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Preference for drugs containing fentanyl from a cross-sectional survey of people who use illicit opioids in three United States cities

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ABSTRACT

Background: Death from fentanyl-related overdose is now a leading cause of mortality among US adults. We sought to characterize fentanyl preference among street-based people who use drugs (PWUD).

Methods: Cross-sectional surveys were administered to PWUD (N = 308) who illicitly used heroin or prescription opioids in the prior six months. Recruitment occurred in 2017 in three US east coast cities with high overdose mortality: Baltimore, Boston, and Providence. Our main outcome was preference for fentanyl (yes/no); exposures included sociodemographics, drug use, and overdose history. Pearson's $\chi 2$, Shapiro-Wilk-Mann rank-sum tests, and tiered log-binomial regression determined sociodemographic and exposure-related factors associated with fentanyl preference.

Results: Preference for nonmedical use of fentanyl was reported by 27% (n = 83) of the sample. Fentanyl preference was associated with non-Hispanic white race (adjusted risk ratio (ARR) = 1.68, 95% confidence interval (CI):1.18–2.40), daily illicit drug use (aRR = 2.2, CI:1.71–2.87), and overdose ≥1 year ago (aRR = 1.33, CI:1.18–1.50). Age (in decades; aRR = 0.77, CI:0.61–0.98) and overdose < 1 year ago (aRR = 0.92, CI:0.87–0.97) were associated with a decreased likelihood of preference. In our model excluding sociodemographics, initiating opioid use with non-prescribed opioids was associated with fentanyl preference (aRR = 1.48, CI:1.26-1.73).

Conclusion: In three cities with high levels of opioid use and overdose, a quarter of street based PWUD reported preferring fentanyl. An opioid use age cohort effect and disproportionate access to prescription opioids by race could be contributing to preference. Frequency of opioid use, not route of administration, was associated with preference. Our data demonstrate the need to consider preferences for fentanyl when targeting services and interventions for PWUD.

1. Introduction

Drug overdose deaths in the United States (US) increased 9% to 70,237 in 2017 over the previous year, resulting in a second consecutive drop in overall average life expectancy. (Kochanek et al., 2017; Xu et al., 2016) Overdose mortality in the US is driven by interwoven epidemics: an ongoing prescription opioid misuse and heroin crisis and the recent proliferation of deaths attributed to synthetic opioids. (Ciccarone, 2017) Deaths from synthetic opioids, predominantly illicitly manufactured fentanyl (IMF) and its analogues, climbed from 3,105 in 2013 to 20,145 in 2016. (Centers for Disease Control, 2018; Drug Enforcement Administration: Strategic Intelligence Section, 2018) While the US continues to have the highest drug-related mortality rate in the world, opioid overdose deaths are also rising in Canada, Australia, and several European Union countries. (Harm Reduction International, 2016; Jannetto et al., 2019; Perraudin, 2018; Roxburgh et al., 2013)

Fentanyl, an opioid clinically indicated for pain management, is approximately 50–100 times more potent than morphine. (Drug Enforcement Administration, 2016) By weight, IMF is many orders of magnitude cheaper than heroin and enters the drug supply primarily as a heroin adulterant (Ciccarone, 2017; Rothberg and Stith, 2018). It is also pressed into counterfeit opioid medication tablets (Arens et al., 2016; Drug Enforcement Administration: Strategic Intelligence Section,

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2016) and mixed with stimulants such as cocaine. (Marinetti and Ehlers, 2014) The US east coast has been heavily impacted, where heroin's similarly powdered form is easily cut with IMF and its analogues (Ciccarone, 2009; DEA Strategic Intelligence Section, 2015).

The presence, dose, and type of IMF in street heroin, illicitly manufactured opioid pills, and other drugs are largely unknown to consumers, placing individuals at high risk of accidental overdose. (Amlani et al., 2015; Ciccarone et al., 2017) North American studies demonstrate the increased risk of fentanyl-related overdose among unaware populations of people who use drugs (PWUD). (Amlani et al., 2015; Park et al., 2018) In Baltimore, Maryland, fentanyl-related overdose deaths increased 249% from 2015 to 2016. (Maryland Department of Health and Mental Hygiene, 2017) Fentanyl was detected in over half of overdose deaths in Rhode Island in 2016, (Marshall et al., 2017) and over three quarters of opioid-related deaths in Massachusetts. (Massachusetts Department of Public Health, 2016) Age-adjusted drug overdose mortality rates (per 100,000) in the cities examined here are among the highest in the nation: 80.6 in Baltimore; 35.3 in Boston, Massachusetts; and 32.5 in Providence, Rhode Island; the US state-wide average is 20.8. (Centers for Disease Control, 2018)

Drug preferences among PWUD are not well understood, particularly as populations adapt to the introduction of novel, highly lethal drugs. Studies demonstrate that some prefer to procure the strongest available heroin, even when implicated in overdose. (Mars et al., 2016, 2015; Prebble and Casey, 1969) Research prior to the arrival of IMF on the market indicated a substantial desirability of pharmaceutical-grade fentanyl. (Comer et al., 2008; Firestone et al., 2009) Qualities associated with fentanyl include a powerful high and concomitant short duration (Ciccarone et al., 2017), in line with fentanyl's pharmacodynamics. (Armenian et al., 2018; MacKenzie et al., 2016) A recent survey reported 31% of people who inject heroin wanted fentanyl but did not characterize this subpopulation. (Peiper et al., 2018)

To better understand the nature of fentanyl preferences among PWUD, this study aims to examine characteristics of individuals across three US cities affected by high rates of fentanyl-related overdose deaths. We address a knowledge gap regarding who prefers fentanyl and provide insight as to why they do so, with an aim to inform the nature and scope of services for PWUD and the broader fentanyl discussion.

