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Quantity fluctuations of illicitly used opioids and overdose risk

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Abstract

BACKGROUND—Reduced opioid tolerance is believed to be associated with overdose risk, although this relationship has primarily been examined in the context of gaps and frequency of opioid use. We sought to assess how changes in the quantity of opioids used, as opposed to periods of abstinence or overall frequency of use, relate to overdose risk.

METHODS—Among repeated visits of participants of a behavioral intervention trial from 2014-2016, we used multivariable logistic regression models fit with generalized estimating equations to examine the relationship between the percentage of opioid use days on which individuals used more or less than the quantity they used on average (i.e., quantity volatility) and the occurrence of opioid overdose.

RESULTS—Our sample included 290 four-month reporting periods among 63 participants (67% male). Opioid overdose events were reported by 28 (44%) participants during 48 (17%) reporting periods. Our measure of quantity volatility had a median of 20% (IQR 0.0-50.0). In multivariable analysis, using a quantity different than the quantity used on average on more than 20% of all opioid use days in the reporting period was significantly associated with odds of any opioid overdose (Adjusted OR=3.55, 95%CI=1.55-8.13, p=0.003), controlling for confounders.

CONCLUSION—Quantity volatility of illicitly used opioids was positively associated with overdose risk and may contribute to the complex system of overlapping factors that influence overdose risk. Future observational research among opioid users should collect detailed opioid use data, including quantity used over time, to clarify the patterns that most elevate overdose risk.

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DECLARATIONS OF INTEREST

None.

DISCLAIMER

The authors are solely responsible for the content of this article, which does not necessarily represent the official views of the San Francisco Department or Public Health.

Keywords

Opioid overdose; risk factors; injection drug use; heroin; prescription opioids

INTRODUCTION

The United States continues to grapple with an unprecedented opioid overdose epidemic. Since 1999, the opioid overdose mortality rate has more than tripled (Rudd, Aleshire, Zibbell, & Gladden, 2016). As this public health crisis expands and evolves, continued research is essential to understanding the key drivers of overdose risk, both distal and proximate.

A large portion of overdose-related research has focused on understanding the role of individual risk behaviors. Correspondingly, history of prior overdose, polysubstance use, and resumption of use after periods of abstinence, perhaps due to rapid changes in physiological tolerance, have all been established as significant drivers of overdose risk among individuals who use opioids (Coffin et al., 2003; Darke, Mills, Ross, & Teesson, 2011; Jenkins et al., 2011; Stoove, Dietze, & Jolley, 2009). These individual-level findings have directly informed the development of interventions aiming to reduce overdose risk among different populations at risk, such as community-based training and education programs or naloxone distribution programs targeting individuals released from prison (i.e., following a period of forced abstinence and reduced tolerance) (Clark, Wilder, & Winstanley, 2014; Parmar, Strang, Choo, Meade, & Bird, 2017).

The relationship between physiological tolerance to opioids and overdose risk has primarily been examined in the context of gaps and frequency of opioid use. Observational studies have identified an increase in overdose risk immediately following periods of incarceration or substance use treatment, theoretically due to changes in tolerance that may accompany periods of abstinence (Alex et al., 2017; Binswanger, Blatchford, Mueller, & Stern, 2013; Binswanger et al., 2007; Clausen, Waal, Thoresen, & Gossop, 2009; Darke, Williamson, Ross, & Teesson, 2005; Groot et al., 2016; Jenkins et al., 2011; Merrall et al., 2010; Moller et al., 2010). Similarly, the enhanced overdose risk associated with injecting heroin versus other routes of administration has been shown to be higher for sporadic users than daily users, perhaps due to lower tolerance among sporadic users (Brugal et al., 2002). Contradicting these findings, multiple observational studies among people who inject drugs have observed a *lower* risk of opioid overdose among low-frequency, sporadic heroin injectors compared to high-frequency heroin injectors (Evans et al., 2012; Harris et al., 2013). Forensic toxicological research using hair analyses among small samples of heroin overdose decedents have also arrived at conflicting conclusions regarding the relative significance of abstinence and frequency of use, compared to other risk behaviors such as polysubstance use, in increasing opioid overdose risk (Druid et al., 2007; Tagliaro, De Battisti, Smith, & Marigo, 1998). It is clear from these mixed findings that the relationship between opioid use patterns, physiological tolerance, and overdose risk is complex and not fully understood.

