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ORIGINAL ARTICLE

Toxicology

Buprenorphine, oxycodone, hydrocodone, and methadone mortality in the United States (2010–2017)

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Abstract

Objective: Opioid overdose survivors present to emergency departments (EDs) and many EDs have developed programs to initiate buprenorphine. The impact of the increasing use of buprenorphine in ED and by other providers is unknown while opioid mortality continues to rise. Public mortality data do not distinguish buprenorphine from other prescription opioids. Our objective was to determine when changes in overdose mortality trends occurred comparing deaths involving buprenorphine to oxycodone, hydrocodone, and methadone.

Methods: This observational study utilized the drug-involved mortality database including US death certificates (2010–2017) in which buprenorphine, oxycodone, hydrocodone, or methadone were contributing causes of death (determined through textual analysis). Population- and drug utilization-adjusted mortality rates were examined using disjointed linear regression. Buprenorphine-involved deaths were stratified by polysubstance involvement.

Results: The population-adjusted mortality rates for buprenorphine-involved deaths were lowest compared to other opioids; however, the change in rate for buprenorphine increased faster than oxycodone, hydrocodone, and methadone at 8.9% each quarter-year (95% confidence interval [CI]: 8.0, 9.8) from 2010 to mid-2016 when it stabilized. After adjusting for changes in dispensing over the study period, buprenorphine-involved mortality rates were increasing at 5.3% (95% CI: 4.6, 6.1) each quarter-year. In 2017, 94% buprenorphine-involved deaths had at least one other drug contributing to the cause of death.

Conclusions: Given the low mortality, high proportions of polysubstance mortality, and the mixed agonist/antagonist mechanism of action, use of buprenorphine alone likely presents a lower risk for overdose than comparators. Mortality rose faster than dispensing, signaling need to ensure people understand buprenorphine risks, particularly polysubstance use, balanced against importance for treating opioid use disorders.

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KEYWORDS
buprenorphine, medication-assisted therapies, overdose mortality, polysubstance

1 | INTRODUCTION

1.1 | Background

Mortality related to the opioid crisis has risen rapidly in the last two decades in the United States. Early in this crisis, overdose mortality primarily involved prescription opioids, followed by increasing heroin-involved overdose mortality and, more recently, by a sharp increase in overdose involving synthetic opioids.[1] By 2017, 70% of all drug overdose deaths involved an opioid, and 60% of opioid deaths involved a synthetic opioid.[2] One tactic to combat the growing opioid epidemic has been increasing access to pharmacological treatments for opioid use disorders (OUDs).

Buprenorphine, which suppresses withdrawal symptoms and attenuates other opioid effects,[3] was approved by the Food and Drug Administration as a treatment for OUD in 2002.[3] Although a waiver was initially required for physicians to prescribe buprenorphine in office-based settings and there were patient limits in place, access to buprenorphine was expanded in 2016,[4] and the waiver requirement was eliminated entirely starting in 2023.[5] Buprenorphine is a partial agonist at the μ-opioid receptor and antagonist at the κ-receptor, which causes it to have different pharmacological profiles than a full agonist treatment, such as methadone.[6] Buprenorphine infusion can also limit respiratory depression caused by other opioids, including fentanyl.[7]

Nonetheless, as a partial μ-opioid receptor agonist, buprenorphine may itself induce respiratory depression[8] and therefore can contribute to cause of death.[9] Therefore, it is important to understand the extent of this risk as emergency physicians will increasingly encounter those who use buprenorphine to treat OUD, may be in active withdrawal, and those who are survivors of opioid overdose as they present to the emergency department (ED). The impact of increasing use of buprenorphine in the ED and by many other providers is unknown. This study was interested in quantifying the contribution of buprenorphine in drug overdose deaths.

1.2 | Importance

Buprenorphine cannot be distinguished in death records using Classification of Diseases (ICD-10) codes. Importantly, publicly available mortality data do not distinguish buprenorphine from other synthetic prescription opioid deaths, a category that includes all fentanyl related deaths as well.[10] To understand the contribution of buprenorphine in cause of death as dictated by coroners and medical examiners, the literal text fields on death certificates must be analyzed. Furthermore, these data are restricted access. With these two features combined, important national trends in buprenorphine-involved mortality are masked in publicly available mortality reports. Ability to access the literal text on death certificates and extract listed drugs involved in the death allows for more specific assessment of drug molecules and more detailed surveillance of individual active pharmaceutical ingredients. In addition, the co-involvement of synthetic opioids is growing across all drug deaths (semi-synthetic opioids, psychostimulants, cocaine, heroin, etc.).[1] Distinguishing between various synthetic opioids could identify uncommon, but relevant, trends in mortality.

1.3 | Goals

The primary objective of this study was to compare change in drug overdose mortality trends among deaths involving buprenorphine versus oxycodone, hydrocodone, and methadone in the United States from health surveillance data from 2010 to 2017. This includes expansion to access that occurred in 2016. One secondary objective included describing regional differences in mortality over time. Finally, given that those who present to the ED likely are complex clinical cases, which involved polysubstance use, another secondary objective was to quantify the percentages of polysubstance deaths.

