THE TROUBLE WITH FENTANYL

TREATING OPIOID ADDICTION IN THE FENTANYL ERA
DISCLOSURES:

• None

• But... if you have some lucrative (and ethical) conflicts of interest I could add here let me know. I got loans.
GOALS

• Why is fentanyl the enormous problem it is in treating OUD?
• What do we do about it as clinicians/researchers?
FIRST: AN EXPERIENCE DISCLOSURE

• I have only ever treated opioid addiction in the fentanyl era.

• So I asked some who have experienced the contrast:
  – Naloxone for methamphetamine?
  – Deadly
  – Variable dosing (see below)
  – Less predictable withdrawal (see above)
  – Much more likely to precipitate withdrawal
  – Test strips: “get what I paid for.”
  – Microinductions? Single day induction?
THE BASICS

• Morphine equivalents per milligram\(^1\)
  – Heroin: 2-4x
  – Fentanyl: \(~100x\)
  – Carfentanyl/carfentanil: \(~10,000x\)
THE ‘WHY’ IS CLEAR...

• “It is better, in every way.”
  – Cheaper
    • Better cutting agent (levamisole or K2 anyone?)
    • No farming required
    • No import/export
    • $4 per pill
  – Much more potent
  – Double trouble
  – Death sells
  – Look of legitimacy for the new user.²⁻⁴

$1.5 million in Fentanyl seized in Vancouver, BC.

Opium poppy field in Dorset, England.
THE PROBLEM WITH SYNTHETIC DRUGS

• What about meth? The most American drug synthesis:\(^\text{5,6}\)
WHAT DID WE GET?

• Herein lies the problem: we’re not dealing with a single drug, but a multitude, all with different (some unknown) properties. Because organic chemistry is messy – even for organic chemists. 6
SO WHAT DO WE HAVE?

• Maybe about a dozen drugs, with mixed pharmacokinetics and pharmacodynamics, widely available, cheaper and adulterating multiple different unrelated classes of illicit drugs.
• Inadequate research on the target chemical to understand its half-life.
  – Theoretical half-life of about 4 hours. In practice, perhaps a week in urine.
• ~100,000 drug related deaths so far this year in the US. Causation by substance is very challenging.
• Let’s look at another issue in depth...
THE LIPOPHILIC PROBLEM

- Fentanyl clearance in persons with OUD is considerably longer than the typical 2-4 day clearance of other short-acting opioids. Up to 7 days renal excretion in chronic users. 8
- Greater lipophilic properties affecting addiction…
  - Ex: benzodiazepines. Re: dose, duration, administration bioavailability, speed in crossing BBB.
- This might be the biggest problem for treatment.
- Some potential solutions…

<table>
<thead>
<tr>
<th>Benzodiazepines</th>
<th>Diazepam Equivalent (10 mg)</th>
<th>Onset of action</th>
<th>Peak onset</th>
<th>Half-life [active metabolite]</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>0.5 mg</td>
<td>Intermediate</td>
<td>0.7-1.6 hours</td>
<td>6-12 hours</td>
<td>High risk of misuse</td>
</tr>
<tr>
<td>Clobazam</td>
<td>20 mg</td>
<td></td>
<td>12-60 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonazepam</td>
<td>–0.25 mg to 0.5 mg&lt;sup&gt;12&lt;/sup&gt;</td>
<td>20 to 40 minutes</td>
<td>1-4 hours (PO)</td>
<td>18-50 hours</td>
<td>Fast onset, long acting, high potency, partial serotonin agonist</td>
</tr>
<tr>
<td>Diazepam</td>
<td>10 mg</td>
<td>Rapid (PO, IV – due to its lipophilic nature)</td>
<td>1 (PO) hours</td>
<td>IV: 33-45 hours PR: 48-68 hours PO: 45-66 hours</td>
<td></td>
</tr>
<tr>
<td>Lorazepam</td>
<td>1 mg</td>
<td>Intermediate (PO) Rapid (SL/IV)</td>
<td>1-1.5 (PO) hours</td>
<td>10-20 hours</td>
<td></td>
</tr>
<tr>
<td>Oxazepam</td>
<td>20 mg</td>
<td>Slow</td>
<td>2-3 hours</td>
<td>4-15 hours</td>
<td></td>
</tr>
<tr>
<td>Trazodone</td>
<td>20 mg</td>
<td>Slow (PO 0.5-2 mg&lt;sup&gt;13&lt;/sup&gt;)</td>
<td>0.75-1.5 hours</td>
<td>8-22 hours</td>
<td></td>
</tr>
<tr>
<td>Triazolam</td>
<td>0.5 mg</td>
<td>Intermediate</td>
<td>0.75-2</td>
<td>2 hrs</td>
<td></td>
</tr>
<tr>
<td>Flurazepam</td>
<td>Rapid</td>
<td></td>
<td>0.5-2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
A QUICK REVIEW ON PARTIAL AGONISTS

