Impact of Fentanyl Use on Buprenorphine Treatment Retention and Opioid Abstinence

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Objectives: There has been a rapid increase in the presence of illicitly manufactured fentanyl in the heroin drug supply. Buprenorphine is an effective treatment for heroin and prescription opioid use disorder; however, little is known about treatment outcomes among people using fentanyl. We compared 6-month treatment retention and opioid abstinence among people initiating buprenorphine treatment who had toxicology positive for heroin compared to fentanyl at baseline.

Methods: Retrospective cohort study of 251 adult patients initiating office-based buprenorphine treatment who had available toxicology testing across an academic health system between August 2016 and July 2017. Exposure was assessed at baseline before initiating buprenorphine and was categorized as negative toxicology (n = 184) versus fentanyl positive toxicology (n = 48) versus heroin positive toxicology (n = 19).

Results: Six-month treatment retention rates were not different between the fentanyl positive and heroin positive groups [38% (n = 18) vs 47% (n = 9); $P = 0.58$], or between the fentanyl positive and the negative toxicology group [38% (n = 18) vs 51% (n = 93); $P = 0.14$]. Opioid abstinence at 6 months among those who had testing did not differ between the fentanyl positive and the heroin positive group [55% (n = 6) vs 60% (n = 6); $P = 0.99$]. The fentanyl positive group had a lower abstinence rate at 6 months compared to those with negative toxicology at baseline [55% (n = 6) vs 93% (n = 63); $P = 0.004$]. Mean initial buprenophine dosage did not differ between groups.

Conclusions: Buprenorphine treatment retention and abstinence among those retained in treatment is not worse between people using fentanyl compared to heroin at treatment initiation. Both groups have lower abstinence rates at 6 months compared to individuals with negative toxicology at baseline. These findings suggest that people exposed to fentanyl still benefit from buprenorphine treatment.

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BACKGROUND

Since 2014, the prevalence of illicitly manufactured fentanyl contamination in the drug supply has been increasing. In Massachusetts, in the first quarter of 2014 autopsies determined 41% of opioid-related deaths involved fentanyl, with 22% fentanyl only and 19% involving heroin as well. Within 2 years, the percent of opioid-related deaths involving fentanyl had increased to 65%, 50% fentanyl only and 15% heroin plus fentanyl (Massachusetts Department of Public Health, 2018). Nationally there has been a 5-fold increase in overdose deaths due to synthetic opioids, driven predominantly by illicitly manufactured fentanyl and related analogues (Rudd et al., 2016; CDC, 2017; O'Donnell et al., 2017). From 2016 to 2017, among a national sample of 11,045 opioid overdose deaths 20.6% of decedents tested positive for any fentanyl analog (O'Donnell et al., 2018). Because of fentanyl's higher binding affinity as compared to other mu-opioid receptor agonists, theoretical concern has been raised regarding buprenorphine's ability to competitively bind to the mu-opioid receptor in the setting of fentanyl use. There is little data exploring the effectiveness of buprenorphine for fentanyl use. A qualitative study among people who use drugs in Rhode Island who were exposed to fentanyl suggested that opioid agonist therapy was still effective (Carroll et al., 2017). Animal studies have demonstrated that pretreatment with buprenorphine before fentanyl infusion does diminish but not completely block the effects of fentanyl (Kögel et al., 2005).

Buprenorphine is a partial mu-opioid receptor agonist with high binding affinity and slow dissociation from the receptor (Ambros, 2016). These unique properties are harnessed in its use as a treatment for prescription opioid or heroin use disorder. Observational studies have repeatedly demonstrated that buprenorphine access is associated with a reduction in overdose death rates (Carrieri et al., 2006; Schwartz et al., 2013; Sordo et al., 2017). As a treatment for prescription opioid or heroin use disorder, buprenorphine improves treatment retention, remission from opioid use disorder, and abstinence compared to non-medication treatment or antagonist treatment (Kakko et al., 2003; Weiss et al.,

2015; Lee et al., 2018). However, no data exists to explore the impact of fentanyl use on buprenorphine's effectiveness as a treatment for opioid use disorder. Amid the current crisis of opioid-related deaths driven increasingly by illicitly manufactured fentanyl, further study of treatment outcomes for buprenorphine among individuals using fentanyl is critically needed.

To examine whether fentanyl use is associated with buprenorphine treatment outcomes, we compared subsequent treatment retention and opioid use among patients initiating treatment with buprenorphine who had either fentanyl positive or negative toxicology at baseline. We hypothesized that compared to individuals with negative toxicology or toxicology positive for heroin, patients with fentanyl positive toxicology would have poorer treatment retention and higher rates of subsequent opioid use.

