TREATMENT OF STIMULANT USE DISORDERS

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GENERAL DISCLOSURES

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SPEAKER DISCLOSURES

✓ No conflicts of interest/disclosures
OBJECTIVES

1. Brief overview of stimulant-related physiology & epidemiology

2. Recognizing & treating stimulant use disorders:
   - Diagnosis & management of acute effects (brief)
   - Psychotherapies (brief)
   - Pharmacotherapies

3. Special populations
   - ADHD in stimulant-abusing pts: to Rx, and how?
STIMULANTS: What Substances Are We Talking About?

Cocaine

Amphetamines:
- Prescription Meds
- Methamphetamine
- Multiple other modified amphetamines

MDMA (3,4-methylenedioxy-methamphetamine)

[Note: mixed stimulant-psychodelic properties, w/↑serotonin > dopamine and abuse >> addiction.]

Others:
- Cathinones: Khat & Synthetics (e.g., “Bath Salts”)
- Piperazine-like substances (various)
- Phenylaklylpyrrolidines (various)
COMMONALITIES
(WHAT MAKES A STIMULANT A STIMULANT?)

Brain reward (dopamine) pathways

These brain circuits are important for natural rewards such as food, music, and sex.

Drugs of abuse increase dopamine

Typically, dopamine increases in response to natural rewards such as food. When cocaine is taken, dopamine increases are exaggerated, and communication is altered.

- Inhibit dopamine & NE reuptake
- Some also potentiate dopamine-release (e.g., amphetamines, methamphetamines, cathinones)

NIDA (2008) Drugs, Brains, & Behavior
COMMONALITIES: Clinical Effects

Short-term (Intoxication & Withdrawal):
- **Psychiatric**: euphoria, ↑energy & activity, alertness, insomnia, restlessness, anxiety/panic, erratic & violent behavior, paranoia, psychosis, poor judgment.
- **Cardiovascular**: vasoconstriction, arrhythmias, MI, ↑HR, HTN
- **Neurologic**: headache, enlarged pupils, stroke, seizure, coma
- **Other**: ↑body temp, dehydration, renal injury, abdominal pain & nausea, ↓appetite, premature delivery & placental abruption
- **Withdrawal**: Depression, fatigue, hypersomnolence, sleep disturbances, motoric phenomena, paresthesias.

Long-term:
- **End organ damage** (CNS, cardiac, renal, hepatic, other) from hypoperfusion, toxic effects, rhabdomyolysis.
- **Nutrition**: poor nutrition & weight loss.
- **Psychiatric**: Prolonged confusion, depression, anxiety, inattention, psychosis, aggression, memory, and sleep issues.
- **Infection**: Risk of HIV, HCV, other infectious diseases.
IDENTIFYING STIMULANT USE DO

Confirm & Characterize Stimulant Use:
– Based on pt’s report, SUDs screening tools, collateral evidence, symptoms/signs, toxicology, etc

DX: Use → impairment/distress:
– Symptoms:
  • Persistent desire or unsuccessful efforts ↓ use.
  • Cravings

– Behaviors:
  • Using ↑ amounts or over longer period than intended.
  • Excessive time obtaining, using, recovering
  • Failure to fulfill major role obligations
  • Use despite consequences
  • Important activities given up/reduced
  • Recurrent use when physically hazardous.
  • Use despite knowledge of physical/psychological problems

– Physiologic Changes:
  • Tolerance, Withdrawal
STIMULANTS: HOW BIG A PROBLEM?

Numbers of Past Month Illicit Drug Users among People Aged 12 or Older: 2015

- No Past Month Illicit Drug Use: 240.6 Million People (89.9%)
- Past Month Illicit Drug Use: 27.1 Million People (10.1%)

- Marijuana: 22.2 Million People
- Misuse of Prescription Pain Relievers: 3.8 Million People
- Cocaine: 1.9 Million People
- Misuse of Prescription Tranquilizers: 1.9 Million People
- Misuse of Prescription Stimulants: 1.7 Million People
- Hallucinogens: 1.2 Million People
- Methamphetamine: 0.9 Million People
- Inhalants: 0.5 Million People
- Misuse of Prescription Sedatives: 0.4 Million People
- Heroin: 0.3 Million People

