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“Unintentional drug overdose: Is more frequent use of non-prescribed buprenorphine associated with lower risk of overdose?”

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Abstract

Background: Unintentional drug overdoses have reached epidemic levels in the U.S. This study tests the hypothesis that people who have used non-prescribed buprenorphine more frequently in the past six months were less likely to experience a drug overdose during that same time period.

Methods: Participants age 18 years or older with opioid use disorder who reported use of non-prescribed buprenorphine in the last six months were recruited from the Dayton, Ohio, area using a combination of targeted and modified respondent-driven sampling. Participants completed a structured interview, including six-month timeline follow-back, after informed consent. Logistic regression was used to test the association between (log-transformed) frequency of non-prescribed buprenorphine use and overdose in the previous six months, adjusted for confounding due to sex, homelessness, incarceration, substance use treatment, previous overdose, heroin/fentanyl injection, psychiatric comorbidity, and (log-transformed) frequencies of other (non-opioid) drug use.

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Conflicts of interest

The authors declare no conflicts of interest.

CRedit author statement

Robert G. Carlson: Conceptualization, Investigation, Writing -Original Draft; **Raminta Daniulaityte:** Conceptualization, Investigation; Writing-Review & Editing; Project Administration, Funding Acquisition; **Sydney M. Silverstein:** Conceptualization, Writing—Review & Editing; **Ramzi W. Nahhas:** Conceptualization, Formal Analysis, Writing-Original Draft; **Silvia S. Martins:** Conceptualization, Writing-Review and Editing.

Results: Almost 89% of 356 participants were white, 50.3% were male, and 78.1% had high school or greater education. Over 27% (n=98) reported experiencing an overdose in the past six months. After adjusting for confounding, greater frequency of non-prescribed buprenorphine use was significantly associated with lower risk of overdose (AOR=0.81, 95% CI=0.66, 0.98; p=.0286). Experiencing an overdose more than six months ago (AOR=2.19, 95% CI=1.24, 3.97); injection as the most common route of administration of heroin/fentanyl (AOR=2.49, 95% CI=1.36, 4.71); and frequency of methamphetamine use (AOR=1.13, 95% CI=1.02, 1.27) were strongly associated with increased risk of recent overdose in multivariable analysis.

Discussion: The findings support our hypothesis that higher frequency of non-prescribed buprenorphine use is associated with lower risk of drug overdose, a potential harm reduction consequence of diversion. Improving the availability of buprenorphine through standard substance use disorder treatment, primary care, and other innovative methods is urgently needed.

Keywords

Unintentional Drug Overdose; Buprenorphine Diversion; Heroin; Non-Pharmaceutical Fentanyl

Introduction

The opioid epidemic in the U.S. shows little signs of diminishing, with unintentional overdose deaths reaching unsurpassed levels, although a small decrease is indicated in 2018 (mainly due to decreases in overdoses in which prescription opioids were involved) (CDCNVSS, 2019; Gladden, O'Donnell, Mattson, & Seth, 2018; Goodnough, Katz, & Sangor-Katz, 2019; Hedegaard, Minino, & Warner, 2018; Rudd, Aleshire, Zibbell, & Gladden, 2016). Drug overdose deaths increased from 47,055 people in 2014 to 70,237 people in 2017 (Hedegaard et al., 2018; Rudd et al., 2016). The recent escalation in the number of unintentional overdose deaths has been linked to the increased presence of non-pharmaceutical fentanyl and its analogues, such as carfentanyl, acryl fentanyl, and others (Centers for Disease Control and Prevention, 2015; Ciccarone, 2017; Jones, Einstein, & Compton, 2018; O'Donnell, Gladden, Mattson, & Kariisa, 2018).

A range of risk factors for opioid overdose have been identified. One of the strongest correlates of overdose risk is having experienced a previous overdose (Coffin et al., 2007; Najman, McIlwraith, Kemp, & Smirnov, 2017; Stoope, Dietze, & Jolley, 2009). Reduced tolerance, as a result of release after forced abstinence resulting from incarceration and abstinence resulting from substance abuse treatment, including detoxification, have also been associated with increased risk of overdose (Binswanger et al., 2007; Kinner et al., 2012; Leach & Oliver, 2011; Murphy et al., 2018; Strang et al., 2003; Wines, Saitz, Horton, Loyd-Travaglini, & Samet, 2007; Maughan and Becker, 2019). Quantity of opioids consumed (Rowe, Wheeler, Vittinghoff, Santos, & Behar, 2018), changes in heroin purity (Darke, Hall, Weatherburn, & Lind, 1999), increased availability of non-prescribed fentanyl analogues with varying levels of potency (Ciccarone, Ondocsin, & Mars, 2017; Daniulaityte et al., 2019-a; Fairborn, Coffin, & Walley, 2018), and injection route of administration increase risk of overdose (Brugal et al., 2002). Combining multiple CNS depressants (Coffin et al., 2003), such as alcohol (Ruttenber & Luke, 1984), use of non-prescribed benzodiazepines (McClure, Niles, Kaufman, & Gudim, 2017; Zedler et al., 2015)

and prescribed tranquilizers (Silva, Schragger, Kecojevic, & Lankenau, 2013) have been associated with increased risk of overdose. Finally, use of stimulants, including cocaine and methamphetamine, often in combination with heroin (Brugal et al., 2002; Coffin et al., 2003; Jalal et al., 2018; Kinner et al., 2012; Ochoa et al., 2005; Warner, Trinidad, Bastian, Minino, & Hedegaard, 2016; Werb et al., 2008) have also been associated with increased overdose risk.

