Methamphetamine in the Era of Fentanyl: Toxicities and Therapies

Phillip Coffin, MD, MIA, FACP, FIDSA
Director of Substance Use Research
San Francisco Department of Public Health
University of California San Francisco

Tuesday, March 9, 2021
12:00 – 1:00 PM ET
Webinar Housekeeping

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To be recognized, type your question in the “Question” box and select send.
Meet Our Speaker

Phillip Coffin, MD MIA FACP FIDSA

• Director of Substance Use Research

• San Francisco Department of Public Health, University of California San Francisco

• Internal medicine, addiction medicine, and infectious disease boarded and practicing physician and NIDA/CDC-funded investigator studying pharmacotherapies and behavioral interventions for substance use, overdose, and infectious diseases.
Disclosures

Phillip Coffin, MD, has disclosed that he does not have a relevant financial relationship with an ACCME defined commercial interest.
Learning Objectives

By the end of this presentation, attendees will be able to:

1. Describe trends in morbidity and mortality related to methamphetamine.

2. Explain the distinctions between non-fatal and fatal acute methamphetamine toxicity.

MA Use Among US Adults
Amphetamine Overdose ED Visits in US

Vivolo-Kantor, DAD, 2020
Stimulant ED Visits in U.S.

Hoots, Addiction, 2020
Amphetamine-Related Hospitalizations by US Region

Tyler, JAMA Netw Open, 2018
What Leads to MA-Related ED Presentations?

• Trauma: 18-33%
• Psychosis: 8-80%
  ▪ Psychiatric admission 14%
  ▪ Psychiatric hold 11%
  ▪ Jones, J Clin Nursing, 2018

• Neurologic harms of MA
  ▪ Stroke: 2-5x risk for hemorrhagic (not ischemic) stroke
  ▪ Cognitive impairment: learning, exec function, concentration, memory
  ▪ Parkinson’s: 1.5-3x
  ▪ Seizures: seems more cocaine-related
  ▪ Psychosis: ~27% in dependent persons
  ▪ Lappin, Addiction, 2019; Kim, Biomol Ther, 2020
Emergency Presentations for MA: Summary

• ED visits and hospitalizations for MA-related causes are rising nationally

• The reasons for MA-related presentations differ from those for opioids, and are led by:
  - Psychiatric disorders
  - Cardiac complaints
  - Trauma
Age-Adjusted Stimulant Overdose Death in the US

Hedegaard, NCHS Data Brief No. 394, 2020
Catecholaminergic Effects of MA

Kevil, Art Thromb Vasc Bio, 2019
CV Effects of MA

Endothelial activation
- Permeability
- ROS
- ICAM-1/VCAM-1

Enhanced Inflammation
- T cells, Macrophages
- ROS
- IL-1β, IL-6, IFNγ
- Mitochondrial dysfunction

Meth

Remodeling
- Structural
- Inflammation
- Fibrosis

Electrical K channels
- L-type
- Ca channels

Arrhythmogenic focus
- Cardiac Arrhythmia

Sympathetic activation
- mV
- P, Q, R, S, T, U
- Prolonged QT

Meth

Dilated Cardiomyopathy

Inflammation, Fibrosis
- Mitochondrial dysfunction
- Myocyte necrosis

Excess Catecholamine Levels

Direct Cardiotoxicity
Cardiac and Cerebrovascular Disease Associated with MA

- Cerebral / coronary vasoconstriction & pulmonary hypertension
- Artherosclerotic disease
  - Likely mediated by inflammation rather than cholesterol
- Cardiomyopathy
  - Often dilated
- Arrhythmias

- National Inpatient Sample, 2014
  - 184,039 patients with MA “abuse or dependence” diagnosis
  - Adjusted OR for stroke 1.19 (1.10-1.28) and sudden cardiac death 1.27 (1.12-1.44)
  - Parekh, JACC, 2018
Standardized Mortality Rates for People Who Use Amphetamines

- Drug Poisonings
- Suicide
- Homicide
- Accidental Injury
- CV Disease

Stockings, Addiction, 2019
2001 opioid and stimulant deaths in San Francisco

<table>
<thead>
<tr>
<th></th>
<th>Cardiac COD</th>
<th>Cerebrovascular COD</th>
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</thead>
<tbody>
<tr>
<td>Stimulant versus opioid</td>
<td>7.88 stimulant; 1.92 opioid</td>
<td>13.1 stimulant; 0.3 opioid</td>
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<tr>
<td>MA versus cocaine</td>
<td>5.5 MA; 10.1 cocaine</td>
<td>15.1 MA; 11.8 cocaine</td>
</tr>
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</table>

Opioid deaths included opioid/stimulant deaths; results were unchanged when excluding opioid/stimulant deaths
Drug overdose deaths by region

Methamphetamine was the top drug involved in overdose deaths in most of the western half of the U.S. while fentanyl pervaded the eastern half.