2. Material and methods

2.1. Design

Data were derived from FORECAST (Fentanyl Overdose REduction Checking Analysis STudy). (Sherman et al., 2018) FORECAST was comprised of three phases: 1) validating three drug checking technologies; 2) a cross-sectional multicity survey of PWUD (N = 334); (Sherman et al., 2019) and 3) exploring stakeholders' and service providers' feelings about drug checking (N = 36). (Glick et al., 2018)

2.2. Setting

Primary data collection with PWUD occurred from June to October 2017 in Baltimore, Maryland (8 sites); Boston, Massachusetts (1 site); and Providence, Rhode Island (3 sites).

2.3. Participants

Study details have been described elsewhere. (Sherman et al., 2019) Briefly, targeted recruitment in Baltimore was based on 2016 drug arrest data to systematically recruit 175 PWUD. Boston and Providence utilized convenience sampling at harm reduction organizations to recruit n = 80 and n = 79 participants, respectively. Participants were screened with the following eligibility criteria: having used heroin, fentanyl, cocaine or methamphetamines, or reported opioid medication misuse in the past 30 days; being 18 years or older; and ability to speak English. Informed consent was provided orally. Eligible participants were administered an anonymous, 30-minute, computer-assisted personal interview. Participants were compensated with a pre-paid $25USD card in Baltimore or $25USD cash in Boston and Providence.

Of screened participants (N = 402), 340 (84%) were eligible, 337 (99%) of whom agreed to participate. For this analysis, the sample was restricted to those who reported any illicit opioid use in the past six months (n = 308). The study was approved by the Johns Hopkins Bloomberg School of Public Health and the Rhode Island Hospital Institutional Review Boards.

2.4. Measurements

The main outcome, individual preference for fentanyl, was assessed by asking participants to indicate their agreement with "I prefer drugs with fentanyl in them." Responses were measured on a four-point Likert scale (strongly disagree, somewhat disagree, somewhat agree, strongly agree); for purposes of analysis, participants were considered to prefer fentanyl if they somewhat or strongly agreed.

The survey ascertained sociodemographics (age, current gender, race/ethnicity, education, homelessness, income sources) as contextual variables, and exposure variables included drug use recency (past 6 months) and frequency, routes of drug administration, ever and past year overdose (experiencing and witnessing), and knowledge of and experiences with fentanyl. Gender was gathered by asking "Do you consider yourself male, female, transgender, or another gender?" Racial and ethnic backgrounds were ascertained with "What is your race or ethnicity?", allowing multiple responses. Due to small sample sizes for Hispanic ethnicity and race outside of white and black, a binary variable was constructed as non-Hispanic (NH) white or other (including multiracial). Income sources were established by asking "In the last three months, what have been your primary sources of income, legal or illegal?", allowing multiple responses; illegal income was defined as sex work, participation in the drug trade, or theft. Participants were asked if they had been arrested or incarcerated within the past year.

Drug use and overdose items were modified from previous studies. (Karamuzian et al., 2018; Park et al., 2018) Opioid medication misuse was ascertained with "Have you ever used any opioids not as prescribed by a doctor or nurse, including taking more, longer, or in a different way than was prescribed?" Drug of opioid use initiation was established by asking age at first use of heroin, prescription and nonprescription therapeutic opioids (when applicable). Daily use of illicit drugs and intravenous drug use (IDU) was established by asking for frequency of drug use in the past six months, separately by drug type and route of administration. Ability to perceive fentanyl adulteration of street drugs was measured by asking participants if "drugs with fentanyl in them look/taste/smell differently than drugs without fentanyl," as separate questions. Overdose history was gathered by briefly describing symptoms to participants, asking participants to only consider overdoses they felt involved opioids.

2.5. Analysis

Participants were compared using Pearson's chi-square tests across fentanyl preference. Correlates significant at the $p < 0.20$ level were considered for inclusion in regression modeling. Shapiro-Wilk-Mann rank-sum tests were performed for continuous variables. Log-binomial regression with robust standard errors clustered by recruitment city determined characteristics with the greatest associations to fentanyl preference.

Pairwise Spearman's correlation coefficients among final covariates demonstrated high levels ($> \pm 0.3$) of correlation with NH white race. NH white race correlation $> \pm 0.3$ were found for: recent IDU (0.63), illicit income (0.48), age (-0.42), and initiating with nonprescription therapeutic opioids (0.33). Variance inflation factors were acceptable

Table 1
Socio-demographic characteristics of people who recently used illicit opioids, stratified by preference for fentanyl: Baltimore, Boston, and Providence, 2017 (N = 308).