METHODS

Study Design

We conducted a retrospective cohort study of adult patients initiating office-based buprenorphine treatment across a large academic health system based on oral fluid toxicology data between August 2016 and January 31, 2018. Oral fluid toxicology testing was performed using liquid chromatography-tandem mass spectrometry (Flood et al., 2016).

Study Participants

We identified all adult patients with an oral fluid toxicology test between August 15, 2016, when fentanyl was added to the testing panel, and July 31, 2017, to ensure each subject had a complete 6-month follow-up period. We restricted our sample to those who had a buprenorphine outpatient prescription (excluding emergency department prescriptions) within 30 days after testing but did not have an outpatient buprenorphine prescription in the 90 days before treatment initiation to identify a newly started treatment episode. At baseline, participants were divided into 3 groups: (1) individuals who were fentanyl positive; (2) individuals who were positive for morphine, codeine, or 6-monoacetylmorphine but not fentanyl; and (3) individuals who had negative toxicology based on the testing result. Fentanyl exposed individuals were defined as those with any oral fluid toxicology positive for fentanyl at baseline. We used morphine, codeine, or 6-monoacetylmorphine as a proxy for heroin use because of the short half-life of 6-monoacetylmorphine alone and its rapid metabolism to morphine and codeine. Cutoffs used for a negative test were less than 2.0 ng/mL for 6-monoacetylmorphine (6-MAM) and fentanyl and less than 4.0 ng/mL for codeine and morphine (Flood et al., 2016). We did not examine toxicology outcomes for prescription opioids, including oxycodone, hydromorphone, and hydrocodone, as previous research has demonstrated worse treatment outcomes among individuals using heroin compared to individuals using prescription opioids, thus we would expect that individuals exclusively using prescription opioids would have better treatment outcomes than individuals using fentanyl (Weiss et al., 2015).

Outcomes

Our 2 primary outcomes were treatment retention at 6 months after initial toxicology testing and opioid abstinence at 6 months. In addition, we examined treatment retention and abstinence at 1 and 3 months. All retention data were obtained from the electronic health record (EHR). Retention was defined based on previous studies of office-based buprenorphine treatment as having had either a medical visit or an active buprenorphine prescription in the EHR (Cunningham et al., 2013a,b). Abstinence was defined as having tested negative for 6-MAM, codeine, morphine and fentanyl at each follow-up. The time frame for 1 month was defined as a 15-day window before or after 30 days from treatment initiation; 3 months was defined as a 30-day window before or after 90 days after treatment initiation; and 6 months was defined as a 30-day window before or after 180 days after treatment initiation.

Analysis

We used ANOVA and chi-square tests to compare baseline patient characteristics among the 3 study groups. We used Fisher's exact tests to compare outcomes between patients positive for fentanyl at baseline to the other 2 study groups at 1, 3, and 6-month follow-up. We limited the analysis to those with toxicology samples available at follow-up for the abstinence outcome. We used 2-sample *t* tests and chi-square tests to compare patient characteristics between those with and without toxicology samples at follow-up. In a sensitivity analysis, we included all subjects in the analysis assuming those without toxicology samples as non-abstinent. Our primary focus was to compare the fentanyl positive group to the other 2 study groups; therefore, a 2-sided *P* value of 0.025 or less was considered as statistical significance. All analyses were conducted using SAS

TABLE 1. Baseline Patient Characteristics

	Fentanyl Positive	Other Positive*	All Negative	
	N = 48	N = 19	N = 184	*P*
Age, mean (SD)	37.8 (10.5)	40.4 (13.9)	40.3 (11.4)	0.40
Male, N (%)	35 (72.9)	15 (78.9)	129 (70.1)	0.69
Race White, N (%)	44 (91.7)	16 (84.2)	160 (87.0)	0.61
Marital status, N (%)				0.25
Single	40 (83.3)	12 (63.2)	131 (71.2)	
Married/partnered	6 (12.5)	3 (15.8)	25 (13.6)	
Other	2 (4.2)	4 (21.1)	28 (15.2)	

*Tested positive for 6-MAM, morphine, or codeine but not fentanyl.

TABLE 2. Outcomes at 1, 3, and 6-Month Follow-up

Outcome	Month	Fentanyl Positive N = 48 (%)	Other Positive* N = 19 (%)	P^1	All Negative N = 184 (%)	P^2
Retention	1	33 (68.8)	17 (89.5)	0.12	144 (78.3)	0.18
	3	26 (54.2)	13 (68.4)	0.41	133 (72.3)	0.023
	6	18 (37.5)	9 (47.4)	0.58	93 (50.5)	0.14
Abstinence among tested[3]	1	13 (54.2)	8 (50.0)	0.99	102 (95.3)	<0.001
	3	9 (42.9)	8 (80.0)	0.068	102 (92.7)	<0.001
	6	6 (54.5)	6 (60.0)	0.99	63 (92.6)	0.004

*Tested positive for 6-MAM, morphine, or codeine but not fentanyl.
[1]Fentanyl Positive group compared to Other Positive group.
[2]Fentanyl Positive group compared to All Negative group.
[3]Testing availability varied by group with 22.6% of fentanyl positive individuals having testing at 6 months, 52.6% of the other opioid positive, and 38.8% of the all negative group.

version 9.4 (Cary, NC). This study was approved by the Partners Healthcare Institutional Review Board.

