HHS Public Access

Author manuscript

J Subst Use Addict Treat. Author manuscript; available in PMC 2024 July 01.

Published in final edited form as:

J Subst Use Addict Treat. 2023 July ; 150: 209053. doi:10.1016/j.josat.2023.209053.

Buprenorphine and opioid analgesics: Dispensation and discontinuity among accidental overdose fatalities in the Indianapolis metropolitan area, 2016–2021.

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Abstract

Background: This study describes overall trends and sociodemographic disparities in buprenorphine and opioid analgesic uptake and prescribing patterns prior to fatal overdose events.

Methods: We examined toxicology data from all accidental overdose deaths from 2016 to 2021 (N=2,682) in a large metropolitan area. These data were linked at the individual-level with a prescription drug monitoring program (PDMP).

Results: Fewer than half of all deaths had any kind of PDMP record (39.9%, *n*=1,070). Among those with a buprenorphine prescription, 10.6% (n=35) of decedents had a buprenorphine dispensation within 7 days of their death, while the majority (64.7%, n=214) were dispensed buprenorphine more than 30 days prior to death. Evidence existed of racial disparities among

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Author Statement

Grant Victor: Conceptualization, Methodology, Writing- Original draft preparation, Editing. **Brad Ray:** Conceptualization, Methodology, Data acquisition, Data analysis, Writing **Brandon del Pozo**: Writing, Editing, Conceptualization, Data Analysis. **Kate Jaffe:** Writing, Editing, Framing, Manuscript Preparation. **Andy King:** Reviewing, Conceptualization, Editing, Framing. **Philip Huynh**: Data analysis, Writing, Manuscript Preparation.

Disclosures of Conflict: The authors have no disclosures to declare.

those with any buprenorphine uptake, whereby Black individuals (7.3%, *n*=24) had significantly fewer any dispensations compared to White individuals (92.7%, *n*=307). Among those with an opioid analgesic prescription, about 12.2% (*n*=90) were dispensed within 7 days of death, with the majority (68.5%, *n*=506) occurring more than 30 days prior to death. Like buprenorphine dispensations, Black individuals were prescribed a significantly smaller proportion of opioid analgesics (21.9%, *n*=162) versus White individuals (77.7%, *n*=574). Buprenorphine was detected in 78.5% of deaths where fentanyl was present in the toxicology record, significantly greater when compared to opioid analgesics (57.5%).

Conclusion: Consistent with prior research, our findings suggest prescription opioid analgesics may protect against fatal overdoses. Access to buprenorphine treatment did not keep pace with the rising lethality of the overdose crisis, and in recent years, a smaller percentage of the people at risk of fatal overdose availed themselves of MOUD preceding their death.

Keywords

Overdose; Prescription drug monitoring program; Buprenorphine; Opioid analgesics

1. Introduction

The United States continues to face an unprecedented drug crisis that has been exacerbated by the COVID-19 pandemic (American Medical Association, 2020). The overdose crisis has evolved across several waves, and each succeeding wave has become more deadly (Ciccarone, 2019). Wave 1 was associated with increases in overdose deaths due to the misuse of opioid analgesics. Wave 2 began as the primary cause of death shifted from opioid analgesics to heroin, and wave 3 began as overdose deaths become primarily linked to illicitly manufactured fentanyl and similar analogs (National Institute on Drug Abuse, 2019). During wave 1, policymakers implemented guidelines meant to taper or discontinue prescription opioid analgesics, which resulted in most states implementing prescription drug monitoring programs (PDMP; Dowell et al., 2016). Research has identified the establishment of PDMPs and resulting curtailment of opioid analgesic prescribing as having unintended consequences—as patients no longer had access to pain medications, some transitioned to illicit opioids as supply dynamics changed, thus elevating their risk for experiencing an accidental overdose (Victor et al., 2017; Phalen et al., 2018; Reuter et al., 2021).