The nature of the relationship between opioid use characteristics and overdose risk is highly relevant to prevention messaging that might hypothetically conflict with efforts to reduce one's drug use. As part of a randomized behavioral intervention trial in San Francisco, California, we collected detailed longitudinal information regarding the frequency and quantity of opioids used illicitly as well as non-fatal opioid overdose events from a sample of opioid users at high risk for overdose. In an exploratory analysis among participants of this intervention trial, we examined the relationship between changes in the quantity of opioids used over time, or quantity volatility, and non-fatal opioid overdose risk. Our aim was to leverage these detailed, novel data regarding opioid use patterns and overdose events to enhance our understanding of the complex relationship between frequency and quantity of opioid use and overdose risk.

METHODS

Study Sample

The present study examines data from the participants of a pilot randomized trial of a repeated-dose behavioral intervention aiming to reduce overdose and risk behaviors among individuals who use opioids illicitly (REBOOT Study; ClinicalTrials.gov Identifier: NCT02093559). Participants were recruited through active outreach and print advertisements at syringe access (i.e., needle exchange) programs in San Francisco, CA from August 2014 to August 2015. Study eligibility criteria included: 18-65 years of age, opioid dependence (as assessed by the Structured Clinical Interview for DSM-IV-TR Axis I Disorders), positive for opioids by urinalysis at screening, self-report of an opioid overdose in the past 5 years, and prior receipt of take-home naloxone. Eligible participants could report using any opioid (heroin, prescription opioids, etc.) by any route of administration (oral, injection, etc.). Study procedures were approved by the Committee on Human Research, University of California San Francisco (CHR#13-11767) and all participants provided informed consent.

Enrolled participants were randomized in a 2:1 ratio to receive either the intervention, a multi-session counseling series that incorporated motivational interviewing and risk reduction counseling methods with the aim of reducing opioid overdose risk, or treatment as usual, which included information and referrals but no counseling. Participants in both the intervention and control (i.e., treatment as usual) groups completed visits at baseline and approximately every four months for 16 months and a total of five visits between August 2014 and December 2016.

Data Collection

At each visit, trained staff administered computer-assisted personal interviews (CAPI) to all participants. At baseline, demographic information and both lifetime and past 120 day (i.e., four month) history of opioid use and non-fatal overdose were collected. At each of up to four follow-up visits, opioid use and non-fatal overdose history was collected for the time period since the last completed visit. For opioid use information, recall was capped at 148 days, so if a participant's last visit occurred greater than 148 days prior to the current visit, they were only asked about the last 148 days.

Because recall of opioid use information during follow-up visits was cut off at 148 days and recall of opioid overdose events was not, there was a difference in recall duration between opioid use and opioid overdose for a total of 19 reporting periods. Of these 19 reporting periods with recall discrepancies, only six of them involved at least one overdose event and only one involved events that that may have occurred prior to the 148 day cut-off for opioid use recall. For this single reporting period, a total of five opioid overdose events were reported and, because dates were only collected for the three most recent events (each of which occurred within the 148 day recall window), it is possible that the two remaining events occurred prior to the 148 day cut-off. As a result, we included a sensitivity analysis in which we exclude this single reporting from the analysis.

Measures

Demographic information collected at baseline included gender, race, ethnicity, age, education history, income, and housing status.

Opioid use information collected for each reporting period at baseline (120 day recall) and follow-up visits (recall since the last visit, up to 148 days) included the frequency and quantity used of the opioid used most frequently by the participant as well as how often they used more or less than their reported average quantity. Frequency of use was collected for all opioids with the options: less than once a month, one, two, or three days per month, and each of one through seven days per week. To be used in subsequent questions related to participants' opioid use frequency, frequency was converted to days of opioid use during each reporting period for the participant's most frequently used opioid. Days of opioid use for the most frequently used opioid was calculated as follows: (1) each frequency option was converted into a fraction corresponding to the ratio of days of use per 30-day month, assuming four weeks in a month (for example, a frequency of three days per month converts to a fraction of 3/30; a frequency of three days per week converts to a fraction of 12/30); (2) for each reporting period, the frequency-based fraction was multiplied by the total number of days in the reporting period to calculate the approximate number of days that the most frequent opioid was used during the reporting period.