Three primary public health interventions have been used to address the increase in overdose deaths, including wide-scale distribution of naloxone to reverse overdose (Bennett, Holloway, & Bird, 2014; Centers for Disease Control and Prevention, 2012; Kinner et al., 2012), and substance use disorder treatment, most often involving the use of medication assisted therapy, including methadone, naltrexone, naltrexone injectable suspension, and buprenorphine (Amato et al., 2005; Degenhardt et al., 2010; C. Jones et al., 2018; Mattick, Breen, Kimber, & Davoli, 2014; Soyka et al., 2011). Supervised injection facilities, although not yet widely adopted in the U.S., are also potentially important public health interventions to address overdose deaths (Irvine, et al., 2019; Tyndall, 2006; Marshall, Milloy, Wood, Montaner, Kerr, 2011).

Approved for treating opioid use disorder in 2002 in the United States, buprenorphine products have filled an exceptionally important role in responding to the opioid epidemics (Yokell, Zaller, Green, & Rich, 2011b). Significantly, buprenorphine was approved for use by private physicians after completing training in its use, thus providing a potentially new means of treating opioid use disorder in primary care settings (Amass et al., 2004; Hser et al., 2015; Johnson et al., 1995; Saloner, Stoller, Alexander, 2018; Zoorob, Kowalchuk, & Mejia de Grubb, 2018).

Not surprisingly, and similar to other pharmaceutical opioids, diversion of buprenorphine products in communities of people who use illicit drugs has become of some concern both in the U.S. (Bazazi, Yokell, Fu, Rich, & Zaller, 2011; Daniulaityte, Falck, & Carlson, 2012; Furst, 2013, 2014; Johanson, Arfken, di Menza, & Schuster, 2012; Kenney, Anderson, Bailey, & Stein, 2017; Wish et al., 2012) and in many other countries (Carrieri et al., 2006; Lofwall & Walsh, 2014; Maria Patrizia et al., 2006; Winstock, Lea, & Sheridan, 2008; Yokell, Zaller, Green, & Rich, 2011a). In the U.S., there are reports that some patients are disregarding physician's directions for the intended use of the drug, using it to make money, often to buy and use heroin and/or other illicit drugs (Lin, Lofwall, Walsh, Gordon, & Knudsen, 2018); others who have prescriptions give buprenorphine to people to help them avoid withdrawal symptoms (Havnes, Clausen, & Middelthun, 2013).

In contrast to the negative sequelae associated with the non-prescribed use of buprenorphine, it has also been suggested that diversion is a sign of the inability of people who use opioids to access buprenorphine treatment or barriers to participation in treatment (Carroll, Rich, & Green, 2018; Cicero, Ellis, & Chilcoat, 2018; Lofwall & Havens, 2012; McLean & Kavanaugh 2019). As such, the use of non-prescribed buprenorphine products may have some unintended public health benefits, such as not (generally) using other opioids when using buprenorphine, perhaps as a way to bridge waiting time to get into treatment without using other opioids, and even, more importantly, as a means to achieve some form of

self-recovery, for some degree of time (Allen & Harocopos, 2016; Mitchell et al., 2009; Monico et al., 2015). Other harm-reduction benefits may also exist.

There is a dearth of research examining the relationship between use of non-prescribed buprenorphine use and unintentional drug overdose (Bretteville-Jensen, Lillehagen, Gjersing, & Andreas, 2015). In the current study, we test the hypothesis that, among individuals with opioid use disorder who have used non-prescribed buprenorphine in the previous six months, those who use non-prescribed buprenorphine more frequently are less likely to experience an unintentional drug overdose. Variables controlled for in the analysis were selected based on previous research as cited above.

Research setting

The study was conducted in the Dayton (Montgomery County), Ohio, area, an epicenter of the opioid overdose crisis. In 2016, Ohio had one of the highest overdose death rates (39.1) per 100,000 in the nation (Hedegaard et al., 2018), and in 2017, Montgomery County had the highest per capita overdose death rate in the state of Ohio, with 521 overdoses, and an age-adjusted death rate of 95.24 per 100,000 (Rossen, Bastian, Warner, Khan, & Chong, 2019). Our study on trends in non-prescribed fentanyl-related overdose deaths in Montgomery County, Ohio, found that overdose deaths involving non-prescribed fentanyl increased 377% from the second half of 2015 to the first half of 2017 (Daniulaityte et al., 2019a). Over that same time period, we found a high presence of fentanyl and variety of fentanyl analogues. Over 75% of all non-prescribed fentanyl positive cases tested positive for fentanyl analogues in the first six months of 2017 (Daniulaityte et al., 2019a).