As overdose deaths increased in recent years—with the exception of a slight decrease in 2018—the expansion of low-threshold evidence-based treatment for opioid use disorder (OUD) remained underutilized in medical (Huhn et al., 2020) and criminal/legal (Ray et al., 2022) systems. Effective agonist medications exist for treating OUD (e.g., buprenorphine), but only a fraction of those who could benefit from treatment are successfully linked to addiction care (Beetham et al., 2020; Krawczyk et al., 2022). One study found that approximately 86% of those who qualify for medications for opioid use disorder (MOUD) do not receive treatment (Krawczyk et al., 2022). In Indiana, the setting of the current study, the adjusted OUD prevalence rate in 2018–2019 was 3,777.7 per 100,000 people, yet the rate of individuals receiving buprenorphine is 309.4 per 100,000 people, which increased from a rate of 272.6 per 100,000 people in 2017–2018 (Krawczyk et al., 2022).

The stark contrast in treatment supply relative to demand is of great concern given the positive outcomes associated with MOUD treatment. Buprenorphine uptake is associated with significantly reduced rates of nonfatal and fatal overdose (Dupouy et al., 2017; Sordo et al., 2017), all-cause mortality (Hser et al., 2016), reduced risk of criminalization (Evans et al., 2019), and with reductions in adverse health events (Wakeman et al., 2020). Despite these positive treatment outcomes, several barriers remain to the widespread uptake of MOUD in the United States. Research shows that MOUD is highly stigmatized as a treatment option (Tsai et al., 2019; Wakeman & Rich, 2018), perceived as "substituting one form of addiction for another", and the requisite financial investment required to build out the necessary treatment infrastructure has not occurred (Saloner & Barry, 2018). Recent research has highlighted how early discontinuation of buprenorphine is associated with increased overdose risk compared to longer term treatment (Glanz et al., 2022). Similarly, recent research has suggested that the discontinuation of opioid analgesics for chronic pain increases an individual's risk of experiencing a subsequent overdose (James et al., 2019) and other opioid-related adverse events (e.g., hospitalization; Mark & Parish, 2019). Moreover, prescribed use of opioid analgesics may also reduce an individual's risk of experiencing an overdose, because analgesics can be dosed with much greater precision than illicitly produced opioids, thereby reducing the overdose risk associated with such uncertainty (Victor et al., 2021). For these reasons, a lack of adequate buprenorphine prescribing, combined with reductions in the availability of opioid analgesics, have left individuals contending with OUD at an elevated risk of overdose.

During the COVID-19 pandemic, rates of overdose increased among racial and ethnic minorities, while prescription refills for buprenorphine declined among the same population —highlighting the underlying and widening inequities in the treatment landscape (Nguyen et al., 2022). As a result, a large gap remains between the need for buprenorphine and the ability of systems of care to deliver it within the context of widely disseminated federal recommendations to taper or discontinue opioid analgesic dispensations. Recently, the Department of Health and Human Services modified clinical practice guidelines to expand access to buprenorphine; although, these changes have not yet been reflected in empirical data (Practice Guidelines for the Administration of Buprenorphine for Treating Opioid Use Disorder, 2021).

The emergence of fentanyl as the dominant drug in many North American illicit drug markets (Reuter et al., 2021) had been associated with an increased risk of fatal overdose, and this risk is amplified for racial and ethnic minority groups (Nguyen et al., 2022; Ray et al., 2020; Schuler et al., 2021). Therefore, we need to understand buprenorphine and opioid analgesic dispensation patterns among decedents in the year prior to fatal overdose, and to explore potential sociodemographic disparities in the provision of evidence-based treatment. To contribute to this body of literature, this study analyzes buprenorphine and opioid analgesic prescribing patterns in the year leading up to a decedent's accidental fatal overdose and the related toxicology findings. We examined toxicology data from all accidental overdose deaths from 2016 through 2021 (N=2,682) in a large metropolitan area. These data were linked at the victim-level with prescription drug monitoring program (PDMP) data to measure buprenorphine dispensations in the year prior to death. This study had three primary aims: 1) to describe the overall overdose trends in a large metropolitan

region from 2016 to 2021; 2) to compare sociodemographic disparities among decedents that had an active buprenorphine or opioid analgesic dispensation to those who did not; and 3) to examine the proportion of opioids and fentanyl in the decedent's toxicology report among those who were dispensed buprenorphine or opioid analgesics.

