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ORIGINAL ARTICLE

Opioid Overdose Deaths with Buprenorphine Detected in Postmortem Toxicology: a Retrospective Analysis

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Abstract

Background Buprenorphine is a unique μ-opioid receptor partial agonist with avid receptor binding, nominal euphoric reward, and a ceiling effect on sedation and respiratory depression. Despite a pharmacologic profile that enhances safety, cases of fatal opioid overdose with buprenorphine on postmortem toxicology are reported, but details of these cases in the literature are limited.

Methods A retrospective review of opioid-involved drug overdose fatalities in Rhode Island (RI) from 2016 to 2018 using the RI Department of Health State Unintentional Drug Overdose Reporting System (SUDORS) database. Deaths with buprenorphine on toxicology testing versus opioid-involved overdose deaths without buprenorphine were compared to assess the type and number of co-exposures.

Results Of 534 opioid-involved deaths, 29 (5.4%) included buprenorphine and/or norbuprenorphine on toxicology. Most frequent co-exposures are as follows: fentanyl (75.9%), norfentanyl (72.4%), cocaine (41.4%), benzoylecgonine (41.4%), cannabinoids (31.0%), ethanol (31.0%), levamisole (31.0%), and free morphine (31.0%). An average number of co-exposures for fatalities with buprenorphine were 9.24 versus 6.68 in those without buprenorphine. In one case buprenorphine was the only drug listed to cause death; all other fatalities with buprenorphine on toxicology reported additional drugs contributing to death.

Conclusion Decedents with buprenorphine detected on toxicology testing commonly had documented polysubstance use. Although data are limited, buprenorphine may provide some risk mitigation against full agonist opioid overdose including fentanyl. Further work should explore the use of postmortem concentrations of buprenorphine, norbuprenorphine, and other opioid metabolites to determine the role of buprenorphine in fatal overdose pharmacology.

Keywords Buprenorphine · Fentanyl · Overdose · Fatality · Polypharmacy · Co-exposure

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Background

Buprenorphine is a unique μ-opioid receptor partial agonist with avid binding to the opioid receptor [1], nominal euphoric reward, and a ceiling effect on both sedation and respiratory depression [2]. Given these properties, buprenorphine may have a risk-mitigating effect in the setting of acute opioid overdose [3–5]. Buprenorphine has successfully been used as rescue therapy from full agonist opioid overdose in cases when opioid antagonist therapy was not readily available [6]. Despite this safety profile, concerns about buprenorphine misuse, abuse, and diversion are often at the forefront of public discourse and policy development [7, 8]. Most notably, perceived risks of buprenorphine became codified into the Drug Enforcement Agency (DEA) Drug Addiction Treatment Act of 2000 (DATA-2000 Act) adding a legal hurdle to buprenorphine prescribing, thereby restricting patient access.

Cases of fatal opioid overdose with buprenorphine detected on postmortem toxicology testing do occur [5, 9], yet they remain understudied, and national statistics are not readily available. Like most drug overdose fatalities, adult opioid overdose fatalities with buprenorphine and/or buprenorphine metabolites (norbuprenorphine) detected on postmortem toxicology testing (BOTT) tend to occur in the context of polysubstance use; however, buprenorphine-only deaths have been reported [10–12]. In cases where buprenorphine is attributed as the sole agent, deaths are more often in children or associated with parenteral use of buprenorphine products [13]. Nonetheless, prior literature evaluating BOTT does not put deaths in which buprenorphine was noted on toxicology testing in context to the actual cause of death or allow comparison with other opioid-related fatalities.

To fill this research gap, we compared BOTT with opioid overdose fatalities with no detectable buprenorphine and/or buprenorphine metabolites (norbuprenorphine) on toxicology testing (NoBOTT) to evaluate the contribution of buprenorphine in such deaths. Toxicologic and pharmacologic evaluation of these cases can add to the information known about buprenorphine, particularly in the context of co-ingestion of other substances and misuse.