Methods

Subject recruitment

Targeted recruitment (Korf, van Ginkel, & Benschop, 2010; Sifaneck & Neaigus, 2001) and modified respondent-driven sampling (RDS) (Biernacki & Waldorf, 1981; Daniulaityte, Falck, Li, Nahhas, & Carlson, 2012; Heckathorn, 1997) methods were used to recruit people in the community who met the following eligibility criteria: 1) at least 18 years of age; 2) current moderate or severe opioid use disorder 3) report use of non-prescribed buprenorphine at least once in the past six months; and 4) residence in the Dayton, Ohio, metropolitan area, including surrounding counties. Recruitment began May 2017 and ended October 2018. Initial sample seeds were identified by recruitment fliers posted in locations such as laundromats, pawn shops, gas stations, and convenience store, and ads on Craigslist, Facebook, and a local paper. Modifications to RDS included having a flexible limit on the number of referrals to improve recruitment. Participants were compensated \$15 for each person he/she referred to the project.

A two-phase process was used to determine eligibility. In Phase I, participants were briefly screened for eligibility by phone. In Phase II, those who were potentially eligible were scheduled for an office interview in which they were screened in more detail after completing an informed consent approved by the Wright State University and Columbia University Institutional Review Boards. If eligible, participants completed a baseline

structured interview, lasting 1.5–2 hours, administered by trained interviewers in private offices. Participants were compensated \$40 for their time participating in research, and \$10 for transportation, by gift card or check. Urine screening was used to enhance the veracity of self-report. Further details regarding recruitment and data collection are available elsewhere (Daniulaityte et al., 2019b).

Variables

Sociodemographic and drug use characteristics were captured using questions developed by the research team, some of which had been used in previous studies (Carlson, Wang, Falck, & Siegal, 2005; Falck, Siegal, Wang, Carlson, & Draus, 2005). Questions covered the following domains: 1) Time since first use of illicit opioids (“How old were you the very first time you used [drug]”); 2) Mode of administration (“In the past six months, how did you most often administer [drug]”); and 3) Lifetime history of unintentional drug overdose (“How many times in your life have you experienced an unintentional drug-related overdose?”).

Past twelve-month psychiatric comorbidity, including post-traumatic stress disorder (PTSD), generalized anxiety disorder (GAD), and major depressive disorder (MDD) were assessed by using the computerized version of the Diagnostic Interview Schedule-V (Compton, Dawson, Goldstein, & Grant, 2013). Severity of lifetime opioid use disorder was assessed using the DSM-IV Checklist, modified for DSM-V (Forman, Svikis, Montoya, & Blaine, 2004; Hudziak et al., 1993).

The time-line follow-back method was used to assess frequency of non-prescribed buprenorphine use, heroin/non-prescribed fentanyl use, cocaine/crack use, methamphetamine use, prescribed and non-prescribed pharmaceutical opioids (excluding illicit buprenorphine), non-prescribed benzodiazepine use, past six-month drug overdose (“did you overdose?”), incarceration, and use of substance use disorder treatment services in the past six months (Ehrman & Robbins, 1994; Epstein-Ngo et al., 2013; Robinson, Sobell, Sobell, & Leo, 2012). Due to the difficulty of participants to distinguish between heroin and fentanyl, these drugs were combined into one category (Daniulaityte et al., 2019b). Data were captured by interviewers who entered responses on laptop computers using REDCap, an electronic data capture system maintained by Wright State University (Harris et al., 2009). The variable “previous overdose” was derived by comparing the number of overdoses reported in the previous six months with the lifetime number of unintentional drug overdoses reported; if the latter was greater, then we concluded the participant had an overdose experience more than six months prior to the interview.

Statistical analysis

Frequencies and proportions were computed for all categorical variables, and means, standard deviations, and medians for all continuous variables, overall and by past six-month overdose status.

Logistic regression was used to test the association between (log-transformed) frequency of non-prescribed buprenorphine use and overdose in the previous six months, adjusted for confounding due to the following covariates: sex, homelessness, incarceration, substance

use treatment, previous overdose, heroin/fentanyl injection, psychiatric comorbidity (PTSD, GAD, or MDD), and (log-transformed) frequencies of use of cocaine/crack, methamphetamine, and non-prescribed benzodiazepines. This test was two-sided and carried out at the $\alpha = 0.05$ level of significance. Data processing was carried out in SAS 9.4 (SAS Institute Inc, 2012) and data analysis was carried out in R 3.6.2 (R Core Team, 2019).

We chose the covariates that we considered *a priori*, based on previous research, to have the most potential for confounding the relationship between exposure (non-prescribed buprenorphine use) and outcome (overdose), without respect to their relationship with the outcome. Frequency of use of other opioids were not included due to their potential role as mediators of the non-prescribed buprenorphine-overdose relationship. While there was additional covariate information we could have included, we limited this list to approximately the number of events divided by 10 to assure reliable parameter estimates (Harrell, 2015). Other methods of variable selection, such as stepwise selection, were not used due to their leading to invalid p-values (Ferenci, 2017; Harrell, 2015; Rothman, Greenland, and Lash, 2008).

