A Novel Approach Toward Treating Fentanyl with Xylazine Dependency

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BACKGROUND

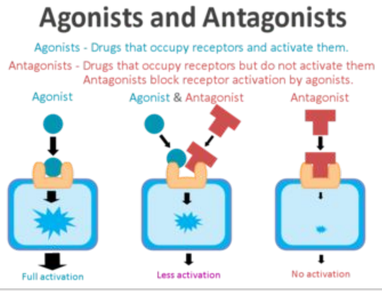
- Opioids can be mixed or adulterated with xylazine to enhance drug effects working synergistically [1]
- Both opioid and xylazine withdrawal must be managed, however, these act through different mechanisms [2]
- Withdrawal can be quantified through Clinical Opioid Withdrawal Scale (COWS). This 11 question assessment looks at domains such as:
  - Subjective symptoms: These are symptoms that are primarily assessed by the patient's report, such as bone or joint aches, anxiety, or restlessness
  - Objective signs: These are signs that can be observed or measured, such as resting pulse rate, pupil size, or sweating
- Patients have a higher chance of turning back to opioid abuse to manage their withdrawal symptoms [3]

Xylazine

- Created in 1962 it first started appearing in the early 2000s in Puerto Rico it then rapidly emerged in Philadelphia and Connecticut [4]
- Strong α-2 adrenergic agonist medication that was initially developed for use in veterinary medicine as an analgesic and sedative for animals [5]

Pharmacological Classification of Opioids

Full Agonist	Morphine, fentanyl, Heroin, methadone	High potency, maximal response even with low receptor occupancy. Fentanyl is a highly lipophilic agent with high affinity for the μ-opioid receptor. It is 75 to 125 times more potent than morphine and has a faster onset of action.
Partial Agonist	Buprenorphine	Partial agonist at the μ-receptor and as an antagonist at the κ-receptor
Mixed antagonist agonist	butorphanol, pentazocine	Agonist -κ-receptor Antagonist - μ-receptor Partial Agonist -σ-receptor
Antagonists	naloxone, naltrexone	Naltrexone competitively binds and may block the effects of endogenous opioids



Opioid Receptors - G protein-coupled receptors (GPCRs)

Receptor	Clinical Effects	Location
μ-receptor (MORs)	Analgesia Changes, Smooth Muscle Tone, Sedation, Mood Alteration, Nausea/Vomiting	Mesenteric Plexus, Central and Peripheral nervous systems, Submucosal Plexus
σ-receptor (DORs)	Decreases colonic transit time	Mesenteric Plexus, Central nervous systems
κ-receptor (KORs)	Central analgesia, Decreases colonic transit time, Visceral nociception antagonist	Mesenteric Plexus, Central and Peripheral nervous systems
nociceptin/orphanin FQ (N/OFQ)	Regulation of instinctive, emotional behaviors	Central and Peripheral nervous systems

CASE

30 year old male presenting with withdrawal after IVDU. Reported abdominal pain with burning sensation, palpitations, profuse vomiting after IVDU 2 hours ago. Endorses 17 year history of IVDU, currently using 20-40 bags per day of Fentanyl and Xylazine. He has had multiple prior rehab and detox attempts, and on Methadone 140 mg daily.

Past medical-psychiatric history

- ❑ Psychiatric History: MDD, GAD, PTSD, ADHD, OUD/CUD/TUD
  - Strong Cluster B components
- ❑ Medical History: Hepatitis C , Peyronie's disease

During the first admission, the patient was started on benzodiazepine-focused treatment with maintaining his Methadone. He remained symptomatic with irritability and tremulousness. Patient then eloped prior to AMA discussion for a treatment length of ~31 hours.

The patient represented 2 weeks later for evaluation of leg wounds and attempting to detox, with symptoms of opioid and xylazine withdrawal. Additional symptomatic management was initiated. He was maintain on the Methadone dose and additionally started on an opioid focused treatment (Oxycodone), but remained symptomatic. This lessened with the introduction of IV Dilaudid, leading to notable improvement. Methadone was titrated and split dosing (100 am and 60 pm). The patient once again eloped prior to AMA discussion, but was treated for ~168 hours, managed to complete a full course of IV antibiotics and outpatient planning for limb debridement/repair.

The patient did appear to be stabilized upon last PSychiatric evaluation. He did represent to our hospital system recently and has maintain abstinence from fentanyl/xylazine for ~5 months with titration of methadone dosing to 200 mg QD, 200 mg QHS.

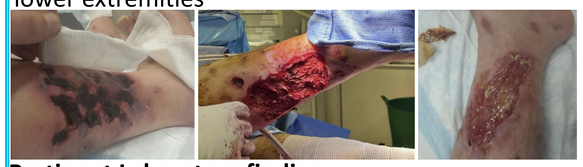
Pertinent Vital Signs

Afebrile, Normotensive-Hemodynamically Stable

Pertinent Physical examination

Constitutional: Alert, nontoxic, Anxious

MSK: Multiple necrotic wounds, primarily to bilateral lower extremities



Pertinent Laboratory findings

UDS positive for Cocaine, Cannabinoid, Opiates, Methadone

EKG: QTC 466 (Bazett); 550/516/466 (Framingham)

Treatment Course

- 1st Admission: benzodiazepine-focused treatment. Unfortunately the patient Eloped prior to AMA discussion. Total length of treatment: ~31 hours 11 mg of ativan, 40mg of valium, methadone 140 mg.
- 2nd Admission: Opioid focused treatment comprising of oxycodone, clonidine, antiemetics, nicotine replacement therapy, PPIs, gabapentin. Symptoms persisted, prompting titration of methadone and of oxycodone. Introducing dilaudid for breakthrough symptoms led to a notable symptomatic and COWS improvement being treated for total of ~168 hours.