2. Methods

2.1 Data and procedures

The data for this study come from Marion County, Indiana, home to Indianapolis, the 12th largest city in the United States, and its metropolitan area. Indiana has an overdose death rate higher than the national average, and a quarter of the state's overdose deaths have occurred in this county (Centers for Disease Control & Prevention, National Center for Health Statistics, 2019). The Centers for Disease Control and Prevention (CDC) has provided ongoing funding to the Indiana Department of Health (Grant #5 NU17CE002721–02 and CDC-RFA-CE19-1904) to rapidly collect toxicology data in Indianapolis to surveil trends in fatal overdose events (Carter et al., 2018; Huynh et al., 2020; Lockwood et al., 2021; Phalen et al., 2018; Ray et al., 2017, 2019, 2020) and reveal gaps in the death investigation process (Gupta et al., 2020; Lowder et al., 2018). These toxicology results include illicit substances such as 6-monoacetylmorphine (heroin), fentanyl (including synthetic analogs such as carfentanyl), methamphetamine, and cocaine. The toxicology panels also screen for the common metabolites of these substances, as well as prescription medications of interest including opioid analgesics such as oxycodone, hydrocodone, oxymorphone, hydromorphone, and tramadol. The study described prescribing patterns as a buprenorphine dispensation seven days, 30 days, and greater than 30 days prior to a fatal overdose event.

Following state legislation in 2016 (Determination of Cause, Manner, Mechanism of Death; Suspicion of Overdose; Certificate of Death; Moving of Body; Autopsy; Coroner Duties, 2019), the Marion County Coroner's Office started including a Prescription Drug Monitoring Program (PDMP) report that detailed all prescribing and dispensing of federally scheduled substances to the decedent in the 365 days prior to death. Prescription drug monitoring is conducted through the Indiana Scheduled Prescription Electronic Collection and Tracking (INSPECT) program and includes drug ingredients, strengths, morphine milligram equivalents (MME), and ontology information from the National Library of Medicine (Indiana Administrative Code IC 35-48-7). Although three FDA approved medications for opioid use disorder exist, the INSPECT system tracks only buprenorphine dispensations. The second agonist medication, methadone, is not tracked because it is administered under direct supervision in federally regulated opioid treatment programs. The third, naltrexone, is not on the federal schedule because as an antagonist it offers no potential for misuse, although research suggests that it is less effective at reducing the adverse effects of OUD than its opioid agonist counterparts (Wakeman et al., 2020).

2.2 Analytic approach

Data from death certificates provided sociodemographic information, coroner data reflects all substances detected in the postmortem toxicology, and the study used PDMP records to identify buprenorphine and opioid analgesic dispensations. The study used a probabilistic

record linkage methodology to identify individuals within the administrative data sets (Asher et al., 2020; Sayers et al., 2016). Each record was linked at the individual level so that those who had a PDMP record from 2016 to 2021 could be merged to accidental overdose death records that spanned the same period. We linked all records by an individual's first name, last name, and date of birth, as used in prior studies (Victor et al., 2021). We established cut-off values by weighting the matched variables (i.e., first name, last name and date of birth) with m (match) and u (unmatch) probabilities and created a composite field weight with positive values being a match and negative a nonmatch. The record match success rate was 99.1%. The study team conducted analyses using Chi-square (χ^2) differences of proportion to look at differences in likelihood of decedents having a PDMP record or prior buprenorphine prescription. We conducted all analyses in IBM SPSS Statistics 27. The university deemed this study to be non– human subjects research, and therefore exempted it.

3. Results

3.1 Overall overdose trends from 2016 to 2021

From 2016 to 2021, the study identified 2,682 accidental fatal overdoses. The study identified 679 overdose deaths in 2021 (70.9 per 100,000) which marked a 97.4% overall increase in overdose deaths since 2016. During the study period (2016 to 2021), we found that a decline in PDMP records occurred among all decedents. That is, in 2016 46.2% (n=159) of all decedents had a PDMP record compared to 43.2% (n=291) of all decedents in 2021. Noting the decrease in overall PDMP records among decedents between 2016 to 2021, we then examined dispensations patters within opioid analgesics and buprenorphine (see Figure 1).