For heroin, quantity used on days of use was collected with the question: "On average, how many bags of heroin have you used each day that you used? A bag of heroin is about 100 milligrams." Partway through the study, we found that most participants thought about their heroin use in terms of grams as opposed to "bags" so the question was reformulated to: "On average, how many grams of heroin have you used each day that you used? A bag of heroin is about 100 milligrams (0.1 gram)." Amounts less than one gram were reportable as decimals with up to two decimal places. For opioid analgesics, quantity was collected in milligrams for all opioid analgesics except for fentanyl, which was collected in micrograms. Common brand names and single pill dosage ranges were provided for each opioid analgesic to facilitate participant recall (e.g., for oxycodone: Percocet, OxyContin, Roxicodone, Percodan were included as common brand names and 5 to 80 milligrams as the single pill dosage range).

To assess changes in opioid quantity, or quantity volatility, for the opioid that participants reported using most frequently, we collected the percentage of use days on which they used

more than the average quantity that they personally reported using and the percentage of use days on which they used less than their individual average quantity. For both of these questions, participants could respond with integer values between 0% and 50% of opioid use days. During the study, it was determined that multiple participants had difficulties conceptualizing their use patterns in terms of percentages, so the question was modified to assess quantity volatility by collecting the *number*, as opposed to the *percentage*, of use days on which they used more and less than the average quantity that they reported using. For participants for whom we collected the *number* of use days on which they used more and less than average, we converted their reported values back to percentages of use days so as to be consistent with the participants who originally reported the *percentage* of use days (see Supplemental Figure for a more detailed description of these calculations). Because we were interested in any volatility in quantity and not just a higher or lower quantity, we created a composite measure corresponding to the percentage of opioid use days on which participant's used more or less (i.e. a different quantity) than they reported using on average. This measure was calculated by summing the percentage of use days on which participant's reported using more than the average quantity and the percentage of use days on which participant's reported using less than the average quantity for each reporting period.

Opioid overdose information was collected as the number of non-fatal overdose events self-reported by participants during each reporting period. Opioid overdose events were defined for participants as when an individual takes opioids and then: (1) "The person is unresponsive when shaken or their name is called"; (2) "The person can't be woken up without help (for example CPR or naloxone)"; (3) "The person's skin, lips, or fingers turn blue; and (4) "The person stops breathing, or breathes really slowly." Because of the small number of events reported, we converted this measure to a binary variable indicating whether or not any non-fatal opioid overdose event was reported during each reporting period.

Analysis

To examine the relationship between quantity volatility and occurrence of opioid overdose events, we used multivariable logistic regression fit with generalized estimating equations (GEE) to account for clustering of multiple visits for each participant. The binary dependent variable was occurrence of any opioid overdose during the reporting period and the primary independent variable was the continuous percentage of opioid use days on which participants' used more or less than their average quantity (i.e., continuous quantity volatility). To further explore the nature of the relationship between quantity volatility and opioid overdose, we built two separate additional models that included our quantity volatility measure as: 1) categorical quartiles and 2) a binary variable indicating a percentage quantity volatility above or below the median. To control for confounding in each of these three models, we included gender; race/ethnicity; age; housing status (i.e., whether the participant slept in traditional housing most nights) during the reporting period; whether the participant used opioids in a new place in which they had never used before during the reporting period; whether they reported any concurrent use of opioids and alcohol, methamphetamine, cocaine, or benzodiazepines during the reporting period (i.e., used at the same time or within two hours of using opioids); number of most frequent opioid use days (i.e., the denominator

used to calculate the continuous quantity volatility measure) during the reporting period; length of the reporting period in days; treatment arm; and a sequential count variable indicating integer months since the first participant enrollment to account for any secular trend in our primary outcome. Due to small cell sizes and invariable outcomes among multiple racial/ethnic groups, race/ethnicity was coded as a binary variable indicating whether or not the participant identified as non-Hispanic white. For housing status, we considered houses, apartments, and rented rooms, as “traditional housing”; we considered cars or other vehicles, abandoned buildings, train stations, shelters, drug treatment centres, medical care facilities, squatting, and the street as not “traditional housing”. To assess the possibility of interaction between quantity volatility and treatment arm, we included an interaction term in all models; if there was no evidence of interaction (p>0.25), the interaction term was removed and treatment arm was included as an independent covariate. All analyses were performed using Stata 14 (StataCorp, 2015).