2 | METHODS

2.1 | Design

This surveillance study used mortality files linked to cause-of-death literal text from death certificates provided in the Centers for Disease Control and Prevention (CDC) restricted-access data from the Research Data Center, the Drug Involved Mortality (DIM) database. The DIM database was essential in this study since it houses the National Vital Statistics System's repository of all deaths with drug-related terms mentioned in the cause-of-death literal text field as determined by medical examiners or coroners. These deaths from 2010 to 2017 in the 50 US states and District of Columbia were included, which was the most recently available data to researchers to request access for use.

Multiple definitions for overdose deaths have been proposed including identification through ICD-10 codes only (the standard National Center for Health Statistics [NCHS] definition), use of substance use disorder codes, and pharmaceutical adverse events.[11] For our analysis, drug overdose deaths were defined utilizing the Vermont Department of Health definition, which includes the standard NCHS definition of identifying poisonings from controlled substances[10] (ICD-10 codes: X40-44 unintentional/accidental poisoning, X60-64 intentional self-harm/suicide, X85 assault/homicide, and Y11-14 undetermined intent)

The Bottom Line

Many emergency departments have developed buprenorphine programs for treating opioid use disorders and addressing overdoses. Compared to population size in the United States, overdose rates for buprenorphine-involved deaths were lowest compared to oxycodone, hydrocodone, and methadone (2010–2017); however, the rates increased from 2010 to mid-2016. Since buprenorphine dispensing has also increased, the rate per prescription was calculated, also increasing over time. In 2017, 94% of buprenorphine-involved deaths had another drug involved. Overall buprenorphine mortality was low, but mortality rose faster than dispensing signaling need to ensure people understand buprenorphine risks, particularly polysubstance use, balanced against importance for treating opioid use disorders.

and adds additional codes to identify drug overdoses including the mental health-related harmful use and dependence syndromes (X45, X60, F10-F19[.0, .1], T36-50, and T51.0).[12] Given buprenorphine was a primary drug of interest and is indicated as treatment for OUD, it was important to include these mental health-related deaths in our definition. Among overdose cases, a drug with involvement in cause of death must have been mentioned on the death certificate based on medical examiners or coroners' determination.

2.2 | Measures/outcomes

In the United States, all deaths that involve a coroner or medical examiner are captured by use of death certificate, which is completed by the coroner or medical examiner performing the examination. The DIM dataset includes all of the drugs mentioned in the literal text fields, which the coroner or medical examiner concluded were causally involved in the death. The primary drug of interest was buprenorphine and must have been mentioned on the death certificate as a contributing cause to the poisoning. Oxycodone, hydrocodone, and methadone-involved deaths were also examined for comparison. Individual substances involved in the death were identified through textual analysis and manual review conducted by NCHS; more details on the specifics of this process can be found elsewhere.[13] Briefly, search terms for each drug substance in the literal text fields completed by medical examiners or coroners were identified through both the listed drugs involved and contextual information. If a search term was isolated in the literal text, the drug was coded as contributing to the cause of death. This provides higher precision for counts of substances involved in deaths since it goes beyond the substances identified by individual ICD-10 codes. If a drug mention is flagged as not being involved in the death through contextual clues in the literal text, the mention was excluded from analysis. If a death record was found to have multiple drugs involved in the cause of death, that death record was included in the analysis for each of the four drugs examined. Among buprenorphine-involved deaths, polysubstance deaths were classified as including any additional cause of death mentions for: any additional drug, alcohol (ethanol), benzodiazepines (eg, alprazolam, diazepam), centrally active psychostimulants (eg, cocaine, amphetamine, methamphetamine), heroin, and other opioid excluding heroin (eg, fentanyl, oxycodone, morphine). Additional information (eg, demographics, geography, date of death) was used as recorded on the death certificate. Sex and race are both determined by the coroner or medical examiner on the death certificates, with known limitations to the accuracy of race and Hispanic origin.[14] Geography is based on the state where the death occurred, presented at the census region level.

Two additional data sources were utilized in this study to scale the rate adjustments by population and amount of drug dispensing which provided context to how opioid dispensing changed from 2010 to 2017. Annual population rates were calculated using population estimates from the US Census Bureau's Population Estimates Program for 1 July of each year both nationally and stratified by census region. For quarterly rates, the population estimates were interpolated via linear regression between years. Population-adjusted rates provide a per capita understanding of drug overdose trends. Projections for amount of drug dispensing were provided by IQVIA's US-Based Longitudinal Prescription Data and are a measure of drug availability by the number of dosage units dispensed in a geographical region. Dosage units were defined as one unit of the dispensed drug, such as a one pill. The IQVIA prescription database uses timely product and geographically specific data obtained from prescription transactions covering approximately 92% of retail pharmacy transactions in the United States to inform their projections. IQVIA uses a proprietary projection methodology to extrapolate from the observed data to the universe of all retail prescriptions in the United States. IQVIA defines the retail prescription channel to include chain pharmacies, independent pharmacies, food store pharmacies, and mass merchandizers with pharmacies. IQVIA data were only available from third quarter 2010 to 2017. Methadone is typically dispensed at opioid treatment centers and therefore not properly accounted for in IQVIA data given it is known to be underrepresented in this data source it was not included in drug utilization analyses. Dispensing adjusted rates provide understanding of drug overdose trends relative to authorized availability.

