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Predictors of future overdose among people who inject drugs in Baltimore, Maryland

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HIGHLIGHTS

- Previous overdose was the most significant predictor of future overdose.
- Participants currently in buprenorphine treatment had elevated overdose risk.
- Contrast of reported fentanyl and positive urine highlights unintended exposure.
- Common use of street-bought non-prescribed medication for opioid use disorder.

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ABSTRACT

Background: Longitudinal studies of future overdose risk among people who inject drugs (PWID) are needed to inform planning of targeted overdose preventions in the United States.
Methods: The Integrating Services to Improve Treatment and Engagement (INSITE) study followed 720 PWID between June 2018 and August 2019 to evaluate the delivery of mobilized healthcare services in Baltimore, Maryland. The present analyses used logistic regression to identify baseline characteristics predictive of non-fatal or fatal overdose during the 6-month follow-up among 507 participants with overdose information. Non-fatal overdoses were self-reported and fatal overdoses were identified through the National Death Index.
Results: At baseline, 121 (23 %) reported an overdose in the prior 6 months. Between baseline and follow-up, 66 (13 %) participants reported a non-fatal overdose and 6 (1 %) experienced a fatal overdose. Overdose during follow-up was positively associated with overdose in the 6 months prior to baseline (6.70 aOR; 95 % CI: 3.51, 12.78) and more than 6 months prior to baseline (2.49 aOR; 95 % CI: 1.52, 4.08) versus no prior overdose. Overdose during follow-up was also positively associated with buprenorphine treatment (2.37 aOR; CI: 1.08, 5.21) and negatively associated with non-prescribed methadone at baseline (0.59 aOR; 0.38, 0.93).
Conclusions: Identifying and intervening with PWID who experienced a recent overdose could reduce short-term elevated risk of future overdose. However, as other PWID reported never experiencing an overdose at baseline nonetheless experienced an overdose during follow-up, targeted approaches should be complemented with population-level interventions. Overdose risk implications of buprenorphine treatment and non-prescribed methadone are also discussed.

1. Introduction

The contemporary drug overdose epidemic is one of the largest public health crises in the history of the United States (US). Fatal drug overdoses have drastically risen over the past two decades in the US, from 17,415 in 2000 to 91,799 in 2020, which corresponds to a 4.6-fold increase in the age-standardized death rate (ASDR) from 6.2 per 100,000 in 2000 to 28.3 per 100,000 in 2020 (Centers for Disease

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Control and Prevention, 2021; National Institutes of Health, 2022). Across the globe, as other countries experience their own version of the overdose epidemic, the US distinguishes itself by leading the ranks of highest drug overdose deaths among high-income countries since the early 2000s (Centers for Disease Control and Prevention, 2021; Ho, 2019). In 2020, the State of Maryland (MD) had the seventh highest drug overdose death rate in the US, with an ASDR of 44.6 per 100,000 (Centers for Disease Control and Prevention, 2021; National Institutes of Health, 2022). In MD and across the US, Baltimore City has been one of the most impacted municipalities by the overdose epidemic and currently leads with the highest overdose death rate across other areas with over 500,000 residents (Centers for Disease Control and Prevention, 2024). In 2020, the fatal drug overdose ASDR in Baltimore was 95.5 per 100,000 with an estimated 89 % of deaths involving opioids (Centers for Disease Control and Prevention, 2021; Maryland Department of Health, 2021).

The US is experiencing an unprecedented magnitude of drug overdose deaths and with the continuing overdose epidemic, it becomes increasingly imperative to identify longitudinal predictors to inform targeted prevention planning to effectively reduce overdose among those at highest risk, people who inject drugs (PWID) (Ho, 2019; Sherman et al., 2007; Snowdon, 2022). While numerous cross-sectional analyses have identified factors associated with overdose, few longitudinal studies in the US have examined predictors of overdose specifically among PWID and during the fentanyl era of the overdose epidemic (Binswanger et al., 2012; Coffin et al., 2007; Colledge et al., 2019; Paquette et al., 2018; Riley et al., 2016; Sherman et al., 2007). To identify candidate predictors of overdose, we analyze data from the Integrated Services to Improve Treatment and Engagement (INSITE) study, a longitudinal cohort of PWID that was established to evaluate a cluster-randomized trial of van-delivered healthcare services in Baltimore, MD (Page et al., 2024).