• Naloxone in suboxone does not cause the withdrawal! (if used properly).
• Buprenorphine is a partial μ-opioid agonist and κ-opioid antagonist
• **Agonist**: A ligand that binds to a receptor and alters the receptor state resulting in a biological response
  • **A full agonist** reaches the maximal response capability of the system
  • **A partial agonist** does not reach the maximal response capability of the system even at full receptor occupancy.⁹
MICROINDUCTIONS

- First described in 2010 as a case study of two patients in Bern, Switzerland. Also known as the Bernese method.
- Goal: Switch to suboxone and avoid withdrawal which will cause treatment failure.
- Allows patients to continue fentanyl use concurrent with suboxone and overcome partial agonist. Buprenorphine has 2-3x greater receptor (Ki =1.35 vs 0.216) affinity than fentanyl (not potency!). Most derivatives (inc. carfentanil) are unknown.
- To be clear... patients will still likely have some withdrawal, but should be mild. This strategy does not work for high dose methadone typically. 10–16
- Example Strategy:
  - Day 1: 0.5mg loading dose (0.5mg total)
    Day 2: 0.5mg BID (1mg total)
    Day 3: 1mg BID (2mg total)
    Day 4: 2mg BID (4mg total)
    Day 5: 3mg BID (6mg total)
    Day 6: 4mg BID (8mg total)
    Day 7: 12 mg (16mg and discontinue other opioids)
  - Option - Day 8: Sublocade 300mg
MICROINDUCTION EFFICACY

- Not yet well established. I’m batting around 50%.
- Pharmacologically suspect

----------------------------------------------

- Two ongoing comparison RCTs.
- Ahmed et al, 2020: 18 papers, 63 patients. Primarily inpatient settings with a variety of opioids, range of dosing all without significant withdrawal. Initial dosing 0.2-0.5 mg and time frame of 3-112 days most over 4-8 days and most completed cross titration between 8-16 mg.
- Most recent reviews suggest available studies are low quality with highly variable dosing strategies. Inconsistent reporting, selection bias, and poor quality evidence limit conclusions regarding optimal dosing, and patient characteristics and clinical settings in which micro-induction is likely beneficial.17-19
SINGLE DOSAGE METHOD

• Mariani et al, 2021: Open-label trial of a single-day induction onto buprenorphine extended-release injection for users of heroin and fentanyl
  – 12-week outpatient clinical trial to test the feasibility of a single-day induction onto extended-release buprenorphine (BXR) injection treatment for five adults (N=5)
  – All 5 received all three injections, with first on first day and all maintained on injections for 3 months. ²⁰

• EX:

<table>
<thead>
<tr>
<th>Time</th>
<th>COWS</th>
<th>Bupe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1020</td>
<td></td>
<td>Buprenorphine 2 mg SL</td>
</tr>
<tr>
<td>1110</td>
<td>8</td>
<td>Buprenorphine 8 mg SL</td>
</tr>
<tr>
<td>1145</td>
<td>9</td>
<td>Buprenorphine 8 mg SL</td>
</tr>
<tr>
<td>1230</td>
<td>15</td>
<td>Buprenorphine 6 mg SL</td>
</tr>
<tr>
<td>1245</td>
<td></td>
<td>XR-Buprenorphine 300 mg SC</td>
</tr>
</tbody>
</table>
CRITIQUE

• Single dosage method may have some benefits, but current method would not be feasible in most treatment settings and would be a small, dedicated subset of our patients – much like microinductions are currently.
• 3 months is insufficient time frame to measure efficacy.
TAKE-AWAYS FOR CLINICIANS

• The fentanyl epidemic is not a problem of fentanyl alone, it is a problem with multiple known and unknown fentanyl analogues with variable receptor affinities, potencies, half-lives, lipophilicities that are created in very different concentrations from multiple different manufacturers.

• This variable affect in regards to reward is likely, in of itself, more addictive (variable number and interval). Like gambling on top of opioid addiction.

• Fentanyl analogues may be the most beneficial thing for cartels since methamphetamine and are nearly impossible to regulate or control.

• Effective ways to address this problem are not yet validated.
WELL THAT WAS DARK... HERE’S THE UPSIDE!

• More research is on the way.

• Microinductions do work\textsuperscript{21}, from my limited experience with them and multiple case studies of short duration. Here is what we’re doing at the VA (Rozylo et al, 2020):

Two quick stories...
QUESTIONS?
THOUGHTS?
DISAGREEMENT?
WORKS CITED:

4. 3 deaths tied to excessive bleeding from synthetic marijuana, possibly tainted with rat poison. Accessed December 5, 2021. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6601a3.htm
8. 1.2262288 1.2262288