	Does not prefer fentanyl		Prefers fentanyl		Total		p-value
	n = 225 (73.0%)		n = 83 (27.0%)		N = 308		
Characteristic	n	(col %)	n	(col %)	n	(col %)	
City - n (row %)							0.062
Baltimore	112	(68.7)	51	(31.3)	163	(100.0)	
Boston	56	(72.7)	21	(27.3)	77	(100.0)	
Providence	57	(83.8)	11	(16.2)	68	(100.0)	
Age - Median (IQR); z ***[a]	45	(37-52)	38	(32-46)	42	(35-51)	< 0.001
Gender							0.574
Male	133	(59.1)	52	(62.7)	185	(60.1)	
Female	92	(40.9)	31	(37.3)	123	(39.9)	
Race / Ethnicity Category ***							< 0.001
NH[b] white	66	(29.3)	49	(59.0)	115	(37.3)	
NH[b] Black	102	(45.3)	20	(24.1)	122	(39.6)	
Hispanic	32	(14.2)	6	(7.2)	38	(12.3)	
Other / Multiracial	25	(11.1)	8	(9.6)	33	(10.7)	
Highest level of education completed							0.764
Some high school	83	(36.9)	31	(37.3)	114	(37.0)	
High school diploma / GED	98	(43.6)	33	(39.8)	131	(42.5)	
Some college / college degree	44	(19.6)	19	(22.9)	63	(20.5)	
Currently homeless	153	(68.0)	58	(69.9)	211	(68.5)	0.231
Main sources of income, last 3 months							
Full or part-time work	33	(14.7)	9	(10.8)	42	(13.6)	0.386
Illegal work ***	93	(41.3)	53	(63.9)	146	(47.4)	< 0.001
Arrested / incarcerated, last year **	95	(42.2)	49	(59.0)	144	(46.8)	0.009
Drug arrest	62	(65.3)	29	(59.2)	91	(63.2)	0.474
Healthcare visit, last 6 months	116	(51.6)	37	(44.6)	153	(49.7)	0.277
NEP use, last 6 months **	140	(62.2)	66	(79.5)	206	(66.9)	0.004
Drug treatment, last 6 months	119	(53.4)	46	(55.4)	165	(53.9)	0.748

Significance (Chi2 p-values): * p < 0.05, ** p < 0.01, *** p < 0.001.
[a] Wilcoxon-Mann-Whitney rank-sum test z-score and *p*-value.
[b] NH = non-Hispanic.

(< 1.6). Due to this correlation, tiered regressions were utilized to distinguish between contextual and exposure variables' effect on fentanyl preference, and a supplemental table stratified by race (NH white *vs*. other) was constructed for selected variables.

All analyses were conducted in Stata/SE 14.2. (StataCorp, 2015). The figure was created with R in RStudio 1.1.456 (RStudio, Inc., 2015).

3. Results

3.1. Sociodemographic characteristics

Fentanyl preference was expressed by 27.0% of participants. Descriptive statistics stratified by fentanyl preference are shown in Table 1. Participants were a median of 42 years old, and PWUD who preferred fentanyl were significantly younger than those who did not (p < 0.001). A greater proportion of participants who preferred fentanyl were NH white (59.0%, n = 49 *vs*. 29.3%, n = 66; p < 0.001). Homelessness was common across stratification (68.5%, n = 211). Participants preferring fentanyl reported participation in the underground economy (63.9%, n = 53 *vs* 41.3%, n = 93; p < 0.001) and arrest in the last year (59.0%, n = 49 *vs*. 42.2%, n = 95; p = 0.009) significantly more often than those who did not. The relationship between age, NH white race, and preference for fentanyl in our sample is demonstrated in Fig. 1. Shapiro-Wilk-Mann rank sum tests for equality of age distribution, stratified by NH white race and fentanyl preference, demonstrated a significant difference in age distribution among NH white participants (p < 0.01). Supplemental table S1 demonstrates differences in selected sociodemographic and exposure variables stratified by NH white race in our sample.

3.2. Drug use and overdose history

Drug and overdose histories are detailed in Table 2. Fentanyl preferers initiated opioid use by misusing opioid medications significantly more frequently than those who did not (50.6%, n = 42 *vs*. 33.8%, n = 76; p = 0.007). Daily drug use rates were significantly higher among those who prefer fentanyl (91.6%, n = 76 *vs* 75.6%, n = 170; p = 0.002), as was recent IDU (83.1%, n = 69 *vs* 68.4%, n = 154; p = 0.011). Injecting heroin was reported more commonly among participants who prefer fentanyl (p = 0.017); the opposite was true for smoking or snorting as route of administration (p = 0.004). Cocaine use (primarily crack cocaine) was common across the sample (70.5%, n = 217) and did not differentiate by fentanyl preference. Recent nonprescription use of benzodiazepines or tranquilizers was more common among people who prefer fentanyl (56.6%, n = 47 *vs*. 41.3%, n = 93; p = 0.013).