Both univariate and adjusted (for all other variables) odds ratios (OR, AOR) and their 95% confidence intervals are presented for all variables listed above. Since our primary analysis (association between non-prescribed buprenorphine use and overdose) consisted of a single test, we did not carry out an adjustment for multiple testing. While 95% confidence intervals and p-values are reported for all variables, only the primary analysis can be considered confirmatory; tests of association for all other variables are considered secondary (exploratory) analyses.

Some variables (listed in Table 3) were skewed and were therefore natural-log transformed to reduce the influence of large values; other than non-prescribed buprenorphine use, which had no zeros, 0.001 was added to each variable prior to transformation.

Since the primary exposure was log-transformed, for explanatory purposes, we carried out the following two secondary analyses to estimate odds ratios that are more easily interpretable: 1) We dichotomized the exposure at the median value (use of non-prescribed buprenorphine on 5.4% of days (10 of 184) in the previous six months) and computed the AOR in the multivariable model for this binary exposure instead of the continuous version; 2) We computed AORs from the primary analysis over a range of exposure values on the original scale. Since this assumes linearity, we also checked the linearity assumption by cutting the exposure into six categories based on equal-length intervals on the log-scale (these correspond to, on the original scale, less than 0.7% (1 day in 184), 0.7% to 1.8% (2–3 days), 1.9% to 5.0% (4–9 days), (5.1% to 13.5% (10–24 days), 13.6% to 36.8% (25–67 days), and 36.9% or more (68 days or more) and computed the corresponding AORs relative to the first group (1 day of use). The resulting AORs and 95% confidence intervals are illustrated, along with the corresponding estimates from the primary analysis.

We hypothesize that at least part of the mechanism by which increased use of non-prescribed buprenorphine lowers risk of overdose is through a corresponding decrease in use of heroin and/or fentanyl. While a full mediation analysis is beyond the scope of this paper, as a

secondary analysis to begin to investigate this hypothesis, we used linear regression to test the association between (log-transformed) frequency of use of non-prescribed buprenorphine and (log-transformed) frequency of use of heroin/fentanyl, and logistic regression to test the association between (log-transformed) frequency of use of heroin/fentanyl and overdose.

Results

Sample characteristics

Overall, 50.3% of the sample of 356 participants were male, almost 89% were non-Hispanic white, and only 23% were married or living with a partner. About 78% had a secondary school/GED or higher education, approximately one-fourth (25.8%) were employed part or full-time, and about half (54.8%) considered themselves as being homeless in the past six months (Table 1). The mean age was 39.2 years (Table 2).

Overdose experience

Almost 28% (27.5%, n=98) of the sample experienced at least one drug overdose in the past six months, and 221 (62.3%) reported at least one prior overdose (more than six months ago) (Table 1). Of those who overdosed in the past six months, 77.3% (75/97) had experienced a prior overdose. In the previous six months, participants experienced 0–10 unintentional overdoses (median = 0, mean = 0.48, SD = 1.02). Over their lifetime, participants experienced 0–200 unintentional overdoses (median = 2, mean = 3.56, SD = 11.5), with 31.8% never experiencing an overdose, 17.5% with one overdose, and 50.7% reporting 2 or more overdoses. Over 95% (95.5%) of lifetime overdoses were related to the use of heroin/non-prescribed fentanyl or non-prescribed pharmaceutical opioids. The mean number of people the participant was personally acquainted with who died from an unintentional overdose was 11.7 (SD=16.0).

Drug use characteristics

Over the previous six months (184 days), participants used non-prescribed buprenorphine 14.6% (26.9 days) of the days on average (SD = 20.4%) (Table 2). Close to 90% of participants reported using non-prescribed buprenorphine for self-treatment of opioid use withdrawal symptoms. Over 50% (56.9%) of the participants reported having ever sold buprenorphine to someone, and 47.9% said they had given buprenorphine prescribed to them, to others.

Participants used heroin/non-prescribed fentanyl a mean of 56.4% of the days in the past six months, cocaine/crack 19% of days, and methamphetamine 11.9% of days (Table 2). 65% reported injection as their most frequent route of heroin/non-prescribed fentanyl use (Table 1). About half (50.6%) had been in substance use treatment in the past six months, and almost 31% had been incarcerated (Table 1). Among the psychiatric comorbidities we assessed, generalized anxiety disorder (45.5%) was most common, followed by major depressive disorder (34.3%), and PTSD (27.5%); overall, almost 59% had at least one of these three in the past year (Table 1).

