Methamphetamine Pharmacology and Treatment Interventions

Control Subject  METH Abuser

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METHAMPHETAMINE
A Brief History

- 1919 Ogata Pharmaceuticals synthesizes methamphetamine from naturally occurring *ephedra*
- manufactured from chemical precursors including *ephedrine* and *pseudoephedrine*
- Methamphetamine a more potent form of amphetamine
- 1930’s pharmaceutical use to treat narcolepsy, ADHD, and obesity.
- 1940’s boost endurance of troops during WWII
- 1970’s Biker gangs are major manufacturers
- 1980’s to present: Mexican Mafia major manufacturers
- Present: Internet revolution. Also, methamphetamine analogs and cathinones like mephedrone (Bath Salts)
Amphetamines are a group of synthetic stimulants with similar effects. Chemical variations include:

- amphetamine;
- methamphetamine;
- dextroamphetamine; and
- dextromethamphetamine or $d$-methamphetamine, the most common form available.
There are also some amphetamine compounds that have an hallucinogenic component such as:

• MDA and

• MDMA or "ecstasy"

(methoxylated amphetamine or methamphetamine)
Although many of the street names are used interchangeably, generally,

- "speed" refers to any amphetamine, methamphetamine, or for that matter, any general stimulant;

- "meth" usually refers to any methamphetamine;

- "crank" usually refers to methamphetamine sulfate or to any methamphetamine that is snorted; and

- "crystal" refers to methamphetamine hydrochloride, which is now almost exclusively \(d\)-methamphetamine hydrochloride.
Case statement:

"When I did 'crank,' it had more of a body effect where with crystal, it was more of an adrenaline thing and it was a lot cleaner of a high".
Methamphetamine HCl
Methamphetamine HCl (smoke-able form) – *Ice, Batu, Glass, Crystal, Shabu, YABA*
Methylenedioxymethamphetamine (MDMA)
Ecstasy, XTC, X
“Bath Salts” (Synthetic cathinones)

MDPV, or methylenedioxypyrovalerone, and newer versions being made by illegal street chemists. The effects can include agitation, paranoia, hallucinations, chest pain, hypertension, and suicidal thinking/behavior. In July 2012, the Synthetic Drug Abuse Prevention Act made it illegal to possess, use, or distribute many of the chemicals used to make bath salts, including Mephedrone and MDPV.
Why Use Speed?

Perceived desirable effects as stated by users:

1. *Weight reduction*
2. Increased energy; increases alertness
3. Lessens desire and ability to sleep
4. Increases sexual arousal
5. Induces sense of self-confidence; productivity
6. Self medicate depression
AMPHETAMINE EFFECTS

- Stimulates excess production and release of the brain chemical, **dopamine**

- Dopamine is key to drug reinforcement through the intense sensation of **pleasure**
ACUTE EFFECTS

- **Behavioral**
  - Talkative, agitated and restless
  - Hypersexuality
  - Sense of power and superiority
  - Aggressiveness or hostility
  - Confusion, poor judgment
  - Paranoid/hyper suspicious
  - Anxiety

  **When dopamine has been depleted:**
  - Depression, suicidality
  - Hyposensitivity
  - Anhedonia (inability to experience pleasure)
  - Lack of motivation
Surging dopamine

Frontal cortex

Nucleus accumbens

VTA

Methamphetamine

Time After Methamphetamine

% of Basal Release

0 1 2 3 4 5 hr

1500 1000 500 0

COCAINEx

Time After Cocaine

% of Basal Release

0 1 2 3 4 5 hr

500 400 300 200 100 0
Methamphetamine: Mechanism of Action

- Blocks reuptake of dopamine into presynaptic nerve terminals and is itself a substrate for the membrane dopamine transporters. Through this mechanism it enters a nerve terminal.

- Inhibits MAO is inhibited where the excess dopamine is available in the synaptic cleft reinforcing effect of methamphetamine.

- Increase in biosynthesis of amino tyrosine into dopamine precursors and ultimately increased dopamine in vesicles.
Addiction: A Brain Disease

The Triune Brain

Our Three Brains

- **Reptilian brain:** Survival—feeding, fighting, fleeing, mating (Keep control)
- **Limbic brain:** memory and emotion—love, attachment, consideration for others, foundation for community and civilization (Keep balanced)
- **Cortical brain:** CEO and operating system—intelligence, intuition, insight, flexibility, speed, efficiency, creativity, morality, free will, meaningful life, uniquely human, under construction (Under construction)
Amphetamines and Love: Chemical Cousins

Dopamine: Euphoria, wanting to repeat.
Conditioned learning and memory
Oxytocin release—Cuddling hormone
Norepinephrine: Excitement, Heart pounding, blood pressure, palm sweating.