2. Methods

2.1. Study design and participants

Between June 2018 and August 2019, 60 participants were enrolled for the INSITE study at each of 12 drug-impacted Baltimore neighborhoods along with syringe service programs (SSP), totaling 720 participants. Sites were randomized to receive the integrated care van services in addition to SSP services or SSP services only. Eligibility criteria for HIV-negative participants included being 18 years of age or older and either injecting drugs four or more times in the past 30 days or injecting with a shared syringe in the last 6 months. Eligibility criteria for HIV-positive participants included being 18 years of age or older and a self-reported history of injection drug use. For this secondary analysis, we applied the same injection drug use criteria to all participants (injected 4 or more days in the past 30 days or shared injection equipment in last 6 months), thus excluding 6 HIV-positive participants without recent injection drug use. The sample was further limited to 507 participants with overdose information during the first 6 months of follow-up, which included participants that either completed a follow-up visit or were identified as having a fatal overdose during the follow-up timeframe through the National Death Index (Centers for Disease Control and Prevention, 2020). Extraction of death records were completed 18 months after the last follow-up assessment to account for potential delays in updated death information. Further scheduled follow-ups at the INSITE study were disrupted and halted due to the COVID-19 pandemic in 2020.

2.2. Data collection

At the combined screening-baseline visit, participants provided written consent to be involved in the study, completed an interviewer-administered questionnaire, and provided biological samples for drug toxicology reports. At the 6-month follow-up, a similar questionnaire was administered, and biological samples for drug toxicology and written consent were reacquired. For each visit, participants were asked to provide extensive sociodemographic and behavioral information, such as marital status, income, education, incarceration history, sexual behaviors, and housing status. Additionally, participants assessed using the Short Form 12 (SF-12) quality of life tool to measure overall physical and emotional health at both baseline and follow-up to compare the sample to the general population (RAND, 2022). To score the SF-12, weights were applied to each item and cross-validated using the recommended package on STATA (RAND, 2022). As for drug-related behaviors, participants were asked about their preferred substance, injection use frequency and sharing of equipment, age of first injection, non-injection substance use, medical history, and previous care provided by the SSP. Participants were also asked health-related questions pertaining to their access to primary care providers, emergency room utilization, recent hospitalization, medication for opioid use disorder (MOUD), access to naloxone, and previous overdoses. Information on non-fatal overdoses were self-reported while fatal overdoses were collected through the National Death Index. A non-fatal overdose was defined if participants self-reported one of the following: an ambulance arrived at the scene, participant was taken to the ED, naloxone was administered, or other medical intervention was provided during overdose. Lastly, for the drug toxicology reports, a Thermo Scientific TSQ Quantum Access MAX Triple Quadrupole Mass Spectrometer was used in selected reaction monitoring mode to detect and quantify substances from the biological samples collected from participants, which was all analyzed at The Johns Hopkins Advanced Clinical Chemistry Diagnostic Laboratory using liquid chromatography-tandem mass spectrometry assay to screen for drug metabolites.

2.3. Statistical analysis

Analyses were completed using STATA SE version 17 (Stata Corp. LLC, College Station, Texas, USA). The outcome of interest was overdose during follow-up, with non-fatal and fatal overdose being combined. Baseline characteristics were analyzed to identify longitudinal predictors of overdose during follow-up using logistic regression models with cluster robust standardized errors to account for clustering of participants within the 12 drug-impacted neighborhoods (Hubbard et al., 2010; Kahan et al., 2016). We did not control for intervention status in the regression models as it was not significantly associated with overdose during follow-up. Finally, a backward-stepwise approach was used to develop a multivariate model to identify baseline predictors of overdose during follow-up and to reduce potential confounding between covariates. The initial model included baseline characteristics associated with overdose during follow-up at $p<0.2$, and then excluded characteristics with $p>0.1$ in the stepwise model.