Association between frequency of non-prescribed buprenorphine use and unintentional drug overdose (primary hypothesis)

Higher mean percentage of days of non-prescribed buprenorphine use in the past six months was significantly associated with a decreased risk of an overdose in the past six months in both unadjusted (OR 0.82, 95% CI=0.70, 0.97, $p = .0180$) and adjusted analyses (AOR = 0.81; 95% CI=0.66, 0.98, $p = .0286$) (Table 3), strongly supporting our hypothesis.

In the secondary analyses, to illustrate the magnitude of the exposure AOR on an understandable scale, the AOR for the binary exposure was 0.67 (95% CI=0.40, 1.13); that is, individuals who used non-prescribed buprenorphine on more than 5.4% of days (10 days; the median) had 33% lower odds of overdose. The AORs after cutting the exposure into six equal-length intervals on the log-scale were, for the upper five intervals, 0.80 (2–3 days; 95% CI=0.31, 2.10), 0.50 (4–9 days; 95% CI=0.20, 1.25), 0.39 (10–24 days; 95% CI=0.15, 1.00), 0.58 (25–67 days; 95% CI=0.22, 1.52), 0.20 (68 or more days; 95% CI=0.05, 0.70), respectively, relative to the first interval. In other words, taking buprenorphine on 2–3 days out of 184 reduced the odds of overdose by 20% compared to just 1 day, with an approximately linear trend of more use associated with even greater reduction in odds of overdose. These estimates are illustrated in Figure 1, which also demonstrates the adequacy of the linearity assumption of the primary analysis.

Regarding our hypothesis that increased use of non-prescribed buprenorphine lowers risk of overdose at least in part through a corresponding decrease in the use of heroin and/or fentanyl, we found that (after adjusting for confounding) *greater* (log-transformed) frequency of use of non-prescribed buprenorphine is strongly associated with *lower* (log-transformed) frequency of use of heroin/fentanyl (beta = -0.076 , 95% CI = -0.098 , -0.053), and *lower* (log-transformed) frequency of use of heroin/fentanyl is strongly associated with *lower* risk of overdose (AOR = 2.77, 95% CI=1.19, 6.70).

Other correlates of unintentional drug overdose (secondary analyses)

In multivariable analysis, odds of past six-month overdose were more than two times greater for those with prior overdose experience (experiencing an overdose prior to the past six months) (AOR = 2.19; 95% CI = 1.24, 3.97; $p < .01$) (Table 3). Similarly, individuals who reported injection as the most common route of heroin/non-prescribed fentanyl administration in the past six months had almost 2.5 times the odds of experiencing an overdose, compared to those who reported a non-injection route (intranasal and/or smoking) (AOR = 2.49; 95% CI = 1.36, 4.71; $p < .01$). Higher frequency of methamphetamine use was also associated with greater odds of overdose in the past six months (AOR = 1.13; 95% CI = 1.02, 1.27; $p < .05$). Incarceration in the past six months and greater percentage of days of crack/cocaine HCl use in the past six months were each strongly associated with greater odds of overdose in unadjusted analyses, but after controlling for other variables these associations were attenuated.

Discussion

The results of this study confirmed our hypothesis that, among people with opioid use disorder who had used non-prescribed buprenorphine recently, more frequent use of non-prescribed buprenorphine is associated with lower risk of non-fatal unintentional drug overdose. Thus, non-prescribed buprenorphine use can potentially be serving harm-reduction purposes. The findings indicate that people who use non-prescribed buprenorphine more frequently are less likely to use heroin/non-prescribed fentanyl on those days and, therefore, reduce their chances of experiencing an overdose.

The relationship is illuminated in our secondary analysis indicating that people who used non-prescribed buprenorphine more than the median number of number of days (10 days) had 33% lower odds of overdose. After dividing non-prescribed buprenorphine use in six equal intervals, the AORs indicated a linear trend where more non-prescribed buprenorphine use was associated with even greater reduction in odds of overdose. This is consistent with the association between being in medication assisted therapy and reduced risk of overdose due to reduction in opioid use (Degenhardt et al., 2010; Soyka et al., 2010). The relationship between more frequent use of non-prescribed buprenorphine and lower risk of overdose is further supported by our findings that *greater* frequency of use of non-prescribed buprenorphine is strongly associated with *lower* frequency of use of heroin/fentanyl, and *lower* frequency of use of heroin/fentanyl is strongly associated with *lower* risk of overdose (Daniulaitye et al., 2019b).

To the best of our knowledge, this is one of the few studies examining the relationship between non-prescribed buprenorphine use and recent non-fatal unintentional overdose. Using latent class analysis to identify classes based on the underlying latent construct, “pattern of opioid use among individuals with current opioid use disorder,” our previous study using the same sample identified a salient subgroup that used diverted buprenorphine more frequently (Daniulaitye et al., 2019b). People in this class were significantly less likely to have experienced an overdose in the past six months.