Methods

A retrospective review of accidental or undetermined opioid-involved overdose deaths (aged 17 to 70) occurring in Rhode Island between July 1, 2016, and June 30, 2018, was performed using data from the Rhode Island Department of Health (RIDOH) State Unintentional Drug Overdose Reporting System (SUDORS) database [14]. SUDORS is a CDC-funded database that contains information abstracted from multiple data sources, including medical examiner records, death certificates, and law enforcement records. Law enforcement and medical records are included as part of the death investigation conducted by the Office of the State Medical Examiner (OSME). Currently 32 states and the District of Columbia (DC) are funded for SUDORS database development as part of the CDC's Enhanced State Opioid Overdose Surveillance Program. Rhode Island is one of the twelve states that have collected data since 2016, and additional twenty states and DC began collecting data in 2017. The information is abstracted by a team of trained abstractors and entered into SUDORS. Variables are coded based on a CDC-provided coding manual. SUDORS includes detailed information on toxicology testing results, demographics, and circumstances surrounding the death. Rhode Island's SUDORS data include cases, both in and outside of a hospital, for which the death was pronounced in Rhode Island, the Office of the State Medical Examiner (OSME) attributed the manner of death to be either "accident" or "undetermined," and an opioid was listed as the primary cause of death or contributing factor.

The forensic toxicology lab at the OSME has a standard testing protocol for analyzing casework. Preliminary drug testing is performed on whole blood specimens using the ELISA (enzyme-linked immunosorbent assay) technique. Drug classes tested include the following: alcohol, amphetamines, antidepressants, benzodiazepines, cocaine, marijuana (cannabinoids), anticonvulsants, muscle relaxants, opioids, barbiturates, and antipsychotics. Presumptive positive results from ELISA testing were subject to more intensive confirmatory testing (e.g., gas chromatography/mass spectrometry (GC-MS) or liquid chromatography/tandem mass spectrometry), which was also performed on a whole blood specimen. Reporting limits of detection for opioids of interest to this study were as follows: buprenorphine 0.5 ng/mL, norbuprenorphine 0.5 ng/mL, fentanyl 0.1 ng/mL, and methadone (25 ng/mL until May 2018 and then 5 ng/mL after May 2018). Fentanyl and fentanyl analogues were detected initially via a GC-MS screening method by the RI OSME and confirmed by an outside laboratory. Naloxone was tested via GC/MS and was reported as positive or negative. Quantification testing for naloxone was not performed.

For this study, data was extracted from SUDORS and de-identified. Demographic data was aggregated to prevent the ability to trace the data back to an individual. Based on RIDOH small numbers reporting policy all data elements and results with numbers less than five were reported as such. Decedents with BOTT versus NoBOTT were compared to assess the type and number of co-exposures/co-intoxicants on toxicology testing. All drugs reported on toxicology testing in SUDORS, whether or not determined by the ME as cause of death, were included. Cases were excluded that did not have testing in all of these drug classes. For comparison purposes, an additional analysis was performed evaluating overdose fatalities with methadone as the only opioid on toxicology testing.

To compare differences, we used the Chi-square test for categorical variables since all expected cell sizes were greater than 5 and the *t*-test for continuous variables. This project was reviewed and deemed exempt status by the Rhode Island Department of Health IRB and the Lifespan IRB because the analysis did not involve living human subjects.

Results

A total of 569 deaths determined by the ME as accidental and/or undetermined opioid overdose fatalities occurred in RI between July 2016 and June 2018. Thirty-five (35, 6.2%) cases were excluded because they did not have comprehensive toxicology testing done, leaving a total of 534 cases in the analytic sample. One excluded fatal overdose case had buprenorphine and/or buprenorphine metabolites (norbuprenorphine) on toxicology testing; the other 34 cases did not.

Of the 534 cases, 29 (5.4%) cases had BOTT. The distribution of BOTT versus all others by age and sex is shown in Table 1. There was no statistically significant difference in the demographics of the two groups.