3. Results

From the total sample of 507 PWID, the majority of participants were male (60 %), 35–59 years of age (75 %), Black (77 %), not currently homeless (93 %), and had an education level equivalent to high school or less (79 %). The majority of participants also reported previous incarceration of three or more days in their lifetime (80 %), but a minority reported incarceration in the past 6 months at baseline (7 %). As for injection drug use, 370 participants (73 %) reported injection drug use of 60 or more times in the past 30 days at baseline and 250 participants (49 %) reported sharing drug injection equipment. Additionally, most participants self-reported use of heroin (99 %), cocaine (91 %), and speedball (71 %), the simultaneous use of heroin and cocaine. Only 129 (25 %) participants self-reported fentanyl use in the past 6 months, yet 425 participants (83 %) tested positive for fentanyl or norfentanyl metabolites at baseline. Among the sample, less than half reported current enrollment in any methadone (31 %) or buprenorphine (6 %)

treatment program. However, a greater proportion of the sample reported non-prescribed or street-bought use of methadone (49 %) and buprenorphine (34 %). When assessing the sample's overall self-perceived health, the SF-12 scores revealed most participants were below the estimated average general population scores for physical (68 %) and emotional health (77 %). Furthermore, during the 6-month follow-up assessment, 72 participants (14 %) experienced an overdose, which included 66 non-fatal (13 %) and 6 fatal (1 %). Among those who overdosed during follow-up, 12 (16 %) had never experienced a previous overdose, 37 (51 %) experienced an overdose in the prior 6 months at baseline, and 23 (31 %) experienced an overdose more than 6 months prior to baseline (Table 1).

3.1. Univariate models

Overall, no sociodemographic or economic factor was found to be predictive of overdose during follow-up among this sample. Previous overdose was an important predictor of overdose during follow-up as those who had recently experienced an overdose in the 6 months prior to baseline or more than 6 months prior to baseline had 7.38 (95 % confidence interval [CI]: 3.89, 14.00) and 2.57 times (95 % CI: 1.54, 4.27) higher odds of overdose during follow-up compared to those who never experienced an overdose, respectively.

More than half of the sample that overdosed during follow-up also reported sharing syringes in the past 6 months at baseline and those reporting sharing syringes had 52 % higher odds of overdose during follow-up (1.52 OR; 95 % CI: 1.01, 2.32) compared to those who did not report sharing syringes. From the urine toxicology reports, fentanyl or norfentanyl was the leading drug positivity among the sample with heroin being second. However, urine detection of fentanyl or norfentanyl was not found to be predictive of overdose during follow-up. As for MOUD, participants had elevated odds of overdose during follow-up if they were currently enrolled in a buprenorphine treatment program at baseline (3.38 OR; 95 % CI: 1.66, 6.89). However, enrollment in a methadone treatment program at baseline was not predictive of overdose during follow-up. Furthermore, those who reported use of non-prescribed methadone in the past 6 months at baseline had reduced odds of overdose during follow-up (0.74 OR; 95 % CI: 0.57, 0.97). However, use of non-prescribed buprenorphine was not predictive of overdose during follow-up.

From the SF-12 quality of life survey, neither aggregated physical nor emotional health scores were associated with overdose during follow-up. However, one of the SF-12 domains for perception of overall health revealed those who self-reported their health as "poor" compared to "excellent" were 7.33 (95 % CI: 1.33, 40.42) times more likely to overdose during follow-up. As for healthcare utilization, emergency department (ED) visits and overnight hospital stays for one or more nights in the past 6 months at baseline were also found to be predictive of overdose during follow-up. Among participants who overdosed during follow-up, 50 % had a past ED visit and 38 % stayed overnight. Those who visited the ER or had an overnight hospital stay had 1.47 (95 % CI: 1.05, 2.05) and 2.34 (95 % CI: 1.15, 4.75) times the odds of experiencing an overdose during follow-up compared to counterparts, respectively.

