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Characteristics and patterns of opioid-related overdoses among veterans

Sara Catherine Warfield

West Virginia University, scwarfield@mix.wvu.edu

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Characteristics and patterns of opioid-related overdoses among veterans

Sara C. Warfield, MPH

Dissertation Submitted to the West Virginia University
School of Public Health

In Partial Fulfillment of the Requirements for the Degree of:

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in
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Robert M. Bossarte, Ph.D., Chair
Christa Lilly, Ph.D.
Mike Brumage, MD, MPH
Thomas Hulsey, Sc.D.

Department of Epidemiology
Morgantown, West Virginia
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ABSTRACT

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BACKGROUND AND OBJECTIVES: The United States is in the midst of an opioid overdose crisis and is now considered a public health emergency. Given the alarming rise in opioid overdose deaths, there is an urgent need to understand the characteristics and risks associated with opioid overdoses. The objectives of this study were 1) to compare factors associated with different type of opioid overdose, 2) to determine the conditional probability of repeat overdose among veterans with a prior overdose event and corresponding probability of mortality for each overdose event and, 3) to identify cause-specific mortality rate of those who experienced a nonfatal overdose during our study period.

METHODS: Using clinical records and mortality files of more than 10.5 million veterans, we extracted data among those with a documented opioid overdose between January 1, 2011 and December 31, 2015. During this time, 13,333 veterans had at least one documented opioid overdose of any intent.

RESULTS: Study 1. Patients who were younger in age (18-44 OR [odds ratio] 7.19, 45-64 OR 4.78) had significantly higher odds of a fatal index overdose and experiencing a repeat overdose (18-44 OR 2.13, 45-64 OR 1.78). Having one or more chronic pain diagnoses was both associated with experiencing a fatal index overdose (OR 3.96) or repeat overdose (OR 1.15). A diagnosis associated with mental health or substance abuse or dependence was significantly associated with experiencing a repeat overdose, (OR 1.54 and 1.25 respectively). Receipt of medication-assisted therapy (MAT) more than one year prior (OR 1.28) to the first (i.e. index) overdose was significantly associated with increased odds of a fatal overdose whereas receiving counseling services prior to index overdose was protective of experiencing a fatal index overdose. Study 2. One fifth of the study sample had a repeat overdose during the study period, with a conditional probability that increased linearly for each subsequent overdose event. The conditional probability of repeat overdose went from 21.1% on the second overdose to 43.2% for five or more overdoses. Mortality was highest among the first documented overdose. Study 3. Overall, veterans with a prior nonfatal overdose more often died from any cause in comparison to their veteran peers and had approximately 26 times the mortality rate to the general U.S. population. Veterans with a prior nonfatal overdose had a higher risk of death from substances (aHR [adjusted Hazard Ratio] 5.0, 95% CI [confidence interval]: 4.4-5.8), including a higher risk of death from drugs (aHR 6.9; 95% CI 5.8-8.1) and alcohol (aHR 2.7, 95% CI 2.1-3.6). For cause-specific mortalities assessed between veterans in our cohort and the general U.S. population, the standardized mortality rate ratio (SMR) was 114 times higher for deaths associated with substances (95% CI: 98.8-128.7), 107 times higher for deaths associated with hepatitis (95% CI: 65.5-152.7) and 68 times higher for deaths associated with liver cancers (95% CI: 47.9-88.7). Overall, veterans in our overdose cohort had an elevated mortality rate than the general public for all the specific causes of death assessed.

CONCLUSION: Although risk factors for opioid overdoses are well studied, there appears to be differences between the type of opioid overdoses documented in a clinical setting. Given that mortality is highest on the first documented overdose suggests that prevention efforts should be further support to reach those patients at highest risk. Furthermore, given that the probability of

experiencing a repeat overdose increases with each overdose event suggest that healthcare settings should be prepared to handle an influx in patients, specifically those with mental health diagnoses. Moreover, given the elevated risk of death from all-causes, specifically those associated with substances suggests the need for an integrated healthcare approach. Understanding risks factors, type of overdose, and cause-specific mortality among patients with an opioid overdose could help to inform healthcare interventions and potentially lead to better patient outcomes.

Dedication

To both of my parents, Randy and Courtney, who always instilled the importance of education but more importantly showed me how to be the voice for those who may not be able to speak.

To all of my family and friends who have been supportive of me, including my second family at the Injury Control Research Center. This experience would not have been the same without you, I deeply cherish you all.

I am also especially grateful for West Virginia University, in particular the School of Public Health, for supporting me and giving me so many opportunities. I will forever be grateful for the numerous opportunities that I have been able to be part.

Last but certainly not least, I dedicate this to my friend, Nick Dibble. You touched the lives of so many people with your wit, humor and love. This epidemic has taken so many lives but yours hit me the hardest.

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List of Abbreviations and Nomenclature

ADD	Attention deficit disorder
CDC	Centers for Disease Control and Prevention
CDW	Corporate Data Warehouse
DoD	Department of Defense
EHR	Electronic health record
HIV	Human immunodeficiency virus
IDU	Injection drug use
ICD-9	International Classification of Disease, Ninth Edition
ICD-10	International Classification of Disease, Tenth Edition
MAT	Medication-Assisted Treatment
MME	Morphine Milligram Equivalence
NDI	National Death Index
OEND	Opioid Overdose Education and Naloxone Distribution program
OSI	Opioid safety initiative
OD	Overdose
PDMP	Prescription drug monitoring program
PTSD	Post-traumatic stress disorder
PWID	Person(s) who inject drugs
SDoH	Social determinants of health
SDR	Suicide Data Repository
SMR	Standardized mortality rate ratio

SSN	Social Security Number
STORM	Stratification Tool for Opioid Risk Mitigation
SUD	Substance Use Disorder
US	United States
VA	Department of Veteran Affairs
VHA	Veterans Health Administration
WHO	World Health Organization
WONDER	Wide-Ranging Online Data for Epidemiologic Research

Chapter 1

Chapter 1. Introduction

1.1 Background

Opioid overdoses have surged in the past decade and deaths from overdose are now considered one of our country's most serious public health crises. Between 2007 and 2017 there were more than 507,000 overdose deaths in the United States; with more than half of these involving opioids [1-4]. Concurrent with the rise in overdose deaths, hospitalizations related to opioid abuse and misuse have also been on the rise [5, 6]. Between 2009 and 2014, opioid overdoses resulting in inpatient hospital admission increased more than 60%, emergency department visits nearly doubled [5] and costs associated with overdose morbidity and mortality have been estimated to exceed \$22 billion annually [7, 8].

Despite the impact associated with opioid overdose on the healthcare system, few studies have examined information available from electronic health records in conjunction with vital records to examine risk for opioid overdose or to inform prevention and clinical programs. There are a number of unanswered questions related to the combinations of medical diagnoses and social conditions as potential risk factors for overdose, particularly among populations with evidence of abuse or misuse. To date, there have been a limited number of studies that examined the etiology of repeated opioid overdoses or compared them with characteristics associated with fatal overdose. [9-11]. Similarly, little is known about the patterns of cause-specific mortality risk among those with history of at least one nonfatal overdose [12, 13]. Understanding risk factors for repeated overdose and mortality following a nonfatal overdose could inform healthcare interventions and in turn, better patient outcomes.

1.1.1 Risk Factors for Overdose

Individual-level risk factors for opioid overdose include sex (male), age (particularly 18 to 45 years), race/ethnicity (non-Hispanic white), and residence in a rural area; particularly the Appalachian region [2, 3, 14-18]. Physical health conditions associated with an increased risk of overdose include diagnoses associated with chronic pain, liver disease, renal disease, chronic pulmonary disease, cardiovascular disease, musculoskeletal injury, cancer, and skin and soft-tissue infections [19-22]. Mental health diagnoses and related factors associated with overdose risk include depression, anxiety, history of suicide attempt or ideation, post-traumatic stress disorder (PTSD), bipolar disorder, attention deficit disorder (ADD), frequent or severe psychological distress, and substance use disorder (SUD) [19-21, 23-27]. While many risk factors for overdoses have been previously studied, they have largely examined risk factors among people who inject drugs (PWID) or individuals taking prescription opioids; primarily due to chronic non-cancer pain [17, 22, 26, 28-32]. Moreover, a majority of studies have focused on identifying risk factors using information obtained from cross-sectional surveys. Risk factors associated with opioid overdose are detailed in Table 1.

1.1.2 Epidemiology of Overdose and Veterans Who Use VHA Services

Evidence suggests that risk factors associated with opioid overdose among veterans who have utilized Veterans Health Administration (VHA) services are similar to those identified among the general U.S. population. Risk factors assessed in previous studies include dosage of prescribed opioids, duration of prescribed opioids [20, 22, 25, 33], medical conditions associated with chronic pain, and diagnoses or symptoms associated with psychiatric disorders [25, 34, 35]. Although risk factors for overdose are similar to those in the general population, research suggests that more veterans who use VHA services have history of some risk factors associated

with overdose morbidity and mortality, such as chronic pain and mental health diagnoses, which in turn may be associated with higher overdose mortality rate among members of this population [24, 36, 37]. Further, previous research among veterans found that over 60% of patients who experienced an unintentional opioid overdose were seen in an outpatient setting in the month prior to their overdose and approximately 30% of those were for mental health treatment [38, 39]. While many risk factors for fatal overdose have been previously identified, existing studies largely examined unintentional overdose death or risk factors for overdose among those with access to prescription opioid pain relievers; primarily due to chronic pain [18, 20, 22, 25, 29, 35, 40, 41]. Although medical diagnoses capture a variety of risk factors associated with overdose mortality, they do not capture all potential risk factors or information available from electronic medical records. Environmental and social stressors have been previously identified as risk factors for substance abuse, yet little is understood about the unique contribution of these factors or the combined influence of environmental and social stressors and medical/psychiatric diagnoses.

Numerous studies have found that social determinants of health (SDoH) are often significantly associated with negative outcomes [42-44]. SDoH that are the most significant for health outcomes are often those associated with socioeconomic status, such as economic instability or inadequate housing [42, 45]. Factors such as homelessness and early life adversity, have also been shown to influence risk for drug use and mental health disorders [46, 47]. Indicators of social determinants of health can be assessed in electronic health records (EHR) through certain V codes (ICD-9) and Z codes (ICD-10). Although these social codes can be used in any healthcare setting, studies have shown they are generally underutilized by most healthcare professionals other than mental health professionals [44, 48].

Looking beyond the primary and secondary diagnostic codes may provide an opportunity to describe the social, behavioral, and environmental factors, also known as contextual factors, which may be associated with overdose risk [48-52]. Such findings could inform additional strategies designed to reduce overdose deaths attributed to opioids. Although studies have examined outpatient visits prior to an overdose, no existing study has examined contextual factors prior to an overdose and few have identified these factors in conjunction with health diagnosis in the veteran population [38, 39].

It is possible that previously identified risk factors may be exaggerated among veteran populations, such as mental health diagnoses (i.e. post-traumatic stress disorder (PTSD) or chronic pain [24, 25, 33, 34, 53]. Studies conducted using data from VHA records have consistently found that veterans have a high rate of mental health diagnoses, including substance use disorder (SUD),[20, 34, 53-55]; a potentially important risk factor to overdose morbidity and mortality[20, 24, 25, 36].

1.1.3 VHA and Electronic Health Records

Data from EHRs can be used in addition to mortality and prescribing surveillance systems to monitor trends as well as identify clinical characteristics associated with a myriad of health outcomes in a timely manner. EHRs hold a comprehensive list of healthcare factors such as diagnosis codes, procedure codes and medication data, allowing for a deeper understanding of various health outcomes. Linking clinical and death records together can leverage data between these two sources to enhance the understanding of corresponding risk for health outcomes. Findings from rich data sources like EHRs can inform future healthcare efforts targeting patients at risk for overdose.

Given the growing concern for opioid overdoses across the U.S., there is a need to enhance information used to understand risk for and prevention of overdose morbidity and mortality. Further, the majority of risk factors identified have focused on single episodes (either fatal or nonfatal) and comparatively little is known regarding the risk factors for repeated overdose.

1.1.4 VHA population

The VHA is one of the largest integrated healthcare system in the United States and collects data on clinical diagnosis, procedures, medications, and sociodemographic information from more than six million patients annually. Currently, the largest proportion of veterans receiving VHA medical care served in the Vietnam Era [56].

Serving more than six million patients annually, the VHA provides an array of comprehensive healthcare services for a myriad of health conditions. VHA services are provided in 170 medical centers and 1,243 outpatient clinics throughout the U.S. [56]. Available data suggests that patients seeking care from the VHA often have poorer health outcomes, such as chronic pain and psychiatric comorbidities, and multi-system diagnoses, which could increase risk of negative health outcomes [57, 58]. In 2003, it was estimated that more than one million veterans who use VHA services have been diagnosed with either a substance abuse disorder or other mental health condition [59]. Accordingly, mental health and substance use disorders are considered a significant issue among the veteran population [60, 61]. Previous research suggests that more than 55,000 veterans who use VHA services have been diagnosed with an opioid use disorder (OUD)[62]. The breadth of data collected by the VHA coupled with the evidence of elevated risk factors among the patient population provides a unique opportunity to use information from this health care system to identify previously unexplored risk factors and targeted strategies to reduce opioid-related morbidity and mortality.

