Guideline Systematic Review

Frequency of Use Links with Social and Health Outcomes

Status of Medication Development for Stimulant Use Disorder

There are no FDA approved medications for stimulant use disorder

No medications that might be FDA approved within the next five years

A small suite of medications have strong evidence of efficacy

Most medications trialed have weak signals for efficacy
Methamphetamine and Cocaine Meds: Strength of Evidence
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
Strongest Evidence for Use: Methamphetamine Use Disorder

XR-NTX @ 3 weeks + bupropion @ 450 q d
Mirtazapine @ 30mg q d
Broadly Effective Medication for Meth Use Disorder

XR-NTX: 380mg @ 3 wks
Bupr: 450mg @ day
NNT 12 Wks=9

Benefits of XR-NTX+Bupropion Continue to Accrue

Figure 1. Marginal predicted mean percentage of methamphetamine-negative urine tests over 12 weeks while on naltrexone plus bupropion versus placebo

Li MJ et al. Submitted
# Culture Links with Medication Effects: MSM vs MSW

## Table 3
Comparison of the adjusted treatment effect for extended-release naltrexone plus bupropion (XR-NTX + BUP) versus placebo for MSM/W and MSW participants.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th># Randomized</th>
<th>Placebo Responder Rate</th>
<th>XR-NTX + BUP Responder Rate</th>
<th># Re-randomized</th>
<th>Placebo Responder Rate</th>
<th>XR-NTX + BUP Responder Rate</th>
<th>Treatment Effect (h)</th>
<th>Standard Error of h</th>
<th>Number Needed to Treat</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSM/W</td>
<td>151</td>
<td>(3/108) 0.1395</td>
<td>(6/43) 0.0278</td>
<td>90</td>
<td>(2/47) 0.0426</td>
<td>(10/43) 0.2326</td>
<td>0.1479</td>
<td>0.0357</td>
<td>6.7</td>
<td>0.04</td>
</tr>
<tr>
<td>MSW</td>
<td>95</td>
<td>(4/69) 0.0580</td>
<td>(2/26) 0.0769</td>
<td>50</td>
<td>(0/22) 0.0000</td>
<td>(1/28) 0.0357</td>
<td>0.0227</td>
<td>0.0484</td>
<td>41.3</td>
<td></td>
</tr>
</tbody>
</table>

MSM/W: men who have sex with men only or with both men and women.
MSW: men who have sex exclusively with women.

Treatment Effect (h): between-group difference (active medication vs placebo) in the weighted average of Stage 1 and Stage 2 respond rates.

*All models were adjusted for study site, age, race, ethnicity, education, employment, HIV serostatus, and baseline methamphetamine use.

Continuing Benefit to Twelve Weeks of Treatment

Li MJ et al. Under Review
Findings and Targets

• Mechanism for combination medication is unknown – but the combination produces the strongest signal of efficacy in over 30 years of addiction research
• Fully powered trial: 403 participants randomized
• Primary outcome response: # participants with two weeks of meth-negative urine screens in weeks 5+6; weeks 11+12
• 450 mg bupropion is a significant dose of a weak stimulant
• XR-NTX produces a significant dose full mu opioid antagonist and kappa opioid antagonist
• Combination produces synergized effect
  • Similarly, lower doses efficacious for weight loss (Contrave™)
Pharmacotherapy for Stimulant Use in MSM: Mirtazapine 30 mg/day

Colfax et al. *Archives Gen Psych*, 2011 68: 1168-1175

Mirtazapine Meta-Analysis

Fig. 2: Forest plot and meta-analysis of reduction in methamphetamine positive urine toxicology screens at 12 weeks.

Fig. 3: Forest plot and meta-analysis of retention in treatment at 12 weeks.

Fig. 4: Forest plot and meta-analysis of reduction in depression symptom severity as measured by the CES-D scale at 12 weeks.