3.2. Multivariate model

Candidate predictors in the final multivariate model included previous overdose, buprenorphine treatment enrollment status, non-prescribed methadone use, injection of prescription opioids, naloxone nearby when injecting drugs, overnight hospital stay, and race. From the adjusted model, those with a previous overdose showed the highest odds of overdose during follow-up as those who reported an overdose in the past 6 months at baseline or more than 6 months prior to baseline were 6.70 (95 % CI: 3.51, 12.78) and 2.49 (95 % CI: 1.52, 4.08) times more likely to overdose compared to those who did not report a previous

Table 1
Baseline characteristics and candidate predictors of overdose during the 6-month follow-up from the univariate and multivariate logistic regressions among PWID in Baltimore, MD (N=507).

Baseline Characteristic	Sample, n (col. %)	Overdosed, n (col. %)	Odds Ratio (95 % CI)	Adjusted Odds Ratio (95 % CI)
Total sample	507 (100)	72 (14.0)		
Age				
18–34	66 (13.0)	8 (11.1)	-	-
35–59	380 (75.0)	54 (75.0)	1.20 (0.47, 3.03)	-
≥60	61 (12.0)	10 (13.9)	1.42 (0.59, 3.36)	-
Race				
Black	391 (77.1)	54 (75.0)	-	-
White	98 (19.3)	13 (18.1)	0.95 (0.42, 2.15)	0.61 (0.27, 1.39)
Other	18 (3.6)	5 (6.9)	2.40 (0.96, 5.98)	1.86 (0.52, 6.67)
Sex				
Male	306 (60.3)	29 (40.3)	-	-
Female	201 (39.7)	43 (59.7)	1.03 (0.65, 1.62)	-
Education				
Less than high school	190 (37.5)	28 (38.9)	-	-
High school or GED	211 (41.6)	27 (37.5)	0.84 (0.37, 1.92)	-
Some college	106 (20.9)	17 (23.6)	1.10 (0.64, 1.88)	-
Homelessness				
No	474 (93.5)	68 (94.4)	-	-
Yes	33 (6.5)	4 (5.6)	0.82 (0.26, 2.56)	-
Incarceration				
Never	63 (12.4)	10 (13.9)	-	-
Past 6 months	37 (7.3)	8 (11.1)	1.43 (0.58, 3.53)	-
More than 6 months ago	407 (80.3)	54 (75.0)	0.79 (0.31, 2.07)	-
SF−12 overall health				
Excellent	23 (4.5)	1 (1.4)	-	-
Very good	108 (21.3)	12 (16.7)	2.74 (0.37, 20.27)	-
Good	173 (34.1)	21 (29.2)	3.03 (0.36, 25.40)	-
Fair	175 (34.5)	31 (43.1)	4.73 (0.67, 33.12)	-
Poor	28 (5.5)	7 (9.7)	7.33 (1.33, 40.42)*	-
SF−12 physical health score				
≥50	159 (31.4)	14 (19.4)	-	-
<50	348 (68.6)	58 (80.6)	2.07 (0.94, 4.54)	-
SF−12 emotional health score				
≥50	113 (22.3)	12 (16.7)	-	-

(continued on next page)

Table 1 (*continued*)