1.1.5 Current Prevention Efforts

Primary prevention strategies for opioid abuse and overdose prevention have largely focused on reducing the excess supply of prescription opioids, including the development and support of safe prescribing guidelines and the implementation of prescription drug monitoring programs (PDMP). Secondary and tertiary efforts have been primarily focused on addressing the gap in treatment and distribution of naloxone, a rapid acting opioid antagonist [63-65]. Importantly, one consequence of the increased distribution and resulting availability of naloxone is the associated increase in probability of surviving an overdose and related history of multiple overdoses.

In recent years, the VHA has amplified efforts to reduce risk of opioid overdose among patients receiving care from clinicians in its facilities. In an effort to promote safer prescribing the VHA introduced the Opioid Safety Initiative (OSI) which leverages prescription data within the VHA and helps clinicians identify patients at risk for adverse risks from opioids. In addition to the OSI, the VHA developed a dashboard to identify patients at risk for an adverse event related to opioids [63, 66]. Furthermore, the VHA has developed academic detailing on opioid abuse and overdose prevention in an effort to provide health care professionals with evidence-based educational tools [66]. To further reduce the burden of opioid overdose among veterans, the U.S. Department of Veterans Affairs also developed the Opioid Overdose Education and Naloxone Distribution (OEND) program. This program primarily focuses on educating health care professionals and high-risk patients on strategies to prevent, identify, and reverse an opioid overdose. Veterans with a history of injection drug use, substance use such as heroin, a diagnosis of opioid use disorder (OUD), or those with a high likelihood of opioid overdose or witnessing an overdose are targeted for the OEND program. These patients' are often identified in medical

settings including but not limited to treatment programs such as Medication-Assisted Treatment (MAT), inpatient withdrawal management, syringe access programs, emergency departments, homeless shelters and other primary health care settings[67].

1.2 Purpose Statement

Given increases in overdose deaths, there is a need to identify opportunities for intervention and prevention services informed by a better understanding of risk for repeat overdose and mortality. The primary aim of this study is to identify and assess the risk factors such as demographic characteristics, medical diagnoses and indicators of social determinants of health associated with risk for repeat overdose and all-cause mortality among patients with a history of one opioid overdose.

The proposed project seeks to expand upon existing efforts using data from VHA administrative records to inform strategies for clinical interventions and preventive services targeting veteran groups at increased risk for a fatal opioid overdose or repeat opioid overdose.

Results from this project will specifically add to the literature in the following ways:

1. Increase understanding of potential differences in risk for nonfatal, repeated and fatal overdose.
2. Calculate associations between an increasing number of nonfatal overdoses and risk for mortality or repeated events.
3. Assess all-cause and cause-specific mortality risk among veterans with a documented opioid overdose.

1.3. Specific Aims

Sample design

Veterans with a documented opioid-related overdose were identified using clinical and administrative records from the Veterans Health Administration (VHA) Corporate Data Warehouse (CDW) and the VA/DoD Suicide (all-cause) Data Repository (SDR) respectively. The process flow of data into the CDW is shown in Figure 1 and specific ICD-9 and ICD-10 codes used for the opioid overdose is in Appendix A and corresponding variables of interest are listed in Appendix B (demographic and diagnostic variables), C (codes which serve as indicators of social determinants of health) and D (codes used to define cause-specific mortality). Underlying cause of death codes used to identify cause-specific mortality can be found in Appendix D.

We identified all veterans who utilized VHA services between calendar years 2011 through 2015 by accessing patient information available from VHA's administrative and EMR data files. Social Security Numbers (SSNs) were used to link to the CDW and SDR records. We extracted potential predictor variables including demographic information such as sex and age, procedural codes and diagnostic codes for the study period (2011-2015). An additional year of data was extracted if the index overdose occurred in the first year of the study period. For instance, if an individual had an opioid overdose (nonfatal or fatal) in January 2011, procedural and diagnosis codes were pulled from one year prior (January 2010) to index overdose.

Inclusion/Exclusion criteria

The cohort was restricted to veterans over 18 years or under 90 years. We excluded patients that did not have a follow-up visit within one year of a non-fatal overdose event. Patients with a death

date prior to an overdose diagnosis date were also excluded from analysis (n=145, 0.89%). Given that repeated overdose occurred on average more than one month after the index overdose (mean=36 days), patients were excluded if the first nonfatal overdose occurred in the last three months of the study period (October 1, 2015 to December 31, 2015). This mitigated potential bias among those with less than three months of documented time at risk following an overdose event.

Opioid overdose cohort

A nonfatal opioid overdose was identified using International Classification of Disease, Ninth Edition (ICD-9) 965.00-965.02, 965.09, E850.0-E850.2. Similarly, ICD Tenth Edition (ICD-10) codes were used to identify opioid overdose: X40-X44, X60-X64, X85, and Y10-Y14 and secondary-axis codes T40.0- T40.4, and T40.6 (Appendix A). The first opioid overdose documented in the compiled records was coded as the index overdose. Multiple opioid overdoses that occurred during an inpatient treatment stay were counted as a single overdose event, based on admission and discharge date. Repeat overdoses were identified among veterans with more than one opioid overdose recorded during the study period. A repeat overdose was defined as a second documented overdose that occurred a) two days after the index event with principal diagnosis of an overdose or b) 3 days or more after a prior overdose. Any record of an overdose within one day of a previous overdose was treated as the same event.

We identified 13,333 patients with a record of an opioid overdose between the calendar years 2011 through 2015. Of those, there were 4,949 (37.1%) opioid overdose deaths, with a majority occurring on the first documented overdose (n=4,890, 98.8%). Furthermore, among these overdose deaths, 85.0% were unintentional (n=4,206), 6.4% were undetermined (n=315), 8.5%

were intentional (n=422) and 0.1% were homicide (n=6). Figure 2 depicts the specific inclusion and exclusion criteria for each of the specific aims.

Predictors

Demographic characteristics were extracted using clinical and administrative rules set by the VHA. For instance, sex was based on last entered value for analysis. Age was static and based on the patient's age on the start of the study period, January 1, 2011.

Date of diagnosis was based on the day of visit for the outpatient population or the date of discharge for the inpatient records. Potential predictors were examined one year prior to first documented overdose and at any point during the study period.

All predictors were dummy coded and additional variables were created based on time of diagnosis, particularly in relation to index overdose. This helped describe the potential relationship between diagnosis and type of overdose experienced.

This study was reviewed and approved by the Institutional Review Board at the Syracuse VA Medical Center, New York.

Analysis plan

For all aims, data management and analysis were conducted using SAS Enterprise Grid software (version 5.1, SAS Institute Inc.). Descriptive analysis for all variables were completed using cross tabulations, column percentages were reported for each outcome of interest. Alpha was set to 0.05 for tests unless otherwise specified.

Specific Aim 1: Characterize differences between those with a fatal index overdose and those with repeated nonfatal overdoses from those with only one nonfatal index overdose.

Based on results from existing studies, we hypothesize that those who experienced repeated overdoses would have a greater number of psychiatric diagnoses and social health indicators than those who died on their first documented overdose [24, 68-71].

Bivariate analyses were conducted using chi-square test of difference among all sociodemographic and diagnostic variables by overdose category: fatal index overdose, repeated nonfatal overdoses, and only one nonfatal overdose. The primary hypotheses was tested using multinomial logistic regression given the polytomous outcome includes three mutually exclusive groups without order. As an extension of logistic regression models, this approach is flexible and allowed three overdose outcome levels using a generalized logit link. In addition, this approach provided a more direct option for interpreting the relationship between the predictors and outcome groups [72], is more robust to violating the assumptions of normality and does not assume a linear relationship between the predictors and outcome [72, 73]. Conversely, this method required additional comparative statements given that this method produced multiple odds ratios for each predictor; which could lead to issues with interpretability [72, 74]. A major limitation of this method may result from the independence of irrelevant alternatives (IIA) assumption which presumes that changing the number of outcomes (e.g. three to five levels) would not affect the odds of the remaining outcomes [75, 76]. Model fit for this multinomial logistic regression model was first assessed by using a series of logistic regression models, controlling for age and gender, which is known to influence overdose risk[74, 77]. Assumptions for multinomial logistic regression models were tested. For example, multicollinearity was assessed by calculating variance inflation factors (VIF). Predictors with a VIF greater than 10 were reassessed for strength of relationship with the outcome. Of those predictors where collinearity was suspected, Wald chi-square tests were conducted to determine which variable

was more appropriate for inclusion in the final models. Weaker predictors were dropped and the model was rerun to only include significant predictors that were not collinear. Goodness of fit indices such as the Type 3 Analysis of Effects and Wald chi-square test were examined for all predictors with the null that all of the coefficients were equal to zero in the model[72].

Interactions between significant predictor variables were tested and significant interactions were left in the model. Odds ratios with a 95% Confidence Interval (CI) were calculated by exponentiating the estimate. The adjusted odds ratio indicate the odds of experiencing a fatal overdose compared to those with one nonfatal overdose as well as the odds of experiencing a repeated nonfatal overdose compared to those with one nonfatal overdose, adjusted for all other predictors in the model.

Specific Aim 2: Calculate the conditional probability of a repeat opioid overdose event (fatal and nonfatal) among those with record of a nonfatal opioid overdose. We expect that the conditional probability for repeated overdose and mortality will increase linearly with each overdose event.

The frequency and conditional probability of nonfatal and fatal overdose was calculated among the VHA patient population with at least one overdose event during the study period (2011-2015). We excluded overdoses that were classified as homicides or suicides. To describe the magnitude of repeated overdose and corresponding mortality for each overdose event, the conditional probability of repeated overdose and associated mortality was calculated for patients with at least one documented overdose in the VHA clinical records. Conditional probability of an overdose was calculated by dividing the proportion of patients experiencing the event by the number of patients at risk for the event [78-80]. The outcome of interest was mortality at each overdose event (e.g., one, two, three, four, and five or more overdoses) as well as conditional

probability for repeated overdose event. Conditional probabilities for overdose death and repeat overdose at each disease event were estimated and 95% CI were extrapolated using the normal approximation method.

Specific Aim 3: Determine the 5-year cause-specific mortality rate of those who experienced a nonfatal opioid overdose. We hypothesize that the mortality rate will be markedly higher among veterans with a prior nonfatal overdose. Further, we hypothesize that select categories of mortality, including suicide and substance-related mortality, will be significantly higher among patients with one or more previously documented overdose events.

The number of person-years at risk of dying and relative frequencies of overall and cause-specific causes of death were compared between those who experienced a nonfatal opioid overdose and a control group. Those who died from a fatal index overdose were excluded from the analysis. We also excluded those with a nonfatal overdose in the last three months of the study period. We evaluated vital status for the nonfatal overdose group and comparison group from the start of the study period, January 1, 2011. Continuous variables were examined to determine overall distribution and bivariate analysis was used to examine bivariate relationships. A 5% stratified random sample was pulled to compare mortality with the nonfatal overdose group. Pulling a stratified random sample allowed the control group to be similar in composition to those with a nonfatal overdose [81]. Given that VHA users are commonly older male with poorer health outcomes, we stratified by sex and age to reduce potential bias that may influence mortality among the control group [56, 58]. This method, using a stratified random sample, has been used in previous VHA research using clinical data due to the large sample size of the population [82-85]. This method allowed for controls to be pulled from a heterogeneous population based on specific strata, specifically sex and age [86-88]. The control group was

constructed to compare differences in mortality between those who experience a nonfatal opioid overdose to those with no documented overdose and allowed for outcome measures to be easily extrapolated for each stratum. We hypothesized that the mortality rate would be markedly higher among the nonfatal overdose group in comparison to the control group, given previous mortality research among a clinical population with a prior nonfatal overdose[12]/

We evaluated mortality from the start of the study period (January 1, 2011) through the end of the study period (December 31, 2015). Follow-up for the study ended the day the patient died or the end of the study period, whichever occurred first. In addition to all-cause mortality, cause-specific mortality was extrapolated for the following categories: external causes of death, suicide, homicide, accidents, substance-related deaths, drug-related deaths, alcohol-related deaths, infectious, viral hepatitis, human immunodeficiency virus (HIV), circulatory system, respiratory system, influenza, chronic respiratory disease, digestive system, cirrhosis and alcoholic liver disease and cancers. Specific types of cancers were categorized into the following groups using the International Classification of Diseases for Oncology [89]: lung and bronchus, liver and intrahepatic bile duct, digestive system cancers, which included esophageal, stomach, small intestine, colon, rectal, anal, gallbladder and pancreatic cancers, lymphoma and leukemia and other cancers. (See Appendix D for the full list of cause-specific mortality and corresponding ICD-10 codes).

To test study hypotheses, cox proportional hazard models were used to calculate relative risk estimates and included demographic factors (e.g. sex and age) as covariates. Using this type of analysis we assumed the following: 1) the hazard ratio remained constant over time, 2) the independence of survival was different between each veteran in the cohort and 3) there was a multiplicative relationship between the predictors [90]. This semi-parametric method has been

used in similar research to elucidate the relationship between multiple predictors and mortality [12, 83, 91]. We assessed the proportional hazard assumption by comparing the observed with the predicted survival curves for categories of the variables in the model, curves that were relatively close indicated the hazard ratio remained constant over time [92]. Significant predictors were identified using Wald Z-tests which evaluated whether hazard ratio was equal to one or equivalently that the slope was equal to zero [92]. Given that a cox proportional hazard model is a likelihood-based method, the overall model fit was evaluated through likelihood ratio (LR) tests. Given the large sample size of the cohort, results from the LR test were close to Wald test. Interactions between two different variables were assessed to determine significance by examining Akaike information criteria (AIC) levels in comparison to the model without interaction terms. We detected violations of the hazard assumption by examining the Schoenfeld residuals [93]. Hazard ratios and corresponding 95% CI were extrapolated for cause-specific mortality.