RESULTS

There were 251 patients who met eligibility criteria for inclusion, 48 tested positive for fentanyl, 19 tested positive for 6-MAM, morphine, or codeine but not fentanyl, and 184 tested negative at baseline. The sample was predominantly male and non-Hispanic white. Individuals with fentanyl positive toxicology were more likely to be single and younger with a mean age of 38 compared to 40 for the other opioid and negative toxicology groups; however, these findings were not significant (Table 1).

For our primary outcome of treatment retention at 6 months, there was no significant difference between individuals who were positive for fentanyl at baseline compared to individuals who were positive for heroin at baseline, with 38% (n = 18) and 47% (n = 9) retained, respectively ($P = 0.58$) (Table 2). Retention rates were also not significantly different between the group that had negative toxicology at baseline compared to those who were fentanyl positive at 6 months [51% (n = 93) vs 38% (n = 18); $P = 0.14$].

Our other primary outcome of opioid abstinence at 6 months could only be assessed among those with testing, which essentially limited this outcome to the subset of patients who were retained in care. There were no significant differences in patient characteristics between those with and without testing during the follow-up period. Among those with testing, there was no difference in abstinence between the fentanyl positive group and the heroin positive group [55% (n = 6) vs 60% (n = 6); $P = 0.99$]. The fentanyl positive group did have a significantly lower abstinence rate at 6 months compared to those with negative toxicology at baseline [55% (n = 6) vs 93% (n = 63); $P = 0.004$] (Fig. 1) The results were similar from a sensitivity analysis where those without testing were assumed as non-abstinent.

Mean initial buprenorphine dosage did not differ between the 3 groups. At initiation the mean dosage of buprenorphine in the fentanyl positive group was 13.7 mg/day compared to 13.9 mg/day in the heroin positive group and 13.4 mg/day in the negative toxicology group. At six months the mean dosages were 15, 18.3, and 15.8 mg/day in the fentanyl, heroin, and negative toxicology groups respectively (Table 3).

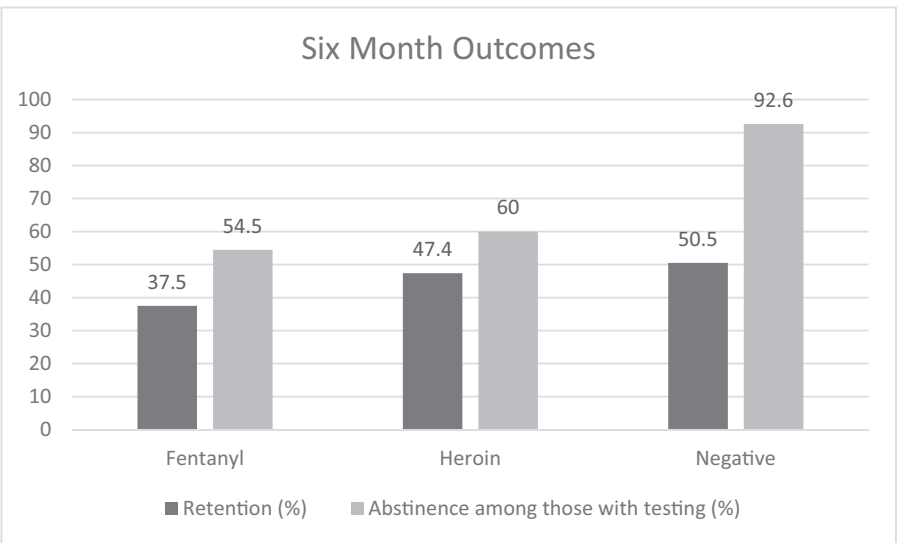

FIGURE 1. Retention and opioid abstinence among those retained at six-month follow-up.

TABLE 3. Buprenorphine Dosage

Buprenorphine Dose mg/day, N, Mean (SD)			
Month	**Fentanyl Positive**	**Other Positive***	**All Negative**
Baseline	48, 13.7 (6.8)	18, 13.9 (5.9)	181, 13.4 (5.5)
1	25, 16.8 (4.6)	17, 17.4 (5.8)	122, 14.8 (6.1)
3	17, 16.7 (4.7)	10, 19.6 (5.5)	109, 15.8 (5.9)
6	12, 15.0 (6.2)	7, 18.3 (6.0)	70, 15.8 (6.3)

*Tested positive for 6-MAM, morphine, or codeine but not fentanyl.