Findings and Targets

• Main strengths for mirtazapine for methamphetamine
  • Study findings replicate! Hardest thing to do in science is the same thing twice
  • Slopes of meth reduction measured by positive urine drug screens over time are parallel in the two trials

• Mechanism of response
  • FDA approved antidepressant – but no meta-analysis support for the depressive symptoms link with discontinuation of methamphetamine
  • More likely mechanism is restoration of sleep architecture – participants all recognized better sleep during the trial; sleep disturbance also is a common depressive symptom

• Potential downsides
  • Weight gain significant, which may be unacceptable for some MSM and for some women
  • Both studies conducted so far are in MSM and trans women; need replication in general broad groups – trial ongoing in Australia to advise use in outpatient clinic settings
    • Many of study assessments in that multisite trial are conducted using telehealth visits
Miguel is a 35-year-old Latino male with severe methamphetamine use disorder who recently had his first heart attack. Miguel is a dedicated father and hardworking shift-worker. The methamphetamine helps Miguel work as a dry-wall hanger and additional gig work as a Lyft driver. On Friday afternoons, Miguel blows off steam by having casual sex with whomever is hanging around the Home Depot men’s room. Miguel is a good family man and meets his family responsibilities. At your clinic, Miguel completed STI screening; he tested positive for syphilis (he’s never had syphilis before).

Miguel tells you he doesn’t believe his health problems are in any way linked with his methamphetamine use. He is unwilling to do much about his situation as he cannot afford time off work for the repeat health visits – or the co-pays for follow-up visits. While in clinic, Miguel is treated for syphilis and says he is willing to try one of the new medications for methamphetamine use, but he can only come in once a month or so.

As a practitioner, what would be the top goal for Miguel’s treatment plan?

A. Do nothing – Miguel’s words and behavior show he’s not ready for treatment
B. Schedule a meeting with Miguel’s wife to discuss her current health risks
C. Prescribe mirtazapine 30mg hs
D. Mandate 30 meetings in 30 days
Strongest Evidence for Use: Cocaine
Cocaine+ADHD: Mixed Amphetamine Salts - ER

Levin F et al. 2015. JAMA Psychiatry, 72(6):593-602
Findings and Targets

• Strength of trial is evaluation of two doses of slow-release d-amphetamine (standard dose (60mg) and higher (80mg) in adults living with ADHD and cocaine use disorder

• Strength of efficacy is the dose-response from placebo, to standard to higher dose slow-release d-amphetamine as measured by cocaine positive urine screens over 12 weeks

• Mechanism of response
  • Powered trial evaluating the rationale for stimulant medications to treat cocaine use disorder
  • Linked with neuropsychological underpinning of treating attention and impulsivity in both ADHD and cocaine use disorder

• Potential downsides
  • Many clinicians uncomfortable prescribing stimulants (even slow-release) to people with cocaine use disorder
  • Need data in people with primary cocaine use disorder to evaluate whether the approach produces remission of symptoms in people without co-occurring ADHD
Mixed Amphetamine Salts-Extended Release + Topiramate

3+ wks Neg UA


Levin FR et al. 2020 DAD 206:107700.
Findings and Targets

• Same group (Frances Levin, John Mariani) conducted two trials showing similar strength of efficacy using 60 mg XR-MAS and topiramate (200 mg) combination compared to placebo

• Strong evidence of using treatment combination

• Mechanism of response
  • Replication trials in cocaine use disorder only show similar signal for producing:
    • Significantly higher percent of participants who achieved 3 consecutive weeks of cocaine negative urine samples (first trial)
    • Reduced cocaine positive urine samples over 12 weeks (second trial)
  • Three studies together with similar signal sizes provide strong evidence supporting use of stimulants to change neuropsychological underpinning of attention and impulsivity
    • Some of the efficacy signal related to topiramate

• Potential downsides
  • Many clinicians uncomfortable prescribing stimulants (even slow-release) to people with cocaine use disorder
Fig. 2. Overall and by dependence drug effect of prescription psychostimulants compared to placebo for outcome sustained abstinence

Findings and Targets

- Meta-analysis of RCTs of psychostimulants for stimulant use disorder show signal for cocaine use disorder for sustained abstinence outcome; less signal for amphetamine/methamphetamine use disorder
  - Psychostimulant strength linked with strength of agonist:
    - Amphetamines > modafinil/atomoxetine/methylphenidate
  - For cocaine use disorder, strong dose effect, with at maximum or above recommended highest dose showing consistent signal for sustained abstinence outcome
- No consistent signal of psychostimulants for treatment retention
- Mechanism of response
  - Relief from attentional problems, energy issues, psychological symptoms in sustained abstinence
- Potential downsides
  - Many clinicians uncomfortable prescribing stimulants (even slow-release) to people with cocaine use disorder
Summary Current Pharmacotherapies