Similar to prior research, we found the vast majority of participants used non-prescribed buprenorphine only to self-treat opioid use disorder withdrawal, and not to achieve euphoric effects (Allen & Harocopos, 2016; Chilcoat, Amick, Sherwood, & Dunn, 2019; Cicero et al., 2018). Our findings extend previous research indicating that non-medical use of medications such as buprenorphine is a lay harm-reduction strategy, resulting in short and longer-term abstinence from heroin/non-prescribed fentanyl use which may reduce injection-related risk behaviors and risk of overdose (Harris & Rhodes, 2013). Our qualitative data indicate that with increased proliferation of non-pharmaceutical fentanyl and other novel synthetic opioids in the Dayton area (Daniulaitye, 2019a; Daniulaitye, 2019c), some individuals sought non-prescribed buprenorphine to intentionally mitigate their risks for an unintentional overdose from highly potent and unpredictable novel synthetic opioid mixtures that were sold as and/or completely replaced heroin (Silverstein, Daniulaitye, Martins, Miller, & Carlson, 2019; Silverstein et al., in review).

Our finding that previous unintentional drug overdose is associated with subsequent overdose is consistent with previous research (Coffin et al., 2007; Larochelle et al., 2018; Olfson, Wall, Wang, Crystal, & Blanco, 2018; Stooove et al., 2009). In a prospective study with 2,317 people who use drugs in Vancouver, Canada, Caudarella and colleagues (Caudarella, Dong, Milloy, Kerr, & Wood, 2016) found a dose response relationship where increases in cumulative non-fatal overdose were associated with future fatal overdose. As Coffin and colleagues (2007) conclude, one of the strongest predictors of a non-fatal overdose among people who use heroin is having experienced a previous overdose. Increased susceptibility to experiencing multiple overdoses may be related to comorbid medical conditions, especially those that impact the respiratory system (Coffin et al., 2007; Olfson et al., 2018), and psychiatric comorbidity (Bohnert & Ilgen, 2019; Fridell, Backstrom, Hesse, Krantz, & Nysten, 2019). Factors of socioeconomic disadvantage may also contribute to heightened risk of multiple overdoses (Nandi et al., 2006).

Our finding that increased risk of unintentional overdose is associated with injection drug use, rather than snorting or smoking, is also consistent with prior research. Injection route of administration increases the speed of onset and rate of drug absorption, thereby increasing overdose risk (Gossop, Griffiths, Power, & Strang, 2010; Samaha & Robinson, 2005; Strang et al., 1998; Strang, Des Jarlais, Griffiths, & Gossop, 1992). Several studies have suggested that harm reduction strategies to reduce overdose risk include switching from injection to smoking or inhaling heroin or non-prescribed fentanyl (Ciccarone et al., 2017; Fairborn et al., 2018; Harris, Forseth, & Rhodes, 2015).

Higher average percentage of days of methamphetamine use in the past six months was a strong correlate of overdose in multivariable analysis. This is also consistent with previous research (Brugal et al., 2002; Kinner et al., 2012; Werb et al., 2008). For example, in a study with 592 people who inject drugs in Denver, Colorado, Al-Tayyib and colleagues (Al-Tayyib, Koester, Langregger, & Raville, 2017) found that those who injected heroin and methamphetamine in the past 12 months were 2.8 times more likely to experience a non-fatal overdose in the same time period, compared to heroin only injectors in multivariable analyses. In addition, participants who injected heroin and methamphetamine at different times were more likely to report an overdose in the past 12 months, compared to people who injected a mixture of the drugs. In contrast, another study with 795 people who inject drugs recruited in San Francisco, Ochoa and colleagues (2005) found that those who injected a mixture of heroin and methamphetamine were more likely to experience an overdose in the previous 12 months, compared to those who did not report an overdose (Ochoa et al., 2005). In Dayton, Ohio, methamphetamine mentions in overdose deaths increased from 18% in 2017 to 26% in 2018, and methamphetamine seizures increased from 68,485 grams in 2017 to 256,766 grams in 2018 (Public Health Dayton and Montgomery County, 2018). A preliminary finding from our current research focusing on methamphetamine suggests the existence of lay beliefs among people who use drugs in Dayton that use of methamphetamine in conjunction with heroin/non-prescribed fentanyl may reduce overdose risk. This incorrect lay belief may contribute to increased methamphetamine use in conjunction with non-prescribed fentanyl, and may, in part, explain the significant role of methamphetamine use as a correlate of overdose.

Limitations

Limitations are noted. The sample was not randomly recruited. However, we used a combination of targeted recruitment and modified respondent-driven sampling to diversify recruitment networks. Nevertheless, the sample may be biased by income level, education, employment, and other factors. Second, the meaning of “experiencing an unintentional overdose” was not further defined; thus, there may be some variability in participants’ interpretations of what constitutes an “overdose.” It is also possible that some overdoses were intentional. However, as noted in previous research, a drug overdose may include elements of both intentionality and unintentionality, perceived intent may change among people with non-fatal overdose after recovery, and some people cannot distinguish whether an overdose was intentional or unintentional (Bohnert & Ilgen, 2019; Bohnert et al., 2018). The findings are based on self-report, and are subject to potential inaccurate recall. However, there is substantial support for the validity and reliability of self-report data among people who use drugs (Adair, Craddock, Miller, & Turner, 1995; Darke, 1998; Passik, Hays, Eisner, & Kirsh, 2006). In addition, we used urine sample testing to increase the veracity of self-report. Finally, although the TLFB has been used with people who use drugs successfully in other studies (Carey, Carey, Maisto, & Henson, 2004; Hjorthoj, Hjorthoj, & Nordentoft, 2012; Robinson et al., 2012), some degree of error in recall accuracy may have occurred.