In sensitivity analyses, we added additional variables to or dropped specific observations from the GEE logistic regression models described above. In the first sensitivity analysis, we included a variable indicating whether the opioid most frequently used during the reporting period was heroin or a prescription opioid, which excludes participants who did not report using opioids during the reporting period. In the second sensitivity analysis, we examined only reporting periods for which heroin was the most frequently used opioid and we included a continuous variable for the quantity of heroin used. We included only reporting periods for which heroin was the most frequently used opioid in the prior sensitivity models because quantity of heroin and prescription opioids used would not be comparable. In the third sensitivity analysis, due to our small sample size and the large number of potential confounders included in our multivariable models, we utilized backwards stepwise selection to remove all covariates with Wald Test p-values > 0.05. In the fourth sensitivity analysis, we excluded the single reporting period during which an overdose event could have occurred outside of the opioid use recall window, as described earlier. Finally, to assess the possibility that the mid-study change in the phrasing of the quantity volatility survey questions could affect our estimates (i.e., from a percentage to an absolute numeric value), we conducted a fifth sensitivity analysis in which included an interaction term between the quantity volatility measure and a variable indicating whether the participant was asked the original or the revised phrasing of the question. Sensitivity analyses were conducted for all three formulations of the quantity volatility measure: continuous, categorical quartiles, and categorical above/below the median.

RESULTS

Study Sample

Our analysis includes a total of 290 reporting periods among 63 participants (Table 1), with the remaining 25 possible reporting periods missing due to either missed participant visits (n=24) or the CAPI survey not being saved (n=1). The majority (n=39; 62%) of participants were non-Hispanic white, eleven (18%) were non-Hispanic Black/African-American, nine (14%) were Hispanic/Latino, and four (6%) were another non-Hispanic race. Forty-two (67%) participants were male and the mean age was 43 years.

Opioid overdose events were reported by 28 participants during 48 (17%) of the 290 reporting periods (Table 2). Our primary continuous measure of quantity volatility, that is, the percentage of opioid use days on which a participant used a higher or lower quantity than the quantity they reported using on average, had a mean of 28.3% (SD = 29.0) and a median of 20.0% (IQR = 0.0-50.0) across all reporting periods; as such, half of all reporting periods involved a quantity volatility greater than 20%. Heroin was the most frequently used opioid in 216 (75%) reporting periods, prescription opioids in 52 (18%), and no opioids were used during 22 (8%) reporting periods. The average quantity of heroin used on each day of use was 805 milligrams (SD = 909).

Multivariable Analysis

In the multivariable model assessing the relationship between continuous quantity volatility and occurrence of opioid overdose events, quantity volatility was positively associated with the odds of any opioid overdose event (Adjusted Odds Ratio [aOR]=1.01, 95%CI=1.00-1.03, p=0.032) (Table 3). In the multivariable model assessing categorical quantity volatility as quartiles, the highest two quartiles of quantity volatility were significantly associated with odds of any opioid overdose event (3^{rd} vs. 1^{st} Quartile: aOR=3.65, 95%CI=1.06-12.55, p=0.040; 4^{th} vs. 1^{st} Quartile: aOR=4.21, 95%CI=1.06-16.75, p=0.042). In the multivariable model assessing categorical quantity volatility as above or equal to and below the median (median=20.0%), quantity volatility above the median was significantly associated with odds of any opioid overdose event (OR=3.55, 95%CI=1.55-8.13, p=0.003). There was no evidence of interaction between treatment arm and quantity volatility in any of the models.