2.3 | Data analyses

First, decedent demographics over the cumulative period from 2010 to 2017 were presented by drug. Second, total number of overdose deaths by drug were calculated as quarterly adjusted rates based on month of death to assess changes over time; quarter 1 included January–March, quarter 2 included April–June, quarter 3 included July–September, and quarter 4 included October–December. Number of overdose deaths with 95% confidence intervals (CIs, cal-

TABLE 1 Demographics characteristics of overdose deaths by involved drug (2010–2017).

Characteristic	Level	Drug listed contributing to cause of death			
		Buprenorphine (*N* = 3241)	Oxycodone (*N* = 46,244)	Hydrocodone (*N* = 26,278)	Methadone (*N* = 31,659)
Gender	Male, *N* (%)	2086 (64.4%)	26,565 (57.4%)	13,518 (51.4%)	19,269 (60.9%)
Age	Median (IQR)	38 (30, 49)	45 (35, 54)	48 (38, 56)	43 (32, 53)
Race	White, *N* (%)	3059 (94.4%)	42,605 (92.1%)	24,192 (92.1%)	28,664 (90.5%)
	Black, *N* (%)	129 (4.0%)	2751 (5.9%)	1532 (5.8%)	2365 (7.5%)
	Native American or Alaskan Native, *N* (%)	26 (0.8%)	560 (1.2%)	350 (1.3%)	448 (1.4%)
	Asian or Pacific Islander, *N* (%)	27 (0.8%)	328 (0.7%)	204 (0.8%)	182 (0.6%)
Most common ICD-10 underlying cause of death codes[a]	Unintentional				
	X41, *N* (%)	34 (1.0%)	118 (0.3%)	74 (0.3%)	119 (0.4%)
	X42, *N* (%)	1004 (31.0%)	15,035 (32.5%)	6940 (26.4%)	13,558 (42.8%)
	X44, *N* (%)	1831 (56.5%)	21,700 (46.9%)	12,753 (48.5%)	13,129 (41.5%)
	Self-harm/suicide				
	X62, *N* (%)	12 (0.4%)	1595 (3.4%)	835 (3.2%)	429 (1.4%)
	X64, *N* (%)	59 (1.8%)	3045 (6.6%)	2701 (10.3%)	658 (2.1%)
	Undetermined intent				
	Y12, *N* (%)	30 (0.9%)	1198 (2.6%)	471 (1.8%)	1444 (4.6%)
	Y14, *N* (%)	89 (2.7%)	1423 (3.1%)	932 (3.5%)	849 (2.7%)

Abbreviations: ICD-10, Classification of Diseases; IQR, interquartile range.
[a]Underlying cause of deaths codes contributing <1% of deaths for all drugs were not displayed.

culated based on the Poisson distribution) were scaled to rates per 1,000,000 population and 1,000,000 dosage units dispensed; national and regional rates were calculated. Joinpoint statistical software was utilized to fit linear disjointed regression slopes, which identified breaks in the national trend at "joinpoints."[15] Briefly, the software utilized the log-transformed mortality rates per quarter and searches the grid space to identify the best fit number of joinpoints, and calculates the average quarterly percent change using a Poisson model.[16,17] This method assumes no prior number of trend breaks, but does assume sequential linear relationships connected at joinpoints. We ensured at least two quarters must be present in between identified segments to ensure the joinpoint method was detecting changes beyond seasonality in deaths. Tests of significance used a Monte Carlo Permutation method. The advantage of this approach was that no a priori assumptions about observed trends were required. Both segmental quarterly percent change and cumulative average quarterly percent change are shown to be interpreted as the change in total counts, or absolute number, of deaths involving each of the drugs of interest without other adjustments.

To understand dispensing changes during the study period, national dispensing per capita (per 1000 population) was calculated for each drug. Buprenorphine dispensing was further stratified by census region. Finally, among 2017 deaths, the annual proportions classified as polysubstance were calculated with 95% Clopper–Pearson CI for each additional substance mentioned for the four drugs of interest. Since reporting of all drug mentions involved in deaths has improved over time, the quantification of each drug involved in the polysubstance nature of the death was only shown for the most recently available data.

For all analyses, if death counts less than 10 occurred, the statistics for that cell were suppressed for confidentiality reasons in accordance with CDC restricted data use agreements. Given this study was conducted on only decedents, it is not considered human subject's research. All analyses were conducted in SAS (version 9.4) and Joinpoint Trend Analysis Software (version 4.9.0.0) for the trend analysis.[18]

3 | RESULTS

3.1 | Characteristics of decedents

From 2010 to 2017 among poisoning overdose deaths, there were 3241 buprenorphine-involved deaths, 46,244 oxycodone-involved deaths, 26,278 hydrocodone-involved deaths, and 31,659 methadone-involved deaths across the 50 US states and the District of Columbia. Decedents with buprenorphine listed on their death certificate as a contributing cause were younger and slightly more likely to be white or male than those with oxycodone, hydrocodone, or methadone listed on their death certificate (Table 1). Across all drugs, accidental poisonings were the most reported underlying cause of death. The inclusion of mental health-related codes, which was intended to yield potentially

TABLE 2 Percent change over time for adjusted mortality rates by drug (2010–2017).