Baseline Characteristic	Sample, n (col. %)	Overdosed, n (col. %)	Odds Ratio (95 % CI)	Adjusted Odds Ratio (95 % CI)
<50	394 (77.7)	60 (83.3)	1.51 (0.67, 3.40)	-
Previous overdose				
Never	213 (42.0)	12 (16.7)	-	-
Past 6 months	121 (23.9)	37 (51.4)	7.38 (3.89, 14.00)***	6.70 (3.51, 12.78)***
More than 6 months ago	173 (34.1)	23 (31.9)	2.57 (1.54, 4.27)***	2.49 (1.52, 4.08)***
Drug injections past 30 days				
0–59	137 (27.0)	18 (25.0)	-	-
≥60	370 (73.0)	54 (75.0)	1.12 (0.84, 1.50)	-
Shared injection equipment past 6 months				
No	257 (50.7)	30 (41.7)	-	-
Yes	250 (49.3)	42 (58.3)	1.52 (1.01, 2.32)*	-
Fentanyl or norfentanyl positive urine toxicology result				
No	82 (16.2)	9 (12.5)	-	-
Yes	425 (83.8)	63 (87.5)	0.97 (0.56, 1.68)	-
Fentanyl injection past 6 months				
No	378 (74.5)	54 (75.0)	-	-
Yes	129 (25.5)	18 (25.0)	1.44 (0.71, 2.91)	-
Speedball injection past 6 months				
No	144 (28.4)	19 (26.4)	-	-
Yes	363 (71.6)	53 (73.6)	0.72 (0.60, 2.09)	-
Prescription opioid use past 6 months				
No	137 (27.0)	18 (25.0)	-	-
Yes	370 (73.0)	54 (75.0)	1.08 (0.74, 1.58)	-
Prescription opioid injection past 6 months				
No	257 (50.7)	30 (41.7)	-	-
Yes	250 (49.3)	42 (58.3)	1.67 (0.94, 2.95)	1.74 (0.91, 3.33)
Methadone treatment status				
Not enrolled	347 (68.4)	56 (77.8)	-	-
Currently enrolled	160 (31.6)	16 (22.2)	0.57 (0.22, 1.47)	-
Non-prescribed methadone use past 6 months				
No	257 (50.7)	41 (56.9)	-	-
Yes	250 (49.3)	31 (43.1)	0.74 (0.57, 0.97)*	0.59 (0.38, 0.93)*
Buprenorphine treatment status				
Not enrolled	474 (93.5)	61 (84.7)	-	-
Currently enrolled	33 (6.5)	11 (15.3)	3.38 (1.66, 6.89)**	2.37 (1.08, 5.21)*
Non-prescribed buprenorphine use past 6 months				
No	331 (65.3)	39 (54.1)	-	-
Yes	176 (34.7)	33 (45.8)	1.72 (0.99, 2.99)	-
Naloxone nearby				
No	302 (59.6)	35 (51.4)	-	-
Yes	205 (40.4)	37 (48.6)	0.68 (0.39, 1.17)	0.67 (0.40, 1.12)
SSP use past 6 months				
No	367 (72.4)	57 (79.2)	-	-
Yes	140 (27.6)	15 (20.8)	0.65 (0.34, 1.22)	-
ED visit past 6 months				
No	295 (58.2)	36 (50.0)	-	-
Yes	212 (41.8)	36 (50.0)	1.47 (1.05, 2.05)*	-
Overnight hospital stay past 6 months				
No	386 (76.1)	44 (61.1)	-	-
Yes	121 (23.9)	28 (38.9)	2.34 (1.15, 4.75)*	1.89 (0.91, 3.94)

Abbreviations: CI = confidence interval, SF-12 = short form, SSP = syringe service program, ED = emergency department.
Two-tailed test *p<0.05, **p<0.01, ***p<0.001.
Note: Adjusted results are based on backward stepwise logistic regression (p-remove=0.20, p-enter=0.10) that initially included all characteristics from the unadjusted model. All models include cluster robust standard errors to account for clustering of participants within study sites.

overdose, respectively. Additionally, current enrollment of a buprenorphine treatment program was associated with higher odds of overdose during follow-up (2.37 aOR; 95 % CI: 1.08, 5.21) compared to those who were never part of a treatment program or previously enrolled in a program more than 6 months prior to baseline. Lastly, use of non-prescribed methadone remained a significant predictor of overdose during follow-up and was associated with reduced odds of overdose (0.59 aOR; 95 % CI: 0.38, 0.93) when compared to those who did not report use of non-prescribed methadone.