In the first set of sensitivity analyses, including a variable in the models indicating whether the opioid most frequently used was heroin or a prescription opioid did not qualitatively change the point estimates of the associations between quantity volatility and odds of any opioid overdose event in any of the models; however, the standard errors of the estimates in the continuous and quartile-categorical models increased, resulting in p-values greater than 0.05 (p=0.053 in continuous model; p=0.080 for both the 3^{rd} to 1^{st} quartile and 4^{th} to 1^{st} quartile comparisons in quartile-categorical model). In the second set of sensitivity analyses, including only reporting periods where heroin was the opioid most frequently used and including quantity of heroin used did not qualitatively change the point estimates or standard errors for the estimated associations between either continuous or categorical quantity volatility (quartiles or above/below median) and odds of any opioid overdose event. In the third set of sensitivity analyses utilizing backwards stepwise model selection, the point estimates for the association between quantity volatility and odds of any opioid overdose event were not qualitatively different for any of the models; however, the standard errors of the estimates in the continuous and quartile-categorical models increased, resulting in p-values greater than 0.05 (p=0.058 in continuous model; p=0.057 for the 3^{rd} to 1^{st} quartile comparison and p=0.062 for the 4^{th} to 1^{st} quartile comparisons in quartile-categorical model). In the fourth set of sensitivity analyses in which we excluded the single reporting period during which an overdose event could have occurred outside of the opioid use recall window, there were no qualitative differences from the main models in point estimates or standard errors. In the fifth and final set of sensitivity analyses, there was no evidence of

interaction between quantity volatility and whether the participant was asked the original or revised phrasing of the quantity volatility questions in any of the models (p>0.25).

DISCUSSION

In this exploratory analysis of opioid users participating in a behavioral intervention trial, fluctuations in the amount of opioids used was associated with an increased odds of reporting a non-fatal opioid overdose. This is the first study to examine this aspect of opioid use patterns over time and how it relates to overdose risk.

The association between changes in quantity of opioids used and overdose risk is biologically plausible. The depressive respiratory effects that lead to opioid overdose are known to be dose dependent (Pattinson, 2008). Although we were unable to determine the exact dose of opioids used, it is likely that changes in quantity represent changes in dose. As such, inconsistent opioid use patterns (i.e, quantity volatility) facilitate more opportunities for an individual's opioid dose to exceed their physiologic tolerance for these respiratory effects. Indeed, for this reason, healthcare providers who prescribe opioids are advised to exercise extreme caution and carefully consider a number of clinical factors when adjusting a patient's opioid dose (Dowell, Haegerich, & Chou, 2016).

Notably, prior studies assessing the relationship between frequency of opioid use and overdose risk have produced mixed results, conversely linking overdose risk to both frequent (Evans et al., 2012; Harris et al., 2013) and infrequent use of opioids (Brugal et al., 2002) in different populations. The ambiguity of such findings may be related to other attributes of an individual's opioid use patterns, such as fluctuations in quantity or dose, that were not evaluated in these prior studies and are rarely examined or incorporated into analyses. Our findings suggests that quantity volatility may play a role in the complex web of overlapping factors that influence overdose risk, along with frequency of use, polysubstance use, the genetic makeup of the individual, and a multitude of other factors.

Alternatively, it is plausible that quantity volatility is associated with chaotic life conditions or engagement with other overdose risk behaviors; however, our main models and sensitivity analyses attempted to suppress these potentially confounding pathways by controlling for relevant individual and opioid use characteristics (e.g., housing status, concomitant polysubstance use, etc.). Although some of our sensitivity analyses resulted in inflated standard errors and thus point estimates that were not statistically significant at the 5% level, the results of our multivariable models suggest that our findings are robust and that fluctuations in opioid quantity may in fact influence overdose risk independent of these other known risk factors. In fact, quantity volatility was a stronger predictor of overdose than other established risk factors in our sample, such as concurrent polysubstance use, further highlighting its potential significance.