	Cumulative percent change[a] (each quarter-year)	Segment percent change[b] (each quarter-year)	
Drug	**Average % (95% CI)**	**Trend segment**	**Year quarter, % (95% CI)**
Population-adjusted mortality rates			
Buprenorphine	7.8 (6.7, 9.0)***	2010Q1–2016Q3	8.9 (8.0, 9.8)***
		2016Q3–2017Q4	2.4 (–3.1, 8.2)
Oxycodone	0.3 (–0.3, 0.8)	2010Q1–2013Q3	–0.9 (–1.8, 0.0)
		2013Q3–2017Q4	1.2 (0.5, 1.9)**
Hydrocodone	–0.1 (–0.4, 0.1)	None observed	–
Methadone	–1.4 (–1.1, –1.7)***	None observed	–
Dosage units dispensed-adjusted mortality rates[c]			
Buprenorphine	5.3 (4.6, 6.1)***	None observed	–
Oxycodone	0.8 (0.2, 1.4)**	2010Q3–2013Q3	–0.6 (–1.7, 0.6)
		2013Q3–2017Q4	1.8 (1.1, 2.4)***
Hydrocodone	2.1 (1.7, 2.4)***	None observed	–

Abbreviations: 20XXQY, year-quarter indication; CI, confidence interval.
[a]Cumulative percent change based on weighted average of segments for entire study period.
[b]Segments based on observed joinpoints identified on log-transformed mortality rates; when no joinpoints were observed no segment data were provided.
[c]Dispensing data available beginning in 2010Q3; methadone dosage units dispensed mortality rates not shown due to known underestimate of methadone dispensing in data.
**$p < 0.01$.
***$p < 0.001$.

missed deaths involving buprenorphine, yielded few additional deaths ($n = 169$) compared to the standard NCHS definition.

3.2 | Main results

Mortality for each of the study drugs increased over the study period except for methadone (Table 2 and Figure 1). At the end of the study period, buprenorphine had a lower population-adjusted mortality rate of 0.67 deaths per 1,000,000 population (95% CI: 0.58, 0.76) compared to rates for hydrocodone (2.32 deaths per 1,000,000, 95% CI: 2.16, 2.48), methadone (2.60 deaths per 1,000,000, 95% CI: 2.43, 2.78), and oxycodone (4.60 deaths per 1,000,000, 95% CI: 4.37, 4.83). However, the cumulative rate of change across the study period for buprenorphine mortality outpaced oxycodone, hydrocodone, and methadone (Table 2).

For the population-adjusted mortality rate trends, there was one joinpoint identified in third quarter 2016 for buprenorphine (Figure 1). Before this time, crude buprenorphine mortality rates were statistically significantly increasing at 8.9% each quarter-year (95% CI: 8.0, 9.8) and then became a non-significant percent change of 2.4% each quarter-year (95% CI: –3.1, 8.2). Oxycodone also had an identified joinpoint in third quarter 2013 where population-adjusted rates before this time were not significantly changing and then rose to significant 1.2% change each quarter-year (95% CI: 0.5, 1.9). Hydrocodone population-adjusted rates were unchanged while methadone rates were significantly decreasing from 2010 to 2017 at –1.4% each quarter-year (95% CI: –1.1, –1.7) with no trend changes identified.

While oxycodone and hydrocodone total dispensing per capita had decreased over the study period, buprenorphine dispensing per capita rose steadily nationally and across all US regions (Figure 2). The Northeast had the highest dosage units dispensed per capita (Figure 2). Combining this dispensing data with mortality, buprenorphine dispensing-adjusted mortality rates had significant growth of 5.3% (95% CI: 4.6, 6.1) each quarter-year (Figure 1) over the study period, with no identified joinpoints. Hydrocodone dispensing-adjusted rates also had a significantly increasing percent change for each quarter-year of 2.1% (95% CI: 1.7, 2.4) across the study period, with no identified joinpoints. For oxycodone, a joinpoint at third quarter 2013 was identified for utilization-adjusted rates, where rates went from non-significant change to significantly increasing by 1.8% (95% CI: 1.1, 2.4) each quarter-year. This oxycodone joinpoint at third quarter 2013 was also found in the population-adjusted rates.

There were observable regional differences in population-adjusted mortality rates both by magnitude and shape of the trend line (Figure 3 and Table S1). In general, oxycodone had the highest population-adjusted rate in every region, and buprenorphine had the lowest rate in every region over the study period. Buprenorphine-involved population-adjusted mortality increased in all census regions. The Northeast and South appear to have the steepest growth, with buprenorphine surpassing the hydrocodone morality rate in the Northeast in 2017.

