Current trends and Treatments in SUD

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Background

- Residency – EM / Fellowship – University At Buffalo – Addiction Medicine
- Current Director of Addiction Medicine MidMichigan Community Health Services
- MOC – University of Michigan - Consulting physician
- Stimulant Grant Medical Director - NMORC
Objectives

1) Describe current Trends in OUD/Stimulant Use Disorder and overdose rates nationwide/statewide and treatment options
2) Understand different analogs of fentanyl and trends in Michigan
3) Recognize the increase of Xylazine related to OUD
4) Describe Kratom and potential risks
# Substance Use Disorder

<table>
<thead>
<tr>
<th>Substance Use Disorder</th>
<th>DSM-IV Abuse^a</th>
<th>DSM-IV Dependence^b</th>
<th>DSM-5 Substance Use Disorders^c</th>
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</thead>
<tbody>
<tr>
<td>Hazardous use</td>
<td>X</td>
<td>–</td>
<td>X</td>
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<tr>
<td>Social/interpersonal problems related to use</td>
<td>X</td>
<td>–</td>
<td>X</td>
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<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^d</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>
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<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>

^a DSM-IV Abuse

^b DSM-IV Dependence

^c DSM-5 Substance Use Disorders

^d Withdrawal
Addiction Definition

Addiction is a treatable, chronic medical disease involving complex interactions among brain circuits, genetics, the environment, and an individual’s life experiences. People with addiction use substances or engage in behaviors that become compulsive and often continue despite harmful consequences.

Prevention efforts and treatment approaches for addiction are generally as successful as those for other chronic diseases.
Wrong direction
Michigan
Figure 6. National Overdose Deaths Involving Stimulants (Cocaine and Psychostimulants*), by Opioid Involvement, Number Among All Ages, 1999-2021

*Among deaths with drug overdose as the underlying cause, the psychostimulants with abuse potential (primarily methamphetamine) category was determined by the T43.6 ICD-10 multiple cause-of-death code. Abbreviated to psychostimulants in the bar chart above. Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2021 on CDC WONDER Online Database, released 1/2023.
National Prevalence
Fentanyl

- Synthetic opioid first synthesized in 1960
- Relatively selective potent agonist at the MORs
  - 50x more potent than morphine and Carfentanil
    10,000x
- Highly lipophilic (lipid soluble)
- Deaths occur quickly – within 5 minutes of injection
- Combo of factors – potency, rate of onset, muscle rigidity, lower susceptibility to naloxone reversal, lack of cross tolerance
Criminal Chemistry

Traffickers manufacturing fentanyl often purchase the key ingredient from China, which doesn't regulate its sale. Here's how the chemical building blocks become a highly profitable street drug.

The key ingredient is NPP, 25 grams of which can be bought from China for about $87.

NPP can be combined with about $720 of other chemicals to produce fentanyl.

The resulting 25 grams of fentanyl cost about $810 to produce... and are equivalent to up to $800,000 of pills on the black market.

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Sources: NES Inc.; Drug Enforcement Administration; Calgary Police

Average current price from Chinese suppliers
Prices from U.S. suppliers

THE WALL STREET JOURNAL.
There are over 40 analogues (variations) of fentanyl.
Emerging trend: Para-Flourofentanyl
What is Para-flourofentanyl

• Scheduled 1 synthetic opioid analgesic first synthesized for research purposes in the 1960’s
• It is a Fentanyl analog with similar structure and synthesis route to fentanyl
• Clinical evidence suggests an even higher potency than fentanyl,
• Has been detected in heroin packets and counterfeit pills in the state
• Linked to multiple overdoses in other states as well
• Signs, symptoms, treatment of overdose that are associated with pFF are like other opioid analgesics
NOT JUST opioids!!
Typical patient

<table>
<thead>
<tr>
<th>Collection Date</th>
<th>12/1/2022</th>
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<th>12/8/2022</th>
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<td>12/13/2022</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Buprenorphine</td>
<td>Negative</td>
<td>Negative</td>
<td>170</td>
<td>187</td>
<td>Abnormal</td>
<td>Specimen Validity</td>
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<tr>
<td>Norbuprenorphine</td>
<td>Negative</td>
<td>Negative</td>
<td>233</td>
<td>216</td>
<td>Abnormal</td>
<td>Specimen Validity</td>
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<tr>
<td>Fentanyl</td>
<td>31</td>
<td>29</td>
<td>10</td>
<td>24</td>
<td>&gt; 161</td>
<td>Specimen Validity</td>
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<tr>
<td>Norfentanyl</td>
<td>&gt; 1.356</td>
<td>873</td>
<td>401</td>
<td>253</td>
<td>&gt; 842</td>
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<tr>
<td>Lorazepam</td>
<td>Negative</td>
<td>Negative</td>
<td>933</td>
<td>364</td>
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<tr>
<td>Hydroxybupropion</td>
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<td>Not Ordered</td>
<td>Not Ordered</td>
<td>Not Ordered</td>
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<td>Quetiapine</td>
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<td>Negative</td>
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<td>Negative</td>
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<tr>
<td>Naloxone</td>
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<td>Negative</td>
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<td>430</td>
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<tr>
<td>Cocaine metabolite</td>
<td>&gt; 8,477</td>
<td>&gt; 11,268</td>
<td>3,012</td>
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<td>&gt; 4,015</td>
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<td>5</td>
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<tr>
<td>Acetyl norfentanyl</td>
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<tr>
<td>Para-fluorofentanyl</td>
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<td>Negative</td>
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<td>Negative</td>
<td>Abnormal</td>
<td>Specimen Validity</td>
</tr>
</tbody>
</table>
How xylazine, a veterinary tranquilizer, is making overdoses even riskier