![Graphs showing the release of various neurotransmitters after different substances](image)
Dopamine

1. Dopamine: Euphoria and desire to repeat.
2. Dopamine: Reward-driven memory, salience, increased drive to repeat.
3. Dopamine releases oxytocin—cuddling hormone

**Conditioned Response: Reward Driven Learning, Memory and Behavior**

Pavlov’s Dog

1849-1936

Conditioned learning incorporates environment into memory and adds weight –salience—to it, giving it higher priority in driving drug use until it takes over everything.
### Comparing Cocaine and Methamphetamine

<table>
<thead>
<tr>
<th>Source</th>
<th>Cocaine</th>
<th>Methamphetamine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Route of Admin</strong></td>
<td>inhaled, injected, snorted,</td>
<td>same. Also ingested orally.</td>
</tr>
<tr>
<td><strong>PK</strong></td>
<td>short-acting (20-30 min). 50% of drug removed from the body in 1 hour. Uses CYP3A4 pathway.</td>
<td>Long-acting (8-24 hours). 50% removed in 12 hours. Uses CYP2D6 pathway.</td>
</tr>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Reuptake blockade DA/5-HT. Alters µ opioid receptors.</td>
<td>Same and also NE. MAOI- like activity (inhibition of enzymatic degradation).</td>
</tr>
<tr>
<td><strong>Neurotoxic Effects</strong></td>
<td>n/a</td>
<td>Reductions in D2 receptors within the orbitofrontal cortex. DAT impairment. Monoamine depletion and compensatory up regulation</td>
</tr>
</tbody>
</table>
## Methamphetamine Symptoms to Complications

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Complications</th>
<th>Ntx</th>
</tr>
</thead>
<tbody>
<tr>
<td>paranoia</td>
<td>psychotic episode</td>
<td>DA</td>
</tr>
<tr>
<td>tachycardia</td>
<td>arrhythmia</td>
<td>NE</td>
</tr>
<tr>
<td>hypertension</td>
<td>cerebral hemorrhage</td>
<td>NE</td>
</tr>
<tr>
<td>increased energy</td>
<td>hyperexcitability/mania</td>
<td>NE</td>
</tr>
<tr>
<td>hyperthermia</td>
<td>heat stroke</td>
<td>NE</td>
</tr>
<tr>
<td>anorexia</td>
<td>malnutrition</td>
<td>NE</td>
</tr>
<tr>
<td>insomnia</td>
<td>adds to paranoia</td>
<td>NE</td>
</tr>
<tr>
<td>euphoria</td>
<td>dysphoria/depression</td>
<td>DA</td>
</tr>
<tr>
<td>hypersexuality</td>
<td>hyposexuality</td>
<td>DA</td>
</tr>
</tbody>
</table>
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
- Hypothermia
- 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

Heart
- Chest pain
- Rapid heart rate
- Heart attack

Liver
- Damage

Kidneys
- Damage
TOLERANCE

Whether the methamphetamine is snorted, injected, eaten, or smoked, tolerance builds rapidly.

A 15 milligram prescribed daily dose can grow to 1500 milligrams during a "speed run."
Case Statement:

“I had an unending supply but there is only so much you can do and after a while, you don't get high anymore. No matter how much more you do, you just need to crash.”
“Tweaking”

- Tweaking lasts 8-12 hours, depending on dose and purity; may last several days from repeated dosing

- Major symptoms may include:
  - Obsessionality, hyper-fixated on trivial “importance”
  - Dilated pupils and staring/trance state
  - May include paranoia and hallucinations
  - Emotionally volatile
“Crashing”

- Withdrawal effect:
  - Extreme exhaustion
  - Sleep deprivation
  - Suicidal ideation
  - Increased generalized anxiety and/or other anxiety disorders
  - Polypharmacy: Using ‘downs’ (sleeping pills) and/or opiates to alleviate withdrawal
The Cycle of Meth Use

**Rush**: lasts 5 – 30 minutes. Increased Hypertension, tachycardia, euphoria

**High**: Lasts 4 – 16 hours. False sense of confidence and power. Grandiosity. Argumentative

**Binge**: Lasts 3 – 15 days.
- User becomes hyperactive mentally and physically, avoiding sleep for days and becoming paranoid and delusional.
- Tolerance to the drug’s effects develops quickly
- User tries to keep the high by taking more meth more often. Effects get less and less until the user cannot day high
The Cycle of Meth Use

