PSYCHOSTIMULANTS

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Disclosers / Background

- Residency – EM / Fellowship – University At Buffalo – Addiction Medicine
- Current Director of Addiction Medicine MidMichigan Community Health Services
- MOC – Consulting physician
- Stimulant Grant Medical Director - NMORC
Morphine was detected, but could not be matched to any of the reported prescriptions. Sources of morphine include Avinza, Kadian, MS Contin, MSIR, & Roxanol and is a metabolite of codeine and heroin. Morphine is also found in poppy seeds. Consumption of bakery products containing poppy seeds may result in urinary morphine levels of up to 3000 ng/mL.
Butch Con’t

- No Cocaine
- Methamphetamine
- Amphetamine
- Valium
- MDMA
- THC
- And a touch of ETOH metabolite
EVERYTHING BAGEL
Objectives

01 Be able to define a psychostimulant

02 Define Stimulant Use Disorder

03 Gain knowledge on History of Psychostimulants and current epidemic

04 Identify most effective strategies and therapies to treat those with SUD (Stimulant Use Disorder)

05 Promote continued discussion and collaboration aimed at potential solutions for SUD
A “psychostimulant” can be defined as a psychotropic substance with the capacity to stimulate the central nervous system.

- Most used psychotropic substances in the world
- Causes excitation and elevated mood, and well as increased arousal and alertness
- Speed up the signals in brain

negatively defined as a substance other than a depressant of a hallucinogenic substance
<table>
<thead>
<tr>
<th>Condition</th>
<th>DSM-IV Abuse</th>
<th>DSM-IV Dependence</th>
<th>DSM-5 Substance Use Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazardous use</td>
<td>X</td>
<td>–</td>
<td>X</td>
</tr>
<tr>
<td>Social/interpersonal problems related to use</td>
<td>X</td>
<td>–</td>
<td>X</td>
</tr>
<tr>
<td>Neglected major roles to use</td>
<td>X</td>
<td>–</td>
<td>X</td>
</tr>
<tr>
<td>Legal problems</td>
<td>X</td>
<td>–</td>
<td>X</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>–</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Tolerance</td>
<td>–</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Used larger amounts/longer</td>
<td>–</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Repeated attempts to quit/control use</td>
<td>–</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Much time spent using</td>
<td>–</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical/psychological problems related to use</td>
<td>–</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Activities given up to use</td>
<td>–</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Craving</td>
<td>–</td>
<td>–</td>
<td>X</td>
</tr>
</tbody>
</table>
Stimulants

- Plant derived Stimulants - several are available for traditional oral use in many area of the world
  - Coca(Cocaine)
  - Ephedra (containing ephedrine in North America and East Asia)
  - Khat (containing cathinone) in East Africa and Arabia
  - Kratom?
  - Nicotine - tobacco – nightshade family
  - Coffee
Synthetic Stimulants

• Available by Rx
  • Amphetamine – Adderall - ADHD
  • Lisdexamfetamine – Vyvanse – ADHD
  • Methamphetamine – ADHD, Weight control
  • Methylphenidate – Ritalin, Focalin, Concerta – ADHD
  • Modafinil – Provigil – Narcolepsy
  • Phentermine – Adipex – Weight control

• Illegal - Synthetic
  • Bath salts
  • MDMA
  • Methamphetamine
Caffeine

• Domesticated in Ethiopia > 800 years ago
• Used regularly by >90% of Americans at an average of 200mg/day
• Adenosine receptor antagonist
  • Does not increase dopamine in the NA, but still highly addictive
  • Adenosine uncouples dopamine receptors from G-proteins, thus reducing dopamine signaling
• Intoxication similar to other stimulant
• Withdrawal is mostly headache, fatigue, difficulty concentrating, and dysphoric mood
• Addiction to caffeine does not typically cause functional impairment
Khat