Overdose history significantly differed across fentanyl preference stratification (p = 0.016). Participants who preferred fentanyl more commonly reported having overdosed, but not within the past year (31.3%, n = 26 *vs*. 17.3%, n = 39). The majority (88.4%, n = 122) of those who overdosed in the past year attributed an overdose to fentanyl. Close to half of those who had ever witnessed an overdose reported having witnessed a fatal overdose (44.7%, n = 122).

3.3. Experiences with fentanyl

Fentanyl experiences are shown in Table 3. Ever receiving a fentanyl prescription did not significantly differ across fentanyl preference groups. Over three-quarters of participants suspected fentanyl adulteration of their drugs in the past six months. Fentanyl preferers reported significantly higher rates of recent exposure (p < 0.001).

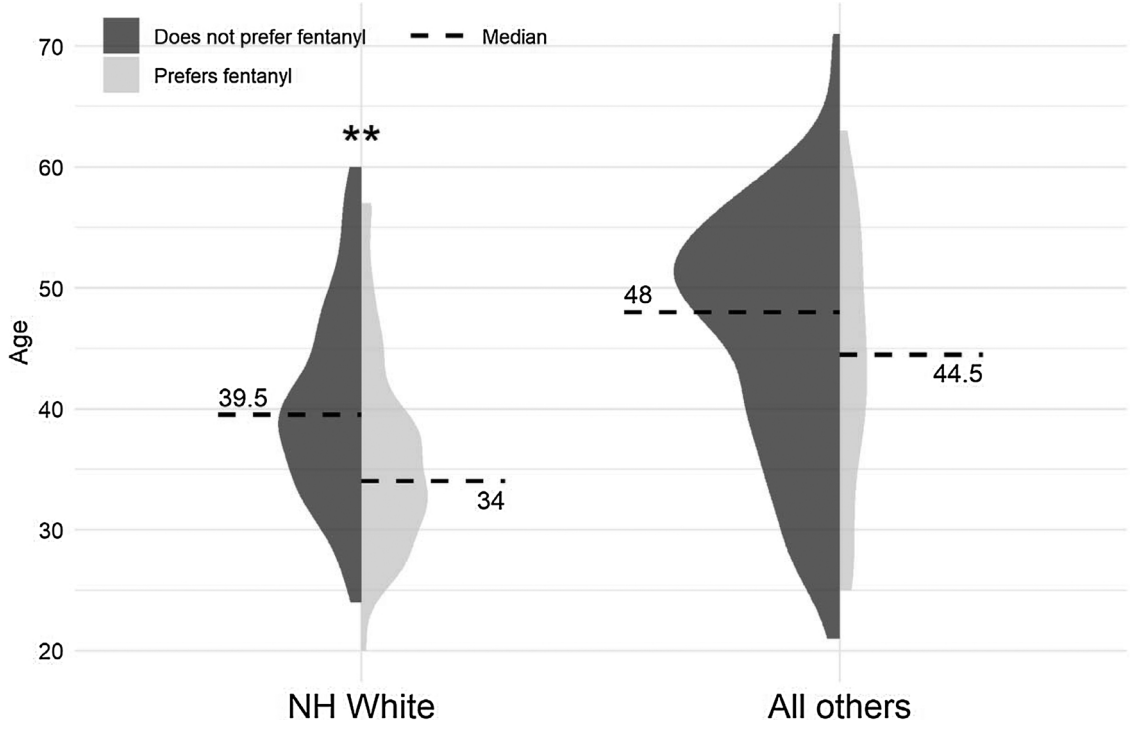

Fig. 1. Frequencies of participants indicating a preference for fentanyl stratified by race and age. NH stands for non-Hispanic. Medians for each group are indicated with a dashed line and their numeric value. Shapiro-Wilk-Mann rank sum test for equality of age distribution p-value is indicated by the two asterisks ($p < 0.01$); test was not significant ($p = 0.23$) in the "all others" group.

Nearly 60% (n = 94) of those who do not prefer fentanyl reported weekly or more frequent exposure in the past six months. Among those that prefer fentanyl, two-thirds reported actually wanting fentanyl at their most recent suspected use. Perceived ability to subjectively discern fentanyl adulteration was common and did not different significantly across fentanyl preference. PWUD preferring fentanyl were more knowledgeable about analogs, such as Carfentanil, compared with those who did not prefer fentanyl (60.2%, n = 50 *vs* 43.1%, n = 97; p = 0.018). Nevertheless, differentiation by fentanyl analog was similarly poor across the sample. The majority (85.4%, n = 263) of all surveyed reported interest in having their drugs checked for fentanyl with an objective method. A significantly larger proportion of preferers would not change their drug usage behavior if they knew beforehand their supply contained fentanyl (16.0%, n = 36 *vs* 71.1%, n = 59; $p < 0.001$), though the most common harm reduction use behaviors did not differ significantly by fentanyl preference.

