Evidence of Buprenorphine-precipitated Withdrawal in Persons Who Use Fentanyl

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Objectives: Buprenorphine can precipitate withdrawal in opioid-dependent persons with recent fentanyl use. However, the prevalence of this phenomenon is not clinically established. We sought to evaluate the incidence of buprenorphine-precipitated withdrawal in persons who use fentanyl.

Methods: We collected self-report data on opioid withdrawal symptoms after buprenorphine use, and, as a comparator, after methadone use, in 1679 individuals seeking treatment for opioid use disorder across 49 addiction treatment centers in the United States.

Results: The odds of developing severe withdrawal symptoms significantly increased when taking buprenorphine within 24 hours after fentanyl use (OR = 5.202, 95% CI = 1.979–13.675, $P = 0.001$), and within 24 to 48 hours after fentanyl use (OR = 3.352, 95% CI = 1.237–9.089, $P = 0.017$). As expected, patients did not report significantly higher rates of withdrawal when taking methadone after fentanyl use. Of those who waited less than 24 hours after fentanyl before using buprenorphine or methadone, 22.19% (n = 152 of 685) and 11.56% (n = 23 of 199), respectively, reported severe opioid withdrawal.

Conclusions: This study supports previous anecdotal reports of buprenorphine-precipitated withdrawal from fentanyl. The odds of withdrawal symptoms significantly increased when taking buprenorphine after recent (within 48 hours) fentanyl use, however, this relationship was not observed in persons taking methadone, suggesting that this effect is specific to buprenorphine. Further research is urgently needed to describe the pharmacokinetics of non-medical fentanyl use to improve buprenorphine inductions strategies.

Key Words: buprenorphine, fentanyl, methadone, opioid use disorder, precipitated withdrawal

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Opioid-related mortality in the United States is increasing due to the clandestine manufacture and sale of synthetic opioids such as fentanyl and fentanyl analogs.[1] Buprenorphine, 1 of 3 FDA-approved medications for opioid use disorder (OUD), is a high-affinity, mu-opioid receptor (MOR) partial agonist. When taken within 6 to 8 hours of a full MOR agonist (eg, fentanyl), buprenorphine can precipitate withdrawal by competitive displacement. Case studies have recently reported buprenorphine-precipitated withdrawal in patients using fentanyl despite 2 to 3 days of observed abstinence.[2–4] The aim of this study was to establish the prevalence of buprenorphine-precipitated withdrawal in persons entering OUD treatment across the United States. We hypothesized that shorter time since last fentanyl use would be associated with increased odds of experiencing severe withdrawal after buprenorphine administration.

METHODS

Sample and Assessments

This study sample consisted of patients entering treatment for OUD at one of 49 addiction treatment facilities across the United States. A third-party aggregation system (Trac9, NLW Partners, LLC, Lubbock, TX) collected these data to track treatment outcomes as part of routine admissions. Patients reported general demographic information. Additionally, individuals whose primary drug was ''opioids'' and who self-reported either ''probably'' or ''definitely'' using fentanyl before treatment were asked whether they had used an opioid treatment medication (buprenorphine or methadone as a comparator) after using fentanyl, the length of time between using the medication and fentanyl, and whether the medication alleviated or exacerbated their opioid withdrawal symptoms. The study team received only de-identified data and the Johns Hopkins University School of Medicine Institutional Review Board determined this study did not constitute human subjects research.

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Statistical Analyses

We calculated descriptive statistics for demographic and fentanyl-related questions (Appendix 1, http://links.lww.com/JAM/A305) and used binary logistic regression to compute the odds of experiencing severe opioid withdrawal symptoms from buprenorphine or methadone after fentanyl use. Analyses were performed with IBM SPSS 27.0.1.0 for Microsoft Windows 10 x64 (IBM, Armonk, NY). Figures were generated with GraphPad Prism 9.1.1 (225) for Microsoft Windows 10 x64 (GraphPad Software, San Diego, CA).

RESULTS

Patient Demographics

In this cohort of persons entering treatment for OUD (N = 1679), 69.3% (n = 1163) of patients reported either ''probably'' (10.7%; n = 180) or ''definitely'' (58.5%; n = 983) using fentanyl before an opioid treatment. Patients were a mean (± SD) age of 30.77 (± 10.23) years, 70.6% (n = 821) male, and 80.4% (n = 935) White. Additionally, 43.9% (n = 510) reported their urine sample tested positive for fentanyl at treatment admission.