We identified person-years of follow-up and mortality rates per 10,000 person-years for the cohort. Crude death rates were calculated and adjusted mortality rates were calculated using Cox proportional hazard models, adjusting for age and sex.

Mortality rates among veterans with a nonfatal overdose were compared to mortality rates in the US population. Standardized mortality rate ratios (SMRs) were calculated using data from the Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER). In order to obtain approximate estimates, age-adjusted mortality rates were pulled for the cause specific deaths of interest among individuals between 15 and 84 years using data from CDC WONDER. SMRs were calculated for specific causes of death by dividing the observed number of deaths to the expected deaths [94, 95].

Limitations

Although the VHA is the largest healthcare system in the United States, a major limitation of this study is that it only examines individuals who access healthcare through the VHA. Moreover, these study results may not generalize to the US population given the homogeneity of the veteran population. Moreover, veterans using VHA healthcare often experience a number of physical and mental health conditions compared to the general population which could result in a higher number of comorbidities or utilization of health care services [57]. These estimates may suffer from Berksonian bias, which appears when the sample is different than the general population leading to biased findings and is common among studies that use electronic health records [95]. However, the use of comparison groups and controlling for potential confounding will reduce potential bias that may occur. In addition, health services could be utilized outside of the VHA which could alter findings, showing a lower utilization of actual health care services. The CDW only captures overdoses documented in the VHA system which may lead to an underestimate on the true number of overdoses. Another potential limitation could occur when linking datasets (CDW and SDR) resulting in missed overdose deaths resulting in an underestimate of total deaths. However, records were required to match fully on SSN and 80-90% based of the additional characteristics including name, date of birth and sex.

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Tables and Figures

Table 1. Risk factors for opioid overdose

Population characteristics	
<i>Demographics</i>	
♦	Male
♦	Ages 18-45
♦	Non-Hispanic white
♦	Rural
♦	Appalachian region
<i>Physical health conditions</i>	
♦	Chronic pain
♦	Liver disease
♦	Renal disease
♦	Chronic pulmonary disease
♦	Cardiovascular disease
♦	Traumatic injury
♦	Cancer
♦	Soft skin and tissue infections
<i>Mental health conditions</i>	
♦	Mental distress
♦	Depression
♦	Anxiety
♦	Previous suicide attempt
♦	PTSD
♦	Bipolar disorder
<i>Substance Use</i>	
♦	Substance Use Disorder (SUD)
▪	History of opioid dependence or abuse

- ◆ Drug use (opioids, specifically heroin)
 - High MME/day (e.g. more than 90 MME/day)
 - Severity of substance use
- ◆ Co-prescribed opioids with benzodiazepines, antidepressants or antipsychotics

Figure 1. Process Flow of CDW

Abbreviations: CDW, Corporate Data Warehouse; VHA, Veterans Health Administration

Figure 2. Sample Design for the Opioid Overdose Cohort

Abbreviations: CDW, Corporate Data Warehouse; SDR, Suicide Data Repository

Chapter 2

2.1 Abstract

Objective

To compare demographic and diagnostic criteria associated with different categories of opioid overdoses including: fatal index (i.e. first recorded), single nonfatal, and repeat overdose (nonfatal).

Methods

Electronic health records (EHR) from the Veterans Health Administration (VHA) and death records from the Department of Veterans Affairs (VA)/Department of Defense (DoD) Joint Suicide (all-cause) Data Repository (SDR) were used to identify veterans with at least one documented opioid overdose between 2011 and 2015. Bivariate analyses were used to describe opioid overdose category and associated variables including sociodemographic characteristics, diagnostic factors such as chronic pain, mental health diagnosis, prior substance use, and codes associated with social determinants of health. Multinomial logistic regression was used to assess factors associated with fatal index overdose versus repeat overdose and one nonfatal overdose.

Results

A total of 12,848 VHA patients had at least one opioid overdose documented in VHA's EHR between 2011 and 2015. Among them, 34.7% (n=4,464) died on their first documented overdose, 20.7% (n=2,659) had at least one additional (i.e. repeat) documented overdose, and 44.6% (n=5,725) had only one nonfatal overdose in their medical records. Patients who were younger in age (18-44 OR [odds ratio] 7.19, 45-64 OR 4.78) had significantly higher odds of a fatal index overdose and experiencing a repeat overdose (18-44 OR 2.13, 45-64 OR 1.78). Having one or more chronic pain diagnoses was associated with experiencing a fatal index overdose (OR 3.96)

or repeat overdose (OR 1.15). A mental health or substance abuse or dependence diagnosis was significantly associated with experiencing a repeat overdose, (OR 1.54 and 1.25 respectively). Receipt of medication-assisted therapy (MAT) more than one year prior (OR 1.28) to the first (i.e. index) overdose was significantly associated with increased odds of a fatal overdose whereas receiving counseling services prior to index overdose was protective of experiencing a fatal index overdose.

Conclusion

To reduce overdose mortality and repeat morbidity, prevention efforts should target younger to middle aged veterans, especially those with a chronic pain diagnosis. Healthcare efforts should focus on treating mental health diagnoses, which are significantly associated with multiple overdoses. Healthcare efforts should consider integrating relapse prevention in primary care settings, to mitigate potential risk among patients with a history of an overdose.

2.2 Introduction

Overdoses are now the leading cause of accidental death in the United States and are a growing concern for public health and clinical medicine. Fatal opioid overdoses have been on the rise since 1999 and have more than quadrupled in the United States during this time period [1-6]. In a similar fashion, nonfatal overdoses have also been increasing. Fatal and nonfatal overdoses are highest among people who inject drugs (PWID) [7-9], have an opioid use disorder (OUD) [10, 11], or consume a high-dose of opioids [12-17].

Prior research has found that risk factors for nonfatal overdose [13, 18-28] are similar in nature to those for fatal overdose [15, 17, 29-32]. The most significant risk factors for overdose include those related to mental health such as a diagnosis of anxiety, depression, or a history of suicide ideation or attempt [7, 22, 23, 28, 33-35]. Diagnostic risk factors such as chronic pain, respiratory disease, renal disease, and cardiovascular disease have also been associated with overdose risk but were not as strong as those associated with mental health diagnoses [22, 23, 33, 34]. Research conducted among PWID suggest that homelessness and early life adversity are also associated with increased risk for substance abuse and overdose [30, 36, 37]. While studies have identified social determinants of health as significant risk factors of overdose, no studies have used EHRs to assess differences across categories of overdoses.

Existing evidence suggests that the number of prior overdoses is directly related to subsequent risk of death from overdose[38]. Furthermore, research suggests there has been a rise in patients hospitalized for repeat overdose events. However, little is known about risk factors for repeat overdose or if they may differ from those identified with increased risk of overdose mortality [39]. The few studies that have examined repeat overdoses have examined intentional overdoses rather than those that were thought to be unintentional or of undetermined intent [40-43].

The purpose of this study was to identify diagnostic factors, including codes related to social determinants of health, associated with different opioid overdose categories including fatal index overdose, a single nonfatal overdose, and repeat overdose (nonfatal) using data from the one of the largest integrated health care systems in the U.S.

2.3 Methods

Study population

We pulled a cohort of veterans who received services from the Veteran Health Administration (VHA) in calendar years 2011-2015. Opioid overdoses were extracted using clinical records from the VHA Corporate Data Warehouse (CDW) linked with death records from the VA/DoD Suicide Data Repository using Social Security Numbers (SSNs) [44-47]. To allow for time to risk, patients were excluded if their first overdose occurred in the last three months of the study (October 1, 2015 through December 31, 2015). Patients were also excluded from the study or if they did not have follow-up records within the year following a nonfatal overdose. This study was restricted to veterans over 18 and under 90 years of age. This cohort identified 13,333 veterans with at least one documented opioid overdose between 2011 through 2015. After excluding those who died from overdoses classified as suicide (n=422) or homicide (n=6), or those that died on a repeat overdose (n=57), the final study cohort was 12,848.

Opioid overdose

Opioid overdose was defined using International Classification of Disease, Ninth Edition (ICD-9) codes: 965.00-965.02, 965.09, E850.0-E850.2 and ICD Tenth Edition (ICD-10) codes: X40-X44, Y10-Y14 and secondary axis codes T40.0- T40.4, and T40.6. Repeat overdose was defined

as either a) a second documented overdose that occurred two days after the previous overdose, with the overdose documented as the principal diagnosis or b) a second documented overdose that occurred three days or more after the previous overdose. An overdose that occurred one day after a prior overdose was treated as the same event. The outcome of interest was category of opioid overdose: including categories for fatal index overdose, repeated nonfatal overdoses, and only one nonfatal overdose, which were constructed as three mutually exclusive groups.

Predictors

We extracted information on six domains of predictors for veterans receiving medical care from the VHA [46, 48]. These domains included demographic, chronic pain, mental health, substance abuse/dependence, MAT, and social codes, which serve as indicators of social determinants of health. Demographic information included age and sex of the patient. Information on race and ethnicity were not included due to limited availability and documented lack of reliability [49, 50]. Age was fixed and determined based on age on the first day of the study period (January 1, 2011). Sex was determined based on last entered value for sex in either the clinical or death records.

Chronic pain

Chronic pain diagnoses were categorized into seven diagnostic groups: arthritis, back pain, migraines, headaches or tension headaches, psychogenic pain, neuropathy, and fibromyalgia. If a patient had a diagnosis of at least one chronic pain diagnosis, a dummy variable was created to identify the association between any chronic pain diagnosis prior to index overdose and type of subsequent overdose (i.e. any chronic pain diagnosis prior to index overdose). Classifications for chronic pain were guided by previous research [51].

Mental health

A broad definition of mental health diagnosis was identified using ICD-9 codes 290.00 to 319.99 or ICD-10 codes F00 to F99, excluding tobacco codes starting with 305 or F17 [52, 53]. Eight specific types of mental health disorders were categorized and included anxiety, depression, bipolar, PTSD, adjustment disorder, schizophrenia or other psychotic disorders, traumatic stress, and personality disorder. Two combination variables were then created to identify potential interactions between types of mental health diagnoses and included: 1) having either depression, anxiety, or PTSD, and 2) having all three mental health diagnoses (i.e. depression, anxiety, and PTSD). Similar to chronic pain diagnoses, a dummy variable indicating any mental health disorder was used to assess the relationship between mental health diagnoses and type of documented overdose.

Substance abuse or dependence

Substance abuse or dependence was measured using seven types of substance abuse or dependency groups including alcohol, opioid, cannabis, sedative, hypnotic, or anxiolytic, cocaine, other stimulant, and hallucinogens. Similar to chronic pain and mental health diagnoses, patients with any type of substance abuse or dependence documented in the clinical record were then categorized as having any type of substance abuse or dependence. Patients with more than one type of substance abuse or dependence were also identified as having polysubstance abuse or dependence to assess the potential relationship between substance abuse/dependence for multiple substances and type of overdose. Due to limited numbers, three types of substance abuse/dependency disorders were not included in tables but were included in the composite variable identifying any substance abuse/dependence or polysubstance abuse/dependence. Type

of substances explored but not specifically retained in tables include the three categories: cannabis, hallucinogens, and sedative, hypnotic, or anxiolytic substances.

MAT

Receiving MAT services was identified by a documented primary or secondary stop code 523, which identifies buprenorphine or methadone treatment in the clinical record [54-56]. Patients who received MAT prior to their index overdose were then further identified as having MAT more than one year prior to overdose. Exploratory analyses identified more than one year as a critical time point for last MAT rather than one, three or six months prior to index overdose.

Social determinants of health

Codes that are indicators of social determinants of health were collapsed into the following 13 categories guided by previous literature (Torres et al., 2017; Gottlieb et al., 2016): 1) problems related to employment or unemployment, 2) problems related to education and literacy, 3) problems related to housing or economic circumstances, 4) problems related to mental or behavioral health, 5) problems related to upbringing, 6) problems related to social environment, 7) problems related to primary support group, 8) problems related to psychosocial circumstances, 9) problems related to environmental psychosocial circumstances, 10) problems related to abuse, 11) problems related to lifestyle or lifestyle management, 12) receipt of counseling services, and 13) receipt of counseling services for substance abuse.

The specific diagnostic codes (ICD-9 and ICD-10) used for the predictor variables can be found in a Supplemental Table 1.

This study was reviewed and approved by the Institutional Review Board at the Syracuse VA Medical Center, New York.

Analysis

Data for this study was analyzed using SAS Enterprise Grid software (version 5.1, SAS Institute Inc.). Descriptive analysis for all potential predictors were completed using cross tabulations for all outcomes and alpha was set to 0.05 for tests unless otherwise specified.

Bivariate analyses were conducted using chi-square test of difference, for all predictor variables with each overdose outcome: fatal index overdose and repeated nonfatal overdoses (Table 1).

The reference group for all analyses was a single nonfatal opioid overdose.