3.4. Regression models

Log-binomial regression results are detailed in Table 4. In bivariate analysis, NH white race (relative risk (RR) = 2.42, 95% confidence interval (CI):1.56-3.76), recent IDU (RR = 1.88, CI:1.04-3.40), illegal income (RR = 1.96, CI:1.33-2.89), and arrest (RR = 1.64, CI:1.17-2.31), initiating opioid use with nonprescription opioid medications (RR = 1.65, CI:1.50-1.82), daily use of illicit drugs (RR = 2.74, CI:1.51-4.96) and overdose history (over a year ago: RR = 2.00, CI:1.30–3.09; within past year: RR = 1.30, CI:1.06-1.61) were significantly associated with an increased risk of fentanyl preference. Age increase (per decade) was bivariately associated with a decrease in risk (RR = 0.70, CI:0.58-0.83). In the presence of other sociodemographic variables (Model 1), fentanyl preference was significantly associated with NH white race (adjusted RR (aRR) = 1.82, CI:1.14-2.90). In the presence of only other exposure variables (Model 2), fentanyl preference was associated with having initiated opioid use with nonprescription therapeutic opioids (aRR = 1.48, CI:1.26–1.73); daily or greater use of an illicit drug (aRR = 2.24, CI:1.46–3.45), and a history of overdose but not in the past year (aRR = 1.54, CI: 1.20–1.97), controlling for IDU in the past six months.

In a fully adjusted model including both sociodemographic and exposure variables (Model 3), fentanyl preference was associated with: NH white race (aRR = 1.68, CI:1.18–2.40), daily or greater use of an illicit drug (aRR = 2.2, CI:1.71–2.87), and overdose ≥1 year ago (aRR = 1.33, CI:1.18–1.50). A decade increase in age (aRR = 0.77, CI:0.61–0.98) and overdose in the past year (aRR = 0.92, CI:0.87–0.97) were independently associated with a decreased risk of fentanyl preference.

4. Discussion

The current study is one of the first to explore characteristics of individuals who prefer fentanyl in the contemporary US opioid overdose crisis. Among PWUD in three cities heavily impacted by a fentanyl-adulterated illicit drug supply, we identify a subset of street-based PWUD who prefer fentanyl and describe how this relates to their experiences with drug use (length and frequency) and racial background. Likelihood of preference for fentanyl decreased with age, while NH white PWUD and PWUD reporting more frequent drug use were significantly more likely to prefer fentanyl, compared with others. Overdose history presented a nuanced picture: compared with those who had never overdosed, PWUD with recent overdose (≤1 year) were less likely to prefer fentanyl, while those who survived an overdose > 1 year ago were more likely to prefer fentanyl. In our exposure-only analysis, PWUD who initiated opioid use with nonprescription opioid medication were more likely to prefer fentanyl.

Approximately a quarter of recent users of illicit opioids preferred fentanyl. Studies support our findings that some PWUD prefer the effects of fentanyl-contaminated heroin and may seek it out, (Macmadu et al., 2017) but the majority find it undesirable. (Carroll et al., 2017) Reports of suspected fentanyl exposure were high, reflecting fentanyl's saturation of the observed cities' drug supply, as other research has

Table 2
Drug use and overdose history among people who recently used illicit opioids, stratified by preference for fentanyl: Baltimore, Boston, and Providence 2017 (N = 308).

	Does not prefer fentanyl		Prefers fentanyl		Total		p-value
	n = 225 (73.0%)		n = 83 (27.0%)		N = 308		
Characteristic	n	(col %)	n	(col %)	n	(col %)	
First opioids used[a]							
Heroin	116	(51.6)	37	(44.6)	153	(49.7)	0.277
Prescribed opioids	86	(38.2)	31	(37.3)	117	(38.0)	0.889
Opioid medication misuse **	76	(33.8)	42	(50.6)	118	(38.3)	0.007
Locations drugs were used most often, last 30 days							0.051
Private	96	(43.2)	23	(28.0)	119	(39.1)	
Semi-public	56	(25.2)	28	(34.1)	84	(27.6)	
Public	70	(31.5)	31	(37.8)	101	(33.2)	
Usually used drugs alone, last 6 months	104	(46.2)	43	(51.8)	147	(47.7)	0.384
Rushed drug purchase or use due to police activity, last year *	175	(77.8)	73	(88.0)	248	(80.5)	0.045
Recent illicit use[b] of 3 or more substances	168	(74.7)	70	(84.3)	238	(77.3)	0.072
Recent use[b] of prescription drugs							
Prescribed opioid use	120	(53.3)	44	(53.0)	164	(53.2)	0.960
Medication-assisted treatment[c]	84	(70.0)	33	(75.0)	117	(71.3)	0.530
Nonprescription therapeutic opioid use	111	(49.3)	42	(50.6)	153	(49.7)	0.843
Nonprescription use of tranquilizers or benzodiazepine medication *	93	(41.3)	47	(56.6)	140	(45.5)	0.017
Recent use[b] of illicit drugs							
Daily drug use **	170	(75.6)	76	(91.6)	246	(79.9)	0.002
Injection drug use *	154	(68.4)	69	(83.1)	223	(72.4)	0.011
Heroin injection *	144	(64.0)	65	(78.3)	209	(67.9)	0.017
Heroin, smoked or snorted **	115	(51.1)	27	(32.5)	142	(46.1)	0.004
Crack cocaine use	156	(69.3)	61	(73.5)	217	(70.5)	0.478
Snort powdered cocaine	63	(28.0)	16	(19.3)	79	(25.6)	0.120
Cocaine injection	79	(35.1)	37	(44.6)	116	(37.7)	0.128
Speedball injection	94	(41.8)	44	(53.0)	138	(44.8)	0.079
Overdose							
Opioid overdose *							0.016
Never	84	(37.3)	21	(25.3)	105	(34.1)	
More than a year ago	39	(17.3)	26	(31.3)	65	(21.1)	
Within last year	102	(45.3)	36	(43.4)	138	(44.8)	
Suspected due to fentanyl	91	(89.2)	31	(86.1)	122	(88.4)	0.617
Witnessed overdose, ever	194	(86.6)	79	(95.2)	273	(88.9)	0.101
Witnessed fatal overdose	84	(43.3)	38	(48.1)	122	(44.7)	0.469
Received naloxone/overdose training, last 12 months	158	(70.2)	57	(68.7)	215	(69.8)	0.793

