Case Report: Buprenorphine-precipitated fentanyl withdrawal treated with high-dose buprenorphine [version 2; peer review: 2 approved]

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Abstract

Background: Buprenorphine, a partial agonist of the mu-opioid receptor, is an increasingly prescribed medication for maintenance treatment of opioid use disorder. When this medication is taken in the context of active opioid use, precipitated withdrawal can occur, leading to acute onset of opioid withdrawal symptoms. Fentanyl complicates use of buprenorphine, as it slowly releases from body stores and can lead to higher risk of precipitated withdrawal.

Objectives: Describe the successful management of buprenorphine precipitated opioid withdrawal from fentanyl with high doses of buprenorphine. We seek to highlight how no adverse effects occurred in this patient and illustrate his stable transition to outpatient treatment.

Case report: We present the case of a patient with severe opioid use disorder who presented in moderately severe opioid withdrawal after taking non-prescribed buprenorphine-naloxone which precipitated opioid withdrawal from daily fentanyl use. He was treated with high doses of buprenorphine, 148 mg over the first 48 hours, averaging 63 mg per day over four days. The patient reported rapid improvement in withdrawal symptoms without noted side effects and was able to successfully taper to 16 mg twice daily by discharge.

Conclusions: This case demonstrates the safety and effectiveness of buprenorphine at high doses for treatment of precipitated withdrawal. While other options include symptomatic withdrawal management, initiating methadone or less researched options like ketamine, utilizing buprenorphine can preserve or re-establish confidence in this life-saving medication. This case also increases the previously documented upper boundary on buprenorphine dosing for withdrawal and should provide additional confidence in its use.

Keywords

Buprenorphine, fentanyl, Opioid-Related Disorders, case report
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Author roles: Bormann NL: Conceptualization, Investigation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; Gout A: Writing – Review & Editing; Kijewski V: Writing – Review & Editing; Lynch A: Conceptualization, Funding Acquisition, Supervision, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

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This article is included in the Addiction and Related Behaviors gateway.
Introduction
Buprenorphine, a partial mu-opioid receptor agonist, has become the most prescribed treatment for opioid use disorder (OUD).1 With greater availability, non-prescribed use has also increased.2 Buprenorphine can precipitate withdrawal by reducing receptor activation through competitive displacement of higher efficacy mu-opioid receptor ligands.3 This rapid onset of opioid withdrawal symptoms including bone and muscle pain, diarrhea, insomnia, dysphoria, and anxiety, causes significant patient discomfort.

The rise of synthetic opioids such as fentanyl has complicated the treatment of precipitated withdrawal. Fentanyl is more potent than heroin, and has high lipophilicity leading to rapid uptake into body tissues and subsequent slow release.4,5 While use of ketamine has been suggested for withdrawal treatment,6 conventional wisdom has been to utilize additional buprenorphine.7 Recent cases in the literature have shown safety and effectiveness of up to 40 mg of buprenorphine early in the withdrawal period.7–11 Herein, we describe the case of a patient who required 148 mg of buprenorphine over 48 hours for successful treatment of buprenorphine-precipitated withdrawal from fentanyl. Consent was obtained from the patient for his case to be used in the academic literature and is available upon request. As such, the University of Iowa Institutional Review Board has deemed this case report exempt from review.

Case description
Individual was a 21-year-old partnered, unemployed Caucasian male with no known past medical history, a psychiatric history of OUD, attention deficit hyperactivity disorder and unspecified anxiety, who presented with his father to our medication for addiction treatment (MAT) walk-in clinic for assistance discontinuing daily fentanyl use. Pertinent family history included an OUD in his brother and both his mother and maternal aunt having an unspecified prescription pill addiction. Initial opioid exposure was through purchasing prescription opioids for six months, before transitioning to use of fentanyl after he had purchased it unknowingly. He endorsed daily fentanyl use of an unknown amount for six months, with an escalation in patient-estimated amount over the preceding two months. His typical method of use was insufflation or vaping. He had attempted to stop multiple times by tapering use with the goal of abstinence, however, was unsuccessful after occurrence of withdrawal symptoms led to eventual return to daily use of the previous amount. Other substance use consisted of non-prescribed alprazolam 1 mg daily that he had started taking in the previous weeks for anxiety symptoms. He denied other active substance use.