Co-exposures

All BOTT cases involved additional co-exposures. The average number of drugs and metabolites found was 9.24 (SD = 3.99) for BOTT versus 6.68 (SD = 3.50) for NoBOTT.

As shown in Table 2, fentanyl and/or metabolites were identified in 76% of the BOTT and 74% of NoBOTT. Norfentanyl was found in 96% (21/22) of the fentanyl fatalities in BOTT, versus 71% in the fatalities in NoBOTT (p = 0.0137). All the BOTT cases that had norfentanyl detected also had fentanyl present. In NoBOTT there were fewer than five cases where norfentanyl was present without fentanyl.

Additional opioids were found on toxicology testing in 89.7% (26/29) of BOTT cases. In the BOTT cases where buprenorphine was the only opioid found on toxicology testing, co-exposures included the following: sertraline and metabolites, ethanol, cocaine, benzoylecgonine, cocaethylene, methylecgonine, norcocaine, gabapentin, quetiapine, levamisole, cannabinoids, and hydroxyzine. In 28 out of 29 BOTT cases, in addition to buprenorphine and/or norbuprenorphine, other substances were identified by the medical examiner as a cause of death.

Of the 29 BOTT cases, norbuprenorphine alone was found in 10 (34.5%) cases, buprenorphine alone was found in less than five cases, and both buprenorphine and norbuprenorphine were found in 16 cases (55.2%). Naloxone was not found on toxicology testing in any of the BOTT and only 1% of the NoBOTT.

Methadone

Among the 534 included opioid-involved fatalities, there were 66 (12.4%) opioid overdose fatalities with methadone on postmortem toxicology testing. NoBOTT cases had methadone detected on toxicology testing. Of the 66 cases with methadone detected, it was the only opioid found in 29 (43.9%) of the cases. After methadone the next most common drugs and/or metabolites found on toxicology testing in cases with methadone on toxicology testing (n = 66) were as follows: fentanyl (38%), norfentanyl (32%), cocaine (32%), benzoylecgonine (30%), cannabinoids (26%), levamisole (21%), alprazolam (18%), and gabapentin (18%). The average number of drugs and metabolites on toxicology testing for opioid-involved overdose fatalities with methadone was 7.80 (SD = 3.65; see Table 3).

Discussion

In this retrospective review of all opioid overdose fatalities occurring in Rhode Island between July 2016 and June 2018, buprenorphine was found on postmortem toxicologic analysis in only 29 (5.4%) cases. All BOTT cases had

Table 1 Demographics of opioid-involved accidental or undetermined fatalities in Rhode Island, July 2016–June 2018.

Fatalities with buprenorphine or norbuprenorphine detected (n = 29)			Fatalities without buprenorphine or norbuprenorphine detected (n = 505)			p Value
Age	Count	Percentage	Age	Count	Percentage	
15–34	9	31.0%	15–34	174	34.4%	0.635
35–54	13	44.8%	35–54	244	48.3%	
55 +	7	17.2%	55 +	87	17.2%	
Sex	Count	Percentage	Sex	Count	Percentage	
Male	20	69.0%	Male	369	73.1%	0.629
Female	9	31.0%	Female	136	26.9%	

p values represent expected differences across all age categories

Table 2 Co-exposed drugs and metabolites found on toxicology testing among opioid-involved accidental and undetermined fatalities in Rhode Island, July 2016–June 2018

Opioid overdoses with buprenorphine or norbuprenorphine detected ($n = 29$)			Opioid overdoses without buprenorphine or norbuprenorphine detected ($n = 505$)		
Agent	Count	Percentage	Agent	Count	Percentage
Fentanyl	22	75.9%	Fentanyl	370	73.3%
Norfentanyl	21	72.4%	Norfentanyl	264	52.3%
Cocaine	12	41.4%	Cocaine	190	37.6%
Benzoylecgonine	12	41.4%	Benzoylecgonine	175	34.7%
Cannabinoids	9	31.0%	Cannabinoids	126	25.0%
Ethanol	9	31.0%	Total morphine	107	21.2%
Levamisole	9	31.0%	Levamisole	107	21.2%
Free morphine	9	31.0%	Free morphine	106	21.0%
Methylecgonine	8	27.6%	Methylecgonine	106	21.0%
Total morphine	8	27.6%	Ethanol	101	20.0%

The top ten substances for each exposure category are shown. The number is greater than the total number of cases due to multiple exposures in individual decedents

co-exposures. On average, BOTT cases had more drugs and metabolite co-exposures compared with NoBOTT cases.