**Tweaking:** Most dangerous time to confront user. Volatile, unpredictable and short tempered.

**Crash:** Long periods of sleep

**Withdrawal:** Depression, suicidal, lethargic, dysphoria, cognitive deficits (memory, tolerance to stress, problem solving, )
Chronic Effects

- **Long-term**
  - Intense craving, increased tolerance of the drug, withdrawal symptoms
  - Neurotransmitters (i.e. dopamine) depleted
  - Tremor, uncontrolled movements
  - Paranoia, hallucinations
  - Weight loss/malnutrition/poor dental hygiene (meth mouth)
  - Insomnia (additive to paranoia)

- **Lethality** results from kidney failure, dehydration, seizures (can occur after single use); cardiovascular events such as heart attack or stroke
Recovery of Brain Dopamine Transporters in Chronic Methamphetamine (METH) Abusers

Normal Control

METH Abuser (1 month abstinence)

METH Abuser (24 month abstinence)

Post Acute Withdrawal Effects

After Meth is stopped:

- At least 6-12 months of symptoms
  - Profound depression, abnormal mood
  - Insomnia
  - Psychosis, paranoia
- Long term brain changes
  - Brain scans show up to 80% reduction in dopamine metabolism
Protracted abstinence and brain recovery

Figure 2. Partial Recovery of Brain Dopamine Transporters in Methamphetamine (METH) Abuser After Protracted Abstinence

Normal Control  METH Abuser (1 month detox)  METH Abuser (14 months detox)

Additional problems with meth:

- Impaired cognitive functioning and short-term memory loss, notably abstract thinking and judgment

- A person’s ability to perceive risks and consequences while tweaking is diminished (person may engage in high risk sexual behavior, linked to HIV infection or other STDs)

- Mixing drugs when crashing: pain killers; sleeping pills
Methamphetamine Use and Pregnancy
Fertility and AOD Use

High-risk or dependent patterns of psychoactive drug use can affect female fertility causing:

- disruption of hypothalamic-pituitary-gonadal axis (alcohol and heroin)
- menstrual irregularities, ovulatory failure, early menopause (alcohol)
- amenorrhoea (heroin, amphetamines, cocaine)
- increased risk of sexually transmitted disease (which affects fertility).
The ‘Drug Vulnerable’ Fetus

Most drugs used in a high-risk manner by the mother can result in:

- increased risk of miscarriage, premature labor, still birth
- fetal distress
- reduced birth size/weight and associated slow growth
- developmental delays

**NOTE:** A negative toxicology screening at birth *does not* mean there was no prenatal alcohol/drug exposure.
METHAMPHETAMINE USE BY THE MOTHER

- ASSOCIATED WITH POLYPHARMACY
  - HIGHER ALCOHOL USE
  - CIGARETTE SMOKING DURING PREGNANCY
  - HIGHER MARIJUANA USE
WITHDRAWAL IN THE MOTHER

- DYSPHORIA
- FATIGUE
- NIGHTMARES
- HYPERSOMNIA (INCREASED SLEEP)
- INCREASED APPETITE
- PSYCHOMOTOR RETARDATION
- AGITATION
Drug Risk for the Fetus: Methamphetamine

- Psychostimulants increase the risk of:
  - maternal hypertension
  - premature labor
  - placental abruption and hemorrhage
  - spontaneous abortion
  - greater number of obstetrical complications

- Effects will vary depending on:
  - the trimester in which drug use occurs
  - frequency, amount, concurrent drug use
FETAL EFFECTS

- INCREASE IN CONGENITAL ANOMALIES
- REDUCTION OF BLOOD FLOW TO THE FETAL BRAIN
- CEREBRAL INFARCTION
- SEIZURES
- SMALLER \ HEAD CIRCUMFERENCE
- DECREASED BIRTH WEIGHT
- INCREASED INCIDENCE OF BIRTH DEFECTS AND MISCARRIAGES
- INCREASED RISK FOR ADHD LATER IN LIFE
NEONATAL EFFECTS

Full-term babies act like premies:

- Difficulty sucking and swallowing
- Sensitive to touch and often shake
- Increased risk for stroke before birth
- Abnormal reflexes and extreme irritability
Treatment Found to Be Effective for Methamphetamine Addiction

• **Motivational Interviewing** - a collaborative, goal-oriented style of communication with particular attention to the language of change. It is designed to strengthen personal motivation for and commitment to a specific goal by eliciting and exploring the person’s own reasons for change within an atmosphere of acceptance and compassion.