Using multinomial logistic regression, the odds ratios for repeat overdose and fatal index overdose were calculated for sociodemographic and diagnostic factors such as chronic pain, mental health diagnosis, prior substance use, and codes associated with social determinants of health. Multinomial regression was used to provide a more direct interpretation for the relationship between the predictors and category of overdose [57, 58]. As an extension of logistic regression, this method was selected because it is more robust to violating assumptions of normality and ability to compare across multiple outcome groups(57, 58). Model fit for this multinomial logistic regression model was assessed by using a series of logistic regression models, controlling for age and gender [59, 60]. Assumptions for this method were testing by assessing multicollinearity among predictors with a variance inflation factor (VIF) with a critical value greater than ten. If evidence of collinearity was identified among predictors, Wald chi-square tests were conducted to determine which variable was best suited for inclusion in the final model. Goodness of fit indices such as the Type 3 Analysis of Effects and Wald chi-square test were examined for all predictors [61]. Interactions between significant predictor variables were tested.

Adjusted odds ratios (OR) with 95% Confidence Intervals (CIs) were calculated for each of the significant predictors in the final model (Table 2). Adjusted odds ratios indicate the odds of experiencing a fatal overdose compared to those with one nonfatal overdose as well as the odds of experiencing a repeated nonfatal overdose compared to those with one nonfatal overdose, adjusted for all other predictors in the model.

2.4 Results

Our cohort consisted of 12,848 veterans with at least one documented overdose between calendar years 2011 to 2015. This retrospective cohort consisted primarily of men (91.5%, n=11,070) between the ages of 45-64 (61.3%, n=7,874). More than half had at least one chronic pain diagnosis (69.6%, n=8,941) the most common types of chronic pain among our cohort was arthritis (55.5%, n=7,129) and back pain (50.8%, n=6,521). Among our study cohort more than 90% had a mental health diagnosis during the study period (91.6%, n=11,768). The most common mental health diagnoses were depression (75.5%, n=9,703) followed by anxiety (60.8%, n=7,807), and PTSD (47.8%, n=6,146). In fact, 84.9% (n=10,906) of our cohort had at least one of those mental health diagnoses and 32.8% (n=4,208) had record of all three. A majority of the cohort (64.6%, n= 8,303) had at least one diagnosis associated with substance abuse or dependence and 40.5% (n=5,203) had more than one substance abuse or dependence diagnosis. Among our entire cohort, 11.1% (n=1,424) received MAT during the study period and among those 76.1% (n=1,084) had MAT before their index overdose. Of those who received MAT prior to their index overdose, 64.9% (n=704) last received MAT more than one year before the first overdose recorded in their VHA medical record.

Diagnostic codes that are known as indicators of social determinants of health, or social codes, were present in the EHR for 92.4% of our cohort (n=11,867). The most common social code

documented for this cohort was receipt of counseling services, with 88.3% (n=11,338) having at least one counseling code on record prior to their index overdose. The other social codes which were frequent among this cohort were those indicating problems with housing or economic circumstances (39.6%, n=5,082) and problems associated with psychosocial circumstances (44.7%, n=5,739). (Table 1)

Bivariate analyses showed notable differences in group compositions between those who died on their first overdose, those with repeat nonfatal overdoses, and those with only one nonfatal overdose (Table 2). There were significant differences in the age distribution for those with repeat overdose and fatal overdose ($p<0.01$). While males more often experienced a fatal index overdose there were no significant differences in sex distribution for those with repeated nonfatal overdose when compared to those with only one nonfatal overdose. Bivariate analysis also suggests that those with repeated overdose events were significantly more likely to have had a mental health or substance abuse diagnosis when compared to those with only one nonfatal overdose ($p<0.01$). Similarly, those who died on their index overdose less frequently had any documented social code ($p<0.01$). Those who died on their first overdose were more likely to have a diagnosis for chronic pain in comparison to those with one nonfatal overdose ($p<0.01$).

A multivariable analysis assessing factors associated with category of overdose is provided in Table 3. Males were more than 50% more likely to experience a fatal overdose when compared to those with a single nonfatal overdose (OR [Odds ratio] 1.57, 95% CIs [confidence interval]: 1.34-1.83). Patients between the ages of 18-44 years were more likely to experience a fatal index overdose (OR 7.19, 95% CI: 5.88-8.78) or repeat overdose (OR 2.13, 95% CI 1.76-2.58) when compared to those who only had record of one single nonfatal overdose. Similarly, patients with a chronic pain diagnosis prior to their first recorded overdose were significantly more likely to

experience a fatal overdose (OR 3.96, 95% CI: 3.56-4.42) or repeat overdose (OR 1.15, 95% CI 1.04-1.27). However, patients with a prior history of polysubstance abuse or dependence were more likely to experience a repeat overdose (OR 1.25, 95% CI: 1.13-1.38) and less likely to experience a fatal index overdose (OR 0.75, 95% CI: 0.68-0.82) compared to those with one nonfatal overdose. Patients who were last received MAT was more than one year prior to their index overdose were 28% more likely to experience a fatal index overdose (OR 1.28, 95% CI: 1.05-1.55). Lastly, the odds of fatal index overdose were significantly lower among those receiving counseling services prior to their first known overdose (OR 0.35, 95% CI: 0.30-0.40).

2.5 Discussion

Overall, these findings suggest that men were more likely to experience a fatal index overdose and younger and middle-aged patients (aged 18-64 years) were more likely to experience either a fatal index overdose or repeat overdose; results that are similar to previously identified associations [4, 5, 15]. These findings suggest the need for targeted overdose prevention programs targeting younger to middle aged men.

Similarly, those who experienced either a fatal index or repeat overdose were also more likely to have a chronic pain diagnosis prior to their index event, underscoring the need for integrated health care, which is consistent with other research findings [22, 23] and supports the need for continued efforts to identify and support alternative approaches to management of chronic pain [62-64]. While the CDC has developed Chronic Pain Guidelines, these findings suggest the need to amplify risk management of chronic pain patients by additional education or co-prescription of naloxone [65].

Interestingly, patients with a mental health diagnosis or polysubstance abuse/dependence were more likely to experience a repeat overdose and less likely to experience a fatal index overdose when compared to those with a single nonfatal overdose. Although there is evidence that mental health diagnoses are more prevalent among those who experience an overdose, this is the first study to identify a difference in magnitude in the associations between mental health diagnosis and category of opioid overdoses [33, 66]. This is an interesting and important finding considering previous reports that suggests repeat overdose trends are increasing [39]. Healthcare systems should be ready for the potential for a higher number of patients and consider integrating mental health services with emergency care and substance abuse treatment.

In addition to one or more mental health diagnoses, receiving counseling services prior to the index overdose was protective against experiencing a fatal index overdose. Conversely, those who received their last MAT services a year or more ago were more likely to experience a fatal index event during our study period. These findings highlight the need for healthcare systems to treat OUD using a disease model approach and suggest the need for relapse prevention in primary care settings [67]. Substance use disorder (SUD) is a chronic disease with relapse rates comparable to other common health conditions, such as hypertension [68-72]. Future clinical efforts should be supported to identify and address SUD in primary care settings similar to other chronic diseases.

Strengths and limitations

To the best of our knowledge, this is the first study to compare risk factors by category of opioid overdose history. This study used data from one of the largest integrated healthcare systems in the United States. However, this study is not without limitations. The information collected on category of overdose which relies on clinical recording and may not be present if an individual

does not seek medical care for an overdose or a clinician does not document the event.

Therefore, the true number of overdoses may be underestimated. This analysis was conducted among the veteran population and results from this study may not be generalizable to the general population. The associations with measures of social determinants of health explored in this study may be biased given that there is evidence that they are more likely to be entered by mental health professionals, particularly psychiatrists, when compared to other medical specialties [73, 74]. The decision to omit patients who die on a repeat overdose could systematically exclude characteristics associated with death after multiple overdoses. However, the small number of cases prevent inclusion as a second category and characteristics among these patients may be different when compared to those who died on their index overdose. Future research should consider characteristics associated with mortality among those with multiple overdose events.

It is important to note that various public health interventions have been implemented to reduce overdose among people at highest risk [16, 75-78]. These efforts have largely been focused on reducing the excess supply of opioids through education programs, surveillance systems designed to reduce the availability of prescription opioids (e.g. prescription drug monitoring programs), and prevention of overdose-related mortality through broad availability of naloxone.

In general, nonfatal and fatal overdoses appear to be impacting younger and middle aged veterans, suggesting that primary prevention efforts in the future may want to tailor the programs to this audience. Chronic pain, psychiatric diagnoses, and contextual factors appear differentially associated with fatal index overdose in comparison to those with repeated nonfatal overdoses.

These findings underscore the need for integrated healthcare to address mental health and chronic pain among patients at risk for an opioid overdose.

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Tables and Figures

Table 1. Demographic and diagnostic characteristics of veterans with a documented opioid overdose, 2011-2015

		n (n=12,848)	%
Demographic			
Sex			
	Female	1,098	8.55
	Male	11,750	91.45
Age (years)			
	18-44	3,879	30.19
	45-64	7,874	61.29
	65+	1,095	8.52
Type of pain diagnosis prior to index OD			
Any chronic pain diagnosis			
	No	3,907	30.41
	Yes	8,941	69.59
Arthritis			
	No	5,719	44.51
	Yes	7,129	55.49
Back pain			
	No	6,327	49.25
	Yes	6,521	50.75
Migraines			
	No	11,978	93.23
	Yes	870	6.77
Headaches or tension headaches			
	No	11,075	86.20
	Yes	1,773	13.80
Psychogenic			
	No	12,586	97.96
	Yes	262	2.04
Neuropathy			
	No	11,804	91.87

	Yes	1,044	8.13
Fibromyalgia			
	No	12,187	94.86
	Yes	661	5.14
Mental health diagnosis			
Any mental health diagnosis			
	No	1,080	8.41
	Yes	11,768	91.59
Anxiety			
	No	5,041	39.24
	Yes	7,807	60.76
Depressive disorder			
	No	3,145	24.48
	Yes	9,703	75.52
Bipolar			
	No	9,764	76.00
	Yes	3,084	24.00
PTSD			
	No	6,702	52.16
	Yes	6,146	47.84
Adjustment disorder			
	No	9,333	72.64
	Yes	3,515	27.36
Schizophrenia or other psychotic disorder			
	No	10,334	80.43
	Yes	2,514	19.57
Traumatic stress			
	No	11,071	86.17
	Yes	1,777	13.83
Personality disorder			
	No	10,090	78.53
	Yes	2,758	21.47

Either depression, anxiety, or PTSD diagnosis			
	No	1,942	15.12
	Yes	10,906	84.88
All three diagnosis (depression, anxiety, & PTSD)			
	No	8,640	67.25
	Yes	4,208	32.75
Substance abuse/dependence			
Any substance abuse/dependence diagnosis			
	No	4,545	35.38
	Yes	8,303	64.62
Polysubstance abuse/dependence diagnosis ^a			
	No	7,645	59.50
	Yes	5,203	40.50
Alcohol abuse or dependence diagnosis			
	No	6,968	54.23
	Yes	5,880	45.77
Opioid abuse or dependence diagnosis			
	No	7,137	55.55
	Yes	5,711	44.45
Cocaine abuse or dependence diagnosis			
	No	10,052	78.24
	Yes	2,796	21.76
Other stimulant abuse or dependence diagnosis			
	No	11,873	92.41
	Yes	975	7.59
Medication-Assisted Treatment			
Ever had MAT			
	No	11,424	88.92
	Yes	1,424	11.08
MAT before index overdose			
	No	11,764	91.56
	Yes	1,084	8.44

MAT more than 1 year before index OD			
	No	12,144	94.52
	Yes	704	5.48
Social determinants of health (SDoH)			
Any code related to SDoH			
	No	981	7.64
	Yes	11,867	92.36
Counseling services			
	No	1,510	11.75
	Yes	11,338	88.25
Problems related to housing and economic circumstances			
	No	7,766	60.45
	Yes	5,082	39.55
Problems related to education and literacy			
	No	11,689	90.98
	Yes	1,159	9.02
Problems related to environmental psychosocial circumstances			
	No	7,109	55.33
	Yes	5,739	44.67
Problems related to mental and behavioral			
	No	12,690	98.77
	Yes	158	1.23
Problems related to social environment			
	No	9,686	75.39
	Yes	3,162	24.61
Other problems related to primary support group			
	No	11,794	91.80
	Yes	1,054	8.20
Problems related to upbringing			
	No	12,620	98.23
	Yes	228	1.77

Abbreviations: OD, overdose; PTSD, post-traumatic stress disorder, SDoH, social determinants of health; MAT, medication-assisted treatment

- a. Polysubstance use or dependence refers to a patient having a diagnosis for more than one substance during the study period (2011-2105).