A significant decrease occurred in opioid analgesic dispensations between 2016 to 2021 among decedents with a PDMP record. In 2016, 79.2% (n=126) of decedents had a PDMP record for opioid analgesics, compared to 2021, where 50.2% (n=146) of decedents had a PDMP record for opioid analgesics (χ^2 (1, N = 1023) = 25.126, p < .001). During the same period (2016–2021), decedents who had a buprenorphine PDMP record increased significantly from 17.0% (n=27) in 2016 to 36.4% (n=106) in 2021(χ^2 (1, N = 450) = 18.673, p < .001).

3.2 Demographic characteristics and correlations with medication dispensation

Among all overdose deaths (N=2,682), the average age was 40.6 years old, predominantly male (68.1%; n=1,827), and White (73.4%; n=1,969). Among decedents with buprenorphine PDMP record, significantly fewer χ^2 (1, N = 1,162) = 33.439, p < .001) were Black individuals (7.3%, n=24) compared to White individuals (92.7%, n=307). The study observed a similar pattern with respect to opioid analgesics, where significantly fewer Black individuals (n=162, 21.9%) had a PDMP record for opioid analgesics χ^2 (1, N = 1,162) = 29.251, p < .001) compared to White individuals (n=574, 77.7%). Decedents with a military background had fewer buprenorphine dispensations compared to opioid analgesic dispensations (3.6%, n=12 and 7.5%, n=62 respectively) χ^2 (1, N = 1,162) = 5.893, p < .05). Age was significantly lower among decedents with a buprenorphine dispensation (M = 38.5,

S.D.= 10.9) compared to those with opioid analgesic dispensations (*M* = 42.9, *S.D.*= 12.7) (*t* (703) = 5.958, $p < .001$).

3.3 Buprenorphine and opioid analgesic prescribing information

Among decedents with a buprenorphine PDMP record (28.5%; *n*=331), the average number of days from the last dispensation event was 11.9 (*SD*=9.0; Range 1–60), with an average quantity of 23.0 (*SD*=19.4; Range 1–120). Only 10.5% (*n*=342) of decedents with a buprenorphine PDMP record had a refill included as part of their prescription. The time between death and most recent buprenorphine dispensation suggests greater than half (64.7%; *n*=214) of the dispensations occurred more than 30 days before death—35.3% (*n*=117) received the medication within 30 days prior to death, and 10.6% (*n*=35) within the week prior to their death.

Among decedents with an opioid analgesic PDMP record (63.6%; *n*=739), the average number of days from the last dispensation was 17.2 (*SD*=12.2; Range 1–190), with an average quantity of 67.3 (*SD*=59.2; Range 1–630). Refills were present in 2.6% (*n*=111) of opioid analgesic dispensations. More than two-thirds (68.5%, *n*=506) of decedents who had an opioid analgesic PDMP record had a dispensation more than 30 days before their death, nearly one-third (31.5%, *n*=233) had an opioid analgesic dispensed within 30 days of their death, and 12.2% (*n*=90) had an opioid analgesic dispensed within 7 days of their death (see Table 1).

3.4 Examination of buprenorphine and opioid analgesics detection in toxicology records

Finally, we analyzed toxicology records to determine the involvement of any opioids, opioid analgesics, and fentanyl among those who had a PDMP record for buprenorphine and opioid analgesic dispensation. Toxicology records suggest that among decedents whose overdose deaths were attributed to any opioid, the proportion of decedents with a PDMP buprenorphine record was significantly greater compared to decedents with no PDMP record (90.9% vs. 82.0%; $p < .001$), and to decedents with an opioid analgesics PDMP record (90.9% vs. 83.6%; $p < .001$). Among decedents whose overdose death was attributed to fentanyl, a significantly greater proportion of decedents had PDMP record for buprenorphine compared to decedents with no PDMP record (78.5% vs. 70.3%; $p < .01$) and to decedents with an opioid analgesics PDMP record (78.5% vs. 57.5%; $p < .001$). Among decedents whose overdose deaths were attributed to any opioid analgesic, a significantly smaller proportion of decedents had a PDMP record for buprenorphine compared to decedents who had an opioid analgesics PDMP record (30.5% vs. 43.2%; $p < .001$). A full description of these findings can be found in Figure 2.