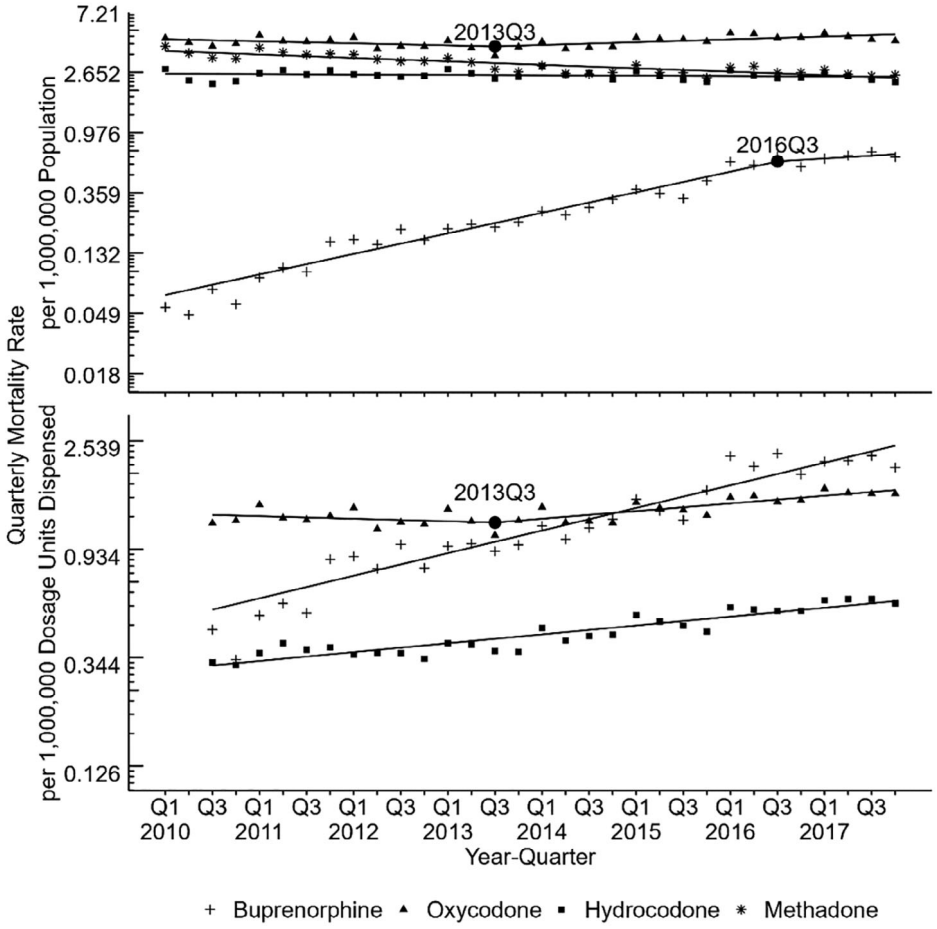

FIGURE 1 Trends over time for quarterly adjusted mortality rates by drug (2010–2017). Overall buprenorphine involved deaths rates are lower than that of oxycodone, hydrocodone, and methadone. Buprenorphine population-adjusted rates had an identified joinpoint at 2016Q3; whereas,) no joinpoint was identified in utilization-adjusted rates. Trends are displayed on log-transformed rate scale to show percent change over time. Dispensing data available beginning in 2010Q3; methadone dosage units dispensed mortality rates not shown due to known underestimate of methadone dispensing in data.

In 2017 among deaths involving buprenorphine, 93.8% also mentioned another specific drug that contributed to the cause of death. In particular, reports also mentioned other substances in the following order: benzodiazepines (46.9%), opioids other than heroin (43.5%), centrally active psychostimulants (32.0%), and alcohol or heroin (<20%). Polysubstance involvement in deaths was high for all four drugs of interest but generally speaking, buprenorphine was co-involved with other substances more often than methadone. All polysubstance proportions and 95% CIs are shown in Table 3.

4 | LIMITATIONS

The DIM database is comprised of all deaths recorded in the 50 US states and the District of Columbia. The literal text extraction, which cannot be extracted in public records, allows for more detailed surveillance of individual active pharmaceutical ingredients. However, deaths from Puerto Rico and US territories are not included, and results are likely not generalizable to these geographies. Additionally, heterogeneity exists between the state and local practices of medical examiners and coroners and toxicology practices have changed over the course of the study period. While standards for the practice of death investigation exist, these were introduced during the timeframe of this study (2014), and the diagnostic acumen of the pool of medical examiners and coroners could change over time.[19] Likely some of the increasing trend in buprenorphine-involved deaths over the study period could be attributed to increased identification of buprenorphine. Identification of specific opioid molecules is often dependent on toxicology screens, and misclassification can occur. The proportion of drug overdose deaths in which no specific drugs are identified varies widely by state.

5 | DISCUSSION

We observed an increase in dispensing-adjusted mortality rates for buprenorphine, hydrocodone, and oxycodone. While the absolute number of deaths involving buprenorphine as a contributing cause