After making plans to present to the MAT clinic, he abstained from using fentanyl to prepare for buprenorphine induction. His father drove him to the MAT clinic sixteen hours after last fentanyl use. While traveling to the clinic, he took non-prescribed buprenorphine-naloxone 8-2 mg, which immediately precipitated withdrawal. On initial evaluation in clinic, he had a clinical opioid withdrawal scale12 (COWS) score of 27, with diffuse pain, nausea, emesis, diarrhea, rhinorrhea, chills, yawning, anxiety, and restlessness. He also was intermittently agitated and having visual hallucinations. Due to lack of readily available medications in the outreach clinic, he was taken to the emergency department (ED) at the main hospital.

At the ED, he was given buprenorphine monoprodut (referred to herein as buprenorphine) 8 mg, which lowered COWS to 19 and provided approximately 45 minutes of relief. Screening labs in the ED consisted of a complete metabolic panel, complete blood count with differential, urinalysis, blood alcohol level, acetaminophen drug level, urine drug screen and electrocardiogram (ECG). This standard screening panel was largely within normal limits, with positive findings of presumptive positive for urine benzodiazepines, a minor elevation in neutrophils (count of 7,850 with normal range of 2,188 – 7,800/mm³), and ECG QTc interval of 463 millisecond (normal less than 430 millisecond). He received an additional 8 mg of buprenorphine 3 hours later which lowered COWS to 9. He subsequently was administered doses of 4 mg three times over the next 8 hours, which he did not feel provided as much relief as higher doses. This was increased to 16 mg doses of buprenorphine, which he tolerated without significant changes in vital signs, and provided symptomatic relief for 2 hours at a time. Medication administration record for buprenorphine can be seen in Table 1.
Over the first 24 hours, he received 68 mg of buprenorphine and was routinely assessed by nursing. He became physically restless with increasing anxiety, however these improved with repeat dosing of buprenorphine. He was seen by a psychiatrist in the ED, who recommended admission to the medical-psychiatry unit for on-going management of the high-doses of buprenorphine. The patient’s goal was long-term abstinence from fentanyl use, and continued treatment with buprenorphine was felt to be the most direct method to accomplish that.

Over the second 24-hour period from initial precipitation of withdrawal, he received an additional 80 mg of buprenorphine in 16 mg doses. His respiratory rate measured consistently between 16 and 18 breaths per minute (normal is typically considered 12 to 16) during this time. His daily buprenorphine dose requirement peaked on day two, with the goal for discharge of 16 mg twice daily, the maximum daily amount his insurance would cover. He tolerated this reduction over three days without exacerbation of symptoms or cravings.

The COWS was scheduled every 4 hours, and his scoring remained low with continued treatment. In addition to buprenorphine, he received gabapentin 300 mg thrice daily titrated to 600 mg thrice daily for physical discomfort and anxiety. His anxiety was worse earlier in his course, and he received lorazepam while on the unit, averaging a daily dose of 2 mg by mouth. He was discharged on 1 mg daily of clonazepam. He is now seen in the MAT outpatient clinic and has a severe opioid use disorder in early remission on buprenorphine-naloxone 24-6 mg once daily. His clonazepam use has been tapered, now taking less than 0.5 mg daily. He reports increased stability in his life, and relayed appreciation for the Table 1. Buprenorphine administration timetable.

| Hospital Day | Time  | Hours post \(t_0\) | Buprenorphine, mg | Buprenorphine 24-hour dose, mg |
|--------------|------|--------------------|-----------------|-----------------------------|
| 1            | 16:27| 2.0                | 8               | 68                          |
|              | 19:27| 5.0                | 8               |                             |
|              | 22:10| 7.7                | 4               |                             |
| 2            | 1:03 | 10.6               | 4               |                             |
|              | 4:03 | 13.6               | 4               |                             |
|              | 6:19 | 15.8               | 8               |                             |
|              | 8:25 | 17.9               | 16              |                             |
|              | 11:21| 20.9               | 16              |                             |
|              | 15:36| 25.1               | 16              | 80                          |
|              | 19:02| 28.5               | 16              |                             |
|              | 22:26| 31.9               | 16              |                             |
| 3            | 0:48 | 34.3               | 16              |                             |
|              | 8:38 | 42.1               | 16              |                             |
|              | 15:15| 48.8               | 16              | 56                          |
|              | 21:59| 55.5               | 16              |                             |
| 4            | 8:58 | 66.5               | 16              |                             |
|              | 11:06| 68.6               | 8               |                             |
|              | 16:12| 73.7               | 8               | 48                          |
|              | 20:24| 77.9               | 8               |                             |
|              | 21:02| 78.5               | 16              |                             |
| 5            | 8:44 | 90.2               | 16              |                             |
|              | 22:24| 103.9              | 8               | 24                          |
| 6            | 8:48 | 114.3              | 16              |                             |
|              | 22:13| 127.7              | 16              | 32                          |
| 7            | 9:35 | 139.1              | 16              |                             |