Conclusions

Use of non-prescribed buprenorphine has been shown to be associated with subsequent substance use treatment entry and retention, and self-treatment, both for short-term detoxification and longer-term opioid abstinence (Allen & Harocopos, 2016; Mitchell et al., 2009; Monico et al., 2015). Our findings suggest that decreased risk of overdose associated with more frequent use of non-prescribed buprenorphine is a harm-reduction consequence of diversion. We cannot establish a causal relationship between higher frequency of non-prescribed buprenorphine use and reduced risk of overdose because of the cross-sectional nature of the study. Additional longitudinal studies are needed to further evaluate our findings.

It is difficult to imagine addressing the opioid epidemic in the U.S., now more than two decades in length, without buprenorphine becoming available for treating opioid use disorder in 2002. Medication assisted treatment reduces the risk of overdose deaths (Degenhardt et al., 2010; Larochelle et al., 2018; Morgan, Shackman, Weinstein, & Walley, 2019), and buprenorphine treatment has played a crucial role in providing a pathway to recovery among people with opioid use disorder. Nevertheless, only about 20% of people with opioid use disorder access treatment (Manhapra, Stefanovics, & Rosenheck, 2019; B. Saloner & Karthikeyan, 2015; Wu, Zhu, & Swartz, 2016). Use of diverted buprenorphine appears to fill needs that are unmet by access to medication assisted therapy and is clearly associated with harm reduction consequences among those who use it. Innovative methods to widely expand access to buprenorphine treatment, such as the use of mobile vans to recruit people into short-term buprenorphine treatment before transitioning to longer-term programs (Krawczyk, Buresh, Gordon, Blue, & Fingerhood, 2019), low barrier buprenorphine treatment among homeless on the streets and in shelters (Carter, Zevin, & Lum, 2019; Chatterjee et al., 2017), buprenorphine treatment provided through harm

reduction programs (Fox, Chamberlain, Frost, & Cunningham, 2015), and buprenorphine induction in emergency departments (D'Onofrio et al., 2017) are urgently needed.

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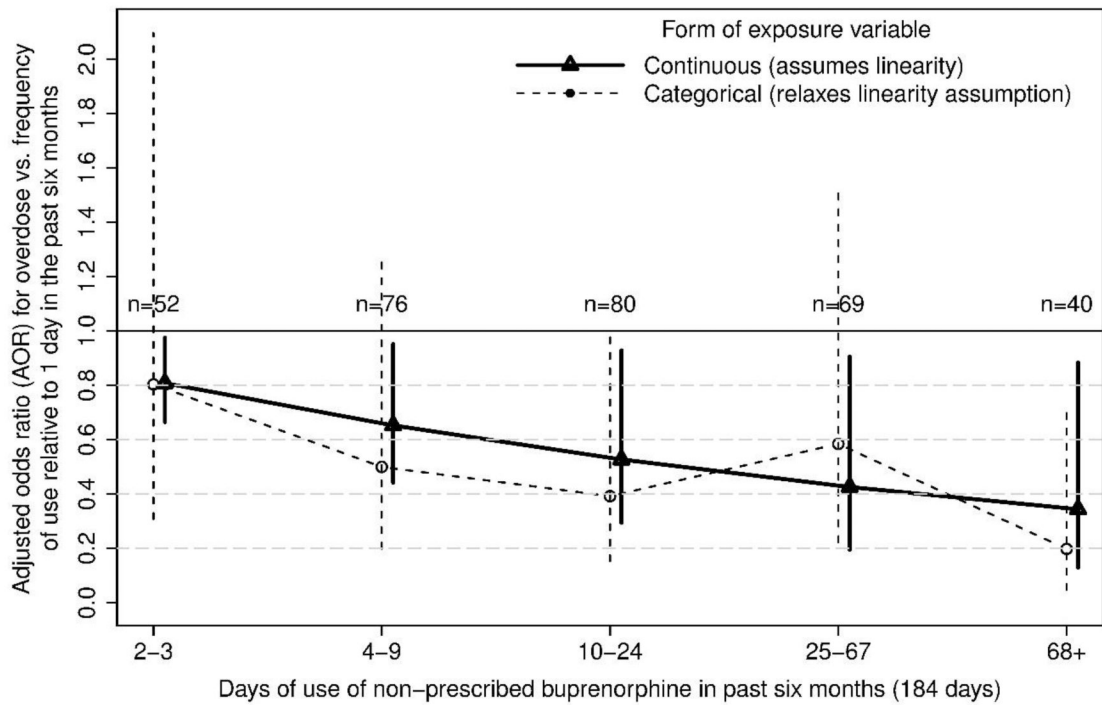


Figure 1. Adjusted odds ratios (AOR) and 95% confidence intervals for overdose vs. increasing frequency of use of non-prescribed buprenorphine in the past six months, relative to one day of use (n = 39).