4. Discussion

Linking PDMP records to toxicology information provided us with a novel means to better understand associations between buprenorphine and opioid analgesic dispensation and subsequent accidental overdose deaths. Among the 2,682 deaths studied, less than half of those had any kind of PDMP record (43.3%, n=1,162) and among those with a PDMP record, only 28.5% (n=331) had a buprenorphine dispensation in the year prior to their

death. Although the total number of buprenorphine prescriptions increased year over year, they did not increase in proportion to the rise in opioid and specifically fentanyl-related deaths. As demonstrated by our toxicology data, prescription opioids are no longer driving overdose deaths in Marion County, Indiana, with fentanyl involved in almost 90% of the cases. It is critically important to acknowledge the broader context of an increasingly toxic supply of unregulated opioids, one in which buprenorphine remains an essential strategy to reducing drug-related overdose.

Most of the decedents who had a buprenorphine prescription had not filled their prescription in the 30 days prior to accidental overdose, which may underscore the challenges of medication adherence and retention. During the same period, overdose deaths continued to rise despite evidence of increasing buprenorphine uptake. While buprenorphine is increasingly accessible, significant barriers exist to starting medication and adhering to treatment. In the era of a fentanyl-saturated drug supply, buprenorphine may be more difficult to initiate, thus lowering the chance of successful treatment. For those accustomed to fentanyl, recommended dosing guidelines for buprenorphine may be sufficient, prompting them to seek unregulated opioids and increasing their risk of overdose.

Barriers to treatment initiation may be exacerbated by treatment systems with poor rates of retention, as evidenced by the fact that many buprenorphine dispensations occurred several months prior to a fatal overdose event. Our findings may underscore the importance of treatment retention, in which modest evidence supports contingency management compared to other behavioral therapies (e.g., supervised medication consumption; Timko et al., 2016). Alternatively, individuals may overdose and be retained in treatment, which may highlight the importance of access and availability of effective harm reduction practices and policies (Dunlop et al., 2020). Prescribing information in the current study may also be suggestive of issues with insurance coverage—if an individual no longer had insurance or qualified for Medicare, they could no longer pay for buprenorphine. Research should continue to explore the manner in which breaks in insurance coverage or periods of incarceration (Khatri et al., 2021) that disenroll people from certain Medicaid benefits can disrupt MOUD, thus potentially increasing the risk of overdose.

Critically, the results of this study reinforce concerns about racially disparate access to effective MOUD (Andraka-Christou, 2021) and chronic pain medication (Hausmann et al., 2013; Morales & Yong, 2021). An accidental opioid-involved overdose death provides strong evidence of OUD, and a prior dispensation of buprenorphine is evidence of utilizing an effective means to treat it. That Black decedents of overdose had significantly fewer buprenorphine dispensations than their White counterparts in the year prior to death, illustrating that these medicines are often not prescribed to Black patients with OUD who would likely benefit from them. The data here cannot speak to whether this disparity was due to lack of intention or lack of access, but research should consider the disparate availability when combined with recent findings that zip codes with a significantly higher proportion of White individuals saw a higher growth in the number of physicians waivered to prescribe buprenorphine (Schuler et al., 2021). Moreover, previous studies have found that treatment disparities in buprenorphine prescribing patterns by race and ethnicity may

be widespread (Lagisetty et al., 2019) and reflect extensive inequalities as they relate to financial barriers (Hansen et al., 2013).