COCAINETH AND ITS CONSEQUENCES

- 1.9 million (> 12yo) used cocaine (crack ~394K users)
- Young adults ~2.5X those > 25yrs old.
- Men >> women (2X use & death rates)
- 423,000 ED visits (2009)
- >5,000 deaths/yr annually

Figure 33. Cocaine Use Disorder in the Past Year among People Aged 12 or Older, by Age Group: Percentages, 2002-2015

SAMHSA (2015) BHTUS; SAMHSA DAWN Study (2010)
METH/AMPHETAMINE MISUSE & ITS CONSEQUENCES

- ~900,000 used Meth in prior month
- 1.7 million misused Rx-ed stimulants in prior month
- ED visits due to illicit meth/amphet effects:
  - ~93,000 (2009)
  - >60% involved at least one other substance.

SAMHSA BHTUS (2015); SAMHSA DAWN Study (2010)
RX STIMULANT MISUSE & DIVERSION

- **HS students** w/stimulant rxs:
  - 15% shared, 7% sold meds to peers in past year

- **College students** w/stimulant rxs:
  - 61.5% shared or sold meds ≥ 1 in their life

- **Adults** w/methylphenidate rxs:
  - 44% diverted, 29% misused in past month

“BATH SALTS”: SYNTHETIC CATHINONES

• MOA like Meth (+ ↑5HT like MDMA)
• Easy access (historically): Internet, head shops
• Not detected on standard tox-screens
• Rates of use uncertain
STIMULANT USE DISORDERS:

TREATMENT
ACUTE INTOXICATION & WITHDRAWAL

Monitor for vitals/lab abnormalities

– Hyperthermia, dehydration, renal function

Supportive

– Cardiac, Renal, Hyponatremia effects may require IVF/electrolytes, HTN control, +/-hospitalization

– Psychiatric symptoms: assess, monitor, +/- ED/hospitalization for safety

• Agitation: Benzodiazepines

• Hallucinations: low-dose antipsychotics for hallucinations

  – Avoid aggressive use of antipsychotics due to increased morbidity
TREATING STIMULANT USE DISORDERS

Components of Comprehensive Drug Abuse Treatment

- Intake Processing/Assessment
- Treatment Plan
- Substance Use Monitoring
- Continuing Care
- Pharmacotherapy
- Behavioral Therapy and Counseling
- Clinical and Case Management

The best treatment programs provide a combination of therapies and other services to meet the needs of the individual patient.
PSYCHOTHERAPIES: A GENERAL APPROACH

↑ intensity for ↑ severity or inadequate response

➢ Outpatient addictions counseling/groups
  ➢ Intensive outpatient tx (largely group-based)
    ➢ Individual therapies (plus groups): CM, CBT
    ➢ Intensive residential, pharmacotherapy

—Note: assess & treat co-morbid psychiatric and other SUDs
TREATING STIMULANT USE DISORDERS

What Works?
PSYCHOTHERAPIES FOR STIMULANT USE

**Therapy Modalities:**
- Contingency Management (CM)
- Cognitive Behav. Therapy (CBT)
- Motivational Enhancement Therapy (MET)
- 12-Step Facilitation
- Family Therapy (esp. for youth)

**Pros:**
- Evidence-based
- Skill-building (often)
- ↑ internal motivation
- Bridge to additional tx
- Can use in multiple settings

**Cons:**
- Time, resource-intensive
- Limited workforce
- Modest effect sizes
- Not suitable for all pts (e.g., cognitive requirements)
- Unclear sustained benefit
PHARMACOTHERAPY FOR STIMULANT USE DISORDERS

Components of Comprehensive Drug Abuse Treatment

- Behavioral Therapy and Counseling
- Treatment Plan
- Substance Use Monitoring
- Self-Help/Peer Support Groups
- Clinical and Case Management
- Pharmacotherapy
- Continuing Care

The best treatment programs provide a combination of therapies and other services to meet the needs of the individual patient.
Question: Which medications are FDA-approved for treatment of a stimulant use disorder?

