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Research Paper

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 to 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.

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

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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 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 g)." 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