DISCUSSION

In our study of patients initiating treatment with buprenorphine in a large urban health care system, we found that abstinence and treatment retention rates were not significantly different between individuals who were exposed to fentanyl compared to those who were exposed to heroin at baseline. Both the fentanyl and heroin positive group had worse abstinence rates at all follow-up intervals compared to individuals with negative toxicology at baseline. At 6 months 38% of those in the fentanyl exposed group were still retained in treatment and among those with testing 55% were abstinent. These results suggest that fentanyl exposed individuals do not have worse treatment outcomes than heroin exposed individuals and are still able to receive notable benefit from buprenorphine treatment. Although this study was limited to buprenorphine treatment, previous studies have demonstrated that treatment retention and abstinence are increased among individuals with opioid use disorder treated with buprenorphine compared to behavioral treatment alone (Kakko et al., 2003).

We limited our analyses to individuals positive for fentanyl or heroin, but not prescription opioids intentionally. While individuals may knowingly choose to use either prescription opioids or heroin, use of fentanyl is thought to be a result of illicit drug supply contamination. Prior research suggests that people who use drugs have attempted to develop methods for discerning whether fentanyl is present as a safety mechanism, suggesting the acquisition of fentanyl is random, rather than something that is being sought out (Ciccarone et al., 2017).

It is important to note that most patients had baseline toxicology that was negative for fentanyl and heroin. This occurred despite our attempts to limit the sample to patients without a buprenorphine prescription in the preceding 90 days and to exclude patients who had an initial prescription identified in the emergency department or inpatient setting, as these individuals may have been previously prescribed buprenorphine outside of our system. This finding suggests some of these individuals were not actually initiating treatment and may have been previously receiving buprenorphine elsewhere or using non-prescribed buprenorphine. Individuals who initiate office-based buprenorphine treatment after a period of using non-prescribed buprenorphine have been shown to have superior treatment retention (Cunningham et al., 2013a,b). Another possibility is that individuals with negative toxicology at baseline had less severe opioid use disorder and may not have been using daily at the time of treatment initiation. This may have affected our results, as the 2 drug positive groups may have included individuals with more severe opioid use disorder or individuals without prior buprenorphine experience. In addition, if the negative toxicology group included individuals who had already initiated treatment, the drug positive groups may have been partially confounded with early treatment non-response. This could explain why these individuals had worse abstinence rates compared to individuals who were abstinent at the start of treatment. Treatment retention rates were lower in this study than in prior naturalistic studies of office-based buprenorphine treatment; however, abstinence rates in the negative toxicology group were significantly higher (Soeffing et al., 2009; Bhatraju et al., 2017). The reasons for these differences are not clear. Initial buprenorphine dosages were not different between the 3 groups, however it may be that individuals using fentanyl require higher buprenorphine dosages. If patients were not able to achieve adequate withdrawal and craving control during treatment initiation, they may have fallen out of care early on. Further study is needed to identify practice, provider, and patient specific factors that contribute to retention and abstinence in the era of illicitly manufactured fentanyl.

The lower abstinence rates for those with positive toxicology at baseline highlight the ongoing challenges experienced by a subset of individuals with opioid use disorder yet at the same time the importance of continued treatment engagement. Despite high rates of drop out in the fentanyl positive group, continued care resulted in 55% of those retained being abstinent after 6 months. This is an important reminder that the response to positive toxicology should be further engagement, rather than termination from treatment. In addition, retention in buprenorphine treatment may have value and offer overdose protection even if an individual is not abstinent from other opioids.

There are important limitations to this study. First it is based on review of EHR and toxicology data without direct patient contact, so the nuances of patient experience, prior treatment experiences, or self-report are lacking. In addition, although our oral fluid toxicology testing has high sensitivity and specificity and is collected under direct observation making false-positive results unlikely, false-negative results are possible in the context of poor collection techniques which could have contributed to the large number of negative tests. Second, our sample size for the fentanyl and heroin positive groups was relatively small. Third, for our abstinence data more than half of the patients did not have any testing in the reference timeframes, which limited our sample size and our findings. However, we did conduct a sensitivity analysis assuming those without testing were not abstinent and the between-group differences were similar. Fourth, the finding that most patients had baseline testing that was negative for heroin or fentanyl was surprising and needs further exploration through chart review. Lastly, this is a non-randomized study and individuals in the fentanyl exposed group differed on key variables which could have affected outcomes, although we attempted to control for these differences in a logistic regression analysis.

CONCLUSIONS

Among patients with opioid use disorder initiating office-based buprenorphine treatment in Massachusetts, people with positive fentanyl toxicology have similar six-month abstinence and treatment retention rates compared to those with heroin positive toxicology at baseline. People who use

illicitly manufactured fentanyl benefit from buprenorphine treatment and should be engaged in care.

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