Racial disparities related to MOUD access underscore the need for expanding the low-cost, availability of MOUD in underserved areas, especially those with a higher concentration of Black residents. The proven effectiveness of buprenorphine (Victor et al., 2021; Wakeman et al., 2020), combined with our findings that people who died of opioid-involved overdoses in this study sample were unlikely to have been taking it in the year before their death—and especially in the weeks before, suggests that low barrier, sustained access to MOUD is critical to reverse the tide of the nation's overdose epidemic (Fiscella et al., 2019). Our findings also suggest that we take up a particular definition of what low-barrier access means, specifically that people with OUD should be inducted into treatment in settings where they feel comfortable and are likely to return, and that we adopt a harm reduction approach that recognizes buprenorphine as an effective means of overdose prophylaxis as much as it is part of a formal, highly-structured, long term treatment protocol (Jakubowski & Fox, 2020).

4.1 Limitations

The limitations to this study center on the limits of its data. Since a PDMP does not capture the use of diverted MOUD, we do not know how many overdose victims may have been self-medicating with diverted buprenorphine in the year prior to their death. Self-medicating is not an uncommon practice (Carroll et al., 2018; Cicero et al., 2018), and research has shown it to be associated with a reduction in the frequency of self-reported accidental overdoses (Carlson et al., 2020). Likewise, we have no way to determine the extent to which people who were dispensed buprenorphine in our study adhered to treatment or instead diverted it to others. We also do not have the data for people who may have died of an accidental overdose in Marion County, but who were prescribed medications at locations outside of the corresponding PDMP's catchment. People may have been prescribed MOUD outside of Indiana but ultimately died of overdose in Marion County, although experience suggests the overall incidence would be rare. Taken together, these limitations come together to stress that although these data pertain to a sequence of events occurring for specific individuals over time, they suggest only associations that can be used to guide further research or inform policy by complementing the results of studies with experimental or quasi-experimental designs. The study does not, however, provide the means to draw firm causal inferences—while the evidence supports the protective effect of buprenorphine against overdoses, we cannot conclude that the decedents in our sample died because they were unprotected by buprenorphine. We can, however, confidently point to the fact that the vast majority were not taking buprenorphine in the months prior to their death.

4.2 Conclusion

The overdose epidemic remains one of the most pressing public health issues in the United States, with more than a half million deaths in the past decade (Seth et al., 2018; Ciccarone, 2017; Hedegaard, 2020). Among decedents with a buprenorphine PDMP record, most had no, abbreviated, or intermittent exposure to a buprenorphine dispensation in the year before their accidental fatal overdose. We also found racial disparities in buprenorphine

dispensation, which may underscore the need to facilitate equitable access to evidence-based practice in addiction medicine. The recent elimination of certain waiver requirements for physicians to prescribe buprenorphine is a promising development (Weimer et al., 2021), but for optimal efficacy, considerations should be given to physicians' willingness to treat patients for OUD, to provide evidence-based treatment (Friedmann et al., 2012), to relax concerns about MOUD diversion (del Pozo et al., 2020), and to ensure equitable access across demographics (Hansen et al., 2013). Last, our findings may represent challenges related to treatment retention, which may have been exacerbated during the COVID-19 pandemic. Future research should continue to explore promising behavioral therapies and service delivery models to increase buprenorphine retention.

Funding:

Support for this project was from the CDC Overdose Data to Action through the Indiana State Department of Health (Award# NU17CE924990).

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Highlights

- The emergence of illicit fentanyl as the dominant drug in many North American illicit drug markets is associated with an increased risk of fatal overdose, and this risk is amplified for racial and ethnic minority groups.
- Our findings indicate that a greater proportion of decedents had no, abbreviated, or intermittent exposure to prescribed buprenorphine in the year before their death.
- We also found racial disparities in buprenorphine dispensation which may underscore the need to facilitate equitable access to evidence-based practice in addiction medicine
- Our findings may represent challenges related to treatment retention, which may have been exacerbated during the COVID-19 pandemic.