The vast majority (26 of the 29) of BOTT cases had norbuprenorphine present; 10 of the 29 deaths had norbuprenorphine detected without any parent compound. The absence of buprenorphine and presence of norbuprenorphine suggest that most individuals who experienced an opioid overdose fatality involving buprenorphine were not recently exposed to buprenorphine, making it unlikely to be the primary cause of death [12, 15]. However, postmortem pharmacokinetics of buprenorphine and its metabolites are complicated and not fully understood, limiting interpretation of their toxic effects. The major active metabolite, norbuprenorphine, has a different pharmacological profile than buprenorphine. Norbuprenorphine is a potent, high affinity agonist at μ-,δ- ,and κ-opioid receptors and acts as a substrate of p-glycoprotein, whereas buprenorphine is a partial agonist at the μ-opioid receptor with antagonist activity at the κ-opioid receptor. As concentrations and ratios change over time due to metabolism and elimination, there is a changing pattern of pharmacologic actions and interactions in vivo, and how this affects postmortem concentrations and interpretation of toxicity requires additional study [9].

Table 3 Fatal opioid-involved overdose postmortem toxicology testing comparison

	Cases with buprenorphine ($n = 29$)	Cases without buprenorphine or methadone ($n = 439$)	Cases with methadone ($n = 66$)
Average age (years)	43.2	40.9	45.3
Average drugs and metabolites on toxicology testing	9.24	6.51	7.8
% with fentanyl	75.9	78.6	37.9

Naloxone was not detected in any of the fatalities with buprenorphine/norbuprenorphine found on postmortem toxicology testing. Unfortunately, in this dataset, the limits of detection for naloxone are unknown, and only qualitative naloxone testing was performed. With therapeutic use of the sublingual transmucosal buprenorphine/naloxone formulation, the peak serum naloxone concentration, Cmax, ranges from 48.5 pg/mL (2/0.5 mg) to 226 pg/mL (16/4 mg); all values below the threshold for detection on most testing [16]. If buprenorphine were injected, higher naloxone concentrations would be expected. This finding may support our hypothesis that the majority of overdose fatalities with buprenorphine detected on toxicology testing in this sample did not experience an acute buprenorphine overdose.

Consistent with current trends in the US overdose crisis (particularly in the northeastern USA), fentanyl was the most common agent found among all cases. Fentanyl/norfentanyl ratios can be used to assist in determining the rapidity of death from opioid overdose [17]. Given the short half-life of fentanyl, norfentanyl should be present together with the parent drug unless the decedent died within minutes of use. In our dataset, norfentanyl was found in 95.5% (21/22) of the fentanyl fatalities with BOTT versus 71% of the NoBOTT fatalities ($p = 0.0137$). This suggests that decedents with some buprenorphine may have survived longer after fentanyl exposure; however, conclusions are limited as drug concentrations to calculate fentanyl/norfentanyl ratios were not available. In the setting of full opioid agonist overdose, binding of opioid to the receptor could be decreased if buprenorphine, which binds with high affinity to the mu opioid receptor, is present. This is consistent with the "euphoria blocking" effect of

buprenorphine on heroin or fentanyl use. However, buprenorphine's avid binding can be overcome if a sufficient amount of full opioid agonist is present [18, 19]. Finally, although data are limited, the increased number of co-exposure drugs and metabolite analysis in BOTT compared with NoBOTT suggests that buprenorphine could provide some risk mitigation against full agonist opioid overdose including fentanyl, the most common agent found in the dataset.