- Cathinone – found in fresh leaves of the khat tree
  - Introduced in Ethiopia to Yemen at least 800 years ago
  - Chewed ubiquitously in Yemen as a social lubricant
  - Used to embolden and desensitize child soldiers
3,4- Methyleneedioxy-methamphetamine (MDMA)

- MDMA, Molly, Ecstasy
  - Often in tablet form, Per NIH most synthesized in Canada and Netherlands

- First used in the 1970's as psychotherapy drug – 1985 DEA labeled as an illegal drug with no medical use

- Typically take with combination other drugs most and usually not “pure”
  - Have found ketamine, caffeine, ephedrine, and dextromethorphan, PCP

- Research varies on the addiction potential

- Alters mood and perception – increased energy, pleasure, emotional warmth and distorted sensory and time perception

- Affects Dopamine, Norepinephrine, and Serotonin system

- Peak effects in 15- 30 minutes
  - Lasts about 3-6 hours - can cause a dangerous increase in body temp shutting down vital organs

- People seeking treatment for MDMA addiction have found behavior therapy helpful
Kratom

- *Mitragyna Speciosa* - tropical evergreen tree native to Southeast Asia - in the coffee family

- Traditional folk medicine to treat a number of conditions, most notably musculoskeletal pain, anxiety and depression.

- May be chewed, smoked, or transformed to powder that can be used as a tea. Largely obtained from internet and “legal high” shops

- Marketed as cheaper alternative to opioid replacement therapy without need for Rx or medical supervision. Opioid dependence treatment
Kratom

- Contains over 40 structurally related alkaloids, most common is mitragynine which acts as a weak mu-opioid agonist and a second key component is 7-hydroxymitragynine (2% kratum by weight),
  - Both act as weak antagonists at the kappa and delta- opioid receptors in vitro.
- Also has a broad affinity for receptors including serotonergic, adrenergic, and GABAnergic pathways
- An estimated 10 -16 million people in the US take Kratom, though current prevalence ranges of 1.3 % - 6.1 % from surveys may underestimate regular Kratom users
- Persons who use Kratom report beneficial effects of relaxation, pain relief, increased energy and decreased depression
Kratom

• Reaches peak concentration at around 1 hour and half life of 23 hours

• Exhibits dose-dependent effects
  • Stimulant at low doses (<5g)
  • Opioid-like effects at 5 to 15 g
  • Sedation at doses >15 g
COCAINE
METH
RX
STIMULANTS
Modern History of Cocaine

- Isolated by a German Ph.D. student in mid-1900s..
- Used to treat morphine addiction 1879.
- Coca-cola (1886) still used coca leaf extract from Stepan Co. in Maywood, NJ. – 1903 removed cocaine from formula
- Sold OTC by Merck and Parke-Davis 1884-1916.
  - Heavily endorsed by Sigmund Freud.
- Use declined in 1920s and 30s with regulation and introduction of amphetamine.
- Resurgence in the 1970s (powder) and 1980s (crack).
Cocaine

- Used in 3 primary preparations
- Crack cocaine low melting point – smoked
  - Mainly mixed with baking soda and heating
- Powdered cocaine – hydrochloric acid is added to make purified, water soluble salt.
- Freebase – adding a base (ammonia or Baking soda) and extracted with either
Cocaine

- Blocks voltage-gated sodium channels
- Blocks NE reuptake causing vasoconstriction
  - Also blocks reuptake of serotonin dopamine
- Activated the dopamine rich Mesocorticolimbic pathway
Adulterants

- Cocaine purity averages 40%.
- Bulking agents/diluents – sugar, talc, cornstarch
- Adulterants – pharmacologically active substances – study found average in seized cocaine averages between 5 and 15 different substances
  - Caffeine, Diltiazem, hydroxyzine, levamisole/dexamisole (horse de-wormer and potent immunomodulator – thought to prolong effect), paracetamol, local anesthetics, phenacetin (pain reliever – removed from market 1983)
- 50-90% of users binge with EtOH. This is processed by the liver to cocaethylene, which is longer-lasting, more rewarding, and more cardiotoxic and liver toxic
# Routes to Brain