\(t_0 = 14:30\); time at which patient took initial buprenorphine-naloxone 8-2 mg dose that precipitated his withdrawal. Each horizontal bolded line signifies separation of a 24-hour period, with initial reference time of \(t_0\). The time column indicates hospital clock time. The values in far-right column are for each subsequent 24-hour period after the initial precipitated withdrawal.
care and assistance he received in transitioning to MAT. He is followed by the senior author, who also saw him at both the walk-in clinic and main hospital. VK was the attending on the inpatient unit during his stay.

**Discussion**

This case builds upon existing literature by extending the upper extreme of known buprenorphine dosing for treatment of buprenorphine precipitated withdrawal. Previous case reports have used between 16 and 40 mg daily. In this case the range was doubled without significant adverse effect. A separate trial showed evidence for tolerability of one-time dosing of up to 96 mg of buprenorphine with goal of craving reduction. This however, to our knowledge, is the first report of a patient tolerating repeated days of high dose buprenorphine, averaging 63 mg per day over the first four days, with maximum 24-hour dose of 80 mg.

The US Food and Drug Administration (FDA) has approved use of buprenorphine up to 32 mg daily. At this dose, the mu-opioid receptor nears saturation. Buprenorphine’s duration of action however is only 6–8 hours, which may partially explain the effectiveness of repeated high doses in this and other cases. Further research is needed to close clinical knowledge gaps, such as incorporation of imaging techniques to quantify changes in receptor occupancy with re-dosing of buprenorphine, fentanyl-specific induction protocols that balance the risk of precipitated withdrawal with treatment retention, and adjunctive treatments such as neuromodulation that may help regulate dysfunctional neural networks.

Opioid withdrawal is a strong negative reinforcer for patients, and the fear of withdrawal may prompt behavior changes intended to avoid such misery. Withdrawal specifically precipitated by buprenorphine is felt by some to be particularly uncomfortable, due to the abrupt displacement of opioid agonist by the high affinity buprenorphine molecule. It is reasonable that an experience with buprenorphine leading to withdrawal would limit one’s willingness to continue taking it or to utilize it for long-term maintenance therapy. However, with only three FDA approved medications for treatment of OUD (buprenorphine, methadone, and naltrexone) and buprenorphine being the most readily accessible, attempts should be made to reassure the patient, optimize the initial exposure to buprenorphine even if use prompted a visit to the ED, and preserve or reestablish the patient’s confidence that this medication can provide benefit.

Along with administering additional buprenorphine, alternative recommendations for the treatment of acute buprenorphine precipitated withdrawal are discontinuation with symptomatic treatment (such as clonidine, ondansetron, loperamide and gabapentin) or utilization of full-opioid agonist such as methadone. In the moment, discontinuing the medication that caused acute withdrawal while providing symptomatic treatment may feel like the safest option, but this strategy misses an opportunity to initiate a potentially life-saving medication. Obtaining a start date for methadone maintenance therapy at an opioid treatment program out of the ED is also a large barrier to care and unrealistic for most parts of the United States. Ketamine has also been suggested, specifically in the ED. A noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, ketamine has the potential to suppress physiologic symptoms of withdrawal. In this patient, continued use of buprenorphine throughout his hospital stay helped the patient develop confidence in the medication and incorporate taking it into his daily routine.

A commonly voiced concern for escalating doses of buprenorphine is respiratory depression. Buprenorphine’s effect on ventilation has been shown to plateau with a ceiling effect, unlike fentanyl, which can lead to apnea with increasing dose. While this case along with others have shown no issues with respiratory depression, it remains a practical concern. Scheduling the COWS can help mitigate this risk by utilizing symptom triggered dosing to inform daily requirement. Contamination of the drug supply, particularly with fentanyl, may also contribute to risk of respiratory depression. The occurrence of hallucinations in the case may be due to opioid withdrawal, which is a documented but less frequent symptom, or from a contaminant.

