



Spring greetings to all,

Some of you remember the days when precipitated withdrawal (PW) felt mostly theoretical. It was before fentanyl suffused the drug supply. At that time, it generally occurred with methadone to buprenorphine transitions or when the advice to wait for moderate withdrawal was not properly heeded. In the last several years, on-the-ground providers have been hearing and seeing more about buprenorphine inductions leading to precipitated withdrawal. This large study reports a remarkably low incidence of precipitated withdrawal and cites it as similar to the pre-fentanyl era. This is perhaps reassuring but also made me wonder –did anxiety bend my risk perception of PW, or is the risk actually this low in my patient population?

Hope you enjoy this little search for illumination,

Andrea

Title: Risk of precipitated withdrawal in the era of fentanyl remains low though is probably more than it used to be

Citation: D'Onofrio G, Hawk KF, Perrone J, et al. Incidence of Precipitated Withdrawal During a Multisite Emergency Department–Initiated Buprenorphine Clinical Trial in the Era of Fentanyl. *JAMA Netw Open*. 2023;6(3): e236108. doi:10.1001/jamanetworkopen.2023.6108

Link:

https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2802898?utm_source=For_The_Media&utm_medium=referral&utm_campaign=ftm_links&utm_term=033023

Funding/Conflicts:

NIDA and NIH Funded trial and investigators. Two of the five investigators received personal fees from companies unrelated to the study drugs.

METHODS

This was an observational cohort study conducted within a randomized controlled trial of weekly depot buprenorphine (CAM2038) versus daily sublingual (SL) buprenorphine given in the emergency dept (ED). It was

conducted in multiple sites across the US from June 30, 2020, to October 26, 2022.

Patients were included if they were 18yrs or older, had a opioid positive and methadone negative urine test and a COWS of 4 or more. Note that opioid positive included buprenorphine. Pregnant and admitted patients were excluded.

If COWS was 8 or more, patients received one of the two buprenorphine formulations while in the ED and were then observed for 2hours. Those given SL were then discharged with a buprenorphine (monoproduct) rx for 16mg daily. Those with COWS 4-7 were given either the depot injection (24mg, estimated equivalent to 16mg SL bup), or instructions for SL home induction with max dose 12mg day 1, and increase to 16mg thereafter.

Precipitated withdrawal (PW) was defined a priori as a COWS increase of ≥ 5 and requiring additional medication. Patients were followed up 7days later (86% retention).

MAIN RESULTS

1200 pts enrolled. (67% men, mean age 38yrs, primarily mix of white (56%) and black race (30%), 14% Latino, 50% unstable housing.) At initial tox testing, 75% of the pts were positive for fentanyl and 37% for buprenorphine (with some overlap in those groups). 85% had some other drug in addition to opioids. Alcohol testing was not reported. 27% reported injection use. Pts reported 5.3 uses in the 7days prior. Time since last use ranged from 8 to more than 24 hours.

PW occurred in 9 people, or 0.76% (0.35-1.43%) of the sample. The authors stated this is not different than with heroin or prescription opioids, citing a study reporting the risk to be <1% in that era.

CONCLUSION

In a clinical trial of people accessing the ED with mod-severe OUD and a COWS of 4 or more, in the era of widespread fentanyl supply, 0.76% of people induced with either sublingual or weekly injectable buprenorphine experienced PW. The risk was slightly higher among those using fentanyl and without recent buprenorphine exposure.

COMMENTARY

Is precipitated withdrawal really not more common than it used to be?

It seems more common! So, are we experiencing a kind of confirmation bias, i.e. we expect to see PW so our antennae are up for it in a way that they weren't 10yrs ago? Or is it an anxiety induced risk perception inflation? Or are we seeing more people with OUD, so it is the same percentage but of a larger pie? Or was it 0.25% before and now its 3times that (but still <1%). It could be a combination of these.

And/or did this study underestimate the likelihood of PW compared to what others see?

The authors do point out that the incidence in this trial is less than that reported in retrospective data sets. For example, in a smaller and much less systematic evaluation done in early 2020 from California Bridge the overall rate of PW was 1.6%, and *among the 44 people reporting fentanyl use* it was 4.5%.

Clearly, the type of opioid being used matters. In this study, 37% of patients had buprenorphine in the urine at initiation, and none of those pts had PW. If we remove them, the rate of PW is $9 / (1200 - 442) = 1.2\%$. If we remove people with opioids other than fentanyl, the rate is $7 / 364 = 1.9\%$.

What if the pharmacokinetics of the injectable medication given to half of the group mitigate risk of PW? In the worst-case scenario, where we say that is true, and all of the PW people were those who got SL bup, then for people using fentanyl only, the risk would have been $7 / 182 = 3.8\%$. Finally, note that the study used buprenorphine monoproduct- not buprenorphine combined with naloxone. Could that make the risk lower than in typical inductions?

Also, this is a study –providers may have been more careful about observing the COWS before induction, and of noting whether there was methadone in the urine (exclusionary). And recall, those with admission worthy psych and medical conditions were excluded.

Did the study give us any hints as to who is more likely to develop PW?

The number of events was small (n=9) so making definitive claims based on this data is sketchy, but a scan of Table 1 shows a few points of interest: Cases reported 6.8 days of use in the past 7, vs 5.3, and while none of the cases tested positive for buprenorphine, all were positive for fentanyl. BMI may impact PW² but BMIs were not reported.

Risk of PW is present, probably higher than it used to be, but remains low.

Patient and provider fear of PW can be a barrier to treatment. This study provides some reassurance that the vast majority of the time PW will not occur, and can help us talk to patients considering induction options. It suggests that in a person not requiring admission, testing positive for fentanyl and negative for buprenorphine, the risk of PW with a relatively standard induction method is probably about 2%, *maybe* up to 4%. And the risk is likely lower in someone who has recently taken buprenorphine, or in cases where fentanyl is not the only opioid being used.

References

1. Snyder, H., Chau, B., Kalmin, M. M., Speener, M., Campbell, A., Moulin, A., & Herring, A. A. (2023). High-Dose Buprenorphine Initiation in the Emergency Department Among Patients Using Fentanyl and Other Opioids. *JAMA network open*, 6(3), e231572. <https://doi.org/10.1001/jamanetworkopen.2023.1572>
2. Luba R, Jones J, Choi CJ, Comer S. Fentanyl withdrawal: Understanding symptom severity and exploring the role of body mass index on withdrawal symptoms and clearance. *Addiction*. 2023 Apr;118(4):719-726. doi: 10.1111/add.16100. Epub 2022 Dec 13. PMID: 36444486; PMCID: PMC9992259.