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October 2024

Hello Colleagues,

Precipitated withdrawal (PW) is a deterrent to initiating MOUD for both patients and providers. Experiencing PW can turn an ambivalent patient further from accepting medication, as can the need to experience withdrawal simply to start treatment. Having a medication at the ready, without the need to wait for withdrawal to ensue is of great appeal. In this multicenter study conducted in EDs, investigators enrolled patients with minimal to mild opioid withdrawal, i.e., COWS of 0-7, and gave them a dose of weekly injectable buprenorphine, CAM2038 (brand name Brixadi) at 24mg (16mg SL “equivalent”)- without prior sublingual dosing. Woah.

Why would the investigators believe this could be successful?... Onset of action. The authors state that CAM2038 blood levels rise more slowly than sublingual, “reaching 1.6 ng/mL in 4 hours compared with 5.6 ng/mL in sublingual dosing”. (SL dose unclear). With this they proceeded.

100 patients enrolled, 70 tested positive for fentanyl on a point of care (POC) test, and 7 patients experienced PW. All of these were in the positive fentanyl group. Five of the seven had a COWS 0-3, and two had a COWS of 4-7. This translates to a risk of PW in fentanyl-positive patients with a COWS 0-3 = 18% and COWS 4-7 = 5%. However, 39 of the 100 had buprenorphine in their initial urine.

It is wonderful to have a new potential approach to initiation, along with data that we can use to make decisions and counsel patients. But as we do that, it is important to consider the influence of the 39% with positive bup. Based on a previous study by this group¹ and knowledge of related pharmacology, we know that presence of BUP can mitigate the incidence of PW. So, while patients with fentanyl-positive POC fentanyl and COWS 4-7 had a 5% incidence of PW in this study, that is likely an underestimate among patients that are negative for buprenorphine. And, for those with fentanyl-positive POC and a COWS of 0-3, it seems worth waiting until more withdrawal symptoms set in, as the risk of PW is at least 18%.

Overall, this is great information and opens the door to treating people earlier in withdrawal with a long-acting medication absent sublingual lead-in. But given

that many patients had buprenorphine “on board,” these numbers should probably be considered underestimates of PW risk for patients who have not taken any buprenorphine in the last 4-5 days.

Please read on for a deeper dive.

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Title: Weekly extended-release injectable buprenorphine carries a relatively low risk of precipitated withdrawal (PW) when initiated during mild opioid withdrawal.

Citation: D’Onofrio G, Herring AA, Perrone J, et al. Extended-Release 7-Day Injectable Buprenorphine for Patients With Minimal to Mild Opioid Withdrawal. *JAMA Netw Open*. 2024;7(7):e2420702. doi:10.1001/jamanetworkopen.2024.20702

Link: <https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2820859>

Funding/Conflicts: Funded by NIH and NIDA. Braeburn provided study med. Two of the 16 authors, though not the primary, reported pharmaceutical funding, and two others grant funding from FORE Foundation for Opioid Response Efforts which was started by McKesson, a pharmaceutical distributor.

BACKGROUND

We need strategies to initiate people to MOUD without them having to experience withdrawal. In many cases, we are looking to do this in a durable fashion. The reported slower rate of rise with injectable weekly bup than sublingual (reaching 1.6 ng/mL in 4 hours compared with 5.6 ng/mL in sublingual dosing) may lend itself to initiation in people who have less than moderate withdrawal.

METHODS

This was a multicenter, single arm prospective 7day study conducted at four urban EDs across the US.

Included were English speaking patients who met DSM5 criteria for moderate to severe OUD, had a COWS 0-8 (minimal to mild withdrawal) and tested positive for opioids on point of care urine drug test. Those with a positive POC for fentanyl only were clinically assessed and included based on that assessment.

Patients were excluded if they had a methadone+ urine, presented with opioid overdose, were pregnant, actively suicidal, needed opioids for pain, required admission or had received MOUD in the last week.