To conclude, this case provides additional evidence for the tolerability of high-dose buprenorphine and how the medication can be successfully tapered to a safe outpatient dose by discharge. There were no identifiable side effects to this total dosing of buprenorphine. As these doses exceeded the FDA approved limit, the use we describe is off label. Clinical trials are needed to bolster existing literature and provide clarity to clinicians practicing in an era where fentanyl use has become increasingly prevalent.

**Data availability**

All data underlying the results are available as part of the article and no additional source data are required.
Reporting guidelines
Open Science Framework: CARE checklist for ‘Buprenorphine-precipitated fentanyl withdrawal treated with high-dose buprenorphine: a case report’. http://doi.org/10.17605/OSF.IO/9M468.23

Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

Consent
Written informed consent for publication of their clinical details was obtained from the patient.

Acknowledgements
The authors extend their gratitude to the patient, who consented to publication to allow his case to help educate providers and improve care of future patients.

References
1. Morgan JR, Schackman BR, Leff JA, et al.: Injectable naltrexone, oral naltrexone, and buprenorphine utilization and discontinuation among individuals treated for opioid use disorder in a United States commercially insured population. J. Subst. Abus. Treat. 2018; 85: 90–96. Publisher Full Text
2. Lofwall MR, Walsh SL: A review of buprenorphine diversion and misuse: the current evidence base and experiences from around the world. J. Addict. Med. 2014; 8(5): 315–326. PubMed Abstract | Publisher Full Text
3. Varshneya NB, Thakrar AP, Hobelmann JG, et al.: Evidence of Buprenorphine-precipitated Opioid Withdrawal in Persons Who Use Fentanyl. J. Addict. Med. 2022; 16(4): e265-e268. PubMed Abstract | Publisher Full Text
4. McClain DA, Hug CC: Intravenous fentanyl kinetics. Clin. Pharmacol. Ther. 1980; 28(1): 106-114. Publisher Full Text
5. Armenian P, Vo KT, Barr-Walker J, et al.: Fentanyl, fentanyl analogs and novel synthetic opioids: A comprehensive review. Neuropsychopharmacology. 2018; 134(9): A1: 121–132. PubMed Abstract | Publisher Full Text
6. Hallozian C, Luftig J, Liang A, et al.: Synergistic Effect of Ketamine and Buprenorphine Observed in the Treatment of Buprenorphine Precipitated Opioid Withdrawal in a Patient With Fentanyl Use. J. Addict. Med. November 2021. PubMed Abstract | Publisher Full Text
7. Oakley B, Wilson H, Hayes V, et al.: Managing opioid withdrawal precipitated by buprenorphine with buprenorphine. Drug Alcohol Rev. 2021; 40(4): 567-571. Publisher Full Text
8. Daniilwitz M, McLean M: High-dose buprenorphine for treatment of high potency opioid use disorder. Drug Alcohol Rev. 2020; 39(2): 135-137. PubMed Abstract | Publisher Full Text
9. Quattlebaum THN, Kiyokawa M, Murata KA: A case of buprenorphine-precipitated withdrawal managed with high-dose buprenorphine. Fam. Pract. June 2021; 39: 292–294. PubMed Abstract | Publisher Full Text
10. Herring AA, Vosoughi AA, Luftig J, et al.: High-Dose Buprenorphine Induction in the Emergency Department for Treatment of Opioid Use Disorder. JAMA Netw. Open. 2021; 4(7): e2117128. PubMed Abstract | Publisher Full Text
11. Jutras-Aswad D, Widlitz M, Scimeca MM: Treatment of buprenorphine precipitated withdrawal: A case report. Am. J. Addict. 2012; 21(5): 492–493. PubMed Abstract | Publisher Full Text
12. Wesson DR, Ling W: The Clinical Opiate Withdrawal Scale (COWS). J. Psychoactive Drugs. 35(2): 253–259. Publisher Full Text
13. Ahmadi J, Jahromi M5, Ghahremani D, et al.: Single high-dose buprenorphine for opioid craving during withdrawal. Trials. 2018; 19(1): 675. PubMed Abstract | Publisher Full Text
14. Greenwald MK, Johanson C-E, Moody DE, et al.: Effects of buprenorphine maintenance dose on mu-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. Neuropsychopharmacology. 2003; 28(11): 2000–2009. PubMed Abstract | Publisher Full Text
15. Foster B, Twycross R, Mihalyo M, et al.: Buprenorphine. J. Pain Symptom Manag. 2013; 45(5): 939–949. Publisher Full Text
16. Volkow ND, Blanco C: Fentanyl and other opioid use disorders: treatment and research needs. Am. J. Psychiatry. 2023; 180(6): 410–417. PubMed Abstract | Publisher Full Text
17. Koob GF: Neurobiology of Opioid Addiction: Opponent Process, Hyperkatifeia, and Negative Reinforcement. Biol. Psychiatry. 2020; 87(1): 44–53. PubMed Abstract | Publisher Full Text
18. Whitey SD, Sohler NL, Kunvis HV, et al.: Factors associated with complicated buprenorphine inductions. J. Subst. Abus. Treat. 2010; 39(1): 51–57. PubMed Abstract | Publisher Full Text
19. Rasmussen K: The role of the locus coeruleus and N-methyl-D-aspartic acid (NMDA) and AMPA receptors in opiate withdrawal. Neuropsychopharmacology. 1995; 13(4): 255–300. PubMed Abstract | Publisher Full Text
20. Dahan A: Opioid-induced respiratory effects: new data on buprenorphine. Palliat. Med. 2006; 20 Suppl 1: s3–s8. PubMed Abstract | Publisher Full Text
21. Varshneya NB, Hassanien SH, Holt MC, et al.: Respiratory depressant effects of fentanyl analogs are opioid receptor-mediated. Biochem Pharmacol Jan 2022; 195: 114805. PubMed Abstract | Publisher Full Text
22. Kumar KM, Grochow LB, Hausheer F: Unusual opioid withdrawal syndrome. A case-report. Lancet (London, England). 1987; 1(8535): 720–721. PubMed Abstract | Publisher Full Text
23. Bormann NL: High dose buprenorphine case report. OSF. April 2022. Publisher Full Text
Open Peer Review