Survey Results

Overall, 29.1% (n = 339/685) of patients reporting fentanyl use took buprenorphine within 24 hours of fentanyl and 36.5% (n = 250/685) of them reported experiencing severe opioid withdrawal (Table 1). In contrast, 11.6% (n = 135/200) of patients reporting fentanyl use took methadone within 24 hours of fentanyl and only 15% (n = 30/200) experienced severe withdrawal. Moreover, fewer patients reported that buprenorphine (38.4%; n = 68/177) completely alleviated opioid withdrawal relative to persons utilizing methadone (44.3%; n = 43/97). Finally, 41.5% (n = 483/1163) of patients knew someone who used fentanyl and experienced precipitated withdrawal symptoms after taking buprenorphine.

TABLE 1. Results for Patients Who Reported ''Opioids'' as Their Primary Drug of Choice and Who Reported ''Probably'' or ''Definitely'' Using Fentanyl

	Buprenorphine* (N = 1163)		Methadone† (N = 1163)	
After Using Fentanyl, What Was the Shortest Amount of Time You Waited to Use Buprenorphine or Methadone?	**n**	**%**	**n**	**%**
Within 24 h of using fentanyl	339	29.1	135	11.6
Within 48 h of using fentanyl	160	13.8	22	1.9
Within 72 h of using fentanyl	97	8.3	21	1.8
Within 1 wk of using fentanyl	52	4.5	13	1.1
Within 1 mo of using fentanyl	37	3.2	8	0.7
Within 1 yr of using fentanyl	57	4.9	29	2.5
Never	421	36.2	935	80.4

	Buprenorphine* (N = 685)		Methadone† (N = 200)	
After Fentanyl Use, Have You Experienced Withdrawal Symptoms When Taking Buprenorphine or Methadone?	**n**	**%**	**n**	**%**
No opioid withdrawal symptoms	177	25.8	97	48.5
Mild opioid withdrawal symptoms	122	17.8	44	22.0
Moderate opioid withdrawal symptoms	136	19.9	29	14.5
Severe opioid withdrawal symptoms	250	36.5	30	15.0

	Buprenorphine* (N = 177)		Methadone† (N = 97)	
Did Buprenorphine or Methadone Decrease Your Withdrawal Symptoms After Fentanyl Use?	**n**	**%**	**n**	**%**
No decrease	29	16.4	18	18.6
Mild decrease	23	13.0	6	6.2
Moderate decrease	57	32.2	30	30.9
Complete alleviation of withdrawal symptoms	68	38.4	43	44.3

	Buprenorphine* (N = 685)			Methadone† (N = 199)		
Odds of Severe Opioid Withdrawal Symptoms After Fentanyl Use	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Within 24 h of using fentanyl	5.202	1.979–13.675	0.001	0.616	0.117–3.247	0.568
Within 48 h of using fentanyl	3.352	1.237–9.089	0.017	0.300	0.035–2.606	0.275
Within 72 h of using fentanyl	2.222	0.780–6.329	0.135	0.316	0.036–2.750	0.297
Within 1 wk of using fentanyl	2.133	0.687–6.620	0.190	0.250	0.019–3.342	0.295

*Buprenorphine (also known as Belbuca, Buprenex, Butrans, Probuphine, Sublocade, Suboxone, and Zubsolv).
†Methadone (also known as Methadose).