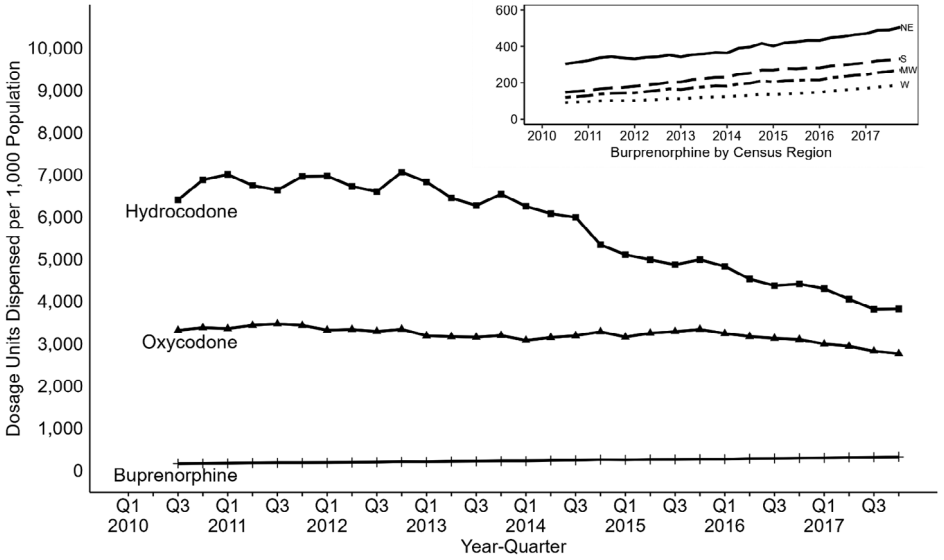

FIGURE 2 Quarterly dosage units dispensed per capita by drug (2010–2017). Buprenorphine dispensing per capita remains lower than hydrocodone and oxycodone. However, buprenorphine dispensing per capita rose across all census regions, with dispensing per capita being greatest in the Northeast and lowest in the West. Dispensing data available beginning in 2010Q3; methadone dosage units dispensed not shown due to known underestimate of methadone dispensing in data.

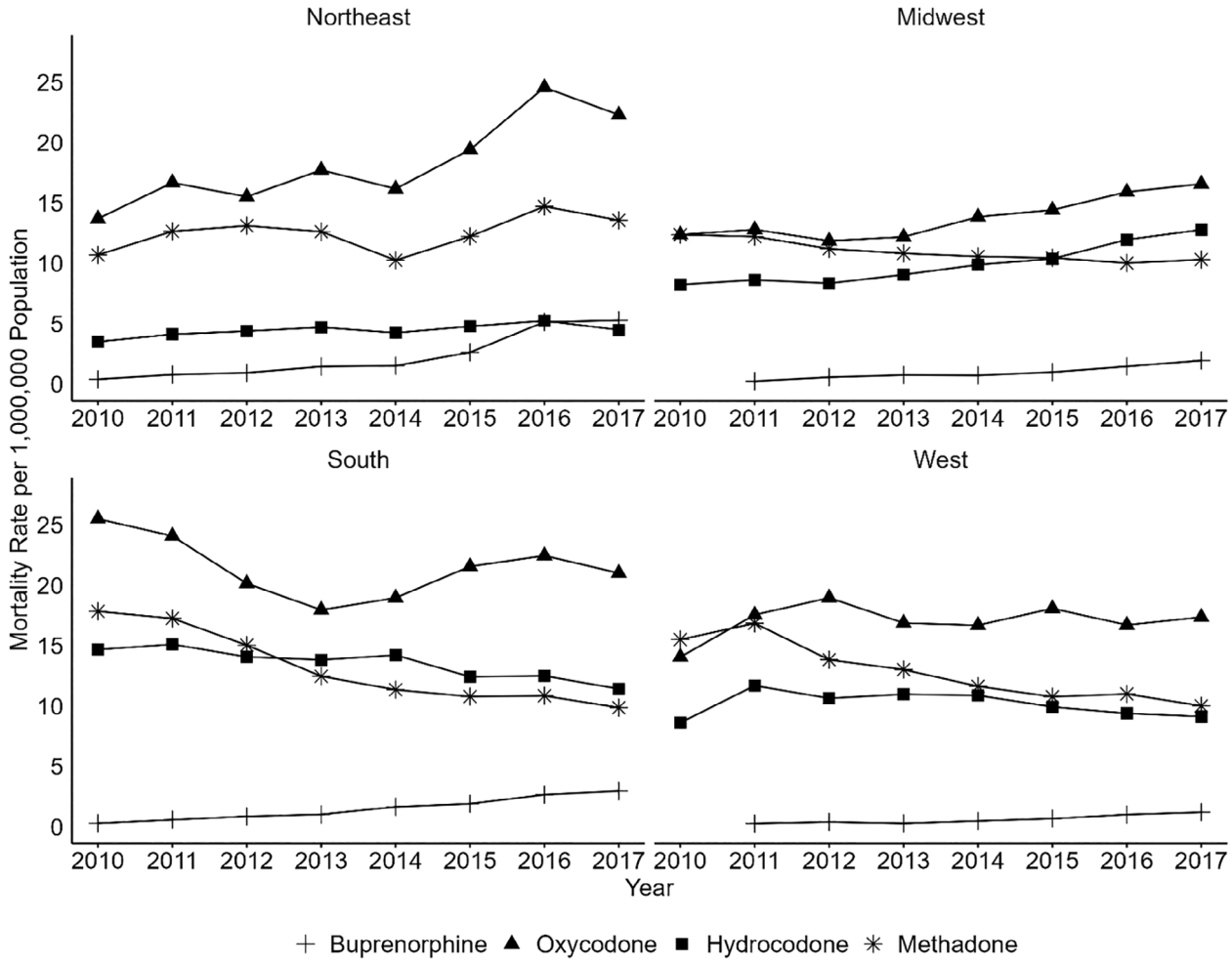

FIGURE 3 Annual regional population-adjusted morality rates by census region and drug (2010–2017). Morality rates per 1,000,000 population by drug differ across census region, with general increases in buprenorphine involved deaths in all regions. Buprenorphine rates from 2010 in the Midwest and West had fewer than 10 deaths and were suppressed for confidentiality reasons.