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

- Mirtazapine effects in MSM are impressive, particularly replication
  - Effect is reduction in use, not abstinence (like naltrexone for heavy alcohol drinking)
  - So far only tested in San Francisco and only 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 effects observed for people with ADHD
- Combination MAS-ER plus topiramate shows two replications
- Support for amphetamine for cocaine use disorder in meta analysis

Evidence to consider medication as a foundation of treatment for stimulant use disorder
Psychotic Symptoms

In the ASAM/AAAP Clinical Practice Guideline for Stimulant Use Disorders, there are 6 antipsychotics that have evidence of efficacy for use in treating psychotic symptoms among people with stimulant use disorders.

Olanzapine and quetiapine are preferred for their antipsychotic effects.

No antipsychotics reduce methamphetamine use – and should be used for psychotic symptomatic relief only.
Withdrawal

- Amineptine is the only medication that shows strong efficacy for withdrawal symptoms (20).
  - Strong stimulant, agonist effects
  - Still off-market in most parts of the world
- Overall, there is inconsistent signal for biomedical treatments on MA withdrawal
- Symptom relief for MA withdrawal seen for a few medications (mirtazapine, naltrexone, bupropion) and repetitive transcranial magnetic stimulation during acute (first week), early protracted (weeks 2–4) and late protracted (> 4 weeks) withdrawal phases
Culture, Epidemiology, Comorbidities: Implications for Medical Treatment of StUD
Implications for Stimulant Use Disorder Treatment

• Professional biases and competencies in treating StUD
  • Understanding of type of treatments (medical, behavioral, community) necessary for success in addressing StUD
  • Identities as a person who uses stimulants (vs person who uses opioids)
  • Cultural factors in addressing StUD in gay/bisexual men, MSM, trans women
  • Cultural factors in addressing persons with minority racial/ethnicity identities
  • Economic factors for persons who use stimulants for work demands
  • New and emerging factors to reduce harm to women and pregnant persons who seek help for StUD

• Academic Detailing
Infectious Diseases
PrEP and ART
- PrEP Persistence
- ART Care – Sustained Viral Suppression
HIV Testing and Counseling
STI Testing and Treatment
Hepatitis A, B, C

Drug and Alcohol Use
- Medications
- Behavioral Therapies
- Harm Reduction

Primary Care
- Cardiovascular care
- Metabolic disorders
- Chronic disease management
- Depression +/- anxiety management

Silo-Busting: Building to Whole Person Care for People with StUD
Your patient is a 32-year-old African American man, James, who is an “out” gay man. You’ve met with James once following referral from his primary care provider. James talked about his concerns over his cocaine use issue, especially fentanyl and xylazine worries. Today’s appointment was for 9:00 am. At 9:45 there was still no sign of James. He hadn’t called to inform the clinic about delays.

You finish your next appointment and walk the individual to the waiting area. It strikes you the clinic is sparsely furnished, with white walls and a few faded framed pictures, some silk plants and outdated magazines. As you look around, you also see James walking out the clinic doors.

At the front desk, the staff member says James arrived at 10:15. The next available session for James is two weeks from today at 9:00 am. James was agreeable to the rescheduled day/time.

Which of the following is something that would be helpful to change to ensure James is likely to return to clinic, and once here, to keep his future addiction medicine appointments?

A. Do nothing – James is scheduled for 9:00 am in two weeks
B. Follow James out to ask if he would spend a few minutes with you in your office
C. Get a urine drug screen from James to confirm recent cocaine use at the next session
D. Require James use treatment goal of absolute abstinence
Summary and Conclusions

- There is strong evidence supporting a limited set of medications for treating methamphetamine and cocaine use disorders
- The treatment with highest efficacy for stimulant use disorder is Contingency Management
  - Several barriers to wide-scale implementation
- Best outcomes for integrating behavior and medication treatments
- Culturally competent treatment for individuals with stimulant use disorder is built upon:
  - The “power of the repeat visit,”
  - Liberal use of structure and positive reinforcement
  - Expertise into effects of stimulants on behavior
  - Commitment to integrated, whole person treatment
  - Respect for cultural differences; reduction in bias/stigma
Thank You!
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