<table>
<thead>
<tr>
<th>Route</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical*</td>
<td>Within 5 minutes</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Intranasal*</td>
<td>Within 5 minutes</td>
<td>15-20 minutes</td>
<td>60-90 minutes</td>
</tr>
<tr>
<td>Intravenous</td>
<td>10-60 seconds</td>
<td>3-5 minutes</td>
<td>20-60 minutes</td>
</tr>
<tr>
<td>Inhalation</td>
<td>3-5 seconds</td>
<td>1-3 minutes</td>
<td>5-15 minutes</td>
</tr>
</tbody>
</table>

*These values represent therapeutic use.*
Benzoylcegonine

Major metabolite in Urine for cocaine

Formed by liver and excreted in urine

Detection window

- Urine – around 4 days – heavy users – longer
- Blood – around 2 days
- Saliva – 2 days
- Hair 3 months
- Positive test UDS is usually cocaine!!
Overdose
Acute Effects

- **low-moderate doses:** euphoria, increased energy and libido, anorexia, impulsivity, grandiosity, increased alertness
- **high doses:** insomnia, anxiety, irritability, confusion, paranoia, panic attacks, hallucinations, hyperpyrexia, hyperreflexia, tremor, diaphoresis, tachycardia, hypertension and tachypnea
- **overdose:** convulsions, cerebral hemorrhage or infarct, cardiac arrhythmias or ischemia, respiratory failure, rhabdomyolysis, placental abruption
Methamphetamine

White powder or pill – easily dissolves in water or alcohol

Looks like pieces of glass or shiny blue-white “rocks” rocks of different sizes

Swallowed, snorted, smoked injected

Called speed, crank, tweak, chalk, tina, gak, ICE, Wash, Trash, Dunk, White cross, Cotton candy, Rocket fuel, scooby snax
HISTORY
2020, approximately 2.5 million adults, on average, used methamphetamine each year.

Nearly 25% of those reported injecting methamphetamine.

Approximately 50% of persons using methamphetamine in the past year met diagnostic criteria for past-year methamphetamine use disorder
  • fewer than one third received substance use treatment.
Overdose
What is Meth made from?

- Meth is produced using chemicals, many of which are toxic and hazardous. For one pound of methamphetamine, there is 5-6 pounds of chemical waste.
- Acetone - found in nail polish remover
- Lithium – used in batteries
- Toluene – used in brake fluid
- Hydrochloric Acid – used to make acid
- Pseudoephedrine – found in cold medicine
- Red phosphorus – matchboxes
- Sodium Hydroxide – lye
Counterfeit pills

- Pill form has appeared in several states in 2019 and 2020
- Most are distributed high purity and high potency across the SWB
- Domestic production continues to decline as meth produced in Mexico remains lower cost, higher purity, and higher potency
**How it works (MOA)**

- Competitively inhibits monoamine reuptake
- Inhibits the VMAT
- Displaces the monoamines from the synaptic vesicles
- Causes reverse transport into the synapse
Drugs of abuse generate a huge spike in dopamine levels in the nucleus accumbens and hijack this survival system.

The drug goes to the head of the line - ahead of food, sex, water, or avoiding danger.
Health Effects

• Short-term increased wakefulness and physical activity; decreased appetite; increased breathing, heart rate, blood pressure, temperature; irregular heartbeat

• Long-term – Anxiety, confusion, insomnia, mood problems, violent behavior, paranoia, hallucinations, delusions, weight loss (malnutrition), severe dental problems, intense itching leading skin sores from scratching, stroke, MI, liver damage, kidney damage, lung damage

• Other Health related issues Pregnancy: premature delivery; Placental abruption; low birth weight; increase risk for defined mortality and morbidity in Pregnancy

• In combination with alcohol - masks the depressant effect of alcohol so can increase overdose; may increase blood pressure
OVERDOSE