3.3. MOUD and urine toxicology

Given the unexpected positive association between current buprenorphine treatment at baseline and overdose during follow-up, we conducted a post-hoc analysis to show the distribution of MOUD enrollment, positive urine toxicology, and non-prescribed MOUD use among this sample. Among the 160 participants who reported current enrollment in a methadone treatment program at baseline, 155 (97 %) tested positive for methadone or 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), and 88 (55 %) reported non-prescribed methadone use. In contrast, among the 33 participants who reported current enrollment in a buprenorphine program at baseline, only 8 (24 %) tested positive for buprenorphine or glucuronide, and 22 (67 %) reported non-prescribed buprenorphine use (Table 2).

Table 2
MOUD program enrollment status, positive urine toxicology test results, and self-reported use of non-prescribed MOUD at baseline among PWID in Baltimore, MD (N = 507).

MOUD treatment status	Total sample, n (col. %)	Positive urine toxicology, n (row %)	Non-prescribed MOUD use, n (row %)
Methadone		Methadone or EDDP	Methadone
Not enrolled	347 (68.4)	86 (24.7)	162 (46.6)
Currently enrolled	160 (31.6)	155 (96.8)	88 (55.0)
Buprenorphine		Buprenorphine Glucuronide	Buprenorphine
Not enrolled	474 (93.5)	8 (1.6)	154 (32.4)
Currently enrolled	33 (6.5)	8 (24.2)	22 (66.7)

Abbreviation(s): MOUD = Medication for Opioid Use Disorder, EDDP = 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine.

4. Discussion

By the 6-month follow-up assessment, 14 % of participants experienced an overdose. After model adjustment, experiencing an overdose in the past 6 months or more than 6 months prior to baseline were the strongest predictors of overdose during follow-up. More than three-fourths of those who experienced an overdose during follow-up also reported ever experiencing an overdose at baseline, thus indicating a need for targeted prevention services for those receiving overdose-related healthcare. However, participants who had not experienced an overdose at baseline did overdose by the follow-up assessment. While targeted approaches are essential for those who have experienced an overdose, there remains a great need for population- level interventions for all PWID as future overdose risk is high regardless of previous overdose. It is noteworthy to emphasize data was collected exclusively from drug-impacted neighborhoods in Baltimore and therefore contextual characteristics were unable to be fully explored for their association with overdose within this study. We know from other investigations that Baltimore neighborhoods with majority Black Census tracks and higher poverty rates have significantly higher overdose rates than non-Black majority and wealthy counterparts (Dayton et al., 2020; Maryland Department of Health, 2021; Thieme, 2024). Moreover, Black people living in higher poverty areas in Baltimore have less engagement with overdose prevention services and experience more chronic injection drug use, which highlights the need for localized community-based interventions for drug-impacted areas experiencing co-occurring racial and economic disparities (Dayton et al., 2020; Nandi et al., 2010).

Reported use of street-bought or non-prescribed methadone was significantly predictive with reduced odds of overdose during follow-up, while current enrollment of methadone treatment was not. Conversely, those who reported current enrollment in buprenorphine treatment were found to have two-fold higher odds of overdose during follow-up, while use of street-bought or non-prescribed buprenorphine was not. Although elevated odds are seen among those enrolled in a buprenorphine treatment program, it is crucial to consider only 24 % of those currently enrolled in buprenorphine treatment tested positive for buprenorphine or glucuronide metabolites compared to 97 % positive for methadone or EDDP metabolites among those currently enrolled in methadone treatment. Therefore, enrollment in a buprenorphine program may lack validity as a reliable predictor of overdose given the low adherence to prescribed MOUD. Nevertheless, it does suggest more patient-centered care is needed to address the other unmet biopsychosocial needs that are preventing people from adhering to treatment. Further investigation through qualitative assessments are needed to understand the notable differences between enrollment in a buprenorphine and methadone program, what role suboptimal medication adherence factors into overdose risk, and what unmet needs remain after receiving treatment among PWID.