Answer: None 😞
POP QUIZ!

Question: Which medication(s) have shown potential benefit for sustaining remission from cocaine use?
POSSIBLE MEDICATION(S) FOR COCAINE USE DISORDER?

Evidence suggestive of likely use-reduction w/Rx:

- Disulfiram, topiramate, methylphenidate

Equivocal, to date:

- Modafinil, amantadine, varenicline, naltrexone, doxazosin, NAC, TA-DC Vaccine

Ineffective (based on available data):

- Lithium, Carbamazepine, TCAs, SSRIs, bupropion, Nefazodone, Selegiline, antipsychotics
DISULFIRAM FOR COCAINE USE DISORDER

Mechanism(s) of Action:

– Inhibits dopamine $\beta$-hydroxylase, $\downarrow$ dopamine $\rightarrow$ norepinephrine
  • Disrupts neurotransmitter balance in reward system?

– $\uparrow$ cocaine plasma levels (MOA unknown) $\rightarrow$ cocaine more aversive?

– FDA approved for ETOH use disorder
  • $\sim$80% of pts w/cocaine use disorder have comorbid ETOH use disorder. Can $\downarrow$ in ETOH use promote $\downarrow$ cocaine use?

Pani et al., 2010
Figure 2. Frequency of cocaine use by treatment week. Effects are estimates from random regression analyses. CBT indicates cognitive behavior therapy; IPT, interpersonal psychotherapy.

Carroll et al., 2004
RX OF COCAINE USE DO:
OTHER (PROMISING) RX OPTIONS

• Topiramate
  – An antiepileptic, increases GABA activation
  – May be especially effective with CBT

• Amphetamine salts
  – Increases dopamine & norepinephrine availability
  – A stimulant “substitution therapy” (like buprenorphine-naloxone)?
  – Mixed results (efficacy improves w/retention?)
Topiramate for Cocaine Use Disorder
- 12 wk trial w/142 Cocaine-dependent pts
- Randomized to CBT +: Placebo vs. Topiramate
  - Target dose, weeks 6-12: 150 mg bid

Johnson et al., 2014
Topiramate for Cocaine Use Disorder:

a) Treatment Retention

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
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<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
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<tr>
<td>Johnson et al. 2013</td>
<td>25</td>
<td>71</td>
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<td>Kampman et al. 2013</td>
<td>29</td>
<td>87</td>
<td>41</td>
<td>83</td>
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<tr>
<td>Umbricht et al. 2014</td>
<td>33</td>
<td>47</td>
<td>26</td>
<td>45</td>
</tr>
</tbody>
</table>

Total (95% CI) 225 219 100.0% 0.85 [0.60, 1.22]

Total events 89 103

Heterogeneity: Tau² = 0.07; Chi² = 7.32, df = 3 (P = 0.06); I² = 59%
Test for overall effect: Z = 0.88 (P = 0.38)

b) Continuous Abstinence

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
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<td>10</td>
<td>20</td>
<td>5</td>
<td>20</td>
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<tr>
<td>Kampman et al. 2013</td>
<td>17</td>
<td>33</td>
<td>8</td>
<td>87</td>
</tr>
</tbody>
</table>

Total (95% CI) 103 107 100.0% 2.43 [1.31, 4.53]

Total events 27 11

Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 1 (P = 0.53); I² = 0%
Test for overall effect: Z = 2.81 (P = 0.005)

c) Adverse Effects

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
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<td></td>
<td>Events</td>
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<td>Johnson et al. 2013</td>
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<td>57</td>
<td>71</td>
</tr>
<tr>
<td>Umbricht et al. 2014</td>
<td>5</td>
<td>45</td>
<td>4</td>
<td>47</td>
</tr>
</tbody>
</table>

Total (95% CI) 116 118 100.0% 1.06 [0.91, 1.23]

Total events 65 61

Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.71 (P = 0.48)

Singh et al., 2015
RX OF COCAINE USE DO: STIMULANTS?