Current Peer Review Status: ✔ ✔

Version 2

Reviewer Report 07 September 2023

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Neil B. Varshneya
Center for Drug Evaluation and Research, Food and Drug Administration, United States Department of Health and Human Services, Silver Spring, MD, USA

The authors satisfactorily addressed my comments.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pharmacology (fentanyl)

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 03 August 2023

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Ethan O Bryson
Icahn School of Medicine at Mount Sinai, New York, USA

This case report describes the use of high-dose buprenorphine in the treatment of buprenorphine-precipitated fentanyl withdrawal. Given the considerable increase in fentanyl-adulterated opioids and non-opioids as well as an increase in persons with opioid use disorder
specifically seeking out fentanyl this report is timely and appropriate.

There are some grammatical errors that need to be addressed prior to indexing, however, specifically:

"While use of ketamine has been suggested, conventional wisdom has been to utilize additional buprenorphine." Please specify that this is for withdrawal treatment to make this a complete thought.

"As such, the University of Iowa Institutional Review Board has deemed it exempt." please specify what is exempt from what.

"A 21-year-old partnered, unemployed Caucasian male with no known past medical history, a psychiatric history of attention deficit hyperactivity disorder and unspecified anxiety, with a pertinent family history of an opioid use disorder in his brother and both his mother and maternal aunt having unspecified addiction to pills per his father, who lived in an apartment with a roommate however was being evicted due to late rent payments, presented with his father to our medication for addiction treatment (MAT) walk-in clinic located at a primary care outreach clinic for assistance. discontinuing daily fentanyl use."

This sentence is too long, and the reader may wonder who (the father? the aunt? or the patient) was late on their rent. Only include details like this if they are relevant. Also, please add "with opioid use disorder" in the patients' history or, if not previously diagnosed, something to that effect as this is more relevant than the other information which is included.