Significance ($\chi 2$ p-values): * - $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.
[a] categories not mutually exclusive.
[b] last 6 months.
[c] methadone, suboxone, subutex, buprenorphine.

shown. (Mars et al., 2018) The majority of PWUD who suspected recent fentanyl exposure did not prefer the drug. Even among preferers, over a third reported not seeking the drug the last time they suspected IMF use. Drug use frequency conferred a preference for fentanyl, potentially reflecting the shorter duration of fentanyl-associated highs and corollary need to use more often demonstrated by prior studies. (Armenian et al., 2018; MacKenzie et al., 2016) Our findings imply that frequency of drug use, rather than route of administration, is a better predictor of fentanyl preference. Fentanyl exposure rates support a supply-side hypothesis of fentanyl market dynamics proposed by other recent North American studies. (Ciccarone, 2017; Gladden et al., 2016; Hempstead and Vildirim, 2014; Unick et al., 2014) Fentanyl preference may be an inevitable response to an illicit drug supply dominated by IMF; increases in (witting and unwitting) fentanyl exposure can result in exacerbated physical dependence and greater tolerance among PWUD. (Carroll et al., 2017; Cicero et al., 2018; Macmadu et al., 2017) Given US drug seizure data (Drug Enforcement Administration, 2015) and the expanding presence of fentanyl and other synthetic opioids globally, (Karila et al., 2019) avoiding fentanyl in street drugs could prove more difficult than finding it. In the absence of reliable and accessible methods for objectively determining IMF adulteration, (*e.g.*, drug checking resources), fentanyl preference can develop unbeknownst to PWUD.

Increase in age significantly decreased likelihood of fentanyl preference, after controlling for race. Prior research on age cohorts of PWUD have demonstrated that opioid use initiation and preference reflect changes in supply—*i.e.*, PWUD born after 1980 preferred opioid medications over heroin, a trend which may be reversing. (Cicero et al., 2018; Novak et al., 2016) This finding may be a harbinger of a younger cohort of PWUD that have adapted to an IMF-saturated market and may now initiate with IMF and prefer it. However, NH white PWUD in our sample were significantly younger than PWUD of other races/ethnicities. This distribution of age by NH white race is likely an artifact of our street-based sampling rather than a reflection of the true American opioid-using population, though our sample size was insufficient to adequately explore an age-race interaction. Future research should help to elucidate whether such a relationship exists.

NH white PWUD were more likely to prefer fentanyl than others, echoing a study which found fentanyl-adulterated heroin use chiefly among NH white youth. (Macmadu et al., 2017) The US overdose epidemic has been perceived as primarily affecting whites, a result of opioid over prescription and transition to illicit alternatives after addiction's establishment. (Hansen and Netherland, 2016) This contrasts with previous US drug crises (*e.g.*, the 1980s crack epidemic), perceived by the mainstream media and politicians to predominately afflict ethnic and racial minority populations—whose drug use was considered a

Table 3
Experiences and opinions about fentanyl among people who recently used illicit opioids, stratified by preference for fentanyl: Baltimore, Boston, and Providence 2017 (N = 308).

