Methamphetamine & Cocaine Use Disorders

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- Some of the medications discussed may not be FDA approved in the manner in which they are discussed including diagnosis(es), combinations, age groups, dosing, or in context to other disorders (e.g. substance use disorders)

*Past 3 years*
Cocaine: Epidemiology

• 4.2 million US residents use cocaine yearly
• >900,000 US residents with cocaine use disorder
• Cocaine is a tropane ester alkaloid found in leaves of the Erythroxylum coca plant, a bush that grows in the Andes Mountain region of South America
• Cocaine is the illegal drug most often associated with visits to US hospital emergency departments

Results from the 2013 National Survey on Drug Use and Health, NSDUH Series H-48, HHS Publication No. (SMA) 14-4863, Rockville, MD 2014
Cocaine: Clinical Effects

- Typical cocaine doses: 12 to 15 g orally (coca leaf), 20 to 100 mg intranasally, 10 to 50 mg intravenously, and 50 to 200 mg smoked
- Potent CNS Stimulation
  - Disinhibition, euphoria, elevation, enhanced sense of self, energy
  - Tachycardia, increased heart rate
- Adverse effects
  - Acute: anxiety, talkativeness, agitation, paranoia, psychosis, stereotypies/picking, dyskinesias, cardiovascular/stroke, hyperthermia, circulatory failure
  - Chronic: sensitization or tolerance, depression, weight loss, neuropsychological impairment, cardiovascular (myocardial infarction, arrhythmias, hypertension), respiratory symptoms (smoked)
- Withdrawal (immediate to 2+ weeks)
  - Intense crash/ sleep
  - Irritability, agitation, depression, urges/cravings
Mechanism of Action of Cocaine


Presynaptic Neuron

Cytoplasmic Dopamine

Storage vesicle

Dopamine Transporter
Norepinephrine Transporter (?)

Cocaine inhibits
Cocaine: Testing

• Screening tests
• Blood (12 hr cocaine, 48 hr benzoylecgonine)
• Oral Fluid (similar to blood, improving detection)
• Urine (benzoylecgonine only)- two to three days after cocaine use, but may be positive up to two weeks after chronic heavy use

Rate of Drug Uptake Into the Brain Linked to Likeability

Cocaine (iv) and methylphenidate [MPH] (iv) produce a “high” but methylphenidate (oral) does not

The slow brain uptake of oral methylphenidate permits effective treatment without a “high”

(Volkow et al., Arch Gen Psych 52:1995, J Neurosci 2001)
Cocaine Treatment

- Some similarities to methamphetamine use disorder
- Smoked cocaine among the most difficult SUD to treat
- Twelve Step (Cocaine Anonymous)/ Rational Recovery
- Cognitive Behavioral Therapy +/- MI
- Contingency Management

Topiramate (n = 71) or placebo (n = 71) in escalating doses from 50 mg/d to the target maintenance dose of 300 mg/d in weeks 6 to 12, combined with weekly cognitive-behavioral treatment.
Treatment of Crack Cocaine with Topiramate

Design: RCT; N=29/group; dosing to 200 mg/day
Adjunct Tx: Motivational interviewing, group Tx
Cocaine: Pharmacotherapy

- Topirimate
- N-Acetylcysteine (NAC)
- Disulfiram (linked to DBH genotype?)
- Modafinil
- Agonist therapies (e.g. stimulants)
- Cocaine vaccine (experimental)

Dackis et al, Neuropsychopharmacology (2005) 30, 205–211
Johnson B et al., JAMA Psychiatry. 2013;70(12):1338-1346
Overshadowed by opioids, meth is back and hospitalizations surge

Publish date: November 27, 2018
By Anna Gorman, Kaiser Health News

Clinical Psychiatry News.

The number of people hospitalized because of amphetamine use is skyrocketing in the United States, but the resurgence of the drug largely has been overshadowed by the nation’s intense focus on opioids.

Amphetamine-related hospitalizations jumped by about 245% during 2008-2015, according to a recent study in the Journal of the American Medical Association. That dwarfs the rise in hospitalizations from other drugs, such as opioids, which were up by about 46%. The most significant increases were in Western states.
Methamphetamine: Epidemiology

- 4.7% lifetime use
- 0.4% past year; 0.2% past month
- Amphetamine type stimulants are second most frequently used illicit class in world
- Use in US for obesity, mood, & ADHD—use peaked in 1967
- Hospitalizations are rising however

Courtney and Roy, Drug Alc Dep 2014: 143: 11-21
Winkelman et al, JAMA (Open): 2018
Methamphetamine Related Hospitalizations are Increasing

(Winkelman et al., JAMA, 2018)
Methamphetamine basics

- Mixture of pseudoephedrine and ephedrine
- New manufacturer decreased with reduced pseudoephedrine availability
- Cost down from 270$/gm in 2007 to 80$/gm currently
- Purity from 40% to 80%
- Available as powder (tablet) or crystalline form ("ice" "Crystal Meth")
- Urine Detection: <4 days (7d if heavy use)
- High: immediate if smoked/injected; slower onset (<20 min) but long duration (8-12h) if po/intranasal/pr
Methamphetamine neurobiology

Related to dopamine, norepinephrine and serotonin systems

- Presynaptic neuronal release with depletion
- Downstream involvement in opioid system
- Reduced anterior circulate and prefrontal cortex activity (linked with diminished cognitive functioning)

Sabrini et al, Drug Alc Dependence, 2019: 194: 75-87
The Mechanisms of Action of (Meth)Amphetamine

(Wilens T. J Clin Psych 2006)