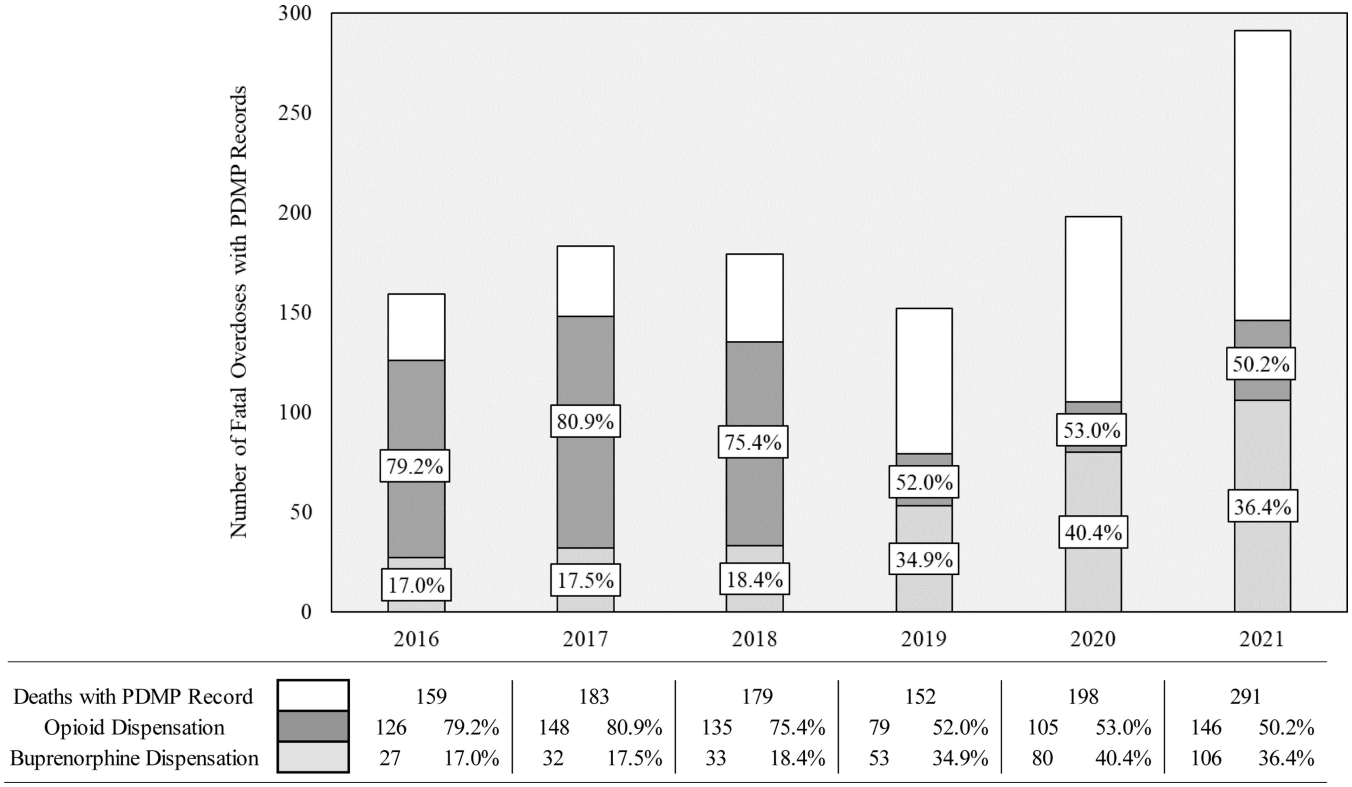

Figure 1.
Buprenorphine and opioid dispensations among decedents with a PDMP Record