Compensation gift cards were provided for enrollment and follow-up. Patients received a 24-mg dose of CAM2038, (equivalent to 16mg of buprenorphine SL daily). They were observed for 4hours after injection and referred to outpatient treatment as usual for each study site.

Primary outcomes were: 1) 5-point increase in COWs within 4hrs XR BUP injection OR 2) COWS ≥ 13 within four hours OR 3) precipitated withdrawal within one hour of XR BUP. Precipitated withdrawal was 'adjudicated by chart review among those with a 5point increase in the COWS.'

COWS was measured prior to and every 30min post injection up to four hours. Pain and tolerability were also evaluated. Craving was evaluated daily for 7days post injection by a text message. On day 7 telephone or in person assessment was conducted and included patient assessment, and report of overdose, engagement in care and udt for those seen in person.

Patients without data were assumed to have had precipitated withdrawal.

MAIN RESULTS

Of 102 eligible patients, 100 enrolled. 7 could not be contacted at 7day follow up (1 incarcerated, 6 no show but 3 contributed to ≥ 1 phone assessment). Initially the sample under-represented those with COWS 0-3 and so recruitment reopened to enrich the sample.

Average age was 36yrs, 28% female, 51% white, otherwise mostly a mix of black (35%) and Latino (13%). Sample was notable for 36% with current unstable housing, 79% Medicaid insured. **70% fentanyl positive. 39% buprenorphine**

positive. Stratification by COWS score showed the higher COWS group having more men, more unstable housing, less private insurance, more amphetamine and methamphetamine, but less cocaine or benzo positive urine, and more IV use.

Primary outcome by COWS and presence of fentanyl are presented here:

Table 2. Summary of Primary Outcomes by Subgroups of COWS Scores and Presence of Fentanyl

		Patients, No. (%) [95% CI] ^b			
COWS score ^a	Patients enrolled, No.	≥5-Point increase in COWS score within 4 h of extended-release buprenorphine	Transition to moderate or greater withdrawal within 4 h of extended-release buprenorphine ^c	Precipitated withdrawal within 1 h of extended-release buprenorphine	Precipitated withdrawal within 4 h of extended-release buprenorphine ^d
At baseline ^e					
4 to 7	63	4 (6.3) [1.7-15.5]	2 (3.2) [0.4-11.0]	1 (1.6) [0-8.5]	2 (3.2) [0.4-11.0]
0 to 3	37	6 (16.2) [6.2-32.0]	5 (13.5) [4.5-28.8]	1 (2.7) [0.1-14.2]	5 (13.5) [4.5-28.8]
With or without fentanyl					
4 to 7 Without	21	0 (0) [0-16.1]	0 (0) [0-16.1]	0 (0) [0-16.1]	0 (0) [0-16.1]
4 to 7 With	42	4 (9.5) [2.7-22.6]	2 (4.8) [0.6-16.2]	1 (2.4) [0.1-12.6]	2 (4.8) [0.6-16.2]
0 to 3 Without	9	0 (0) [0-33.6]	0 (0) [0-33.6]	0 (0) [0-33.6]	0 (0) [0-33.6]
0 to 3 With	28	6 (21.4) [8.3-41.0]	5 (17.9) [6.1-36.9]	1 (3.6) [0.1-18.4]	5 (17.9) [6.1-36.9]
Total	100	10 (10.0) [4.9-17.6]	7 (7.0) [2.9-13.9]	2 (2.0) [0.2-7.0]	7 (7.0) [2.9-13.9]

Abbreviations: COWS, Clinical Opiate Withdrawal Scale.

^a In this trial, scores range from 0 to 7, with higher scores indicating increasing withdrawal.

^b Calculated using the exact Clopper-Pearson method.²⁵

^c Includes COWS scores of 13 or greater.

^d Adjudicated by an expert panel (M.R.L. and S.L.W.).

^e One participant had a missing COWS score at baseline and is categorized using their screening value of 0.