• **Cognitive Behavioral Therapy** is based on the idea that thoughts and feelings cause behaviors, not external factors such as people, situations, and events. This type of therapy aims to help the addict change the way they think and behave to increase coping skills with the stresses of life.

• **Motivational Incentives for Enhancing Drug Abuse Recovery (MIEDAR):** an incentive based treatment promoting meth abstinence is another treatment that has shown efficacy in meth abusers through the National Drug Abuse Clinical Trials Network.

• **The Matrix Model** includes intensive individual and group therapy to promote behavioral changes needed to prevent relapse, be abstinent, and establish a lifestyle unrelated to drugs. This can include changing their where they live, the people they associate with, and even their profession.
Medication-Assisted Treatment for Methamphetamine Abuse: Recent Advances

- No approved medications to help staying off stimulants
- Medications with some support of efficacy:
  - Bupropion
  - Naltrexone
  - Methylphenidate
  - Modafinil
  - Buprenorphine

“Sorry, no water. We’re just a support group.”
Medications Under Study

- Depot naltrexone
- Dextroamphetamine
- N-acetylcysteine
- D-cycloserine
- Sigma receptor antagonists
- MA binding vaccine
Medications: What Do They Do?

- Medications ultimately aim to help the addicted person stay off drugs.

- Staying off drugs —relapse prevention— requires replacing drug memories with non-drug memories.

- Pharmacotherapy is not substituting one drug with another drug; it is replacing one memory with another.

- An addicted brain has not gained a disease; it has lost the memory of a meaningful life.
Relapse: A Three-Act Play

- Drug memories: “Everything, seems to bring, memories of you”; seeds waiting for the rain.
- Cues and triggers: craving and desire for love lost; provides the moisture to sprout the seeds.
- Emotional buildup: justification for drug use—the internal dialogue making use acceptable and natural; the growing process leading to relapse.

Relapse does not happen by accident!
Staying Off Drugs (Relapse Prevention):

- Relapse depends on memory: no memory, no relapse.
- Relapse prevention means replacing the old drug memories with new non-drug memories.
- Limited success in research on “forgetting.”
- Practical old-fashioned ways to create new memories that work.
Two Ways to Forget

● Suppression: blocking out memory
  - Hippocampus inhibited by dorso-lateral prefrontal cortex; cognitive strategy unclear; not sure what is happening but protein synthesis is important.

● Substitution:
  - Dependent on caudal and mid-ventro-lateral prefrontal cortex which brings specific memories into focus in the presence of distracting memories.
Forgetting by Creating Non-drug Memories: The Old Fashioned Way

- Change your memory, change your brain; change your brain, change your life.
- Experience—activities—leads to protein synthesis, activates new gene expressions, creates new brain connections, and produces new memories.
- New memories create new belief systems and new behaviors that determine how things will turn out.
- The way to change your life is to do things differently so they will turn out different.
Things that Help Build Non-drug Memories

- Sound physical health
- Sound mental health
- Stay off drugs and stay busy
- Take personal responsibility
- Live in harmony with family and friends
- Be a good member of the community
- Become a new “self”; search for a meaning in life.
Success in Long-term Follow-up

- Sustained abstinence; over 5 years
- Employment: taking personal responsibility
- Connected to others: family and friends
- Community: social support and contribution
- New sense of self, new world view and new life story: spirituality and meaningful life.
Environmental Impact of Methamphetamine
Illicit manufacturing: How is meth made? Chemicals from common household substances including:

- Pseudoephedrine – decongestant
- iodine crystals
- battery acid
- red phosphorus – match boxes and road flares
- anhydrous ammonia – fertilizer or countertop cleaner
- toluene – brake fluid
- hydrochloric acid
- acetone – nail polish remover or paint thinner
- sodium hydroxide – lye
- sulfuric acid – drain or toilet bowl cleaner
Pseudoephedrine Cold & Allergy
Nasal Decongestant, Antihistamine
Nasal & Sinus Congestion due to Colds & Allergies
Sneezing & Runny Nose
Itchy, Watery Eyes
Maximum Strength

ALL DAY COLD & SINUS
PROXEN SODIUM 220 mg and PSEUDOEPHEDRINE
EXTENDED-RELEASE TABLETS
PAIN RELIEVER, FEVER REDUCER, NASAL
ALL DAY RELIEF of MINOR PAIN and CO
• Nasal Congestion & Sneeze Prep
plus Headache & Body Aches
10 CAPLETS
Drug users making meth in soda bottle

By Justin Juozapavicius
Associated Press

TULSA, Okla. — This is the new formula for methamphetamine: a two-liter soda bottle, a few handfuls of cold pills and some noxious chemicals. Shake the bottle and the volatile reaction produces one of the world’s most addictive drugs.