Table 2. Bivariate analysis of demographic and diagnostic characteristics by type of opioid overdose among veterans, 2011-2015 ^a

		No repeat OD (n=5,725)		Repeat non-fatal OD (n=2,659)			Fatal index OD (n=4,464)		
		n	%	n	%	p	n	%	p
Demographic									
Sex									
	Female	528	9.22	261	9.82		309	6.92	
	Male	5,197	90.78	2,398	90.18		4,155	93.08	
						0.39	<0.01		
Age									
	18-44 years	1,488	25.99	853	32.08		1,538	34.45	
	45-64 years	3,494	61.03	1,630	61.30		2,750	61.60	
	65+ years	743	12.98	176	6.62		176	3.94	
						<0.01	<0.01		
Type of pain diagnosis prior to index OD									
Any chronic pain diagnosis									
	No	2,112	36.89	900	33.85		895	20.05	
	Yes	3,613	63.11	1,759	66.15		3,569	79.95	
						<0.01	<0.01		
Arthritis									
	No	2,915	50.92	1,269	47.72		1,535	34.39	
	Yes	2,810	49.08	1,390	52.28		2,929	65.61	
						<0.01	<0.01		
Back pain									
	No	3,226	56.35	1,440	54.16		1,661	37.21	
	Yes	2,499	43.65	1,219	45.84		2,803	62.79	
						0.06	<0.01		
Migraines									
	No	5,390	94.15	2,489	93.61		4,099	91.82	
	Yes	335	5.85	170	6.39		365	8.18	
						0.33	<0.01		
Headaches or tension headaches									
	No	5,042	88.07	2,323	87.36		3,710	83.11	
	Yes	683	11.93	336	12.64		754	16.89	
						0.36	<0.01		
Psychogenic									
	No	5,647	98.64	2,627	98.80		4,312	96.59	

	Yes	78	1.36	32	1.20		152	3.41
						0.55		<0.01
Neuropathy								
	No	5,207	90.95	2,444	91.91		4,153	93.03
	Yes	518	9.05	215	8.09		311	6.97
						0.15		<0.01
Fibromyalgia								
	No	5,483	95.77	2,526	95.00		4,178	93.59
	Yes	242	4.23	133	5.00		286	6.41
						0.11		<0.01
Mental health diagnosis								
Any mental health diagnosis								
	No	261	4.56	61	2.29		758	16.98
	Yes	5,464	95.44	2,598	97.71		3,706	83.02
						<0.01		<0.01
Anxiety								
	No	1,920	33.54	772	29.03		2,349	52.62
	Yes	3,805	66.46	1,887	70.97		2,115	47.38
						<0.01		<0.01
Depressive disorder								
	No	1,005	17.55	397	14.93		1,743	39.05
	Yes	4,720	82.45	2,262	85.07		2,721	60.95
						<0.01		<0.01
Bipolar								
	No	4,232	73.92	1,900	71.46		3,632	81.36
	Yes	1,493	26.08	759	28.54		832	18.64
						0.02		<0.01
PTSD								
	No	2,760	48.21	1,502	56.49		2,800	62.72
	Yes	2,965	51.79	1,157	43.51		1,664	37.28
						<0.01		<0.01
Adjustment disorder								
	No	3,930	68.65	1,765	66.38		3,638	81.50
	Yes	1,795	31.35	894	33.62		826	18.50
						0.04		<0.01
Schizophrenia or other psychotic disorder								
	No	4,277	74.71	2,079	78.19		3,978	89.11
	Yes	1,448	25.29	580	21.81		486	10.89
						<0.01		<0.01
Traumatic stress								
	No	4,778	83.46	2,213	83.23		4,080	91.40

Yes	947	16.54	446	16.77		384	8.60
					0.80		<0.01
Personality disorder							
No	4,316	75.39	1,934	72.73		3,840	86.02
Yes	1,409	24.61	725	27.27		624	13.98
					<0.01		<0.01
Either depression, anxiety, or PTSD diagnosis							
No	575	10.04	197	7.41		1,170	26.21
Yes	5,150	89.96	2,462	92.59		3,294	73.79
							<0.01
All three diagnosis (depression, anxiety, & PTSD)							
No	3,573	62.41	1,512	56.86		3,555	79.64
Yes	2,152	37.59	1,147	43.14		909	20.36
					<0.01		<0.01
Substance abuse/dependence							
Any substance abuse/dependence diagnosis							
No	1,897	33.14	661	24.86		1,977	44.29
Yes	3,828	66.86	1,998	75.14		2,487	55.71
					<0.01		<0.01
Polysubstance abuse/dependence diagnosis^b							
No	3,337	58.29	1,323	49.76		2,985	66.87
Yes	2,388	41.71	1,336	50.24		1,479	33.13
					<0.01		<0.01
Alcohol abuse or dependence diagnosis							
No	2,993	52.28	1,239	46.60		2,736	61.29
Yes	2,732	47.72	1,420	53.40		1,728	38.71
					<0.01		<0.01
Opioid abuse or dependence diagnosis							
No	3,070	53.62	1,189	44.72		2,878	64.47
Yes	2,655	46.38	1,470	55.28		1,586	35.53
					<0.01		<0.01
Cocaine abuse or dependence diagnosis							
No	4,509	78.76	1,945	73.15		3,598	80.60
Yes	1,216	21.24	714	26.85		866	19.40
					<0.01		0.02
Other stimulant abuse or dependence diagnosis							
No	5,225	91.27	2,371	89.17		4,277	95.81
Yes	500	8.73	288	10.83		187	4.19
					<0.01		<0.01
Medication-Assisted Treatment							
Ever had MAT							

No	5,097	89.03	2,264	85.14		4,063	91.02	
Yes	628	10.97	395	14.86		401	8.98	
					<0.01			<0.01
MAT before index OD								
No	5,297	92.52	2,398	90.18		4,069	91.15	
Yes	428	7.48	261	9.82		395	8.85	
					<0.01			0.01
MAT more than 1 year before index OD								
No	5,433	94.90	2,476	93.12		4,235	94.87	
Yes	292	5.10	183	6.88		229	5.13	
					<0.01			0.95
Social determinants of health								
Any code for social determinant of health								
No	237	4.14	120	4.51		624	13.98	
Yes	5,488	95.86	2,539	95.49		3,840	86.02	
					0.43			<0.01
Counseling services								
No	450	7.86	200	7.52		860	19.27	
Yes	5,275	92.14	2,459	92.48		3,604	80.73	
					0.59			<0.01
Problems related to housing and economic circumstances								
No	3,482	60.82	1,535	57.73		2,749	61.58	
Yes	2,243	39.18	1,124	42.27		1,715	38.42	
					<0.01			0.43
Problems related to education and literacy								
No	5,143	89.83	2,398	90.18		4,148	92.92	
Yes	582	10.17	261	9.82		316	7.08	
					0.25			<0.01
Problems related to environmental psychosocial circumstances								
No	2,901	50.67	1,396	52.50		2,812	62.99	
Yes	2,824	49.33	1,263	47.50		1,652	37.01	
					0.12			<0.01
Problems related to mental and behavioral								
No	5,653	98.74	2,618	98.46		4,419	98.99	
Yes	72	1.26	41	1.54		45	1.01	
					0.29			0.24
Problems related to social environment								
No	4,111	71.81	1,975	74.28		3,600	80.65	
Yes	1,614	28.19	684	25.72		864	19.35	
					0.02			<0.01
Other problems related to primary support group								

No	5,193	90.71	2,427	91.27	4,174	93.50	
Yes	532	9.29	232	8.73	290	6.50	
					0.40		<0.01
Problems related to upbringing							
No	5,603	97.87	2,611	98.19	4,406	98.70	
Yes	122	2.13	48	1.81	58	1.30	
					0.33		<0.01

Abbreviations: OD, overdose; PTSD, Post-Traumatic Stress Disorder; MAT, Medication-Assisted Treatment

- a. Bivariate analysis examined patient characteristics that were different among those with a repeated overdose and fatal index overdose in comparison to those with only non-fatal overdose.
- b. Polysubstance use or dependence refers to a patient having a diagnosis for more than one substance during the study period (2011-2105).

Table 3. Multinomial regression analysis of factors associated with type of opioid overdoses among Veterans, 2011-2015

		Repeat OD (n=2,659)		Fatal index OD (n=4,464)	
		OR	95% CI	OR	95% CI
Sex					
Male		0.98	(0.83-1.14)	1.57	(1.34-1.83)
Female		1.00	Ref	1.00	Ref
Age (years)					
18-44		2.13	(1.76-2.58)	7.19	(5.88-8.78)
45-64		1.78	(1.49-2.13)	4.78	(3.95-5.78)
65+		1.00	Ref	1.00	Ref
Chronic pain diagnosis					
Yes		1.15	(1.04-1.27)	3.96	(3.56-4.42)
No		1.00	Ref	1.00	Ref
Mental health diagnosis					
Yes		1.54	(1.15-2.07)	0.18	(0.15-0.22)
No		1.00	Ref	1.00	Ref
Polysubstance abuse or dependence ^a					
Yes		1.25	(1.13-1.38)	0.75	(0.68-0.82)
No		1.00	Ref	1.00	Ref
MAT more than 1 year prior to index OD					
Yes		1.18	(0.97-1.44)	1.28	(1.05-1.55)
No		1.00	Ref	1.00	Ref
Received counseling services					
Yes		0.93	(0.78-1.12)	0.35	(0.30-0.40)
No		1.00	Ref	1.00	Ref

Abbreviations: OR, Odds Ratio; CI, Confidence Interval; OD, overdose; MAT, Medication-Assisted Treatment

a. Polysubstance use or dependence refers to a patient having a diagnosis for more than one substance during the study period (2011-2105).

Supplement Table 1. Corresponding ICD-9 and ICD-10 Codes for Variables

Characteristic	ICD-9 and ICD-10 code
<i>Psychosocial & related mental health diagnoses</i>	
Any mental health diagnosis	ICD-9: 290.00 to 319.99, excluding tobacco codes starting with 305 ICD-10: F00 to F99, excluding tobacco codes starting with F17
Anxiety	ICD-9: 300 ICD-10: F40, F41
Depression	ICD-9: 296.2, 296.3, 300.4, 311 ICD-10: F32, F33, F34.1
Bipolar	ICD-9: 296.0, 296.1, 296.4, 296.5, 296.6, 296.7, 296.8 ICD-10: F31
PTSD	ICD-9: 309.81 ICD-10: F43.1
Adjustment disorder	ICD-9: 309.0, 309.24, 309.28, 309.3, 309.4, 309.9 ICD-10: F43.20- F43.25
Schizophrenia or other psychotic disorders	ICD-9: 295.90, 295.40, 295.70, 297.1, 297.3, 298.8, 293.81, 293.82, 298.9 ICD-10: F20.9, F20.81, F25.0, F25.1, F22, F24, F23, F06.2, F06.0, F29)
Traumatic stress	ICD-9: 308.9, 309.89, 309.9 ICD-10: F43.0 F43.8, F43.9
Personality disorder	ICD-9: 301.83, 301.7, 301.81, 301.50, 301.4, 301.82, 301.6, 301.0, 301.20, 310.1 301.9 ICD-10: F60, F61
Opioid abuse/dependence	ICD-9 codes: 304.0, 304.7, 305.5 ICD-10 codes: F11
Alcohol abuse/dependence	ICD-9: 303, 305.0 ICD-10: F10
Cannabis abuse/dependence	ICD-9: 304.3, 305.2 ICD-10: F12
Sedative, hypnotics, or anxiolytic abuse/dependence	ICD-9: 304.1, 305.4 ICD-10: F13
Cocaine abuse/dependence	ICD-9: 304.2, 305.6 ICD-10: F14
Other stimulant abuse/dependence	ICD-9: 304.4, 305.7 ICD-10: F15
Hallucinogen abuse/dependence	ICD-9: 304.5, 305.3 ICD-10: F16
Any substance abuse/dependence	Any diagnosis for substance abuse/dependence
Polysubstance abuse/dependence	At least two combinations of the substance abuse/dependence diagnosis
TBI	ICD-9: 800.0-801.9, 803.0-804.9, 850.0-854.1, 950.1-950.3, 995.55, 959.01 ICD-10: S02.0, S02.1, S02.8, S02.91, S04.02, S04.03, S04.04, S06, S07.1, T74.4

Medication-Assisted Treatment (MAT)	
Record of MAT	Using stop code 523 (primary or secondary stop code) to identify MAT services
Chronic pain before index OD	
Back pain	ICD-9: 720.0-724.9 ICD-10: M45.9- M46.1, M46.90, M47.812, M47.12, M47.814, M47.817, M48.20, M48.10, M48.30, M48.9, M50.20, M51.9, M50.30, M51.34- M51.37, M48.02, M54.2, M53.0, M53.1, M54.12, M54.13, M43.6, M54.02, M67.88, M53.82, M54.6, M54.5, M54.30, M54.14-M54.17, M54.89-M54.9, M43.27, M43.28, M53.2X7, M53.3, M54.08, M43.8X9, M53.9
Arthritis	ICD-9: 710.0-739.9, excluding back pain codes ICD-10: M00-M02, M36.2, M36.3, M12, M35.3, M15, M16-M19, M05-M08, M1A, M10-M14
Migraines	ICD-9: 346.0-346.9 ICD-10: G43.0, G43.1, G43.4, G43.5, G43.6, G43.7, G43.8, G43.9, G43.A, G43.B, G43.C, G43.D
Headaches or tension headaches	ICD-9: 784.0 and 307.81 ICD-10: G44.1, R51, G44.209
Psychogenic	ICD-9: 307.80 and 307.89 ICD-10: F45.41, F45.42
Neuropathy	ICD-9: 355.0, 355.9, 356.0, 357.2, 357.9 ICD-10: G57.00, G58.9, G60, E08.42, E09.42, E10.42, E11.42, E13.42, G61.9
Fibromyalgia	ICD-9: 729.1 ICD-10: M60.9, M79.1, M79.7
Any chronic pain diagnosis	Any of the diagnoses for chronic pain
Social determinants of health (SDoH) codes prior to index OD	
Problems related to housing and economic circumstances	ICD-9: V60.0, V60.1, V60.89, V60.6, V60.2, V60.9 ICD-10: Z59 (Z59.0-Z59.9)
Problems related to support group, including family and relationships	ICD-9: V61.0, V61.05, V61.8, V61.01, V61.06, V61.07, V61.08, V62.82, V61.03, V61.49, V61.02, V61.41, V61.3, V61.04, V61.09, V61.8, V61.9 ICD-10: Z63 (Z63.0-Z63.9)
Problems related to social environment	ICD-9: V60.3, V62.4, V62.89 ICD-10: Z60.0, Z60.2, Z60.3, Z60.4, Z60.5, Z60.8, Z60.9
Problems related to upbringing	ICD-9: V61.29, V61.8, V60.81 ICD-10: Z62.0, Z62.1, Z62.2, Z62.3, Z62.6, Z62.8
Problems related to environmental psychosocial circumstances	ICD-9: V62.5, V62.89, V62.81, V62.9 ICD-10: Z65.0, Z65.1, Z65.2, Z65.3, Z65.4, Z65.5, Z65.8, Z65.9
Problems related to abuse	ICD-9: V61.21, V61.22, V62.83, V61.11, V61.12, V65.49 ICD-10: Z69.0, Z69.01, Z69.02, Z69.1, Z69.8
Counseling services	ICD-9: V65.49, V61.2, V61.1, V65.40, V65.9 ICD-10: Z71.81, Z71.89, Z71.9
Other problems related to mental and behavior	ICD-9: V40.0, V40.2, V40.3, V40.31, V40.39, V40.9 ICD-10: F48.9, F69

Any SDoH	Any of the above SDoH codes captured before index OD
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Abbreviations: ICD, International Classification of Disease; ICD-9, International Classification of Disease, Ninth Edition; ICD-10, International Classification of Disease, Tenth Edition; PTSD, Post-traumatic stress disorder; TBI, Traumatic Brain Injury; MAT, Medication-Assisted Treatment; OD, overdose; SDoH, social determinant of health

Chapter 3

3.1 Abstract

Objective

To determine the conditional probability of repeat overdose among patients with one or more prior overdose events and corresponding probability of overdose mortality.