- 12wk, multi-center, double blinded, placebo-controlled
- 73 pts w/cocaine & heroin SUDs on methadone
- Randomized to placebo vs dextroamphetamine SR 60mg/day
- Days of cocaine-use ↓ 26% on Rx stimulant

<table>
<thead>
<tr>
<th>Primary outcome</th>
<th>Sustained-release dexamfetamine group (n=38)</th>
<th>Placebo group (n=35)</th>
<th>Exp(B) (95% CI)</th>
<th>Wald χ² (df=1)</th>
<th>p value</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days of cocaine use during 12-week study</td>
<td><strong>44.9 (29.4)</strong></td>
<td><strong>60.6 (24.3)</strong></td>
<td><strong>1.67 (1.05-2.67)</strong></td>
<td><strong>4.66</strong></td>
<td><strong>0.031</strong></td>
<td><strong>d=0.58</strong></td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Secondary cocaine use-related outcomes</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Longest period of consecutive cocaine abstinence (days)</td>
<td>17.9 (24.9)</td>
<td>6.7 (11.7)</td>
<td>2.69 (1.66-4.36)</td>
<td>16.17</td>
<td>&lt;0.0001</td>
<td>d=0.58</td>
</tr>
<tr>
<td>Consecutive cocaine abstinence for ≥21 days</td>
<td>11 (29%)</td>
<td>2 (6%)</td>
<td>6.72 (1.37-32.97)</td>
<td>5.52</td>
<td>0.019</td>
<td>NNT=4.3</td>
</tr>
<tr>
<td>Days of cocaine abstinence in final 4 weeks</td>
<td>15.2 (10.8)</td>
<td>7.5 (9.1)</td>
<td>2.04 (1.26-3.31)</td>
<td>8.45</td>
<td>0.004</td>
<td>d=0.77</td>
</tr>
<tr>
<td>Proportion cocaine-negative urine samples in final 4 weeks</td>
<td>10.6 (25.1)</td>
<td>3.9 (17.9)</td>
<td>2.60 (1.14-5.94)</td>
<td>5.11</td>
<td>0.024</td>
<td>d=0.31</td>
</tr>
</tbody>
</table>

Data are mean (SD) or n (%), unless otherwise specified. Exp(B)=exponentiated value of regression coefficient B; odds ratio. df=degrees of freedom. d=Cohen’s d, which is a standardised effect size. NNT=number needed to treat.
POP QUIZ!

**Question**: What medication has good evidence of promoting abstinence from methamphetamine among chronic users?
PHARMACOTHERAPY FOR METHAMPHETAMINE USE DISORDER:

– No accepted treatments 😞
– There have been small studies suggesting potential benefit from mirtazapine, bupropion
– Equivocal or negative results for naltrexone, atomoxetine, buprenorphine-naloxone, stimulants
PHARMACOTHERAPY FOR METHAMPHETAMINE USE DISORDER: MIRTAZAPINE (30MG)

Colfax et al. (2011)
PHARMACOTHERAPY FOR METHAMPHETAMINE USE DISORDER: BUPROPION (300MG)

Design:
• 12wk, 151 Meth-dep pts
• Randomized to CBT +:
  – Placebo
  – Bupropion 300mg Qday

Results:
– No diff in abstinence in total sample
– Improvement w/bupropion among light-users

Shoptaw et al. (2008)
A SPECIAL CASE?

PRESCRIBING STIMULANTS FOR CO-MORBID ADHD & STIMULANT USE DISORDERS?
DOES RX OF ADHD WITH STIMULANTS IMPACT DEVELOPMENT OF SUDS?

Risk of Developing Cocaine Abuse or Dependence

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect Size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barkley et al\textsuperscript{26}</td>
<td>0.79 (0.03-20.04)</td>
</tr>
<tr>
<td>Biederman et al\textsuperscript{27}</td>
<td>0.10 (0.01-1.00)</td>
</tr>
<tr>
<td>Burke, unpublished data</td>
<td>2.25 (0.20-25.40)</td>
</tr>
<tr>
<td>Hechtman et al\textsuperscript{31}</td>
<td>1.74 (0.15-20.21)</td>
</tr>
<tr>
<td>Huss et al\textsuperscript{32,33}</td>
<td>0.20 (0.01-4.25)</td>
</tr>
<tr>
<td>Lambert and Hartsough\textsuperscript{35}</td>
<td>2.11 (0.98-4.55)</td>
</tr>
<tr>
<td>Mannuzza et al\textsuperscript{16}</td>
<td>1.09 (0.36-3.34)</td>
</tr>
<tr>
<td>Combined</td>
<td>1.10 (0.51-2.38)</td>
</tr>
</tbody>
</table>