Although quantity volatility could perhaps be addressed alongside other risk behaviors as part of educational harm reduction efforts, it is not likely to be as amenable to modification as other risk behaviors such as syringe sharing in the case of HIV prevention. The ability to access, obtain, and use consistent quantities of illicit opioids plays out in the broader context

of the global and local illicit drug trade and the social and economic circumstances of the individual (Rhodes, 2009). In contrast to addressing quantity volatility as part of a behavioral intervention, medication assisted treatment (MAT), such as methadone or buprenorphine maintenance therapy, attempts to reduce harms associated with illicit opioid use by maintaining opioid-dependent individuals on safe and consistent doses, outside of these broader, and potentially volatile, contexts. As such, expanded access to MAT represents one possible strategy to reducing quantity and dose volatility and associated harms among individuals who use opioids illicitly. In addition, although our study was not designed to assess specific causes of quantity volatility, it is possible that interventions targeting greater stability (e.g., income, housing, etc.) among opioid users may achieve ancillary benefits by reducing quantity volatility.

A study of individuals who inject drugs in Vancouver, Canada found that those who injected heroin were at significantly greater risk for overdose than those who only injected prescription opioids (Lake et al., 2015), a finding that may be explained by the volatile potency and composition of heroin (Darke, Hall, Weatherburn, & Lind, 1999; Smithson, McFadden, Mwesigye, & Casey, 2004), which contrasts with the reliable dosage and composition of prescription opioids. Although we examined self-reported quantities of opioids used and not empirically determined doses, these findings may be tapping into the same underlying relationship between volatility in actual dose, tolerance, and overdose risk. Better understanding this relationship as well as any other novel overdose risk factors is particularly important in context of the evolving opioid epidemic, where opioid stewardship initiatives are constricting prescribing and the availability of diverted prescription opioids (Chang et al., 2016; Lyapustina et al., 2016; Rutkow et al., 2015) and both rates of heroin use (United Nations Office on Drugs and Crime, 2016) and deaths from synthetic opioids (Rudd, Seth, David, & Scholl, 2016) are increasing.

This exploratory study has numerous limitations. First, our convenience sample of 63 participants is relatively small and not necessarily generalizable to broader populations of opioid users.. Second, all data assessed in this analysis was collected by self-report, which is vulnerable to both recall and social desirability bias; however, we have no reason to believe that any exposure or outcome misclassification would occur differentially based on a participant’s quantity volatility. As such, any nondifferential misclassification would bias the results of our multivariable models towards the null. Third, reports of heroin use made up the majority of our analysis and, as previously discussed, we did not collect any empirical data on potency or dose. Therefore, in the case of heroin, our primary measure of quantity volatility is likely to be an imprecise measure of actual dose. Fourth, our measure of quantity volatility included only the opioid used most frequently by each participant during a reporting period and thus does not capture quantities used for any opioids used less frequently. Lastly, the phrasing of key survey questions used in this analysis was modified during the course of the study, which may have affected our ability to measure quantity volatility consistently; however, it is not possible to assess how the different phrasings may have affected the validity of our quantity volatility measure. Notably, in sensitivity analyses, estimates of the association between quantity volatility and overdose did not differ between recall periods in which the different versions of the questions were asked, suggesting a continuity in this association across the two versions of the questions. Given these

limitations and the exploratory nature of this study, our findings should be interpreted as hypothesis-generating.

Despite these limitations, the present study offers a novel contribution to the literature and to our present understanding of the relationship between opioid use patterns and overdose risk. Whereas prior research has focused on frequency or gaps in opioid use to better understand the role of physiological tolerance in opioid overdose events, our findings highlight the potential importance of also considering quantity volatility. Future research among opioid users should collect these types of detailed opioid use data to clarify the patterns that most elevate overdose risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic characteristics, overdose events, and opioid use characteristics of study participants (n=63)

	n	(%)
n	63	(100.0)
Race/Ethnicity		
White	39	(61.9)
Black/African-American	11	(17.5)
Hispanic/Latino	9	(14.3)
Other	4	(6.3)
Gender		
Male	42	(66.7)
Female	21	(33.3)
Age, *mean (sd)*	43.3	(11.7)
Homeless in lifetime *	60	(95.2)
Education at Baseline		
Less than high school graduate	16	(25.4)
High school graduate or GED	21	(33.3)
Some college, 2-year college degree, or	22	(34.9)
Bachelor's degree	4	(6.3)
Number of Visits, *mean (sd)*	4.6	(1.0)

* From the question, "Have you ever been homeless?" at baseline.