Methods

Clinical records were extracted between 2011 through 2015 for veterans receiving medical care from the Veterans Health Administration (VHA). Vital status was determined by linking data from the patient's medical record to information contained in the VA/DoD Joint Suicide (all-cause) Data Repository (SDR). Conditional probability of repeated overdose and mortality was calculated among patients with at least one recorded overdose.

Results

There were 12,905 veterans with at least one opioid overdose between 2011 and 2015. Among this study sample, one fifth (n=2,716) had a repeated opioid overdose during the study period. The conditional probability for repeated overdose more than doubled for each overdose event from 21.1% for a second overdose to 43.2% for five or more overdoses. Mortality was highest for the first documented overdose (34.6%).

Conclusion

Overdose prevention efforts should be expanded and include primary prevention efforts targeting those at highest risk for overdose morbidity and mortality; including those not currently receiving treatment for opioid abuse or misuse. Additional research is needed to identify risk factors for repeated overdose and corresponding mortality to curtail the current opioid crisis.

3.2 Introduction

Opioid overdoses are a growing public health concern. In the United States, the opioid overdose mortality rate increased by 413% since 1999, from a rate of 2.9 to 14.9 per 100,000 [1-5]. In addition to fatal overdoses, nonfatal overdoses resulting in either inpatient admission or emergency department visits have been substantially increasing in the past decade [6, 7]. Despite the observed rise in overdoses, little is known about the risk of repeated overdose events and corresponding mortality. Prior research suggests that a history of overdose and psychiatric diagnoses are risk factors for repeat overdose among persons who engage in self-harm behavior or inject drugs [8-11]. However little is understood regarding the risks associated with repeat overdose among patients in a general patient population.

The overall objective of this study was to calculate the conditional probability of a repeat opioid overdose event and mortality for each overdose event among veterans who use VHA services. This research is important because it will elucidate the number of documented opioid overdose events a patient experiences and will identify the overdose event associated with highest overdose mortality using data from the largest integrated health care system in the U.S..

3.3 Methods

Sample design

This study cohort included 13,333 veterans with at least one documented opioid overdose between January 1, 2011 and December 31, 2015. Opioid overdoses were extracted using clinical records from the VHA Corporate Data Warehouse (CDW) [12]. CDW records were linked with mortality records from the VA/DoD Suicide (all-cause) Data Repository using Social Security Numbers (SSNs) [13, 14]. Vital status was determined for these patients through the 2015

calendar year. Sex and age were extracted from clinical and mortality files. Age was static and determined on the start of the study period (January 1, 2011).

Opioid overdose

An opioid overdose was identified using International Classification of Disease, Ninth Edition (ICD-9) codes: 965.00-965.02, 965.09, E850.0-E850.2 and ICD Tenth Edition (ICD-10) codes: X40-X44, Y10-Y14 and secondary axis codes T40.0- T40.4, and T40.6. The first opioid overdose documented in the clinical records between calendar years 2011 to 2015 was used as the index overdose. Repeat overdose was defined as a second documented overdose that either occurred two days after the previous overdose with the overdose documented as the principal diagnosis or a second documented overdose that occurred or more than three days after the prior overdose.

The study sample was restricted to veterans between 18 and 90 years old. To allow time for repeated events, we excluded patients that had no follow-up visits within one year of the first overdose event or had their first overdose in the last three months of the study period (October 1, 2015-December 1, 2015). For this study, we excluded patients with an opioid overdose death that was classified as intentional or homicide, yielding a total of 12,905 patients.

This study was reviewed and approved by the Institutional Review Board at the Syracuse VA Medical Center, New York.

Analysis plan

The frequency and conditional probability of nonfatal and fatal overdose were estimated among the total VHA patient population with at least one overdose event during the study period (2011-2015). Conditional probability of an overdose was calculated by dividing the proportion of

patients experiencing the event by the number of patients at risk for the event [15-17]. The conditional probability of interest was mortality at each overdose event for each disease event (e.g., one, two, three, four or more overdoses) as well as conditional probability for repeated nonfatal overdose event. Conditional probabilities for overdose death and repeat overdose at each disease event were estimated and 95% confidence intervals were extrapolated using the normal approximation method.

3.4 Results

There were 12,905 veterans with at least one overdose event documented in VHA's electronic medical record (EMR). The conditional probability of repeated overdose increased directly with the number of overdose events. The conditional probability for repeated overdoses more than doubled from 21.1% following one nonfatal overdose event to 43.2% for experiencing four or more overdoses (Table 1). In total, 4,521 veterans experienced a fatal overdose; accounting for 35.0% of the VHA patients with a recorded overdose. The proportion of deaths was highest for the first documented overdose (98.8%) compared to subsequent fatal overdose events (Figure 1).

3.5 Discussion

More than twenty percent of patients with a documented opioid overdose had at least one repeated overdose documented in the records during the five year study period (January 1, 2011-December 31, 2015). With every overdose event, the probability of experiencing an additional overdose continued to increase but the probability of overdose death was consistently low.

Patients were 17 times more likely to die from an opioid overdose on their first documented overdose event during the study period. Given that overdose mortality was highest among patients with no prior overdose during this time period, prevention efforts should be focused on

amplifying resources to those without documented overdose risk. Additional research is needed to understand the risks associated with repeat overdose to inform future clinical and public health interventions directed at those with history of multiple overdoses.

Although overdose was obtained from one of the nation's largest healthcare records, this study has several limitations. Findings relied on patients seeking medical care for an overdose which could underestimate the true number of overdoses an individual experienced. Data collected was among the veteran population so results may not be generalizable to the general population or users of other health systems. Additional studies are needed to understand if these results hold true in other healthcare populations. Due to the limited scope of this analysis additional factors may be present which in turn increase the risk of repeat overdose and associated fatality. Finally this project only included overdoses that were documented by VHA clinician during the study period. It is possible that previous overdoses outside of the study period or those were otherwise undocumented were not captured. Inclusion of these may change distribution across categories or estimated conditional probabilities.

These results suggest the need for additional research, specifically examining potential unique risk factors for experiencing a repeat overdose. Given the rates of repeat overdose increased in a linear fashion, these findings suggest that healthcare systems should be ready for an influx in patients with opioid overdoses. Furthermore, these findings underscore the urgent need to expand overdose prevention efforts, such as naloxone distribution to patients with no history of an overdose.

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Tables and Figures

Table 1. Repeated opioid overdoses and subsequent mortality among patients between 2011-2015

No. of overdoses	No. of fatal OD	No. of OD^a	Conditional probability of repeated OD	95% CI of repeated event^a	Probability of overdose mortality	95% CI of mortality^a
One overdose	4,464	12,905			34.59	(33.77-35.42)
Two overdoses	30	2,716	21.05	(20.35-21.76)	1.10	(0.76-1.59)
Three overdoses	15	954	35.13	(33.33-36.96)	1.57	(0.92-2.64)
Four overdoses	8	396	41.51	(38.37-44.72)	2.02	(0.94-4.10)
More than 5 overdoses	4	171	43.18	(38.27-48.23)	2.34	(0.75-6.26)

Abbreviations: OD, overdose; CI, confidence interval; No., Number

a. Number of total overdoses indicate the total number of overdoses a patient experienced during the study period.

Figure 1. Mortality for each opioid overdose event recorded, 2011-2015

Abbreviations: CI, Confidence Interval

Chapter 4

4.1 Abstract

Objective

To identify cause-specific mortality rates and calculate standardized mortality rate ratios (SMRs) among veterans with a prior nonfatal opioid overdose.

Methods

We followed 8,370 veterans who received medical care for a nonfatal opioid overdose between January 1, 2011 and December 31, 2015 or date of death, whichever occurred first. Mortality records were extracted from the Department of Veteran Affairs (VA)/Department of Defense (DoD) Joint Suicide (all-cause) Data Repository (SDR) and linked to clinical records from the Veterans Health Administration (VHA). We compared the mortality rates among those with a nonfatal opioid overdose to a 5% stratified random sample of patients accessing services during the same time period (n=325,073). SMRs were calculated using age-adjusted cause-specific mortality rates for the general U.S. population obtained from the Centers for Disease Control and Prevention's Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER).

Results

The study cohort included 8,370 veterans with history of a nonfatal opioid overdose resulting in a total of 39,207 person-years of follow-up. The crude mortality for veterans with a history of a nonfatal overdose was 370.6 per 10,000 person years and SMR was 26.2 (95% CI [confidence interval]: 24.6-27.6). The most common causes of death among these veterans of interest were deaths associated with the circulatory system (26.7%), cancer (19.3%), deaths associated with the respiratory system (13.1%) and drug-related deaths (11.6%). Those with a prior nonfatal overdose had a higher risk of substance-related mortality (aHR [adjusted Hazard Ratio] 5.0, 95%

CI 4.4-5.8), including a higher risk of death from drugs (aHR 6.9; 95% CI 5.8-8.1) and alcohol (aHR 2.7, 95% CI 2.1-3.6). For cause-specific mortalities assessed between veterans and the general U.S. population, SMRs were also highest for deaths associated with substances (114.0, 95% CI 98.8-128.7), including drugs (139.3, 95% CI 118.6-160.7) and alcohol (72.7, 95% CI 53.5-92.4). As expected, SMRs for viral hepatitis (107.4, 95% CI 65.5-152.7) and liver cancers (68.2, 95% CI 47.9-88.7) were substantially higher when compared to rates for these outcomes in the U.S. general population. Other cause-specific diseases that were elevated included suicide (29.0, 95% CI 20.0-38.2) and HIV (34.9, 95% CI 10.7-58.9). Deaths related to the digestive system (45.2, 95% CI 36.7-53.7) and respiratory system (35.4, 30.4-40.4) were also markedly higher than the general population.

Conclusion

Veterans with a prior nonfatal overdose experienced a substantially higher mortality rate when compared to other veterans or the general U.S. population. Specific causes of death that were significantly higher include those related to substance use and mental health, highlighting the importance of integrated treatment and recovery services for patients with record of one or more opioid overdose. The significant increase in suicide deaths among veterans, especially among those with history of a prior overdose, supports the need for continued mental health screenings. These findings highlight the need for additional research examining substance use, in particular polysubstance use and associated risk for subsequent mortality among persons with history of one or more nonfatal overdose. Future research should consider whether associations identified in these analyses are different for patients from other health care systems or for those without history of U.S. military service.

4.2 Introduction

Overdoses have surged in the past decade and are now the leading cause of accidental death in the United States. More than 60% of overdose deaths across the nation can be attributed to opioids[1] [2-5]. Between 2007 and 2017 the opioid overdose death rate more than doubled, from 6.1 per 100,000 to 14.9 per 100,000 [6]. Around the same time, nonfatal opioid overdoses resulting in inpatient and emergency department visits substantially increased, by more than 60% and 99% respectively[7]. The rise in opioid overdoses across the United States has been estimated to cost more than \$740 million annually [8]. Despite the recent surge of nonfatal overdoses and associated mortality associated with opioid abuse/misuse, little is known regarding the patterns of mortality following a nonfatal opioid overdose.