In contrast to this study's findings, prescribed buprenorphine has lower misuse potential and is known to be an effective MOUD as it is associated with reduced all-cause and opioid-related mortality (Johnson and Richert, 2019; Kelty and Hulse, 2017; Larochelle et al., 2018; Mattick et al., 2014; Sordo et al., 2017; Wakeman et al., 2020). As fentanyl continues to drive the illicit opioid market, there are new risks worth considering when prescribing or receiving MOUD as those who previously used fentanyl may require higher dosages than are typically used to manage withdrawal and craving symptoms (Chambers et al., 2023; Herring et al., 2021). From a qualitative study among people with OUD, participants shared how fentanyl negatively impacted the effectiveness of their prescribed buprenorphine and motivated them towards seeking street-bought or non-prescribed buprenorphine to alleviate symptoms and avoid further fentanyl exposure (Silverstein et al., 2019). Other studies have also documented the use of non-prescribed MOUD being driven by therapeutic motives for self-treatment and the lack of access to prescribed MOUD (Gryczynski et al., 2013; Johnson and Richert, 2019). Among this sample, the high proportion of those who used non-prescribed MOUD highlights a healthcare disparity, and the challenges of living in a low-income context with limited access to treatment or preventive care during the fentanyl era of the opioid overdose epidemic (Buresh et al., 2020; Lewis et al., 2016; Rouhani et al., 2020; Silverstein et al., 2019). Furthermore, an inclusion criterion of this study required participants to be actively injecting drugs, which contributes to the mixed findings on MOUD.

Synthetic opioids have been a primary cause of the opioid overdose epidemic across the US, and especially in communities like Baltimore, MD (Genberg et al., 2021; Schneider et al., 2019). In this sample, only 25 % of participants self-reported intentional injection of fentanyl in the past 6 months at baseline yet 83 % participants tested positive for fentanyl metabolites. Testing positive for fentanyl at baseline was common, although self-reporting fentanyl use was not. Despite the implications of fentanyl on overdose mortality, testing positive for or intentional injection of fentanyl at baseline were not found to be predictive of overdose during follow-up among this sample. The lack of an association between baseline fentanyl injection or positive urine toxicology and overdose during follow-up was unexpected. Given the short window of detection of fentanyl in urine following exposure, fentanyl may be a near-ubiquitous risk factor that raises overdose risk, and urine toxicology results may provide little discriminant power for overdose risk among PWID in Baltimore (Hadland and Levy, 2016; Pearce, 2011; Substance Abuse and Mental Health Services Administration, 2018; Verstraete, 2004). The difference between intentional and unintentional fentanyl use among this sample further demonstrates the need for improved access to preventive healthcare to combat the increasing contamination of fentanyl in the illicit drug market. As Baltimore and the nearby geographical areas experience an increase in overdose rates attributed to fentanyl with each passing year, the availability of harm reduction resources, such as naloxone and fentanyl testing strips, for safer drug consumption become ever more essential to help reduce the risk of overdose mortality among PWID (Buresh et al., 2020; Lewis et al., 2016; Park et al., 2020, 2018).

As for drug-related behavior, the analyses identified potential key time points for overdose prevention intervention as participants who utilized ED services or had an overnight hospital stay were more likely to experience an overdose during follow-up. While an overnight hospital stay was not associated with overdose during follow-up in the multivariate model and utilizing ED services was not included in the multivariate model due to issues of collinearity, it is important to consider that EDs and hospitals are critical places to reach PWID who are at elevated risk of a future overdose. In other studies, hospital admissions are associated with increased risk of fatal overdose as most EDs are not equipped or intended to provide the primary and tertiary preventive care needed to prevent future overdose among PWID (Krawczyk et al., 2020; Lewer et al., 2023). Nevertheless, studies that have incorporated