	Does not prefer fentanyl		Prefers fentanyl		Total		p-value
	n = 225 (73.0%)		n = 83 (27.0%)		N = 308		
Characteristic	n	(col %)	n	(col %)	n	(col %)	
Prescribed fentanyl, ever	14	(6.2)	7	(8.5)	21	(6.8)	0.477
Use of drug thought had fentanyl in it, last 6 months **	163	(72.4)	74	(89.2)	237	(76.9)	0.002
Frequency of fentanyl exposure ***							< 0.001
Less than monthly / once a month	69	(42.3)	8	(10.8)	77	(32.5)	
Once a week	31	(19.0)	8	(10.8)	39	(16.5)	
Almost every day	33	(20.3)	22	(29.7)	55	(23.2)	
Once a day or more	30	(18.4)	36	(48.7)	66	(27.9)	
Wanted fentanyl, last suspected fentanyl use[a] ***	16	(9.4)	50	(66.7)	66	(26.8)	< 0.001
Thinks drugs with fentanyl look, smell, or taste differently	173	(76.9)	65	(78.3)	238	(77.3)	0.791
Heard of different types of fentanyl *	97	(43.1)	50	(60.2)	147	(47.7)	0.018
Suspected use of drug with other type of fentanyl, ever	25	(26.0)	17	(34.0)	42	(28.8)	0.360
Interested in having their drugs checked for fentanyl	195	(86.7)	68	(81.9)	263	(85.4)	0.296
Drug use behavior if knew their drugs had fentanyl[b]							
Use as originally intended ***	36	(16.0)	59	(71.1)	95	(30.8)	< 0.001
Use less than originally intended	30	(13.3)	6	(7.2)	36	(11.7)	0.139
Use more slowly / do a tester shot	22	(9.8)	8	(9.6)	30	(9.7)	0.971
Use with someone else around	10	(4.4)	4	(4.8)	14	(4.6)	0.889

Significance ($\chi 2$ p-values): * - $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.
[a] among participants who ever suspected using a drug with fentanyl (n = 246).
[b] categories not mutually exclusive.

moral failing. These populations in turn were heavily criminalized in ways that carried profound, long-term consequences. (Netherland and Hansen, 2017) While opioid prescription history was common in our sample, more people of color had never been prescribed an opioid. NH white participants more commonly initiated opioid use with therapeutic opioids (prescribed or not), reinforcing prior work on structural advantages in health care access among white patients contributing to increased opioid accessibility. (Pletcher et al., 2008; Tait and Chibnall, 2014; Tamayo-Sarver et al., 2003) Fentanyl-associated mortality is not just a phenomenon among whites: 2016 US mortality rates indicate that overdose fatality is rising most steeply among Blacks. (Jamison et al., 2018; Katz and Goodnough, 2017; Spencer et al., 2019) The cumulative effects of fentanyl-contaminated heroin appear to be divided along racial lines in the US.

We found no association between fentanyl prescription history and preference for fentanyl, echoing a prior study. (Gladden et al., 2016) However, in our exposure-only model (Model 2), people initiating opioid use with nonprescription opioid medications were more likely to prefer fentanyl. IMF-adulterated heroin's effects may be more similar to therapeutic opioids (compared to pure heroin). It is possible that users accustomed to such highs may prefer fentanyl-adulterated heroin—a phenomenon reinforced by racialized opioid availability in the US and age cohort. As opioid use grows globally (Harm Reduction International, 2016; Martins and Ghandour, 2017) and illicit market forces bring powdered heroin (easily adulterated with IMF) to different geographies, (United Nations Office on Drugs and Crime, 2018) this association is concerning. Notably, this association is nonsignificant when controlling for sociodemographics in our analysis, but in other settings race and ethnicity may play very different roles due to local histories.

Nearly two-thirds of our sample experienced an opioid overdose, with nearly half in the past year—the majority of whom suspected fentanyl involvement. Despite higher exposure rates among preferers, no association was established between fentanyl preference and attribution of a recent overdose to the drug. Preferers were more likely to have ever overdosed, but slightly less likely to have overdosed in the

Table 4
Correlates of fentanyl preference among people who use illicit opioids – multitier log-binomial regression with standard errors clustered by city: Baltimore, Boston, and Providence, 2017 (N = 308).

	Bivariate		Model 1: Sociodemographic		Model 2: Exposure		Model 3: Full	
Variable	RR	95% CI	aRR	95% CI	aRR	95% CI	aRR	95% CI
Age (in decades)	0.70 ***	(0.58-0.83)	0.79	(0.62-1.01)			0.77 *	(0.61-0.98)
Gender								
Male	1	(Ref)	1	(Ref)			1	(Ref)
Female	0.90	(0.73-1.10)	0.81	(0.59-1.13)			0.88	(0.70-1.11)
Race / Ethnicity								
Other than NH White	1	(Ref)	1	(Ref)			1	(Ref)
NH[a] White	2.42 ***	(1.56-3.76)	1.82 *	(1.14-2.90)			1.68 **	(1.18-2.40)
Illegal income, past 3 months	1.96 **	(1.33-2.89)	1.43	(0.88-2.33)			1.26	(0.78-2.05)
Arrest in last year	1.64 **	(1.17-2.31)	1.18	(0.67-2.07)			1.21	(0.61-2.39)
Initiated opioid use with nonprescription therapeutic opioids	1.65 ***	(1.50-1.82)			1.48 ***	(1.26-1.73)	1.10	(0.80-1.49)
Daily use of illicit drugs	2.74 **	(1.51-4.96)			2.24 ***	(1.46-3.45)	2.22 ***	(1.71-2.87)
IDU, past 6 months	1.88 *	(1.04-3.40)			1.53	(0.85-2.74)	0.97	(0.51-1.85)
Overdose history								
Never	1	(Ref)			1	(Ref)	1	(Ref)
Over a year ago	2.00 **	(1.30-3.09)			1.54 ***	(1.20-1.97)	1.33 ***	(1.18-1.50)
Within past year	1.30 *	(1.06-1.61)			1.02	(0.78-1.34)	0.92 **	(0.87-0.97)