People who inject drugs (PWID), people diagnosed with an opioid use disorder (OUD) and those taking more than 90 morphine milligram equivalent (MME) are at highest risk for experiencing an opioid overdose [9-12]. Although overdoses are the leading cause of death among PWID, research has found that PWID more often die from infection-related causes such as human immunodeficiency virus (HIV), Hepatitis C (HCV), and other substance-related deaths [13-15]. Similarly, research suggests that people with an OUD more often die from infectious disease and liver disease when compared to the general population [13, 16]. Patients taking a high volume of MME are often suffering from terminal cancer or chronic diseases associated with severe pain [9, 12, 17]. Several public health interventions have been developed to encourage safer prescribing practices and educate patients on opioid use, especially for those with high MME such as those with chronic non-cancer pain [9, 18]. Although many of these programs have been found to reduce the supply of prescription opioids [11], there is still little known regarding the complex nature of overdose and subsequent mortality. Research among Medicaid enrollees

suggests that mortality following a nonfatal overdose are often associated with substances, suicide, cancer, and the circulatory system however, cause-specific mortality among veterans using VHA services has yet to be examined [19]. The overarching objective of this study is to assess the cause specific mortality among veterans with a documented nonfatal opioid overdose. In order to describe the mortality for specific causes of deaths among veterans with a nonfatal overdose, we will examine the mortality following a nonfatal overdose to a comparison group comprised of a 5% random sample of other veterans using VHA services. We will then compare the mortality among veterans with a nonfatal opioid overdose to the general population.

Given previous research examining mortality among veterans with an OUD, we expected substance-related deaths to be significantly higher among this population [13, 16, 19-21]. We also expected suicide death rates to be substantially higher given that veterans have almost double the suicide death rate than the general population and previous research suggest that people with a history of a nonfatal overdose had higher suicide death rates [19, 22, 23].

Similarly, we expected deaths attributed to hepatitis to be significantly higher among our veteran cohort, given that prevalence of hepatitis is two-times higher than non-veterans and is higher among those with a history of drug use [13, 16, 24-26].

4.3 Methods

In order to determine mortality following a nonfatal overdose among veterans, we examined causes of death linking clinical and mortality files from the Veterans Health Administration (VHA), which is the largest integrated healthcare provider in the United States. We extracted records on individuals with a documented opioid overdose between January 1, 2011 and September 30, 2015 and identified corresponding causes of death, if any, among this cohort.

The study cohort examined clinical and death records for 10,522,835 records to identify veterans with a documented opioid overdose and veterans with no documented overdose for the comparison group. Veterans were identified as having an opioid overdose using clinical records from the VHA Corporate Data Warehouse (CDW)[27]. CDW records were linked with the VA/DoD Suicide Data Repository, using Social Security Numbers (SSNs)[28, 29]. Sex and age were extracted from the SDR and CDW. Age was fixed and determined at the start of the study period. Age-adjusted mortality rates for each cause of death of interest were pulled from the Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER) Detailed Compressed Mortality Files from 2011 through 2015 [6]. To more precisely compare age-adjusted mortality rates with the veteran population we pulled age-adjusted rates among 15-84 year old U.S. residents using CDC WONDER.

This study was reviewed and approved by the Institutional Review Board at the Syracuse VA Medical Center, New York.

Study sample

A nonfatal opioid overdose was identified using International Classification of Disease, Ninth Edition (ICD-9) codes: 965.00-965.02, 965.09, E850.0-E850.2 and ICD Tenth Edition (ICD-10) codes: X40-X44, X60-X64, X85, Y10-Y14 with secondary axis codes: T40.0-T40.4 and T40.6. The first opioid overdose documented in the clinical records was used as the index overdose. Those who died from a fatal index overdose were excluded from analyses.

A control group was constructed by extracting a 5% random sample of veterans, stratified by sex and age. Age was collapsed into three categories: ages 18-44, 45-64 and over 65 years old.

Pulling a stratified random sample allowed the control group to be similar in composition to

those with a nonfatal overdose[30]. Given that VHA users are primarily older males, we intentionally stratified by sex and age to reduce potential bias that may influence observed mortality among the control group. The use of stratified random sample control populations has been used in previous research among the VHA patient population [20, 31, 32].

Exclusion criteria

The study cohort was restricted to veterans between 18 and 90 years old. We excluded patients that had no follow-up visits within one year of the first overdose event or had a nonfatal overdose in the last three months of the study period (October 1, 2015 - December 1, 2015). This mitigated potential bias among those with less than three months of risk for mortality. After applying this inclusion and exclusion criteria, 8,370 veterans were identified for the nonfatal overdose group and 325,073 veterans with no documented overdose as the comparison group.

Mortality

We evaluated mortality from January 1, 2011 through December 31, 2015. Follow-up for the study ended the day the veteran died or the end of the study period, whichever occurred first. In addition to all-cause mortality, cause-specific mortality was considered for the following: all external causes of death, suicide, homicide, accidents, substance-related deaths, drug-related deaths, alcohol-related deaths, infectious, viral hepatitis, human immunodeficiency virus (HIV), circulatory system, respiratory system, influenza, chronic respiratory disease, digestive system, cirrhosis and alcoholic liver disease and cancers. Specific types of cancers were categorized into the following groups using the International Classification of Diseases for Oncology[33]: lung and bronchus, liver and intrahepatic bile duct, digestive system cancers, which included esophageal, stomach, small intestine, colon, rectal, anal, gallbladder and pancreatic cancers,

lymphoma and leukemia and other cancers. (See Supplement Table 1 for the full list of cause-specific mortality and corresponding ICD-10 codes).

Analysis

We identified person-years of follow-up and mortality rates per 10,000 person-years for the entire cohort to compare mortality among veterans with a history of nonfatal overdose to a comparison group of veterans. Crude death rates were calculated and mortality rates were estimated using Cox proportional hazard models, adjusting for age and sex. Survival curves were relatively close, indicating the hazard ratio remained constant over time [34]. Adjusted hazard ratios [aHR] and corresponding 95% confidence interval [CI] were calculated for cause-specific mortality.

We calculated the standardized mortality rate ratios (SMRs) to compare the observed number of deaths among our overdose cohort to the number of expected number based on rates of mortality among members of the U.S. general population [35, 36]. The expected number of deaths was calculated using age-adjusted mortality rates from CDC WONDER and corresponding cohort size[6].

Alpha was set to 0.05 for all statistical tests. We analyzed data using SAS Enterprise Grid software (version 5.1, SAS Institute Inc.).

4.4 Results

This study identified 8,370 veterans with a history of nonfatal opioid overdose and a total follow-up of 39,207 person-years. Among this cohort of veterans with history of a nonfatal overdose, approximately 17.4% (n=1,453) experienced death during the follow-up period. The proportion of veterans who died following a nonfatal overdose was similar to the proportion of veterans

who died in the control group (17.6%, n=57,099). Despite the similar proportion of deaths among each group, there were distinct differences in cause-specific mortality rates and corresponding SMRs. The overall crude mortality rate for veterans with a prior overdose was 370.6 per 10,000 person-years and for the control group was 384.1 per 100,000 person-years. Compared to the control group, veterans with a nonfatal opioid overdose had a higher risk of all-cause mortality after adjusting for age and gender (aHR 1.5; 95% CI 1.4-1.5). (Table 1)

The most common causes of death among veterans with a prior nonfatal overdose were disorders of the circulatory system (26.7%), cancer (19.3%), respiratory disorders (13.1%), and drug-related deaths (11.6%). The veteran cohort with a prior nonfatal overdose was more than six times likely to die from substance-related diseases (aHR [Adjusted Hazard Ratio] 5.0, 95% CI [Confidence Interval]: 4.4-5.8) and more than six times (aHR 6.9, 95% CI 5.8-8.1) likely to die from drug-related diseases compared to their veteran peers. These veterans were more than three times as likely to die from hepatitis (aHR 3.2, 95% CI: 2.1-4.9) and cirrhosis or alcoholic liver disease than their veteran peers (aHR 3.1, 95% CI: 2.4-3.9). Veterans with a prior overdose were also more than two times more likely to die from suicide than their veteran peers (aHR 2.2, 95% CI: 1.6-3.1). Further, these veterans were twice as likely to die of diseases associated with the digestive system (aHR 2.3, 95% CI: 1.9-2.8), chronic respiratory disease (aHR 2.2, 95% CI: 1.6-3.1) and HIV (aHR 2.6, 95% CI: 1.3-5.4).

Similarly, they had an elevated risk of death from viral hepatitis (aHR 3.2, 95% CI 2.1-4.9) and cirrhosis and alcoholic liver disease (aHR 3.1, 95% CI 2.4-3.9). These veterans had a higher risk of death attributed to HIV (aHR 2.6, 95% CI 1.3-5.4), cancer of the liver or intrahepatic bile duct (aHR 2.3, 95% CI 1.7-3.2), or death associated with the digestive system (aHR 2.3, 95% CI 1.9-2.8). Of note, death from suicide was markedly higher among veterans with a prior

nonfatal overdose compared to the control group of veterans (aHR 2.2, 95% CI 1.6-3.1).

Conversely, veterans with history of an overdose were significantly less likely to die from lymphoma or leukemia (aHR 0.5, 95% CI 0.2-0.9) compared to veterans in the control group.

Among cause-specific mortalities assessed and compared to the US population, SMRs were more than eight times higher among veterans with a prior overdose. SMRs were highest for deaths associated with substances (114.0, 95% CI: 98.8-128.7); including drugs (139.3, 95% CI: 118.6-160.7) and alcohol (72.7, 95% CI: 53.5-92.4). SMRs for viral hepatitis (107.4, 95% CI: 65.5-152.7) and liver cancers (68.2, 95% CI: 47.9-88.7) were substantially higher among veterans with history of a nonfatal opioid overdose. Other cause-specific disease that were elevated in this population include HIV (34.9, 95% CI: 10.7-58.9), suicide (29.0, 95% CI: 20.0-38.2), and deaths related to the digestive system (45.2, 95% CI: 36.7-53.7). (Table 2)

4.5 Discussion

Veterans with a documented nonfatal opioid overdose died at 26 times the rate of the general U.S. population aged 15-84 years. Moreover, mortality was markedly higher among veterans with a prior nonfatal overdose when compared to a comparison population of veterans who use VHA services or the general U.S. population (aHR 1.46, 95% CI: 1.39-1.54). These findings suggest that excess mortality among veterans with a prior nonfatal overdose may be associated with patterns and consequences of substance use. Mortality associated with substance use for veterans with a prior nonfatal overdose was significantly elevated among those with a prior nonfatal overdose. The rate of alcohol-related deaths was 72 times higher than the rate of alcohol-related deaths in the general population.

Similarly, veterans with a prior nonfatal overdose had noticeably higher rates of death compared to other veterans, specifically for deaths associated with drugs (aHR 6.85 95% CI: 5.79-8.09), viral hepatitis (aHR 3.22, 95% CI: 2.11-4.93), cirrhosis and alcoholic liver disease (aHR 3.05, 95% CI 2.38-3.90). These findings suggest excess mortality among veterans with a nonfatal overdose can be largely attributed to substance abuse. Although deaths associated with substance use accounted for a majority of deaths, disease of the digestive and respiratory system were elevated in this population as well. Additional research is need to understand the intersection of certain comorbidities related to the digestive system and overdose risk.

There were some distinct differences when comparing results from this study to an existing study examining mortality following a nonfatal overdose among a sample of Medicaid enrollees [19]. The all-cause SMR and drug-related deaths were similar between both the veteran population and Medicaid enrollees. In general, the cause-specific deaths listed in both studies were elevated among the veteran population and HIV was the only cause-specific death in both studies that was lower among the Medicaid population. The most notable difference in our study was the SMR for alcohol-related deaths, the veteran population had an SMR more than seven times higher than the study article. Deaths associated with cirrhosis and alcoholic liver disease were more than four times higher and deaths associated with viral hepatitis were more than three times higher. This finding may be attributed to high rates of HCV among veterans from the Vietnam Era [24-26].

These findings parallel previous research suggesting a deeper understanding of the complex relationship between overdose and self-harm [23, 37-39]. Importantly, deaths from suicide were markedly higher among our cohort of veterans with a prior opioid overdose compared to the general population and a random sample of veterans from the VHA using population. This finding alone suggests the need for continued support and comprehensive services aimed at

reducing suicide among veterans. Mental health services, such as post-discharge psychiatric care may benefit patients with history a nonfatal overdose [40-42]. A documented overdose may provide opportunities to initiate treatment or other prevention programs such as naloxone distribution or provide mental health screening given the elevated mortality associated with suicide and substance-related deaths.

Strengths and limitations

Although this study utilized data from one of the nation's largest healthcare networks, analyses were contingent on patients seeking medical care for healthcare needs such as an overdose. The large sample size provided the statistical power needed to detect differences in risk for mortality. Despite the large sample size, this study had several limitations. Previous studies have shown that barriers often impede healthcare treatment for OUD, which could influence findings from this study[43]. Results from this study may underestimate the magnitude of nonfatal overdoses and subsequent mortality among veterans[44]. Furthermore, these results may not be generalizable to the US population given the heterogeneous composition of veterans seeking healthcare [45-47].

Conclusion

Given the rise in opioid overdoses across the US, there is an urgent need to understand excess mortality among people who experience a nonfatal overdose to inform future clinical and public health efforts. Veterans with a history of nonfatal overdose are significantly more likely to die from any cause, specifically deaths associated with substance use and suicide. Additional research is needed to determine the relationship between psychiatric diagnoses, substance use

and overdose risk over time. These findings underscore the need for coordinated health care, with particular emphasis on mental health care among those with a prior overdose.