AMPH inhibits AMPH is taken up into cell causing DA/NE release into synapse

AMPH diffuses into vesicle causing DA/NE release into cytoplasm

AMPH blocks uptake into vesicle

AMPH is taken up into cell causing DA/NE release into synapse

Presynaptic Neuron

Cytoplasmic DA/NE

Synapse

Storage vesicle

DA/NET? Transporter Protein

AMPH Inhibits
Methamphetamine: Presentation

- Drawn face
- Weight loss
- Skin erosions
- Mucosal infarcts
- Skin erosions, scars
- MSE: Anhedonia/depression, anxiety, executive functioning deficits (prominent)
- Severe urges and cravings

Methamphetamine: Clinical Effects

• Potent CNS Stimulation
  – Disinhibition, euphoria, elevation, enhanced sense of self, energy
  – Tachycardia, increased heart rate
• Adverse
  – Acute: anxiety, talkativeness, paranoia, psychosis, stereotypies/picking, dyskinesias, cardiovascular/stroke, hyperthermia, circulatory failure
  – Chronic: depression, neurotoxicity & neurocognitive dysfunction (executive dysfunction), cardiovascular
• Withdrawal (immediate to two+weeks)
  – Depression most common (anhedonia)

Sabrini et al, Drug Alc Dependence, 2019: 194: 75-87
Adverse (negative) effects of Methamphetamine

Psychological
- Insomnia
- Aggressive behavior
- Paranoia
- Incessant conversations
- Decreased appetite
- Increased alertness
- Irritability
- Slurred speech
- Dizziness
- Confusion
- Hallucinations
- Obsessive behaviors
- Depression
- Panic attacks

Systemic
- Hyperthermia
- Malnutrition
- Impaired immune system

Circulatory
- High blood pressure
- Vessel damage in brain
- Clotting and stroke

Eyes
- Dilated pupils

Mouth
- Grinding of teeth

Skin
- Sweating
- Numbness

Respiratory
- Shortness of breath

Muscular
- Jerky movements
- Increased activity
- Convulsions
- Loss of coordination

Kidneys
- Damage

Heart
- Chest pain
- Rapid heart rate
- Heart attack

Liver
- Damage

Methamphetamine Treatment

- Some similarities to cocaine use disorder
- Amongst the most difficult SUD to treat
  - Engagement and Retention
- Most data suggest psychosocial interventions most effective
- Twelve Step/ Rational Recovery (no empirically based data in meth use disorders)
- Motivational interviewing (data on success in MSM)
- Cognitive Behavioral Therapy
  - Caveat: Executive functioning deficits (less PFC/ACC activity)
  - Focused CBT/MI for MSM useful for sexual behavior and Meth
- Contingency Management
- Time abstinent

Cadet and Gold, Curr Psychiatry, 2017: 11: 15-20
Methamphetamine: Recovery Takes Time
Atomoxetine for amphetamine-type stimulant dependence during buprenorphine treatment: A randomized controlled trial


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ABSTRACT

Background: Amphetamine type stimulants (ATS) use is highly prevalent and frequently co-occurs with opioid dependence in Malaysia and Asian countries. No medications have established efficacy for treating ATS use disorder. This study evaluated the safety, tolerability, and potential efficacy of atomoxetine for treating ATS use disorder.

Methods: Participants with opioid and ATS dependence (N = 69) were enrolled in a pilot, double-blind, placebo-controlled randomized clinical trial; all received buprenorphine/naloxone and behavioral counseling and were randomized to atomoxetine 80 mg daily (n = 33) or placebo (n = 33). The effect size of the between-group difference on the primary outcome, proportion of ATS-negative urine tests, was estimated using Cohen’s d for the intention-to-treat (ITT) sample and for higher adherence subsample (≥60 days of atomoxetine or placebo ingestion).

Results: Participants were all male with mean (SD) age 39.4 (6.8) years. The proportion of ATS-negative urine tests was higher in atomoxetine- compared to placebo-treated participants: 0.77 (0.63–0.91) vs. 0.67 (0.53–0.81, d = 0.26) in the ITT sample and 0.90 (0.75–1.00) vs. 0.64 (0.51–0.78, d = 0.56) in the higher adherence subsample. The proportion of days abstinent from ATS increased from baseline in both groups (p < 0.001) and did not differ significantly between atomoxetine- and placebo-treated participants (p = 0.42). Depressive symptoms were reduced from baseline in both groups (p < 0.02) with a greater reduction for atomoxetine- than placebo-treated participants (p < 0.02). There were no serious adverse events or adverse events leading to medication discontinuation.

Conclusions: The findings support clinical tolerability and safety and suggest potential efficacy of atomoxetine for treating ATS use disorder in this population.
Methamphetamine: Treatment (2)

- No FDA approved agents for meth use disorder
- Bupropion effective in less severe cases
- Modafinil + CBT effective in HIV+ cases
- Naltrexone for general amphetamine misuse
  - Implantable or high dose may be preferred
- Topiramate reduced meth in MSM-short but not longer term
  - May be better for relapse prevention (e.g. abstinent at start)
- Mirtazapine (30 mg)-
  - RCT: tested in MSM (improved meth and risk behaviors)
- Craving reduction
  - Multiple attempts have not been successful
  - Some efficacy with substitution therapy (e.g. d-amphetamine), cholinesterase inhibitors, NAC, bupropion, nicotine, naltrexone
- Treating psychosis (2nd > 1st generation antipsychotics): careful with EPS

Knight et al, Drug Alc Dep, 194: 2019: 410-429
Summary: Cocaine & Methamphetamine

- Both classes of substances with pronounced “stimulant-like” effects
- Nonfatal but intense withdrawal and cravings
- Treatment engagement and retention challenging
- Use of psychosocial treatments necessary
- Limited replicated trials demonstrating medication efficacy
- Somewhat longer time for brain recovery relative to other misused substances