Significance (*p*-values): * - $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.
[a] NH = non-Hispanic.

past year. Preferers were no more or less likely to indicate they would practice common harm reduction usage techniques (*e.g.*, using a smaller quantity, using more slowly, doing a tester shot) if they were confident their supply contained IMF—a fuller examination of these behaviors in our sample have been documented elsewhere. (Rouhani et al., 2019) Given the established links between suspected exposure to fentanyl and the occurrence of non-fatal overdose (Park et al., 2018) and high mortality rates associated with fentanyl use, (Spencer et al., 2019) the null association may be due to increased tolerance among survivors who prefer fentanyl, an adaptation to the market and circumstances. The trauma often associated with surviving an overdose and fentanyl's lethality may serve as negative reinforcement for PWUD who recently experienced overdose and thus influence a preference against fentanyl. (Carroll et al., 2017; Sherman et al., 2019) Additionally, nonprescription use of benzodiazepines was more commonly reported among fentanyl preferers. Benzodiazepines are clinically indicated for treatment of chest-wall rigidity, a common fentanyl side effect, but are also known for their drug-drug interaction with opioids, increasing central nervous system and respiratory depression. (Mayumi et al., 1990; Pérez-mañá et al., 2018) Fentanyl preferers' increased reports of benzodiazepine exposure may reflect their adoption of the drug class to counteract such side effects, though this is concerning considering the increased risk of overdose associated with the drug combination. (Park et al., 2015) Among the most frequently exposed to fentanyl (every other day and higher), there was no association between fentanyl preference and suspected use: preferers and non-preferers were exposed at roughly equivalent rates. If tolerance and exposure to fentanyl are positively associated, it seems likely that preferers are a uniquely high-risk subpopulation of PWUD, and that a "protective" effect of recent overdose on fentanyl preference is a result of high mortality.

4.1. Limitations

Our results should be seen in light of several limitations. Given our cross-sectional design, findings should be interpreted as a snapshot of a rapidly changing risk environment. Due to fentanyl's association with high mortality, survivor bias likely influenced our results. Desirability bias may have impacted participant's willingness to disclose certain aspects of their experience, including fentanyl preference. Interviews were conducted in English—non-English speaking PWUD were therefore excluded. To keep the survey concise, we were unable to ask reasons for or against preference for fentanyl; we hope future ethnographic research can better tackle this subject. Other unmeasured variables, such as the policy environment and local drug market fluctuations in recruitment cities, could have unknown effects on the experiences of participants.

4.2. Conclusion

To our knowledge, this is the first quantitative study examining fentanyl preference among PWUD surviving the contemporary opioid overdose crisis. We demonstrate the role that systemic factors may play in the development of preference, such as fluctuating drug supplies and racialized access to opioid prescriptions, as well as the role of individual user experience of overdose and drug use. Recent trends in political and media discourse around the opioid overdose crisis have suggested that high rates of overdose and the prevalence of fentanyl in markets are due to PWUD pursuing an "ultimate high."(Carroll et al., 2017; National Crime Agency, 2017) We counter that fentanyl preferers are a minority of PWUD, and suggest that PWUD are not inflexible consumers driven chiefly by addiction's compulsions. Narratives attempting to place the onus of the fentanyl crisis on consumers could lead to implementations of ineffective carceral measures, such as the adoption of mandatory minimum sentencing for fentanyl possession or "drug-induced homicide" laws which unfairly target close relations of overdose victims and precisely those most vulnerable to fentanyl overdose.

Secondly, user education about the presence of fentanyl in the drug supply and its lethality will be insufficient to reduce users' risk of overdose so long as they are unable to control whether fentanyl is in the drugs they purchase. Checking drugs for fentanyl presence could be an important component of staving off further increases in opioid overdose fatalities. Given the high rates of exposure to fentanyl among both preferers and non-preferers, it is unlikely that drug checking would "enable" preferers to pursue fentanyl and may in fact help non-preferers avoid fentanyl.

Finally, we provide key information for targeting harm reduction services to PWUD who may be at a higher risk of overdose in the US—namely, young and white urban residents, but also people who smoke, snort or swallow their drugs. Syringe exchange programs in the US have proven efficacious, but there are few established systems of outreach for PWUD who do not inject. We demonstrate that frequency of use, not route of administration, is the most important factor for determining fentanyl preference. Should US drug markets continue to be as saturated by fentanyl as at the time of study, broader groups of PWUD will need to be specifically targeted for services.

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Contributors

S.G. Sherman and T.C. Green conceived and supervised the study. K.B. Morales completed the analyses and led the writing. J.N. Park, J.L. Glick, and S. Rouhani assisted with the study and analyses. All authors provided critical revisions and approved the final manuscript. K.B. Morales confirms that he had full access to all data and had final responsibility for the decision to submit for publication.

Declaration of Competing Interest

Dr. Sherman is an expert witness for plaintiffs in opioid litigation. Remaining authors report no conflicts of interest nor financial disclosures.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2019.107547.

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