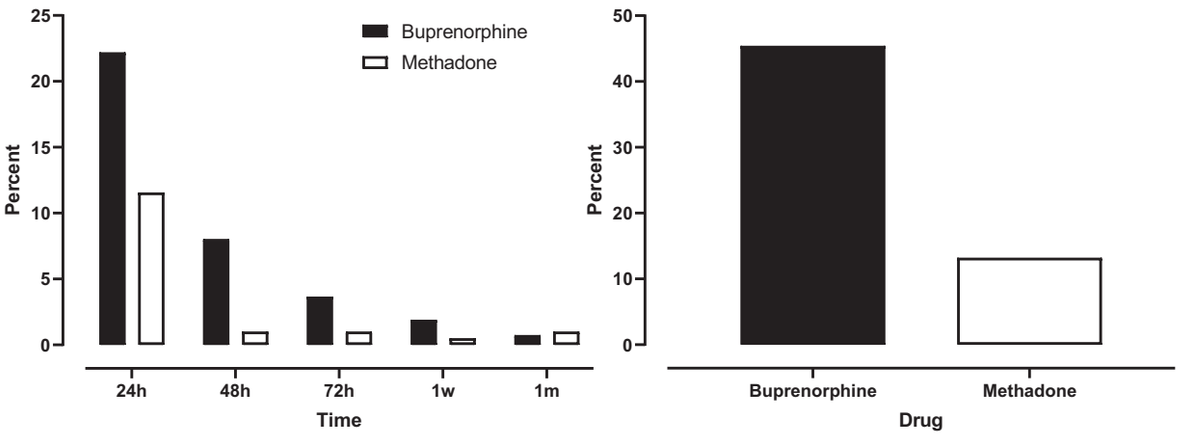

FIGURE 1. (Left), Percentage of patients who endorsed ''probably'' or ''definitely'' using fentanyl and who reported severe withdrawal after use of buprenorphine (n = 250) or methadone (n = 30) as a function of the shortest amount of time endorsed (24, 48, or 72 hours, 1 week, and 1 month) after fentanyl use. (Right), Percentage of patients who endorsed ''probably'' or ''definitely'' using fentanyl and who reported severe withdrawal after use of buprenorphine (n = 69) or methadone (n = 20) after taking fentanyl; only patients with experience with both buprenorphine and methadone after fentanyl use were included this analysis.

Odds of Severe Opioid Withdrawal

Individuals who used buprenorphine within 24 hours of fentanyl had the highest odds (OR = 5.202, 95% CI = 1.979–13.675, $P = 0.001$) of developing severe withdrawal followed by those who used buprenorphine within 48 hours of fentanyl (OR = 3.352, 95% CI = 1.237–9.089, $P = 0.017$) (Table 1). Patients who used methadone after fentanyl did not have increased odds of severe withdrawal within 24 (OR = 0.616, 95% CI = 0.117–3.247, $P = 0.568$) or 48 (OR = 0.300, 95% CI = 0.035–2.606, $P = 0.275$) hours. There was no increase in odds of severe withdrawal when taking buprenorphine or methadone within 72 hours to 1 week after fentanyl use.

Figure 1 shows the percentage of patients who reported severe withdrawal after buprenorphine (n = 250) or methadone (n = 30) use, as a function of the shortest amount of time (less than 24, 48, or 72 hours, 1 week, 1 month) after taking fentanyl. Of those who waited less than 24 hours after taking fentanyl before using buprenorphine or methadone, 22.19% (n = 152/685) and 11.56% (n = 23/199), respectively, reported severe opioid withdrawal. Of those who waited less than 48 hours, 8.03% (n = 55/685) and 1.01% (n = 2/199), respectively, developed severe withdrawal. In addition, among a subset of patients who endorsed experience with both buprenorphine and methadone after fentanyl use (n = 152), 45.4% (n = 69) reported severe opioid withdrawal symptoms after taking buprenorphine compared to 13.2% (n = 20) for methadone.

DISCUSSION

In this cohort of 1163 individuals entering addiction treatment with self-reported fentanyl use, buprenorphine preceded severe withdrawal symptoms in more than a third of patients and taking buprenorphine within 24 to 48 hours of fentanyl significantly increased the odds of severe withdrawal. In contrast, those who used methadone after fentanyl reported a lower incidence of severe withdrawal; this was not associated with time since last fentanyl use.