Those without fentanyl had none of the primary outcomes. N=10 (10%) of the total sample, had a 5point+ increase in COWS within 4hrs. 7 of those progressed to a score of 13 or more and were judged to have precipitated withdrawal. All 7 of these were among the 70 pts who had tested positive for fentanyl. Those results are summarized here:

Incidence of PW among 70 patients positive for fentanyl by initial COWS score:

COWS	Incidence of PW	95% CI
0-3	N=5, 17.9%	6.1-36.9%
4-7	N=2, 4.8%	0.6-16.2%

Of interest, only 2/7 who had withdrawal experienced it within one hour of injection. And, 3 of 100 pts had a 5point cows increase but did not progress to PW.

Other outcomes:

Few patients received ancillary medication. Pain and erythema up to four hours post injection were minimal. At 7days, 11/93 reported tenderness and 7/93, pain. Medication was rated as mostly effective (0-5 completely effective to 0 completely ineffective). 52% rated 5, 25% rated 4, 4% rated 0. Six pts reported an overdose in the week prior to injection, 0 in the week following. 60% reported no opioids on any day that week, and higher cravings were associated with use. Among the ~40% who responded during the first week, cravings were median 10/100 throughout the week. Urine point of care at day 7 was available for 81 pts and of those 43 had any opioid, 22 methamp (vs 34/100 at baseline). 73% received OUD treatment on day 7, all of which was buprenorphine. 5 serious AEs, 2 precipitated withdrawal, 1 depression, 1 other mental health do, 1 cellulitis.

CONCLUSION

Weekly injectable buprenorphine has a reportedly slower onset of action than sublingual. When given to those with positive fentanyl POC and a COWS of 4-7 the risk of precipitated withdrawal was 5%. For those who tested fentanyl positive with COWS 0-3, the risk was much higher and probably not acceptable (18%). Given that patients with buprenorphine in their urine were included in this evaluation, these are probably underestimates of PW risk for those who have not taken buprenorphine in the last 4-5days. We need to know more about the incidence of PW in those who are not buprenorphine positive at initiation to better advise those patients.

COMMENTARY

In May 2023, this group [published a paper reviewed here](#) where patients were initiated using 8mg sublingual bup vs 24mg CAM 2038 but with COWS 8 or more. That data suggested that in a person testing positive for fentanyl and negative for buprenorphine, the risk of PW was about 2%, *maybe* up to 4%. (The PW rate

headlined in the paper was <1% because that was rate including people who were using opioids other than fentanyl or methadone, many of whom also had bup positive urine). In that study, no patient with buprenorphine presence experienced PW.

Looking at a group of people with milder withdrawal (COWS 0-7) was brave and helpful, but as with the first study, the numbers may be underestimating risk. Similar to that previous study, 39% of patients were positive for buprenorphine. Based on what we know from low-dose initiation and principles of pharmacology, having any buprenorphine present on opioid receptors probably mitigates the risk of PW. How much of an underestimate might this be? In the prior study, the risk of PW in those without bup was 63% higher than in the full sample (0.76% full sample vs 1.2% negative for bup).

Also, the use of POC testing presents some limitations – perhaps some fentanyl or methadone was missed - though this would tend to overestimate the PW risk. A false positive, on the other hand, would underestimate the PW risk.

Limitations notwithstanding, this study provides a new buprenorphine initiation strategy to consider, as well as some quantitative information for patients who do not want to go through a period of withdrawal as they start medication. And though we all want to lower barriers to treatment 1) keep in mind the potential impact of a precipitated withdrawal event on motivation to retry MOUD, 2) be clear with patients about the risk so that the 5% or more who do develop symptoms will trust us next time, and 3) have a plan to manage PW (ie, ED plan, way to obtain additional buprenorphine to treat the withdrawal).

REFERENCES

1. D'Onofrio, G., Hawk, K. F., Perrone, J., Walsh, S. L., Lofwall, M. R., Fiellin, D. A., & Herring, A. (2023). Incidence of Precipitated Withdrawal During a Multisite Emergency Department-Initiated Buprenorphine Clinical Trial in the Era of Fentanyl. *JAMA network open*, 6(3), e236108.
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