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Table 2

Overdose events and opioid use characteristics by study visit (n=290)

	Visit 1		Visit 2		Visit 3		Visit 4		Visit 5		All Visits	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Number of Participants with Complete Data	63	(100. 0)	61	(100 .0)	56	(100 .0)	56	(100 .0)	54	(100 .0)	290	(100 .0)
Length of Reporting Period (days), ***mean (sd)***	120	(0.0)	117 .4	(16. 4)	119 .6	(31. 3)	132 .9	(38. 5)	119 .9	(31. 4)	121 .9	(27. 1)
Number of Reporting Periods with Any Overdose Event	21	(33.3)	11	(18. 0)	6	(9.5)	7	(11. 1)	3	(4.8)	48	(16. 6)
Opioid Dose Volatility *												
Percentage of Opioid Use Days with higher/lower dose than typical, mean (sd)	44. 2	(30.2)	31. 0	(27. 3)	27. 2	(30. 2)	18. 7	(23. 9)	18. 0	(24. 9)	28. 3	(29. 0)
First Quartile (0% - 1.5%)	6	(9.5)	10	(16. 4)	17	(27. 0)	21	(33. 3)	20	(31. 7)	74	(25. 5)
Second Quartile (1.5% - 22.5%)	11	(17.5)	18	(29. 5)	13	(20. 6)	15	(23. 8)	17	(27. 0)	74	(25. 5)
Third Quartile (22.5% - 50%)	26	(41.3)	22	(36. 1)	17	(27. 0)	15	(23. 8)	12	(19. 0)	92	(31. 7)
Fourth Quartile (50% - 100%)	20	(31.7)	11	(18. 0)	9	(14. 3)	5	(7.9)	5	(7.9)	50	(17. 2)
Percentage of Opioid Use Days with higher dose than typical, mean (sd)	25. 2	(19.3)	18. 5	(19. 2)	13. 2	(17. 7)	9.0	(14. 3)	8.4	(15. 6)	15. 2	(18. 4)
Percentage of Opioid Use Days with lower dose than typical, mean (sd)	19	(19.8)	12. 5	(17. 5)	13. 9	(19. 2)	9.7	(14. 2)	9.5	(15. 1)	13. 1	(17. 6)
Most Frequent Opioid Used During Reporting Period												
Heroin	52	(82.5)	43	(70. 5)	38	(60. 3)	42	(66. 7)	41	(65. 1)	216	(74. 5)
Quantity used (mg), *mean (sd)*	674	(1010 .5)	422 .1	(515 .7)	760 .5	(886 .1)	105 5	(997 .7)	115 4	(867 .0)	805 .4	(909 .0)
Prescription Opioid	11	(17.5)	15	(24. 6)	12	(19. 0)	8	(12. 7)	6	(9.5)	52	(17. 9)
No Opioids Used	0	(0.0)	3	(4.9)	6	(9.5)	6	(9.5)	7	(11. 1)	22	(7.6)
Days of Opioid Use During Reporting Period, ***mean (sd)***	101 .3	(36.3)	91	(42. 5)	76. 1	(50. 3)	72. 3	(52. 2)	68. 4	(51. 8)	82. 5	(48. 1)
Participant Spent Most Nights in Non-Traditional Housing †	27	(42.9)	26	(42. 6)	23	(36. 5)	27	(42. 9)	25	(39. 7)	128	(44. 1)
Participant Used Opioids Concurrently with Other Substances ‡	51	(81.0)	49	(80. 3)	42	(66. 7)	37	(58. 7)	33	(52. 4)	212	(73. 1)
Participant Used Opioids in a New Place	32	(50.8)	31	(50. 8)	22	(34. 9)	21	(33. 3)	17	(27. 0)	123	(42. 4)

*Opioid dose volatility is measured as the percentage of opioid use days on which participant used more or less than the quantity they reported using on average. Opioid use days and quantity used pertain only to the opioid used most frequently during each recall period.

†Non-traditional housing defined as cars or other vehicles, abandoned buildings, train stations, shelters, drug treatment centers, medical care facilities, squatting, and the street.

‡"Other substances" includes alcohol, methamphetamine, cocaine, and benzodiazepines. "Concurrently" refers to use at the same time or within two hours of using opioids during the reporting period.