- Hot, flushed or sweaty skin
- Severe headaches
- Chest pain
- Unsteady walking
- Difficulty breathing
- Psychotic symptoms
- Feeling panicked or very agitated
- Confusion or disorientation
- Tremors, spasms, jerky movements or seizures
WITHDRAWAL SYMPTOMS
Rx Stimulants

• Among people 12 and older in 2020, 1.8 percent (5.1 million people reported misuse)

• Highest among young adults ages 18-25
Treating Stimulant Use Disorder

• Not great options

• Mainstay of treatment is periods when symptoms of intoxication or withdrawal resolve

• May occur during residential treatment that follows an acute inpatient care or during long-term outpatient treatment

• Clinic goal is to retention of treatment and keep patients alive

• “there is no universally accepted evidence – based treatment model that integrates the psychosocial and medical approaches and offers treatment to individuals depending on psychostimulants that parallels treatment of alcohol and OUD – from UNODC statement (United Nations office on drugs and crime)
Treatment options

- NO FDA approved medications
- First line treatment is individual or group counseling
- IOP up to 16 weeks
- CBT therapy
- Contingency management – motivational incentives
- The Matrix model
- 12-step facilitation therapy
Contingency management

• Motivational incentives
• Level 1 evidence
• Hard to get grants and funding – insurance system
  • Progressive schedule
  • Bonuses for 3 consecutive Stimulant free urine
  • Reset with 5 stimulant free
  • Earnings up to $1200 dollars
  • 12 weeks
  • Poor compliance after completed

Voucher-Based Reinforcement
Here, patients receive a voucher for each drug-free urine sample or negative breathalyzer result. Each voucher has a value that can trade for goods, services, retail items, or more.

Prize Incentives
Here, patients supplying drug-negative urine or breath tests draw from a fishbowl at least once a week for the opportunity to win a prize.
The Matrix Model

- Manualized outpatient approach
- Has some good evidence
- IOP for 16 weeks
  - Incorporates variety of therapies
  - Structured
Other

- CBT – have been found to be efficacious
- 12 Step facilitation therapy – limited
- Mobile Medical application: reset
  - More data on opioid use disorder
- Recently integrative models vs parallel models
  - Studied more in OUD – patients getting Obstetric care, addiction care, mental health care, supportive services in 1 location show better addiction end obstetric and neonatal outcomes
- Acupuncture
- Residential
Medications

- It is postulated that treatment with medication will normalize some of the changes in the brain functioning, decreasing impulsivity and craving for the drug, allowing individuals to decrease or stop drug use and benefit from psychosocial treatment.

- More than 100 various medications have been clinically tested over the past 30 years, yet no medication that has shown to have a large and reproducible beneficial effects and therefore no medication has been approved in any country.
Medications

Recent study – Adapt 2 trial

- Naltrexone 380 mg IM Q3 weeks
- Bupropion 450 mg XL daily

- Limited success
  - Defined as negative UA for 3 out of 4 at the end of stage 1 and 2 (6 weeks and 12 weeks)
  - Compared to placebo arm had a higher response
  - 13.6% compared to 2.5% placebo with an overall treatment effect of 11.1
  - NNTT was 9!
Other Medication

- If considering off label medications for methamphetamine abuse
  - No accepted treatments
  - There have been small studies suggesting potential benefit from Mirtazapine, Bupropion, Disulfiram and Topiramate, stimulants
  - Equivocal or negative results for Naltrexone alone, Atomoxetine, NAC, Suboxone, and stimulants
  - Evident of Stimulant?
    - Literature is not great – limited concern for diversion or abuse
    - Potential – Do they have cooccurring ADHD –
    - Strongest evidence supports use of extended release methylphenidate in treatment for amphetamine use disorder and use extended release formulations of amphetamine products in Cocaine use disorder.
    - Higher dosed where more effective
    - Admin under observations / individualize decision making
PRINCIPLES OF HARM REDUCTION:

• Non-judgmental approach that meets people where they are at
• Treating all individuals with dignity, compassion, and respect
• Opposition to the stigmatization of substance use disorder
• Use of evidence-based policy and practice
• Accepting behavior change as an incremental process. Small gains for many people have more benefit for a community than large heroic gains achieved for a select few. People are much more likely to take multiple tiny steps, rather than one or two huge steps
• Inclusion of individuals in active addiction, in recovery, and within the community to shape policies and practices
• Focus on quality life improvements over abstinence
• Commitment to universal human rights
• Empowerment of the individual as the primary agent responsible for reducing the harms related to their substance use
Patient Samantha

• 37 yo presented to office for “Help” from everything

• Around 2.5 years ago. Lived in town

• PHM – Polysubstance use disorder, Depression, Anxiety Hep C,

• Social – overdosed 3 times, currently using IV Meth about 0.5 g 3 x week, 0.5 g Heroin daily. Smoked cigarettes, occasionally did Benzos and Cocaine

• Has been to rehab 7 times, never in sustained SUD clinic, arrested 3 times, no Job, has 2 sons but never sees them, lives with mother in law (sig other in prison)

• “I cant believe im here right now and talking to you – last use was yesterday – feels terrible
Initially discussed treatment options - outpatient vs residential
  - Bio/Psych/Social/Spiritual

DX: OUD, SUD, Nicotine use disorder, Cocaine abuse, Benzodiazepine abuse, Anxiety depression, Hepatitis C

Started that day with Suboxone 8mg BID, Set her up with counseling (wasn’t ready to do yet) hx of Sexual mental and physical abuse – just wants to take one thing at a time
  - Discussed “Off Label” Stimulant Use Disorder Medications – not interested
  - “No way am I going to stop smoking” and Psych meds were not an option

Got her in at least with our recovery coach and agreed to see weekly for foreseeable future

Given Narcan, Lab work, follow-up via phone in 2 day then next week in office.
• Over the next month she did pretty well on Suboxone and Heroin use started to decrease, Meth use was consistent at 2-3 week

• Made it into the office weekly, meet with our recovery coach

• By second month was ready to possibly try counseling and had been looking into the “meetings “ possibly with the recovery coach and asked about AA/NA

• Finally agreed to get labs and felt more and more comfortable every week

• Over the next 2-6 months she started counseling – slowly, got her bloodwork and discussed treatment for hepatitis C – she 3-4 “lapses on Heroin “ for 1-2 days but kept coming back.

• Started 1 celebrate recovery meeting weekly and agreed to discuss meds for anxiety depressions and MUD
  • Started on NAC, Wellbutrin for combined Nicotine use disorder, Remeron for sleep issues and comorbid depression, and Zoloft
Patient Con’t

- 6-18 months
  - We still continued with Suboxone, weekly to bi weekly visits, kept journal of Meth use – started to really come down – positive reinforcement and increased counseling. Keeping Journal of use
  - Treated Hep C
  - Started to see improvement in mood, function, Amount and frequency of use, developed coping skills and relapse prevention techniques, made inroads with sons.

- 12-24 months – has had no opioid use in over 1 year, transitioned to weekly to biweekly smoking small amount of meth, got a job cleaning, speaking at celebrate recovery and making tremendous progress.
  - Success?!!!!
Takeaways

• No Universal treatment modality for Treating Stimulant Use Disorder
• All Medications are “off Label”
• Consider treatment of cofounding Polysubstance use disorder, Psychosocial support, comorbidities like depression
• Remember recovery takes time!
• Harm Reduction – meet people where they are at
• Retention of Treatment and keep patients alive
• Everyone has their own path and definition of recovery
• Biological, psychological, social, spiritual
DON’T FORGET
References/Articles

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- Dubin, Jeremy. “MAT and Stimulant Abuse: From Harm Reduction to Treatment.” Lecture, 51st Annual ASAM conference April 2-5, 2020 Denver CO
- https://nida.nih.gov/research-topics/methamphetamine
- https://nida.nih.gov/research-topics/mdma-ecstasymolly