TABLE 3 Percentages of deaths identified as polysubstance overdose deaths by drug (2017).

	Proportion of deaths (95% CI)			
Additional drug mentioned	**Buprenorphine**	**Oxycodone**	**Hydrocodone**	**Methadone**
Any specific drug mention	93.8 (92.0, 95.3)	87.7 (86.9, 88.5)	90.2 (89.1, 91.2)	79.9 (78.5, 81.2)
Benzodiazepines	46.9 (43.6, 50.2)	41.6 (40.4, 42.8)	43.0 (41.3, 44.8)	31.8 (30.3, 33.4)
Other opioids excluding heroin	43.5 (40.2, 46.9)	48.6 (47.4, 49.9)	51.7 (49.9, 53.4)	38.1 (36.5, 39.7)
Centrally active psychostimulants	32.0 (29.0, 35.2)	20.0 (19.0, 21.0)	17.4 (16.1, 18.7)	26.0 (24.6, 27.5)
Alcohol	17.8 (15.3, 20.5)	16.3 (15.4, 17.2)	18.0 (16.7, 19.4)	11.5 (10.4, 12.6)
Heroin	17.8 (15.3, 20.5)	10.9 (10.1, 11.7)	9.1 (8.1, 10.1)	16.6 (15.4, 17.9)

Abbreviation: CI, confidence interval.

was fewer than the comparator drugs, the mortality rates for both population-adjusted and dispensing-adjusted increased more rapidly than other medications. By end of 2017, the mortality rate of buprenorphine had been increasing almost 8% per year since 2010.

There are several possible explanations for the increased mortality involving buprenorphine. First, prescribing of buprenorphine has increased following extensive efforts to increase the number of health care providers that prescribe buprenorphine.[20] If increased availability resulted in the same rate of deaths per unit dispensed, then the expected result would be that the number of deaths would increase while the dispensing-adjusted mortality rate would remain unchanged over time. Instead, the mortality rate for buprenorphine after adjustment for dosage units dispensed has increased and lacks the flattening observed after mortality rate adjustment for population. Thus, it is unlikely that increased prescribing of buprenorphine is the cause of the increasing mortality rate.

Second, most buprenorphine is prescribed to patients with OUD who are at a high risk of opioid overdose. However, expansion of prescribing may have included patients who are even higher risk of overdose such as those patient presenting after an acute opioid overdose. While it clinically appropriate for a patient to be started on buprenorphine after an overdose, this practice may shift in the cohort of patients receiving buprenorphine resulting in buprenorphine use by more individuals at high risk for drug overdose.[6,21] If patients treated with buprenorphine were at increased risk of death from underlying comorbidity, then the buprenorphine mortality rate might increase as more high-risk patients received the drug. For example, if more patients with recurrent, relapsing polysubstance overdose were prescribed buprenorphine, the apparent mortality rate might increase if these patients subsequently died. We did observe larger proportions of polysubstance mortality among buprenorphine-involved deaths (vs. comparators). Similarly, an increase in mortality might develop if efforts to expand prescribing recruited clinicians who were inexperienced in the use of buprenorphine. Of note, most clinicians that prescribe buprenorphine do so infrequently and tend to have a low caseload.[22] Of interest, the number of prescriptions written by emergency physicians is low and unlikely to affect our results, but prescriptions written by advanced practice providers have increased. However, better information is needed to address the risks associated with prescribers. The removal of the buprenorphine waiver requirement in 2023 may create similar concerns. The expanded use of buprenorphine is desirable, but monitoring for safe use in important.

Third, the nature of buprenorphine overdose is evolving. Our period of study occurred during a time when polysubstance use was increasing. Buprenorphine is a partial μ-receptor agonist,[23] which results in a ceiling for respiratory depression when used alone.[24] Furthermore, the binding affinity of buprenorphine is much higher than full agonists.[25] These properties may contribute to its lower mortality rates relative to full agonists. Both real-world mortality evidence and pharmacologic evidence support the relative safety of buprenorphine compared to full agonists. However, buprenorphine effects can be overcome with high doses of full agonists,[26] and does not protect against the respiratory depression caused by non-opioids (e.g., benzodiazepines), which offers a rationale for why polysubstance involvement was frequently observed among buprenorphine involved deaths. As the serum concentration of buprenorphine decreases, the use of a highly potent opioid would be more likely to produce an overdose. Elevated, sustained concentrations of buprenorphine may be needed to protect against such high potency agonists, such as fentanyl.[27] Unfortunately, the concentration of buprenorphine is not included in mortality data.

Furthermore, substances such as xylazine, fentanyl, and fentanyl derivatives have contributed to the marked increase in polysubstance mortality.[28] The impact of increasing polysubstance misuse is still being evaluated, but the presumption is that the involvement of multiple drugs that may affect multiple nervous system or myocardial conduction pathways will increase the risk of death. The interaction of this factor with other factors such as prescribers remains to be determined.