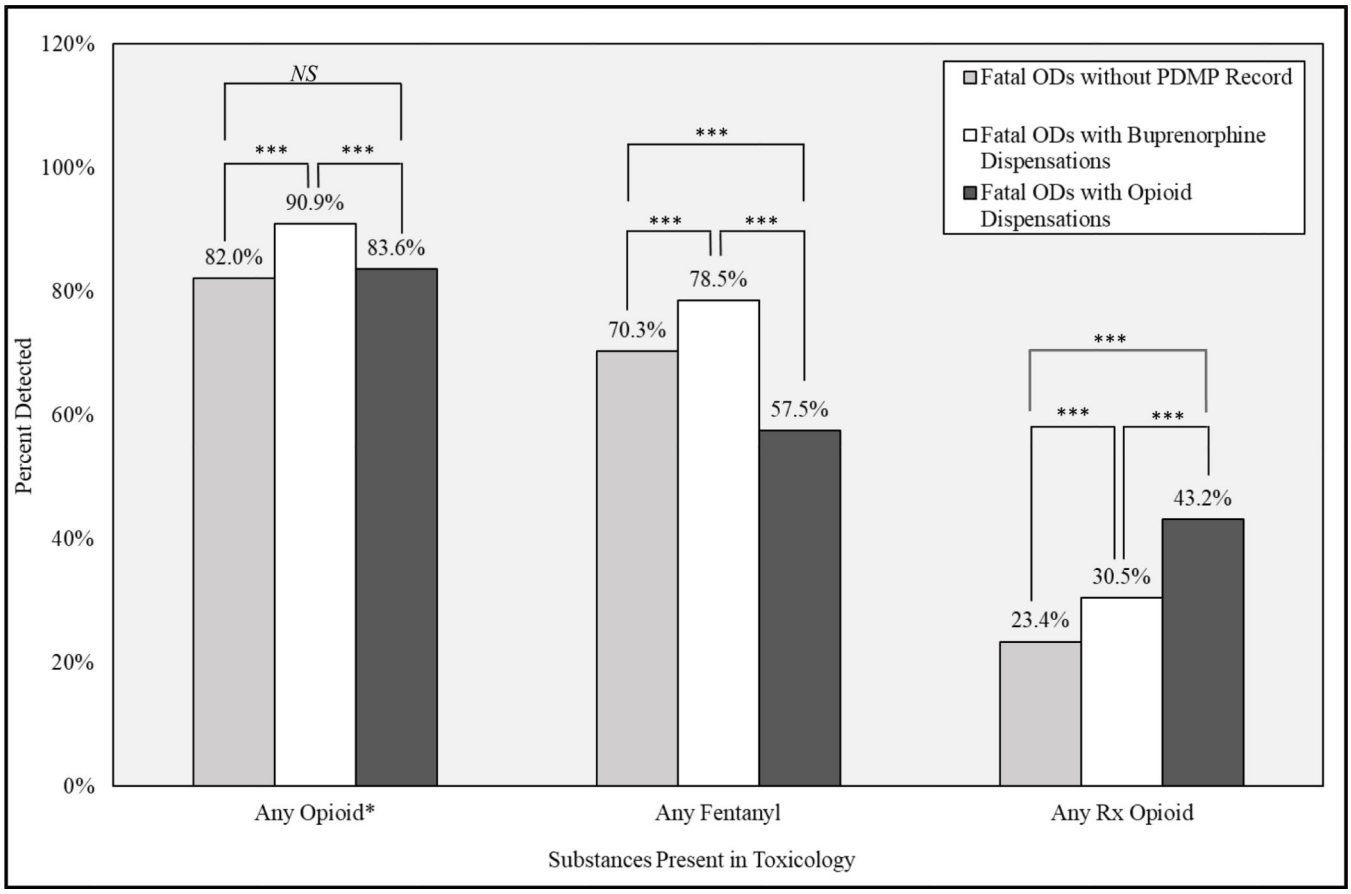

Figure 2.

Substances detected in toxicology reports

*Includes Rx opioids, heroin, and fentanyl

*p<.05, **p<.01, ***p<.001

Table 1:

Patterns of buprenorphine and opioid prescription dispensation

N	**1162**			
Prescribing Information	**Buprenorphine Rx**		**Opioid Rx**	
Number of Decedents with Rx	331	28.5%	739	63.6%
Total Rx Filled	3244		4280	
Days				
Mean (S.D.)	11.9 (9.0)		17.2 (12.2)	
Range	1 – 60		1 – 90	
Quantity				
Mean (S.D.)	23.0 (19.4)		67.3 (59.2)	
Range	1 – 120		1 – 630	
Refills (Any)	342	10.5%	111	2.6%
Mean (S.D.)	1.7 (1.1)		2.2 (1.9)	
Range	1 – 9		1– 13	
Fill date of Rx received prior to death *				
Within 7 days	35	10.6%	90	12.2%
Within 30 days	117	35.3%	233	31.5%
More than 30 days	214	64.7%	506	68.5%

*From most recent script to death