Methamphetamine use disorder: current trends and treatment

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• none
Objectives

- Describe current trends in WA state
- Describe complications of short and long term use
- Review treatment strategies
Case: John

- 37yo man with history of HTN, polysubstance use disorder (primary methamphetamine), depression, PTSD, schizoaffective d/o

- Relevant medications:
  - Suboxone 8mg daily
  - Bupropion XR 150mg q24h
  - Buspar 50mg TID
  - Seroquel 50mg QD
  - Geodon 40mg qAM + 60mg qPM

- Can I have a prescription for Adderall for methamphetamine replacement?
What is methamphetamine?
Methamphetamine Use in WA State

Stimulant-caused death rates per 100,000 Washington State residents 2008-2016

Sources: Washington State Department of Health (deaths), state Office of Financial Management (population)

Ref: Stoner SA 2018
Deaths by county

Deaths involving methamphetamine, per 100,000 residents, 2003-2004
State: 1.51

Deaths involving methamphetamine, per 100,000 residents, 2015-2016
State: 4.96

Ref: Stoner SA 2018
Concomitant substances

Bottom line:
• ~1/2 of meth overdose deaths involve an opioid
• Treat underlying OUD
• Primary meth users should carry naloxone

Ref: Stoner SA 2018
Mechanism of action

Increases synapse of monoamine neurotransmitters including dopamine, norepinephrine and serotonin

Ref: UTD 2021, Bloom K 2021
## Mode of administration

<table>
<thead>
<tr>
<th>Method</th>
<th>Time to brain circulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>6-8 sec</td>
</tr>
<tr>
<td>Injecting</td>
<td>10-15 sec</td>
</tr>
<tr>
<td>Snorting</td>
<td>3-5 min</td>
</tr>
<tr>
<td>Ingesting (PO)</td>
<td>180 min</td>
</tr>
</tbody>
</table>

Ref: Gisborneherald.co.nz
Short-term effects

Sympathetic nervous system activation

Ref: Verywell / Joshua Seong
Long-term effects

- Addiction
- Increased risk HIV, Hep B/C
- Extreme weight loss
- Intense itching, formication, skin sores
- Severe dental decay

Ref: https://facesofmeth.us/
Ref: CBS news, 2011
Long term cognitive changes

• Anxiety

• Psychosis
  • paranoia, persecutory delusions, auditory, visual, and tactile hallucinations

• Moderate Cognitive Deficits

• Neurotoxicity

• Increased risk of Parkinson’s dementia

Blum K 2021
Effects in Pregnancy

- Low birth weight
- Premature birth
- Postpartum hemorrhage
- Retained placenta
- Poor nutrition, sleep, inattention to prenatal care
- Possible increase in anxiety and impulse control in children
Withdrawal Timeline

CRYSTAL METH WITHDRAWAL TIMELINE

Withdrawal usually lasts for 1-2 weeks

The first phase is usually the most intense, during the first 24 hours

Symptoms can sometimes last up to 4 weeks

Acute withdrawal syndrome can mean users experience symptoms for months

THE RECOVERY VILLAGE
Withdrawal symptoms

CRYSTAL METH WITHDRAWAL SYMPTOMS

- Anxiety and nervousness
- Depression
- Increased appetite
- Increased need for sleep
- Fatigue
- Itching
- Dry mouth
- Mood swings
- High body temperature
- Mild paranoia
Behavioral/Psychosocial treatments

- Matrix Model
- Cognitive behavioral therapy (CBT)
- Contingency management (CM)
- Motivational interviewing (MI)
- Brief intervention
- Residential rehab programs
- Exercise
- Repetitive transcranial stimulation (rTMS) and Transcranial Direct Current Stimulations (tDCS)
Matrix model

• 16 week behavioral health intervention

• Group CBT (36 sessions), individual counseling (4 sessions), family education groups (12 sessions), group social support (4 sessions) and urine and weekly breath alcohol testing.

• Encourages attendance at 12-step meetings like Crystal Meth Anonymous

• 4 studies 2004-2018 showed positive result

• Conclusions:
  • Decreased risky behaviors, days of meth use
  • Effect lasted 18 months

Ref: Siefried KJ 2020, AshaRani P 2020
Contingency Management (CM)

- Encourages positive behavior change by providing positive reinforcement
- Positive reinforcement:
  - vouchers exchangeable for money or prizes
- Consequences:
  - withholding vouchers
  - Resetting earned vouchers to 0
  - punishment by making an unfavorable report to a parole officer
- 7 studies 2006-2019 showing positive outcomes
- Conclusions:
  - CM associated with decreased positive utox

Ref: Siefried KJ 2020, AshaRani P 2020
Medications

• None FDA approved

• Lots of research on antidepressants, antipsychotics, substitution/replacement therapy
Research on Pharmacotherapies