Is the background of the case's history and progression described in sufficient detail?
Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Yes

Is the case presented with sufficient detail to be useful for other practitioners?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Addiction, Anesthesiology, Electroconvulsive therapy

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
Bormann et al. describe the successful management of buprenorphine-precipitated fentanyl withdrawal with high-dose buprenorphine and provide valuable insights into the management of opioid use disorder and the challenges associated with fentanyl exposure. This case report underscores the importance of individualized medication management in patients with opioid use disorder. The patient in this case had a history of opioid use disorder, including repeated fentanyl self-administration (with daily fentanyl use and dose escalation for 6 months), and developed severe withdrawal symptoms following non-medical, unsupervised self-treatment with buprenorphine/naloxone. The patient was subsequently managed in a medical setting with high doses of buprenorphine, which provided symptomatic relief in two hours intervals. The patient was eventually stabilized on a lower dose of buprenorphine and was discharged without exacerbation of symptoms or cravings. The report highlights the need for careful monitoring and tailored treatment plans for patients with opioid use disorder, especially in cases of fentanyl exposure. The report also underscores the importance of proper medication management for the acute onset of opioid withdrawal symptoms.

Overall, this is a well-written an interesting manuscript and is timely given the role of fentanyl and its analogs in the ongoing opioid crisis. In general, the data are clearly presented. However, there are a few minor issues that deserve attention:

1. The authors write: “When buprenorphine is taken after recent use of a full-agonist opioid, buprenorphine displaces the lower affinity molecule, causing a precipitated withdrawal.” I think there are instances in which buprenorphine, with high enough doses, would still precipitate withdrawal by reducing receptor activation when competing with mu-opioid receptor ligands of higher affinity and efficacy. You should consider rewriting this sentence as follows: “Buprenorphine can precipitate withdrawal by reducing receptor activation through competitive displacement of higher efficacy mu-opioid receptor ligands”. Thank you for citing my work here.

2. The authors write: “Further research is needed in this area, such as incorporation of imaging techniques to quantify changes in receptor occupancy with re-dosing of buprenorphine.” You should consider including additional research strategies from the following article and cite it here:

Volkow, N. D., & Blanco, C. (2023, Jun 1). Fentanyl and Other Opioid Use Disorders: Treatment and Research Needs. Am J Psychiatry, 180(6), 410-417.
The authors write: “However, with only three FDA approved medications for treatment of OUD and buprenorphine being the most readily accessible, attempts should be made to reassure the patient, optimize the initial exposure to buprenorphine even if use prompted a visit to the ED, and preserve or reestablish the patient’s confidence that this medication can provide benefit.” Please list the three FDA approved medications in parentheses following “only three FDA approved medications for treatment of OUD”.

3. The authors write: “A commonly voiced concern for escalating doses of buprenorphine is respiratory depression. Buprenorphine’s effect on ventilation has been shown to plateau with a ceiling effect, unlike fentanyl, which can lead to apnea with increasing dose.” You might consider citing the following study showing demonstrating the respiratory-depressant ceiling of buprenorphine vs fentanyl in animal models:

Varshneya, N. B., Hassanien, S. H., Holt, M. C., Stevens, D. L., Layle, N. K., Bassman, J. R., Iula, D. M., & Beardsley, P. M. (2022, Jan). Respiratory depressant effects of fentanyl analogs are opioid receptor-mediated. Biochem Pharmacol, 195, 114805. https://doi.org/10.1016/j.bcp.2021.114805

4. The authors write: “This report builds upon existing literature and should provide additional confidence for providers in the emergency setting to opt for treatment of precipitated withdrawal with high-dose buprenorphine.” I wouldn’t say that N = 1 exactly inspires confidence, so I suggest using different language here to state that further research is needed.

5. The authors write: “This report builds upon existing literature and should provide additional confidence for providers in the emergency setting to opt for treatment of precipitated withdrawal with high-dose buprenorphine.” I wouldn’t say that N = 1 exactly inspires confidence, so I suggest using different language here to state that further research is needed.

References
1. Volkow ND, Blanco C: Fentanyl and Other Opioid Use Disorders: Treatment and Research Needs. Am J Psychiatry. 2023; 180 (6): 410-417 PubMed Abstract | Publisher Full Text
2. Varshneya N, Hassanien S, Holt M, Stevens D, et al.: Respiratory depressant effects of fentanyl analogs are opioid receptor-mediated. Biochemical Pharmacology. 2022; 195. Publisher Full Text

Is the background of the case's history and progression described in sufficient detail? Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes? Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment? Yes

Is the case presented with sufficient detail to be useful for other practitioners? Yes
**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Pharmacology (fentanyl)

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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