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Table 3

Three multivariable generalized estimating equation (GEE) logistic regression models assessing the odds of reporting any overdose event in during a reporting period (n = 290 reporting period among 63 participants)

	Model I			**Model II**			**Model III**		
	Dose Volatility as a Continuous Measure			**Dose Volatility as a Categorical Measure (Quartiles)**			**Dose Volatility as a Categorical Measure (Above/ Below Median)**		
	Odds of Any Opioid Overdose Event			**Odds of Any Opioid Overdose Event**			**Odds of Any Opioid Overdose Event**		
	aOR*	**(95% CI)**	***p*-value**	**aOR***	**(95% CI)**	***p*-value**	**aOR***	**(95% CI)**	***p*-value**
Continuous Quantity Volatility†	1.01	(1.00- 1.03)	0.032	–	–	–	–	–	–
Categorical Quantity Volatility (Quartiles)†									
First Quartile	–	–	–	Reference			–	–	–
Second Quartile	–	–	–	1.11	(0.28- 4.40)	0.866	–	–	–
Third Quartile	–	–	–	3.65	(1.06- 12.55)	0.040	–	–	–
Fourth Quartile	–	–	–	4.21	(1.06- 16.75)	0.042	–	–	–
Categorical Quantity Volatility (Above/ Below Median)*									
Below Median	–	–	–	–	–	–	Reference		
Equal to or Above Median	–	–	–	–	–	–	3.55	(1.55- 8.13)	0.003
Gender									
Female	Reference			Reference			Reference		
Male	0.39	(0.15- 1.00)	0.051	0.38	(0.15- 1.00)	0.050	0.39	(0.15- 1.01)	0.053
Race									
Non-White	Reference			Reference			Reference		
White	0.75	(0.31- 1.80)	0.521	0.71	(0.29- 1.73)	0.454	0.71	(0.29- 1.71)	0.441
Age	1.03	(1.00- 1.08)	0.086	1.03	(1.00- 1.08)	0.085	1.03	(1.00- 1.07)	0.088
Spent Most Nights in Non-Traditional Housing‡	0.36	(0.15- 0.83)	0.017	0.36	(0.15- 0.84)	0.018	0.36	(0.15- 0.85)	0.019
Used Opioids Concurrently with Other Substances§	1.42	(0.53- 3.82)	0.483	1.20	(0.44- 3.30)	0.719	1.19	(0.44- 3.22)	0.728
Used Opioids in a New Place	4.50	(1.99- 10.17)	<0.001	4.33	(1.39- 9.83)	<0.001	4.35	(1.92- 9.88)	<0.001

	Model I Dose Volatility as a Continuous Measure Odds of Any Opioid Overdose Event			Model II Dose Volatility as a Categorical Measure (Quartiles) Odds of Any Opioid Overdose Event			Model III Dose Volatility as a Categorical Measure (Above/ Below Median) Odds of Any Opioid Overdose Event		
	aOR*	**(95% CI)**	***p*-value**	**aOR***	**(95% CI)**	***p*-value**	**aOR***	**(95% CI)**	***p*-value**
Days of Opioid Use During Reporting Period	1.00	(0.99- 1.01)	0.993	1.00	(0.99- 1.01)	0.967	1.00	(0.99- 1.01)	0.892
Length of Reporting Period in Days	1.00	(0.99- 1.02)	0.534	1.01	(0.99- 1.02)	0.449	1.01	(0.99- 1.02)	0.426
Secular Trend in Months	0.93	(0.87- 0.99)	0.023	0.93	(0.87- 1.00)	0.039	0.93	(0.87- 0.99)	0.033

*Adjusted odds ratio

†Opioid dose volatility is measured as the percentage of opioid use days on which participant used more or less than the quantity they reported using on average. Opioid use days and quantity used pertain only to the opioid used most frequently during each recall period.

‡Non-traditional housing defined as cars or other vehicles, abandoned buildings, train stations, shelters, drug treatment centers, medical care facilities, squatting, and the street.

§"Other substances" includes alcohol, methamphetamine, cocaine, and benzodiazepines. "Concurrently" refers to use at the same time or within two hours of using opioids during the reporting period.