The opioid overdose risk profile of buprenorphine needs to be placed in context. The risks and benefits of buprenorphine prescribing should be compared to alternate therapies for opioid dependence. Both buprenorphine and methadone are widely used to control the physiologic and psychological effects of opioid withdrawal and to treat opioid use disorder. Compared with buprenorphine (half-life 2–9 hours), methadone has a prolonged half-life of 15–72 hours, which increases the risk of drug accumulation from one dose to the next increasing risk of toxicity and death. Although both buprenorphine and methadone are subject to postmortem redistribution, methadone is a more lipid soluble, resulting in greater postmortem redistribution and higher blood concentrations post-death [20].

In 2016, out of a total population of 1.057 million, approximately 26,000 Rhode Islanders had been diagnosed with opioid use disorder [21]. According to state surveillance data, during the study period, an average number of patients actively receiving buprenorphine and methadone for the treatment of OUD in Rhode Island respectively were 4707 (monthly range 4395–5214) and 5377 (monthly range 5139–5695) [22]. Over our study period, there were 66 deaths (12% of all included opioid-involved drug fatalities) with methadone found on toxicology testing compared with 29 (5.4% of all included opioid-involved drug fatalities) with buprenorphine on toxicologic analysis. Of the 66 methadone fatalities, 29 had methadone listed as the only opioid detected on toxicology testing versus less than five fatalities with buprenorphine/norbuprenorphine as the only opioid detected on toxicology testing ($p < 0.001$). Our findings are congruent with prior studies that demonstrated fewer deaths in patient on buprenorphine use versus methadone [23, 24].

Limitations

This study has a number of limitations. The sample is limited to overdose death surveillance data from only a single state in New England, which limits generalizability. The time from death to sampling for toxicology testing for cases was not reported in this dataset, which may make it difficult to contextualize the toxicology testing results in some cases. Additionally, individual variation in tolerance to opioids, clinical information not available in this de-identified dataset, can limit the ability to interpret the significance of blood concentrations postmortem. It is difficult with some substances to differentiate between parent compound and metabolite identified on toxicology testing. For example, for deaths involving heroin, it is common to find morphine on toxicology testing, and it is difficult to determine with certainty whether the morphine found was a separate exposure or a heroin metabolite. For this reason, all drugs and metabolites were recorded as unique agents to ensure uniformity across comparison groups. Postmortem toxicology testing presented is qualitative, and drug concentrations are not available. The source of buprenorphine and methadone, (e.g., illicit vs. prescribed) in fatalities is unknown, which limits the ability to make conclusions about mortality rates among individuals engaged in MAT.

Conclusion

Decedents with buprenorphine detected on toxicology testing commonly had documented polysubstance use. Although data are limited, buprenorphine may provide some risk mitigation against full agonist opioid overdose including fentanyl, the most common agent found in the dataset and the fastest rising cause of opioid overdose death nationally. Further work should explore the use of postmortem concentrations of buprenorphine, norbuprenorphine, and other opioids and metabolites to determine the role of buprenorphine in fatal overdose.

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Authors' Contributions Rachel S. Wightman, MD: Dr. Wightman was involved in study design, data analysis and interpretation, and manuscript creation.

Jeanmarie Perrone, MD: Dr. Perrone was involved in study creation, design, data analysis and interpretation, and manuscript editing.

Rachel Scagos, MPH: Rachel Scagos was involved in study design, data extraction, interpretation, and analysis as well as manuscript creation.

Maxwell Krieger, BSc: Maxwell Krieger was involved in study design, data extraction and acquisition, and data analysis and graphical representation of study findings.

Lewis S. Nelson, MD: Dr. Nelson was involved in data analysis and interpretation as well as manuscript editing.

Brandon D.L. Marshall, PhD: Dr. Marshall was involved in study creation, design, data analysis and interpretation and manuscript editing.

Compliance with Ethical Standards

Conflict of Interest None.

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