Humphreys et al (2013)

Conclusions:
- Neutral > protective effects; not harmful
Comorbid ADHD & amphetamine use disorders:
• Very little research
• Rx w/stimulants $\rightarrow$ no difference in ADHD or SUD (Konstenius et al 2010.)

Comorbid ADHD & Cocaine use disorder:
• More research
• Results suggesting...
STIMULANTS FOR RX OF COMORBID ADHD & STIMULANT ABUSE...MAYBE

Levin et al 2007:

Design:
- 14 week double-blinded, placebo-controlled trial
- 106 adult w/ADHD + Cocaine UD
- CBT + SR-MPH (60mg) vs CBT + placebo

Results:
- Decreased probability of cocaine+ UDAS w/MPH
- No difference in ADHD symptoms
Riggs et al (2011)

Design:
• 16 wk, double-blinded placebo controlled
• 303 teens w/ADHD + active SUD
• Methylphenidate (Concerta) 72mg/day + CBT vs placebo + CBT

Results:
• No diff in ADHD or substance use
• Drugs of abuse: Cannabis > Alcohol > other drugs
STIMULANTS FOR COMORBID ADHD & STIMULANT ABUSE...MAYBE YES!

Levin et al 2015:

Design:
• 13 wk double-blinded, placebo-controlled 3-arm trial
• 126 adult w/ADHD + Cocaine UD
• CBT plus: Placebo vs. SR-mixed Amph (60mg) vs. SR-mixed Amph (80mg)

Results:
• Rx w/Stimulant ↓ prob. cocaine-use (UDAS or self-report)
• Rx w/Stimulant ↓ ADHD symptoms
STIMULANTS FOR COMORBID ADHD & STIMULANT ABUSE – SUMMARY

Studies suggest:

– No worsening of substance of use disorders
– Unclear utility in amphetamine use disorder
– Accumulating evidence for role in cocaine use disorder
  • May ↓ cocaine use
  • May ↓ ADHD symptoms
STIMULANTS FOR COMORBID ADHD & STIMULANT ABUSE – TREATMENT APPROACH

Tailor to individual pt:
- Actual AD/HD & of what severity?
- Has SUDs treatment been +/- optimized?
- Hx/risk of mis-use or diversion?

Would non-abusuble Txs work for pt?:
- e.g., atomoxetine, bupropion, CBT

Consider long acting stimulant, as appropriate:
- ↑outcomes w/pre-rx abstinence
- Coordinate w/other providers
- Treatment agreement/contract
- Monitor (tox screens, call-backs PRN)
- Use adequate/higher doses
PRESENTATION SUMMARY:

– Stimulant misuse:
  • Modestly prevalent; often severe individual & social costs

– Acute symptom management: supportive

– Psychosocial Txs are 1st Line:
  • Conting. Management, CBT have most evidence

– Pharmacotherapies:
  • Cocaine:
    – Disulfiram; some evidence for topiramate, stimulants, others
  • Methamphetamine:
    – Small studies ~ potential benefit from mirtazapine, bupropion
  • Consider co-morbid psychiatric DOs in Rx decision /selection

– Tx of AD/HD in stimulant-abusing pts:
  • Case by case, prescribed stimulant can be helpful
QUESTIONS & DISCUSSION

MANY THANKS!
- The PACC community
- Andy Saxon, MD
- Jonathan Buchholz, MD
- Mark Duncan, MD
COCAINE USE AND ITS CONSEQUENCES

- Men (0.8%) vs. women (0.4%)
- >5,000 deaths/yr annually (2014)

Source: National Center for Health Statistics, CDC Wonder

SAMHSA (2015) BHTUS: Results from the 2015 National Survey on Drug Use and Health