NOTE: Data from 2017. Deaths may include additional drugs.
SOURCE: NCHS National Vital Statistics System
Relative Change in Age-Adjusted Drug Overdose Death Rate from 2018-2019

Mattson, MMWR, 2021
Distribution of Opioids/Stimulants in Overdose Deaths in SUDORS Regions, Jan-Jun 2019
Potential Opportunities for Intervention in SUDORS Regions, Jan-Jun 2019

Hedegaard, NCHS Data Brief No. 394, 2020
MA Overdose Deaths in San Francisco

![Graph showing the number of MA overdose deaths in San Francisco from 2006 to 2019. The graph compares deaths involving methamphetamine, methamphetamine without opioid, methamphetamine in combination with any opioid, and methamphetamine in combination with fentanyl.]
MA Overdose Deaths: Summary

• MA overdose deaths are rising nationally
  ▪ Western states have had higher MA death rates, but eastern states are rising

• "Overdose" death from MA is poorly understood, but likely related to cardiac and cerebrovascular disease – not a toxicity that can be consistently addressed by reversing drug effects

• MA/fentanyl deaths are rising most rapidly for unclear reasons
  ▪ Are they really fentanyl overdose deaths, with MA incidental?
    − Does fentanyl use result in higher rates of MA use?
  ▪ Does MA contain fentanyl or are there frequent counterfeit/mistaken products?
  ▪ Does MA interact with fentanyl to increase overdose death risk?
Bradford Hill Criteria for Causality of Substance Use for HIV

<table>
<thead>
<tr>
<th>Drug</th>
<th>Strength</th>
<th>Consistency</th>
<th>Temporality</th>
<th>Biological gradient</th>
<th>Causal criteria plausability</th>
<th>Coherence</th>
<th>Specificity</th>
<th>Experimental evidence</th>
<th>Analogy</th>
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</thead>
<tbody>
<tr>
<td>Methamphetamine</td>
<td>+++</td>
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<td>MDMA</td>
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<tr>
<td>Ketamine</td>
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<td>+++</td>
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<td>GHB</td>
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<tr>
<td>LSD</td>
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<tr>
<td>Flunitrazepam</td>
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<tr>
<td>Sildenafil</td>
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<td>Volatile nitrites</td>
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*0, no evidence to meet criterion; +, very poor evidence to meet criterion; ++, some evidence to meet criterion; ++++, good evidence to meet criterion; ++++, very strong evidence available to meet criterion.
Stimulant Use Disorder: DSM-V

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

**Drug effects**
- 1. Tolerance
- 2. Withdrawal

**Use patterns**
- 3. Used for longer periods than intended
- 4. Can’t cut down or quit
- 5. Time spent getting, using or recovering

**Harms**
- 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
MA Use Disorder Medication Trials

- 23 pharmacotherapies have been tested in RCTs, with some potential in the following products:
  - Dexamphetamine, methylphenidate
  - Naltrexone
  - Topiramate
  - Bupropion
  - Mirtazapine
  - Riluzole

- Potential future agents
  - NAC
  - Pomaglumetad
  - mAbs
  - Vaccines

### Some Classes Without Signal

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
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<tbody>
<tr>
<td>SSRIs</td>
<td>GABA agents</td>
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<tr>
<td>TCAs</td>
<td>BDZ antagonist</td>
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<tr>
<td>5HT3R</td>
<td>Nicotinic agonist</td>
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### Limitations

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<th>Limitation</th>
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<tr>
<td>Measure of MA use &amp; outcome of choice</td>
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<tr>
<td>Co-morbid mental illness</td>
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<tr>
<td>Co-morbid cardiac disease</td>
</tr>
<tr>
<td>Medication adherence</td>
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Siefried, CNS Drugs, 2020
Mirtazapine for MA Use Disorder

Mirtazapine 1.0 (N=60; MSM)

Mirtazapine 2.0 (N=120; MSM/TGW)