These results support emerging anecdotal evidence that individuals with prolonged fentanyl use face an increased risk of severe withdrawal from buprenorphine.[2,5,6] Fentanyl, a full MOR agonist, accumulates in adipose with repeated use and can take weeks for renal clearance when used by persons with OUD.[7] Buprenorphine, a high-affinity MOR partial agonist can competitively displace fentanyl from the receptor binding pocket resulting in precipitated withdrawal. This interaction may contribute to the increased incidence of buprenorphine-precipitated withdrawal within 48 hours of fentanyl use, even when clinicians follow conventional buprenorphine-induction procedures.[8] Future pharmacokinetic studies of fentanyl and other substances found in the illicit drug supply may further elucidate this mechanism. We hypothesize that the individuals who experienced severe withdrawal after methadone may have reported poor management of their withdrawal related to insufficient MOR agonism, since initial doses of methadone are limited to 30 mg in the outpatient setting and since methadone takes >1 week of daily dosing to reach steady state concentrations that consistently suppress withdrawal.[8]

Fentanyl and its analogs are rapidly spreading across North America, adulterating and replacing heroin in non-medical drug markets.[9] Fentanyl and other synthetic opioids may be a common terminus for these markets; given supply-side factors such as the availability of precursors, ease of production, and access to online marketing and distribution, fentanyl is likely here to stay.[10] This could have dire consequence if patients decline buprenorphine out of fear of precipitated withdrawal or if clinicians are dissuaded from prescribing buprenorphine.[11]

Overall, this study expands upon a small number of case reports of buprenorphine-precipitated withdrawal after fentanyl use despite extended (24–48 hours) periods of fentanyl abstinence. Further research is urgently needed to identify patients at risk, develop effective treatments for fentanyl-related precipitated withdrawal, and to compare conventional buprenorphine induction procedures to novel,

low-dose (also known as ''micro-dosing'') inductions to avoid precipitated withdrawal.[12,13]

CONCLUSIONS

Persons who use buprenorphine within 24 to 48 hours of fentanyl use are at significantly greater risk of developing severe opioid withdrawal symptoms relative to those who wait >48 hours.

REFERENCES

1. Centers for Disease Control and Prevention. *Multiple Cause of Death 1999-2019 on CDC WONDER Online Database, released in 2020. Data are from the Multiple Cause of Death Files, 1999-2019, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program.* National Center for Health Statistics; 2020.
2. Antoine D, Huhn AS, Strain EC, et al. Method for successfully inducting individuals who use illicit fentanyl onto buprenorphine/naloxone. *Am J Addict*. 2020;30:83–87.
3. Johnson R. Buprenorphine: How to use it right. *Drug Alcohol Depend*. 2003;70(2):S59–S77.
4. Moe J, O'Sullivan F, Hohl CM, et al. Short communication: Systematic review on effectiveness of micro-induction approaches to buprenorphine initiation. *Addict Behav*. 2021;114:106740.
5. Silverstein SM, Daniulaityte R, Martins SS, et al. ''Everything is not right anymore'': Buprenorphine experiences in an era of illicit fentanyl. *Int J Drug Policy*. 2019;74:76–83.
6. Bisaga A. What should clinicians do as fentanyl replaces heroin? *Addiction*. 2019;114(5):782–783.
7. Huhn AS, Hobelmann JG, Oyler GA, et al. Protracted renal clearance of fentanyl in persons with opioid use disorder. *Drug Alcohol Depend*. 2020;214:108147.
8. Rastegar DA, Fingerhood MI, American Society of Addiction Medicine. *The American Society of Addiction Medicine Handbook of Addiction Medicine*. Second ed. Oxford University Press; 2020, 464.
9. Shover CL, Falasinnu TO, Dwyer CL, et al. Steep increases in fentanyl-related mortality west of the Mississippi River: Recent evidence from county and state surveillance. *Drug Alcohol Depend*. 2020;216:108314.
10. Pardo B, Taylor J, Caulkins J, et al. The dawn of a new synthetic opioid era: the need for innovative interventions. *Addiction*. 2021;116(6):1304–1312.
11. Practice Guidelines for the Administration of Buprenorphine for Treating Opioid Use Disorder (Federal Register) (2021).
12. Button D, Hartley J, Robbins J, et al. Low-dose buprenorphine initiation in hospitalized adults with opioid use disorder: A retrospective cohort analysis. *J Addict Med*. 2021. doi:10.1097/ADM.0000000000000864.
13. Thakrar AP, Jablonski L, Ratner J, et al. Micro-dosing intravenous buprenorphine to rapidly transition from full opioid agonists. *J Addict Med*. 2021. doi:10.1097/ADM.0000000000000838.