- Antidepressants: Amineptine, Mirtazapine, Bupropion, Bupropion + naltrexone, Sertraline, Atomoxetine
- TCAs: Imipramine
- Atypical antipsychotics; Aripiprazole, Aripiprazole + methylphenidate
- Anticonvulsants: Topiramate
- CNS stimulants: Dextroamphetamine/dexamphetamine, methylphenidate
- Other CNS agents: Modafinil
- GABA agonist/GABAergic agents: Baclofen, gabapentin
- Opioid agonists: Buprenorphine, Buprenorphine + methadone
- Partial cholinergic nicotinic agonist: Varenicline
- Glutamatergic agents: N-acetyl cysteine, N-acetyl cysteine + naltrexone, Riluzole
- CRF1 antagonist: Pexacerfont
- Benzodiazepine antagonist/GABA agonist/H1 histamine receptor: Flumazenil + gabapentin + hydroxyzine
Mirtazapine

• Proposed mechanism of action (MOA):
  • Noradrenergic and specific serotonergic antidepressant
  • Mixed monoamine agonist/antagonist -> release of norepinephrine, serotonin and dopamine in the CNS
Mirtazapine

- Kongsakon, 2005: n= 20, mirtazapine 15-60mg PO QD
  - Improvement in withdrawal symptoms
- Cruickshank, 2008: n=31, mitrazapine 30mg PO QD
  - No difference in retention or withdrawal symptoms
- Colfax, 2011: n= 60, mirtazapine 30mg QD in MSM
  - Reduction in use, reduction in high-risk sexual behaviors

Conclusion: Conflicting results
- May improve withdrawal symptoms
- Reduction in use, reduction in high risk behaviors

Buprenorphine

- Proposed MOA:
  - μ-opioid receptor partial agonist, κ-opioid receptor antagonist

- 2015: buprenorphine 6mg PO QD for 16 weeks, n=40
  - Decreased MA cravings while taking buprenorphine, benefit stopped when off medication

- 2017: buprenorphine 8 mg vs. methadone 40 mg OD over 17 days, n=40
  - Reduced cravings in both groups
  - No control
  - No UDS

- Conclusions:
  - May help with cravings while taking
  - Use to treat co-occurring OUD

Ref: Salehi M 2015, Ahmadi J 2017, Siefried KJ 2020
Agonist therapy

• Proposed MOA: replacement with alternative CNS stimulant

• Cochrane review, 2013: 4 randomized trials, total n=162

• 2013, 2014, 2015, 2020: 3 randomized trials, total n=307
  • Examined dexamphetamine, methylphenidate

• Conclusions:
  • No reduction in use
  • No increase in sustained abstinence
  • Possible reduction in severity of withdrawal symptoms

Bupropion and Naltrexone in Methamphetamine Use Disorder

Bupropion + Naltrexone: proposed MOA

- **Bupropion:**
  - inhibits reuptake of NE and dopamine
  - minimal effect on the reuptake of serotonin
  - no inhibitory effect on monoamine oxidase; nicotinic acetylcholine receptor agonist

- **Naltrexone:** Opioid receptor antagonist
Bupropion + Naltrexone

- Trivedi, 2021: n=403
  - Stage 1: naltrexone ER 380mg q3wks IM + bupropion ER 450 mg per day QD vs placebo x 6 weeks
  - Stage 2: non-responders in stage 1 randomized to additional 6 weeks
  - Primary outcome = at least ¾ methamphetamine-negative urine samples
Bupropion + Naltrexone

- Primary outcome:
  - 2 stages over 12 weeks: treatment effect of 11.1%

- Secondary outcomes:
  - Reduction in negative uTox-6.8%
  - Decreased cravings -9.7%
  - Decreased PHQ9 score: -1.1
  - Treatment Effectiveness Assessment: -4.0%

- Conclusion: small but statistically significant response
Case: John

• 37yo man with history of HTN, polysubstance use disorder (primary methamphetamine), depression, PTSD, schizoaffective d/o

• Can you prescribe me Adderall?

• Relevant medications:
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Summary

• Greatly increasing methamphetamine use in WA state over last several years

• >50% deadly overdoses associated with co-occurring use with opiates
  - Treat underlying OUD
  - Consider prescribing naloxone to patients who use methamphetamines

• First line treatment: behavioral health interventions (matrix model, contingency management)

• Consider mirtazapine 30mg PO QD, mixed results in studies

• Consider bupropion PO + naltrexone IM for patients without contraindications

• Amphetamine replacement not effective

• Further research needed on pharmacotherapies
Questions?

https://www.123rf.com/clipart-vector/methamphetamine.html
References

- Paulus, Martin. Methamphetamine use disorder: Epidemiology, clinical manifestations, course, assessment, and diagnosis. Up-to-date. Apr 2021