Colfax, Arch Gen Psych 2011, Coffin JAMA Psych 2020
## Mirtazapine for HIV Risk Reduction

<table>
<thead>
<tr>
<th>Behavior</th>
<th>M1.0 Risk Ratio for Treatment Arm @ 12 weeks</th>
<th>M2.0 Risk Ratio for Treatment Arm @ 24 weeks</th>
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</thead>
<tbody>
<tr>
<td># Male Partners with whom MA used</td>
<td>0.45 (0.24-0.82)</td>
<td>0.52 (0.27-0.97)</td>
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<tr>
<td># Male Partners</td>
<td>0.20 (0.04-0.93)</td>
<td>0.54 (0.27-1.14)</td>
</tr>
<tr>
<td>Episodes Anal Sex with Serodiscordant Partners</td>
<td>0.31 (0.14-0.66)</td>
<td>0.42 (0.28-1.01)</td>
</tr>
<tr>
<td>Episodes UAI with Serodiscordant Partners</td>
<td>0.34 (0.17-0.70)</td>
<td>0.47 (0.23-0.97)</td>
</tr>
<tr>
<td>Episodes Insertive UAI with Serodiscordant Partners</td>
<td>0.29 (0.14-0.58)</td>
<td>0.56 (0.24-1.31)</td>
</tr>
<tr>
<td>Episodes Receptive UAI with Serodiscordant Partners</td>
<td>0.27 (0.05-1.57)</td>
<td>0.37 (0.14-0.93)</td>
</tr>
</tbody>
</table>

Colfax, Arch Gen Psych 2011, Coffin JAMA Psych 2020
Bupropion + ER-Naltrexone for MA Use Disorder

Trivedi NEJM 2021
Contingency Management for MA Systematic Review

27 studies (15 RCT)

- SUD treatment
  - MSM community programs

- Reduced MA use (20/21 studies)

- Improved treatment engagement, affect, etc

- Reduced sexual risk behaviors (7/9 studies)
MA Use Disorder: Summary

• Addressing MA use is essential for “Getting to Zero” HIV cases

• MA use disorder is diagnosed with the same criteria as other substance use disorders

• The most consistently proven therapy for MA use disorder is contingency management

• There are several medications that show some promise for MA use disorder, but none are FDA-approved for that indication
  ▪ Effective therapy most likely involves targeting multiple neurotransmitter systems
  ▪ Addiction medicine providers have sufficient tools for trials of promising agents and carefully-selected combinations in appropriate patients
Conclusions

• MA use is concentrated in the west, but increasingly prevalent across the U.S.

• Emergency medicine presentations related to MA are likely dominated by psychiatric complaints

• Acute toxicity deaths from MA are likely predominantly due to cardiac and cerebrovascular events

• The relationship between MA and fentanyl is complex and further research is needed to understand the rapidly rising mortality rate due to these drugs combined

• There are no FDA-approved medications for treating MA use disorder
  ▪ Contingency management has demonstrated benefit
  ▪ Several medications show some promise, warranting trials and novel combinations in appropriately-selected patients
References

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- Colfax et al., Archives of General Psychiatry, 2011
- Drumright et al., Journal of Acquired Immune Deficiency Syndrome, 2006
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Upcoming Webinars

Treatment of Opioid Use Disorder in the Emergency Department: Should it be a Choice?

Dr. Gail D’Onofrio, MD

Tuesday, April 13, 2021
12:00 – 1:00 PM ET
PCSS is a collaborative effort led by the American Academy of Addiction Psychiatry (AAAP) in partnership with:

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<th>American Society of Addiction Medicine</th>
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<td>American Academy of Family Physicians</td>
<td>American Society for Pain Management Nursing</td>
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<tr>
<td>American Academy of Pain Medicine</td>
<td>Association for Multidisciplinary Education and Research in Substance use and Addiction</td>
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<tr>
<td>American Academy of Pediatrics</td>
<td>Council on Social Work Education</td>
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<td>American Pharmacists Association</td>
<td>International Nurses Society on Addictions</td>
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<td>American College of Emergency Physicians</td>
<td>National Association for Community Health Centers</td>
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<td>American Dental Association</td>
<td>National Association of Social Workers</td>
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<td>The National Judicial College</td>
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<td>American Psychiatric Association</td>
<td>Physician Assistant Education Association</td>
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<td>American Psychiatric Nurses Association</td>
<td>Society for Academic Emergency Medicine</td>
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