Table 1.

Descriptive statistics for categorical variables, overall and by overdose in the previous 6 months (n=356)

Characteristic (# of missing values, if any)	Overall (n=356)		Did not overdose (n=258, 72.5%)		Overdosed (n=98, 27.5%)	
	N	%	N	%	N	%
Sex = Male	179	50.3	128	49.6	51	52.0
Race/Ethnicity = White/Non-Hispanic	316	88.8	226	87.6	90	91.8
Education = Secondary school or greater	278	78.1	197	76.4	81	82.7
Employed	92	25.8	67	26.0	25	25.5
Married/living with partner	82	23.0	61	23.6	21	21.4
Homeless (past 6m)	195	54.8	134	51.9	61	62.2
Incarceration (past 6m)	110	30.9	67	26.0	43	43.9
Substance use treatment (ever past 6m)	180	50.6	123	47.7	57	58.2
Previous overdose (more than 6m ago) (1)	221	62.3	146	56.6	75	77.3
Heroin or fentanyl injection (most common route, past 6m) (10)	225	65.0	145	58.5	80	81.6
Psychiatric comorbidity (GAD, MDD, or PTSD) past 12m)	209	58.7	144	55.8	65	66.3

Table 2.

Descriptive statistics for continuous variables, overall and by overdose in the previous 6 months (n=356)

Characteristic	Overall (n=356)			Did not overdose (n=258, 72.5%)			Overdosed (n=98, 27.5%)		
	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Age (years)	39.2	9.5	37.8	39.4	10.0	38.3	38.5	8.2	37.0
Time since first illicit use of opioids (years)	18.5	9.6	17.3	18.4	10.1	17.1	18.5	8.2	18.3
NP buprenorphine frequency of use (% of days, past 6m)	14.6	20.4	5.4	16.4	22.3	6.8	10.0	13.5	4.3
Heroin/fentanyl frequency of use (% of days, past 6m)	56.4	36.5	67.4	52.5	37.9	60.1	66.6	30.8	76.1
Prescribed pain pill frequency of use (% of days, past 6m)	2.7	10.3	0.0	2.9	11.1	0.0	2.3	8.1	0.0
NP pain pill frequency of use (% of days, past 6m)	11.6	22.5	0.5	12.8	24.2	1.1	8.4	16.9	0.0
Cocaine/crack frequency of use (% of days, past 6m)	19.0	27.8	4.3	17.6	27.1	3.3	22.6	29.4	6.3
Methamphetamine frequency of use (% of days, past 6m)	11.9	23.0	0.5	10.8	22.8	0.0	14.8	23.5	4.3
NP benzodiazepine frequency of use (% of days, past 6m)	12.9	23.1	1.6	11.6	20.8	1.1	16.6	28.3	2.2

Table 3.

Correlates of overdose (yes/no) in the previous 6 months (98 of 356 (27.5%) individuals overdosed, 97 of 345 (28.2%) for the multivariable model; OR = unadjusted odds ratio; AOR = adjusted odds ratio, all variables in the model simultaneously.

Correlate (# of missing values, if any)	Univariate		Multivariable	
	OR	95% CI	AOR	95% CI
Primary Exposure				
NP buprenorphine frequency of use (LN of % of days, past 6m) ^a	0.82	(0.70, 0.97)	0.81	(0.66, 0.98)
Confounders				
Sex = Male	1.10	(0.69, 1.76)	1.18	(0.70, 2.00)
Homeless (past 6m)	1.53	(0.95, 2.47)	0.94	(0.54, 1.63)
Incarceration (past 6m)	2.23	(1.37, 3.63)	1.65	(0.96, 2.82)
Substance use treatment (past 6m)	1.53	(0.96, 2.45)	1.22	(0.72, 2.07)
Previous overdose (more than 6m ago) (1)	2.62	(1.55, 4.55)	2.19	(1.24, 3.97)
Heroin or fentanyl injection (most common route, past 6m) (10)	3.16	(1.82, 5.72)	2.49	(1.36, 4.71)
Psychiatric comorbidity (past 12m)	1.56	(0.96, 2.55)	1.62	(0.94, 2.84)
Cocaine/crack frequency of use (LN of % of days + 0.001, past 6m) ^a	1.13	(1.02, 1.25)	1.05	(0.93, 1.18)
Methamphetamine frequency of use (LN of % of days + 0.001, past 6m) ^a	1.21	(1.10, 1.34)	1.13	(1.02, 1.27)
NP benzodiazepine frequency of use (LN of % of days + 0.001, past 6m) ^a	1.05	(0.96, 1.16)	1.05	(0.94, 1.18)

^aThese variables were skewed and were therefore natural-log transformed to reduce the influence of large values. Other than NP buprenorphine, which had no zeros, 0.001 was added to each variable prior to transformation.