By Nadia Kounang, CNN
Published 6:30 AM EDT, Thu March 17, 2022
Xylazine

- FDA warns about risk of xylazine exposure in humans – November 8, 2022
- Called “Tranq-dope”
- Seen uptick in Philadelphia and northeast US
- Non-opioid agent the FDA originally approved in 1972 as a sedative for use in veterinary medicine,
- Structurally similar to clonidine, and tizanidine and may share clinical effects
  - Doesn’t seem to have affect on the imidazoline receptor – hypotension and bradycardia
Michigan Xylazine-involved fatalities

*2019-2022 The Swift Toxicology of Overdose-Related Mortalities (STORM) Program at Western Michigan University Homer Stryker MD School of Medicine (WMed)*
Harms

• Combined effect may increase overdose potential
• May worsen withdrawal symptoms
• Has been associated with severe, necrotic skin lesions that differ from other soft-tissue infections – may develop in sites away from the site of injection
• NOT currently known to be reversed by naloxone – wont hurt
• NOT detected by routine toxicology screens
  • Hard to diagnose with a half life of 23-50 minutes
Drug Combinations

Figure 2. Percent of Xylazine-Positive Decedents (n=206) Testing Positive for Other Substances, October 2019 - September 2022*

- Methamphetamine: 31%
- Cannabinoids: 32%
- Benzylecgonine: 35%
- Morphine: 50%
- Fentanyl: 100%

*2019-2022 The Swift Toxicology of Overdose-Related Mortalities (STORM) Program at Western Michigan University Homer Stryker MD School of Medicine (WMed)
Xylazine withdrawal

- Major symptom is Anxiety
- Duration few days to weeks
- Overlap with opioid withdrawal syndrome
- Anxiety irritability, restlessness
- Some corollary to clonidine withdrawal
  - Hypertension, tachycardia, diaphoresis, anxiety and agitation
  - Manage with sedative/hypnotic withdrawal
    - First line – benzo, phenobarbital
    - Adjunct – Clonidine, Tizanidine, lofexidine, gabapentin, antipsychotics – not great anecdotal effect
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 (partial) and a second key component is 7-hydroxymitragynine (2% kratom by weight).

• Both act as weak antagonists at the kappa and delta-opioid receptors in vitro.

• 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
Key points

- Common side effects reported by users include stomach upset, vomiting, tachycardia, agitation, drowsiness, nausea and hypertension.

- Case series of 12 patients from poison control main clinical effects are seizure, AMS, agitation, CNS depression and tachycardia.

- Not detected by conventional drug screening tests; requires advanced test like liquid chromatography-tandem or mass spectrometry.

- Unsure how long detectable in urine - cases showed in urine 2-4 days - may be very lipophilic and stored in lipid tissue longer.

- Given the increased use for self-treatment and lack of regulation, much needed safety studies and evidence on addictive potential.

- No systematic human studies on the addictive potential of Kratom.
## Kratom Metabolism/clearance

<table>
<thead>
<tr>
<th>Collection Date</th>
<th>5/17/2022</th>
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<td>6/10/2022</td>
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<table>
<thead>
<tr>
<th>Analyte</th>
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<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td>Negative</td>
<td>98</td>
<td>295</td>
<td>134</td>
<td>283</td>
<td>190</td>
</tr>
<tr>
<td>Norbuprenorphine</td>
<td>Negative</td>
<td>80</td>
<td>299</td>
<td>799</td>
<td>1,576</td>
<td>2,117</td>
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<tr>
<td>7-Amino-Clonazepam</td>
<td>207</td>
<td>241</td>
<td>215</td>
<td>184</td>
<td>312</td>
<td>378</td>
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<tr>
<td>Hydroxybupropion</td>
<td>5,059</td>
<td>6,165</td>
<td>5,894</td>
<td>Not Ordered</td>
<td>Not Ordered</td>
<td>Not Ordered</td>
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<tr>
<td>Trazodone</td>
<td>414</td>
<td>212</td>
<td>268</td>
<td>153</td>
<td>578</td>
<td>Negative</td>
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<tr>
<td>Naloxone</td>
<td>Negative</td>
<td>425</td>
<td>1,061</td>
<td>305</td>
<td>533</td>
<td>631</td>
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<tr>
<td>Mitragynine (Kratom alkaloid)</td>
<td>734</td>
<td>158</td>
<td>58</td>
<td>6</td>
<td>1</td>
<td>Negative</td>
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<tr>
<td>7-OH-Mitragynine (Kratom alkaloid)</td>
<td>&gt; 749³</td>
<td>371</td>
<td>120</td>
<td>6</td>
<td>1</td>
<td>Negative</td>
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</tbody>
</table>
Key points

• OUD and Stimulant use disorder are increasing in prevalence and see co-occurring often
• Educate patient on dangers of Xylazine and Fentanyl
• Ask about Kratom use
• Don’t forget Narcan – practice Harm Reduction
Don’t Forget

NARCAN® (naloxone HCl)
NASAL SPRAY 4 mg

DO NOT TEST DEVICES OR OPEN BOX BEFORE USE.
Use for known or suspected opioid overdose in adults and children.
This box contains two (2) 4-mg doses of naloxone HCl in 0.1 mL of nasal spray.
Two Pack
CHECK PRODUCT EXPIRATION DATE BEFORE USE.
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