strategies, such as providing buprenorphine treatment or naloxone, in low-resourced EDs showed significant improvement of treatment adherence and decreased number of future overdose events compared to those who did not receive the intervention (Binswanger et al., 2012; Carroll et al., 2022; Griffith et al., 2023; McCormack et al., 2023; Solomon et al., 2023). Integration of educational and social services, such as overdose prevention training and case management, should also be available at EDs to complement treatment and address other social, physical, or mental comorbidities that negatively impact PWID (McNeil et al., 2014; Motavalli et al., 2021; Paquette et al., 2018; Stoové et al., 2009). PWID who have received health education and overdose prevention training are less likely to consume drugs alone or without naloxone, share drug injection equipment, and are more likely to engage with SSPs, test drugs prior to consumption, and have naloxone readily available (Maxwell et al., 2006; Park et al., 2020; Samuels et al., 2022; Walley et al., 2013). Providing prevention-centered training to complement treatment is necessary to address the overdose epidemic.

4.1. Limitations

This study has important limitations to consider. First, subject retention in the study was moderate as only 70 % of participants completed the follow-up visit. Loss to follow-up introduces potential bias as there could be differences between participants who completed the trial and those who did not. Second, the toxicology report may not fully represent drugs used by participants. The detectable window for drugs is relatively short, and in some cases, only if consumed in the last 24–48 h. Third, analyses based on self-reported information may be subject to measurement errors and therefore introduce bias when retrospective questions are included. Despite the timeframe for the questionnaire being only 6 months, recall bias could factor into the results. Fourth, social desirability bias may be a factor given the stigma associated with injection drug use and the outcome of interest. Fourth, data collection was intended to continue beyond 6 months, but was interrupted by the COVID-19 pandemic. Derailing the primary study from the proposed length of follow-up not only limited identifying significant predictors of overdose for this secondary analysis, but also negatively impacted how follow-up was maintained as data collection was in-person and on-site at the specified neighborhoods. Lastly, it is important to acknowledge the historical contexts and unique characteristics of the US and Baltimore that helped shape the drug-related behaviors and negative health experiences of PWID involved in this study, which limits the inferences from this analysis to other PWID from dissimilar areas and outside of the US.

5. Conclusions

Previous overdose is an important predictor of overdose during follow-up, and opportunities to interact with individuals who have overdosed, whether though emergency medical services, the ED, or hospital encounters, should be leveraged to provide needed services, including drug testing strips, naloxone kits, overdose prevention education, and linkages to drug treatment services. However, many of the study participants who overdosed at follow-up did not report medical encounters or previous overdose at baseline. This demonstrates the imperative for effective population- and community-level approaches to overdose prevention for all PWID and drug-impacted areas as overdose risk remains elevated with the current fentanyl-dominant illicit drug market. Improved access to drug testing, naloxone kits, and safe injection facilities with careful consideration of the existing racial and economic disparities that negatively impact engagement are essential for reducing morbidity and mortality among PWID in Baltimore and elsewhere.

Ethics approval

All procedures were performed in compliance with relevant laws, institutional guidelines, and received IRB approval from the Johns Hopkins School of Medicine (IRB00147873).

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CRediT authorship contribution statement

Brian W. Weir: Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Gregory M. Lucas:** Writing – review & editing, Resources, Project administration, Investigation, Funding acquisition. **Susan G. Sherman:** Writing – review & editing, Investigation. **Michael P. Ramirez:** Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Oluwaseun Falade-Nwulia:** Writing – review & editing, Investigation. **William Clarke:** Writing – review & editing, Investigation. **Robert Harris:** Data curation. **Suzanne M. Grieb:** Writing – review & editing, Investigation. **Miles Landry:** Project administration, Data curation. **Amanda Rosecrans:** Writing – review & editing, Investigation, Data curation. **Kathleen R. Page:** Writing – review & editing, Resources, Project administration, Investigation, Funding acquisition. **Katie Zook:** Project administration, Funding acquisition, Data curation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Due to the sensitive nature of the questions asked throughout this study and the outcome of interest, participants were assured raw data would remain confidential and not be shared outside of the research institution.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.dadr.2024.100286.

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