Lastly, drug-involved death attribution over time is subject to ascertainment bias, which is both a limitation of the study and a possible partial explanation of the observed trends. The increase may be at least partially attributed to changes and improvements in toxicology screening practices and increased identification of buprenorphine-involved deaths.[19] Federal mortality data are comprised of medical death certificates completed by local authorities in hundreds of jurisdictions across the United States and practices could vary, not only by jurisdiction, but within a jurisdiction, as well as over time. Buprenorphine is not necessarily part of standard toxicology panels, but testing has increased since the introduction of buprenorphine treatment for OUD in 2002. Therefore, mortality data could suffer from increased reporting over time due to local preferences and budgetary concerns.

It is important to understand that being listed as a contributing drug in these data does not mean buprenorphine was the primary cause of death, but rather a medical judgement made on a local basis, not determined by national guidelines. For example, if a decedent was treated with buprenorphine but relapsed and inadvertently ingested a counterfeit oxycodone that actually contained a lethal dose of fentanyl, it is conceivable that buprenorphine might be listed as involved even though fentanyl was most likely the primary cause of death. However, the stabilization of buprenorphine-involved deaths seen in the population rates suggest identification practices would have had lower impact on data quality in more recent years. Furthermore, a recent study found that the stabilization of buprenorphine-involved overdose deaths was sustained in 2019–2021.[29]

Separately from the findings around the change in trends, it is important to note that in 2017 nearly all deaths involving buprenorphine included another specific substance (94%), with almost half of deaths including benzodiazepines and opioids other than heroin. This suggests the emergency treatment of opioid overdose may become more complicated. Benzodiazepines can act synergistically with buprenorphine pharmacodynamically resulting in respiratory depression[30] and patients with comorbid sedative use disorders are at increased risk of adverse events,[31] which may partially explain the large percentage of polysubstance deaths involving benzodiazepines. Among deaths involving opioids other than heroin, fentanyl is a large contributing factor based on total mortality trends caused by synthetic opioids[1]; however, these data in our study were not delineated this way. Other authors have quantified the complex nature of polysubstance mortality more comprehensively.[32] This work further supports the general trend indicating the continued need for overdose prevention strategies, which focus on polysubstance use and diverse treatment approaches.[1] Emergency physicians, whether they utilize buprenorphine or other treatments, can guide patients who misuse opioids into treatment where long-term care addressing these complexities can be given.

In summary, it is important to understand and interpret the data regarding mortality associated with buprenorphine use carefully. Buprenorphine-involved mortality remains lower than mortality involving oxycodone, hydrocodone, or methadone; however, buprenorphine-involved mortality is rising faster than dispensing would fully explain and, after adjustment for dispensing, was highest in 2017 compared to prior years of study. The sources of the observed mortality may arise from a combination of factors including prescribing to higher risk patients, the involvement of less-experienced prescribers, and perhaps ascertainment bias. Educational efforts addressing the complicated utilization of buprenorphine and subsequent consequences, both in EDs and treatment clinics, would ensure risks and benefits are well understood by practitioners.

AUTHOR CONTRIBUTIONS

Joshua C. Black, Gabrielle E. Bau, and Karilynn Rockhill had access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Concept and design*: Joshua C. Black, Janetta Iwanicki, Richard Dart, Angela DeVeaugh-Geiss, and Howard Chilcoat. *Data acquisition and analysis*: Joshua C. Black, Gabrielle E. Bau, and Karilynn Rockhill. *Drafting manuscript*: Karilynn Rockhill. *Critical revision of manuscript*: All authors. *Obtained funding*: Angela DeVeaugh-Geiss and Howard Chilcoat. *Administrative and technical support*: Joshua C. Black, Karilynn Rockhill, and Gabrielle E. Bau.

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CONFLICT OF INTEREST STATEMENT

Karilynn Rockhill, Gabrielle E. Bau, Richard Dart, Dr. Iwanicki, and Joshua C. Black are employed by the Denver Health and Hospital Authority. The RADARS system is supported by subscriptions from pharmaceutical manufacturers, government and non-government agencies for surveillance, and research and reporting services. RADARS system is the property of Denver Health and Hospital Authority, a political subdivision of the State of Colorado. Subscribers neither participate in data collection nor do they have access to the raw data. Angela DeVeaugh-Geiss and Howart Chilcoat are employees of Indivior, Inc. and own stock in the company. The findings and conclusions in this paper are those of the authors and do not necessarily represent the views of the Research Data Center, National Center for Health Statistics (NCHS), or the US Centers for Disease Control and Prevention.

DATA AVAILABILITY STATEMENT

Data used in this study are restricted access through the National Vital Statistics System and therefore cannot be shared; this request process can be accessed at the following URL (https://www.cdc.gov/rdc/b1datatype/dt1229.html). After approval of the project, a dataset is created that has a de-identified row for every death in the United States including demographic, geographic, and cause-of-death variables. More documentation can be found here about this dataset including an example data dictionary (https://www.cdc.gov/rdc/b1datatype/datafiles/Drug-Involved-Mortality-Data-Documentation.pdf).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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