CONCLUSIONS

- Despite initial optimism, the patient's withdrawal symptoms persisted, prompting the addition of methadone and titration of oxycodone. Subsequent adjustment involved introducing Dilaudid for breakthrough symptoms, leading to a notable improvement in withdrawal management. This initially was met with push back from the hospital system/team.
- This case highlights the challenges of managing fentanyl and xylazine withdrawal and the importance of tailoring treatment strategies to individual patient responses. The successful outcome underscores the efficacy of a flexible, multimodal approach in addressing complex withdrawal syndromes. This underscores the importance of continual reassessment and adjustment of treatment plans to optimize patient outcomes in substance withdrawal management.

DISCUSSION

- The increasing prevalence of adulterated IVDU which was once only heroin has now become majority fentanyl and addition of xylazine. This presents unique challenges in both clinical management and patient engagement. Unlike traditional opioid use, the synergistic effects of xylazine and fentanyl create a significantly heightened risk for lethality and complex withdrawal syndromes. Xylazine, an alpha-2 adrenergic agonist, adds a distinct layer to the already dangerous effects of fentanyl. Furthermore skin wounds, such as open sores (ulcers) and abscesses from IVDU with xylazine add additional complexity to treating patients whom often require IV antibiotics and prolonged inpatient admission.
- Importantly, managing these patients effectively requires physicians to adopt a patient-centered, harm-reduction approach. This perspective emphasizes meeting patients where they are in their addiction journey, balancing respect for their autonomy with the ethical obligation of beneficence—working toward their best interests. Physicians must negotiate realistic, individualized treatment goals with patients, understanding that immediate cessation of substance use may not be achievable or realistic for every individual. This approach encourages engagement in care, prioritizing harm reduction, and improving health outcomes over time.
- *"My heart pounded so hard and so long I could feel it getting sore. I would sweat so profusely that I would stay constantly drenched as long as I was sick. If I took a baby sip of water, I would projectile vomit within 5 minutes"*
- *"Fentanyl/Xylazine is different, it's not an enjoyable high that you can go and do stuff on. It's oppressive and it completely knocks you out then you wake up, and you're sick already. Even if you only slept 2-3 hours. - I know rehabs/detoxes don't know what they're doing at all. Staff there hasn't even heard of it. They need to be more liberal with the meds. A little clonidine and Motrin is a joke!"*

TREATMENT PROTOCOLS

Buprenorphine

A. Standard Dosing
   a. 12–18 hours after last short-acting agonist (heroin, oxycodone), 24–48 hours after long-acting agonist (methadone)
   b. 4–16 mg per day and then the dose is tapered over time
B. Macro induction
   a. COWS ≥ 13, at least 18 hours elapsed since last fentanyl use (not necessary post-naloxone reversal)
   b. 16 mg buprenorphine. Reassess hourly. Repeat buprenorphine 8–16 mg q1–2h until withdrawal is resolved or sedation (recommended Day 1 maximum is 32 mg)
C. Micro induction Belbuca
   a. Day 1: 150 mcg QID or q3-q4h PRN
   b. Day 2: 300 mcg QID or q3-q4h PRN
   c. Day 3: stop belbuca, Suboxone 2-0.5mg SL QID or q4h PRN
   d. Day 4: stop methadone/oxycodone/dilaudid, suboxone 4-1mg BID or 4-1mg TID

Methadone

A. 10–30 mg with reassessment in 3–4 hours, and a 2nd dose not to exceed 10 mg

Opioid

A. IV 1-2mg dilaudid q4h PRN or IV morphine 4-6 mg q4h PRN
B. PO oxycodone 15-20 mg q4h PRN as necessary for withdrawal or pain; titrate to response

Ketamine

A. Ketamine IV over 10 minutes 0.2 mg/kg
B. Ketamine IV over 60 minutes 0.3 mg/kg

Clonidine

Clonidine 0.1-0.3 mg TID

Benzodiazepine - Clinical induced withdrawal assessment (CIWA)

A. CIWA-2mg Ativan or Valium 5mg PO/IM (8-15, >15)

Additional Rx for Symptomatic Management

1. Robaxin/methocarbamol 750mg TID
2. Zofran 4mg q6h/Tigan 300mg TID
3. Tylenol/Ibuprofen
4. Gabapentin TID
5. Imodium 2mg q2h
6. Nicotine Patch 14/21mg patch q24hr, Nicorette gum 2mg q2h
7. Zanaflex 2 mg q6h
8. Maalox 30 mL q6h
9. Pantoprazole 40 mg
10. Trazodone 50mg QHS
11. CIWA additions: IV thiamine for 9 doses, Folic Acid 5 mg QD, B12 1000 mcg QD, MultiVitamin QD

RECOMMENDATIONS

- Clonidine and Benzodiazepine Protocols seem to be suboptimal compared to opioid driven protocols
- Start with non-invasive tests and limit unnecessary Labs. Is a daily CBC/BMP really necessary?
- A harm-reduction approach may conflict with typical hospital practices around substance use, especially given staff assumptions about what constitutes the patient's best interest and safety, as well as concerns about losing control over the treatment process.
- Supportive Psychotherapy and Motivational interviewing work do not ignore their role in treatment of lieu of addressing withdrawal
- Harm reduction and meeting patients where they are at still are the gold standard approach!