



# Precipitated Withdrawal Refractory to High-Dose Buprenorphine: A Cautionary Tale

Lisa W. Vercollone, MD, PharmD, Edmond Hakimi, DO, David B. Hathaway, MD, Joji Suzuki, MD

Brigham and Women's/Faulkner Hospitals, Boston, MA

Harvard Medical School, Boston, MA

(None of the authors have any disclosures to report)

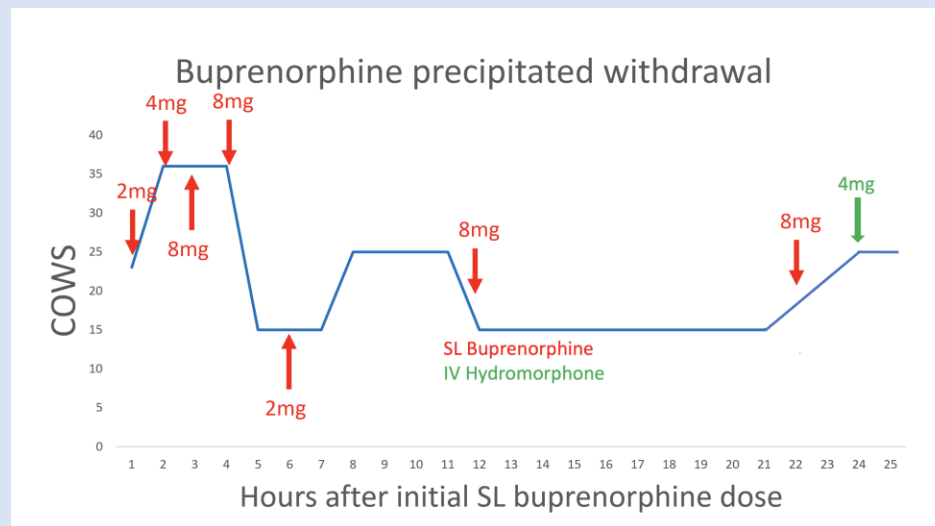


## BACKGROUND

In the fentanyl era, traditional approaches to initiating buprenorphine for persons who use non-prescribed opioids on a daily basis carry significant risk of buprenorphine precipitated opioid withdrawal (BPOW). These continued challenges have recently sparked interest in an alternative approach called "macro dosing," or high-dose buprenorphine initiation (HDBI). As its name implies, HDBI entails the administration of large doses of buprenorphine in a short period of time. The intent of using macro dosing/HDBI is to "flood" mu-opioid receptors with buprenorphine in order to rapidly ameliorate opioid withdrawal symptoms. Yet data supporting the safety or effectiveness of macro dosing/HDBI remains limited. Here we present a case where macro dosing/HDBI was employed to treat BPOW occurring after a traditional buprenorphine initiation attempt.

## REFERENCES

- 1- Herring AA et al. High-Dose Buprenorphine Induction in the Emergency Department for Treatment of Opioid Use Disorder. JAMA Network Open. 2021 Jul 1;4(7)
- 2 - Oakley B et al. Managing opioid withdrawal precipitated by buprenorphine with buprenorphine. Drug Alcohol Rev. 2021;40(4):567-571.
- 3 - Quattlebaum THN et al. A case of buprenorphine-precipitated withdrawal managed with high-dose buprenorphine. Fam Pract. 2022;39(2):292-294.
- 4 - Huhn AS et al. Protracted renal clearance of fentanyl in persons with opioid use disorder. Drug Alcohol Depend. 2020;214.



## DISCUSSION

Case reports suggest that treatment of BPOW with macro dosing/HDBI may ameliorate withdrawal symptoms within 12 hours (1,2). This patient continued to experience severe BPOW 24 hours after macro dosing/HDBI. Many factors were considered.

- Fentanyl is highly lipophilic and has delayed renal clearance leading to the accumulation of high blood levels (4). Given the patient's heavy, chronic fentanyl use, coupled with class II obesity, a significant amount of fentanyl may have persisted despite the fact that over 40 hours had elapsed from last use.
- Concurrent withdrawal syndromes from alcohol, stimulants, and possibly xylazine
- Immediately after buprenorphine is administered at high doses, relatively few opioid-mu receptors remain unoccupied; this may render full mu-opioid receptor agonists with lesser affinity than buprenorphine ineffective and may contribute to severe, persistent BPOW refractory to reversal with full agonist opioids.
- It is also possible that there was a strong contribution of spontaneous opioid (fentanyl) withdrawal, complicated by the patient's poor distress tolerance in the setting of a history of significant life traumas and adverse childhood experiences (ACEs).

Caution is warranted regarding approaches employing high-dose buprenorphine to treat buprenorphine-precipitated opioid withdrawal

## RESULTS

A 26-year-old man with multiple substance use disorders including intravenous (IV) fentanyl, stimulants, and tobacco, depressive disorder, PTSD, and class II obesity (BMI 35) admitted for cellulitis.

- Reported a 4-day "binge" of IV fentanyl, methamphetamine, crack cocaine, and alcohol (2 pints vodka daily) with a baseline use of intravenous fentanyl "2 gm" daily for many months.
- Last use of fentanyl was 2 hours prior to presentation. One week prior to this admission, he had received methadone for 3 days in tapering doses of 30 mg, 20 mg, and 10 mg.
- During this admission, he was started on chlordiazepoxide 75 mg PO q6h for alcohol withdrawal syndrome.
- 28 hours after admission, he was found pacing around the room, diaphoretic, anxious, crying, with piloerection and a COWS of 23. Subsequently, he received bup/nal 2 mg/0.5 mg SL x 1 dose.
- 20 minutes later, a repeat COWS was > 36 consistent with severe BPOW.
- Over the next 6 hours, he received a total of bup/nal 24 mg/6 mg SL. COWS improved to a nadir of 15.
- He received an additional bup/nal 8 mg/2 mg SL dose on the initiation day and was placed on TID dosing.
- The following morning, 24 hours after his initial bup/nal dose, his COWS had increased to 25. In response, he received hydromorphone 4 mg IV which he reported made his symptoms worse and he refused additional doses.
- He stated, "I feel like I'm dying. I am very sorry, I need to leave to use and drink and then I will come back," and he left via a self-directed discharge.
- Total: bup/nal 40 mg/10 mg, chlordiazepoxide 375 mg, lorazepam IV 8 mg, hydromorphone IV 4 mg.
- Quantitative urine drug screen collected 40 hours after admission later revealed a urine concentration of fentanyl 62 ng/mL and norfentanyl 399 ng/mL. Urine methadone was detected but not quantified.