Only a few years ago, making meth required an elaborate lab — with filthy containers simmering over open flames, cans of flammable liquids and hundreds of pills. The process gave off foul odors, sometimes sparked explosions and was so hard to conceal that dealers often “cooked” their drugs in rural areas.

But now drug users are making their own meth in small batches using a faster, cheaper and much simpler method with ingredients that can be carried in a knapsack and mixed on the run. The “shake-and-bake” approach has become popular because it requires a relatively small number of pills of the decongestant pseudoephedrine — an amount easily obtained under even the toughest anti-meth laws that have been adopted across the nation to restrict large purchases of some cold medication.

“Somebody somewhere said ‘Wait, this requires a lot less pseudoephedrine and I can fly under the radar,’” said Mark Woodward, spokesman for the Oklahoma Bureau of Narcotics and Dangerous Drugs Control.

An Associated Press review found that the new method is rapidly spreading across the nation’s midsection. Using the new formula, batches of meth are much smaller but just as dangerous as the old system, which sometimes produces powerful explosions, touches off intense fires and releases drug ingredients that must be handled as toxic waste.
Toxic Meth Labs
Methamphetamine is often made in make-shift labs. There are abundant health and safety concerns for: Explosive chemicals, Toxic waste, Contaminated/Tainted final products that can be neurotoxic to users
Meth Lab Human Toxicity

- What toxins are in a home meth lab?
  - Methamphetamine powder and solution
  - Flammable solvents
  - Phosphorus
  - Lye
  - Acid
  - Iodine
Labs are dirty resulting in drugs that can be contaminated and full of potentially toxic impurities.

Chemicals in labs are dangerous, volatile and potentially explosive.
Meth Lab Human Toxicity

- Phosphorus - Inhalation of phosphine gas is lethal
- Lye or Acid - Concentrated caustic substance produces severe burns
- Iodine – eyes, nose, skin irritation or burn, abdominal pain, thyroid disease
Meth Labs also effect innocent victims – Child Endangerment
Meth Lab Impact: Child Endangerment

Meth residues left on countertops, floors, carpets and appliances are common sources of child exposure to the drug and its precursor chemicals.

U.S. Dept of Human Services reports that by age of 7, children in meth environments exhibit:

- Higher levels of aggressive behavior
- Problems adjusting to environments
- Higher rates of school failure
- Delayed speech and language skills
Meth Lab Impact: Child Endangerment

- Children removed from meth homes commonly experience:
- Respiratory problems (similar to asthma and bronchitis)
- Higher risk for kidney problems and leukemia
- Lead poisoning
- Skin disorders, burns and lesions
- Test positive for meth (second hand exposure, accidental ingestion)
Meth Lab Human Toxicity

- Methamphetamine labs emit strong chemical odors, such as ammonia, acetone or urine smell.
- Labs are at high risk for explosion.
- Labs are often booby trapped against unwanted visitors when “cookers” are away.
Meth Labs & Contamination

Produce about 7 pounds of waste for every pound of drug manufacture. Only specialized trained personnel can clean up a meth lab safely.

Nationally, the average clean up cost is $150,000 per lab.
Take-home Messages

- Becoming addicted is not the same as staying addicted.
- Getting off drugs is not the same as staying off drugs.
- The problem of addiction is not getting off drugs; it’s staying off drugs.
- Staying off drugs — relapse prevention — requires replacing drug memories with non-drug memories.
- An addicted brain has not gained a disease; it has lost the memory of a meaningful life.
- There are evidence-based treatments specific for methamphetamine addiction.
- There are several medicines in development to treat methamphetamine addiction.
Treatment for Methamphetamine

Order these from http://www.samhsa.gov
Treatment for Methamphetamine

Client’s Handbook: Matrix Intensive Outpatient Treatment for People with Stimulant Use Disorders

Order this manual by going to www.samhsa.gov and refer to HHS publication No. (SMA) 09-4145