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Tables and Figures

Table 1. Mortality rate (per 10,000 person-years) among veterans with a nonfatal index OD (n=8,370) compared to a 5% stratified random sample of veterans (n=325,073) ^a

Cause of death	Nonfatal OD		Control group		Hazard ratio of mortality	95% CI Hazard Ratio	Adjusted Hazard ratio of mortality ^b	95% CI Adjusted Hazard Ratio ^b	p-value
	No. of deaths	Crude mortality rate	No. of deaths	Crude mortality rate					
Opioid overdose	59	15.05	-	-	-	-	-	-	-
External Cause of death	69	17.60	1,509	10.15	1.74*	(1.36-2.21)	1.82*	(1.43-2.32)	<0.001
<i>Suicide</i>	39	9.95	651	4.38	2.27*	(1.65-3.14)	2.24*	(1.62-3.10)	<0.001
<i>Homicide</i>	5	1.28	98	0.66	1.93	(0.79-4.75)	1.71	(0.70-4.23)	0.24
<i>Accidents</i>	25	6.38	760	5.11	1.25	(0.84-1.86)	1.43	(0.96-2.13)	0.08
Substance-related	223	56.88	1,474	9.91	5.74*	(4.98-6.61)	5.03*	(4.36-5.80)	<0.001
<i>Drug-related</i>	169	43.10	871	5.86	7.36*	(6.24-8.68)	6.85*	(5.79-8.09)	<0.001
<i>Alcohol-related</i>	54	13.77	603	4.06	3.40*	(2.57-4.49)	2.73*	(2.06-3.61)	<0.001
Infectious	55	14.03	1,393	9.37	1.50*	(1.14-1.96)	1.89*	(1.44-2.49)	<0.001
<i>Viral hepatitis</i>	24	6.12	203	1.37	4.48*	(2.94-6.84)	3.22*	(2.11-4.93)	<0.001
<i>HIV</i>	8	2.04	83	0.56	3.66*	(1.77-7.56)	2.63*	(1.27-5.44)	0.01
Circulatory system	388	98.96	18,312	123.17	0.80*	(0.73-0.89)	1.29*	(1.16-1.42)	<0.001
Respiratory system	191	48.72	6,730	45.27	1.08	(0.93-1.24)	1.87*	(1.61-2.16)	<0.001
<i>Influenza & pneumonia</i>	23	5.87	1,219	8.20	0.72	(0.47-1.08)	1.32	(0.87-2.00)	0.19
<i>Chronic respiratory disease</i>	139	35.45	4,051	27.25	1.30*	(1.10-1.54)	2.18*	(1.83-2.58)	<0.001
Digestive system	109	27.80	2,036	13.69	2.03*	(1.68-2.46)	2.27*	(1.87-2.75)	<0.001
<i>Cirrhosis & alcoholic liver disease</i>	70	17.85	763	5.13	3.48*	(2.72-4.44)	3.05*	(2.38-3.90)	<0.001
Cancers	280	71.42	14,585	98.10	0.73*	(0.65-0.82)	1.00	(0.88-1.12)	0.97
<i>Lung & bronchus</i>	80	20.40	4,347	29.24	0.70*	(0.56-0.87)	0.90	(0.72-1.13)	0.38
<i>Liver & intrahepatic bile duct</i>	43	10.97	699	4.70	2.33*	(1.71-3.17)	2.31*	(1.69-3.16)	<0.001
<i>Digestive system</i>	42	10.71	2,780	18.70	0.57*	(0.42-0.78)	0.77	(0.57-1.05)	0.09
<i>Lymphoma & leukemia</i>	9	2.30	1,116	7.51	0.31*	(0.16-0.59)	0.47*	(0.24-0.90)	0.03
<i>Other cancers</i>	106	27.04	5,643	37.96	0.71*	(0.59-0.86)	1.06	(0.88-1.29)	0.55
Any type of death	1,453	370.59	57,099	384.06	0.97	(0.92-1.02)	1.46*	(1.39-1.54)	<0.001

Abbreviations: No, Number; CI, Confidence Interval; SMR, Standardized Mortality Rate Ratio; OD, overdose; HIV, human immunodeficiency virus

a. For those with a nonfatal OD there were 39,207 person-years follow-up. A control group was constructed using a 5% random sample of veterans, stratified by sex and age stratum.

b. Adjusted for age and sex.

Table 2. Standardized Mortality Ratios, observed, and expected number of deaths for veterans with a nonfatal index overdose for all causes and selected causes, 2011-2015

Cause of death	Nonfatal OD		US Age-adjusted rates ^a	Standardized Mortality Rate Ratio (95% CI)	
	No. of deaths	Crude mortality rate	Expected number of deaths ^b	SMR ^b	95% CI
Opioid overdose	59	15.05	0.91	64.73	(48.29-81.38)
External Cause of death	69	17.60	4.19	16.47	(12.58-20.35)
<i>Suicide</i>	39	9.95	1.34	29.01	(19.97-38.24)
<i>Homicide</i>	5	1.28	0.54	9.25	(1.14-17.38)
<i>Accidents</i>	25	6.38	2.30	10.85	(6.61-15.13)
Substance-related	223	56.88	1.96	113.96	(98.84-128.71)
<i>Drug-related</i>	169	43.10	1.21	139.25	(118.62-160.73)
<i>Alcohol-related</i>	54	13.77	0.74	72.65	(53.51-92.44)
Infectious	55	14.03	1.65	33.36	(24.52-42.14)
<i>Viral hepatitis</i>	24	6.12	0.22	107.39	(65.45-152.74)
<i>HIV</i>	8	2.04	0.23	34.88	(10.68-58.89)
Circulatory system	388	98.96	15.27	25.41	(22.88-27.94)
Respiratory system	191	48.72	5.40	35.40	(30.35-40.39)
<i>Influenza & pneumonia</i>	23	5.87	0.94	24.45	(14.47-34.47)
<i>Chronic respiratory disease</i>	139	35.45	3.35	41.48	(34.59-48.39)
Digestive system	109	27.80	2.41	45.15	(36.74-53.72)
<i>Cirrhosis & alcoholic liver disease</i>	70	17.85	1.07	65.29	(50.09-80.75)
Cancer	280	71.42	15.29	18.32	(16.17-20.46)
<i>Lung & bronchus</i>	80	20.40	4.17	19.20	(14.98-23.39)
<i>Liver & intrahepatic bile duct</i>	43	10.97	0.63	68.23	(47.85-88.65)
<i>Digestive system</i>	42	10.71	3.14	13.36	(9.33-17.42)
<i>Lymphoma & leukemia</i>	9	2.30	1.06	8.47	(2.94-14.04)
<i>Other cancers</i>	106	27.04	6.14	17.27	(13.98-20.55)
Any type of death	1,453	370.59	55.41	26.22	(24.87-27.57)

Abbreviations: No, Number; CI, Confidence Interval; SMR, Standardized Mortality Rate Ratio

a. Mortality for US population was from the Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research data (CDC WONDER).

b. Mortality rates and expected counts is by using age-adjusted mortality rates among 15-84 year olds.

Supplemental Table ICD-10 Codes for cause-specific mortality

Cause of death	ICD-10 Codes For Underlying Cause of Death
Opioid overdose	X40-X44, X60-X64, X85, Y10-Y14 with secondary axis codes T40.0-T40.4, T40.6
External Cause of death	X60-X84, Y87.0, X85-Y09, Y87.1, V01-X39, X46-X59, Y85-Y86
<i>Suicide</i>	X60-X84, Y87.0
<i>Homicide</i>	X85-Y09, Y87.1
<i>Accidents</i>	V01-X39, X46-X59, Y85-Y86
Substance-related	F11.0-F11.5, F11.7-F11.9, F12.0-F12.5, F12.7-F12.9, F13.0-F13.5, F13.7-F13.9, F14.0-F14.4, F14.7-F14.9, F15.0-F15.5, F15.7-F15.9, F16.0-F16.5, F16.7-F16.9, F17.0, F17.3-F17.5, F17.7-F17.9, F18.0-F18.5, F18.7-F18.9, F19.0-F19.5, F19.7-F19.9, X40-X44, Y10-Y14, F10, G31.2, G62.1, I42.6, K29.2, K70, R78.0, X45, Y15
<i>Drug-related</i>	F11.0-F11.5, F11.7-F11.9, F12.0-F12.5, F12.7-F12.9, F13.0-F13.5, F13.7-F13.9, F14.0-F14.4, F14.7-F14.9, F15.0-F15.5, F15.7-F15.9, F16.0-F16.5, F16.7-F16.9, F17.0, F17.3-F17.5, F17.7-F17.9, F18.0-F18.5, F18.7-F18.9, F19.0-F19.5, F19.7-F19.9, X40-X44, Y10-Y14
<i>Alcohol-related</i>	F10, G31.2, G62.1, I42.6, K29.2, K70, R78.0, X45, Y15
Infectious	A00-B99
<i>Viral hepatitis</i>	B15-B19
<i>HIV</i>	B20-B24
Circulatory system	I00-I99
Respiratory system	J00-J98
<i>Influenza & pneumonia</i>	J09-J18
<i>Chronic respiratory disease</i>	J40-J47
Digestive system	K00-K92
<i>Cirrhosis & alcoholic liver disease</i>	K70, K73-74
Cancer	C00-D48
<i>Lung & bronchus</i>	C34
<i>Liver & intrahepatic bile duct</i>	C22
<i>Digestive system</i>	C15-C21, C23-C26
<i>Lymphoma & leukemia</i>	C82-C85, C91-C95
<i>Other cancers</i>	C00-C14, C27-C33, C35-C81, C86-C90, C96-D48

Abbreviations: ICD-10, *International Classification of Diseases, Tenth Edition*

Chapter 5

5.1. Summary

This retrospective cohort study consisted of 13,333 patients with a documented opioid overdose, of any type, from January 1, 2011 to December 31, 2015. Among our cohort, 4,949 persons experienced a fatal overdose during the study period. Of note, we found that mortality from an opioid overdose was highest for an individual's index (i.e. first recorded in the electronic medical record) overdose (98.8%, n=4,890), with only 1.2% (n=59) dying on a repeat overdose. Of those who survived their first overdose, 31.5% (n=2,659) had one or more repeat overdoses. Among those with a repeat overdose, we found that the conditional probability of repeat overdose increased in a linear fashion with the number of additional overdoses in the patient's medical records. In other words, the probability of having a fourth overdose was higher than the probability of having either a third or second overdose.

Although the U.S. has been experiencing an increase in overdoses for more than a decade there is still a limited understanding of risk for repeat overdose or whether factors associated with increased risk for repeat overdose are also associated with risk for overdose mortality. To answer these questions, we identified and compared risk factors for different overdose outcomes, including repeat overdose, available in VHA's electronic health record.

Patients between the ages of 18-64 years were the most likely to have record of a repeat overdose or fatal index overdose compared to those with record of only one non-fatal overdose. Men were more likely than women to die on their index overdose when compared to either repeat or single non-fatal overdose. (OR [odds ratio] 1.57, 95% CI [confidence interval]: 1.34-1.83). Similarly, those with a chronic pain diagnosis were more likely to experience either a repeat overdose (OR 1.15, 95% CI: 1.04-1.27) or fatal index overdose (OR 3.96, 95% CI: 3.56-4.42), when compared to those with report of only one non-fatal overdose. Surprisingly, we found that patients with a

mental health and substance abuse/dependence diagnosis were more likely to experience a repeat overdose and were less likely to die from a fatal index overdose. We also identified associations between patients receiving counseling prior to an overdose and lower likelihood of experiencing a fatal overdose (OR 0.35, 95% CI: 0.30-0.40) and those who had been in MAT more than one year prior were more likely to experience a fatal index overdose (OR 1.28, 95% CI: 1.05-1.55). Neither of these factors were significantly associated with repeat overdose.

Among those with a non-fatal overdose during the study period, we identified significantly increased rates for all-cause mortality when compared to risk for death among other veterans receiving VHA services. Veterans with record of a non-fatal overdose were five times (aHR 5.03, 95% CI: 4.36-5.80) more likely to die from substance-related deaths than their veteran peers. Furthermore, they were more than three times as likely to die from viral hepatitis (aHR 3.22, 95% CI: 2.11-4.93) or cirrhosis and alcohol-related liver disease (aHR 3.05, 95% CI: 2.38-3.90). Despite the higher rate of suicide among veterans who use VHA services [1-3], those with a history of an opioid overdose were twice (aHR 2.24, 95% CI: 1.62-3.10) as likely to die from suicide as their veteran peers who also used VHA services.

Standardized mortality rate ratios (SMR) were calculated to identify differences in the number of observed deaths to the number of expected deaths for cause-specific mortality in the general U.S. population. Of the categories examined, veterans with a non-fatal overdose died at more than 139 times the rate of drug-related deaths, more than 114 times the rate for substance-related deaths and more than 72 times the rate for alcohol-related deaths than the general U.S. population. Moreover, veterans with a history of an opioid overdose died at more than 100 times the rate from viral hepatitis, more than 68 times the rate of liver and intrahepatic bile duct cancer, and more than 65 times the rate for cirrhosis and alcoholic-related liver disease than the general

population. Overall, we found that veterans with a history of non-fatal overdose died at approximately 26 times the rate of all-cause mortality than observed in the general population. Overall, these findings highlight the need for additional public health and clinical interventions for those at risk of overdose. Prevention programs designed to reduce opioid overdose mortality should focus on primary prevention efforts, such as reaching veterans who may not have been identified as having a substance abuse or dependence problem and should tailor these programs to engage veterans who are young to middle aged adults. These findings suggest healthcare providers and health system administrators should prepare for a rise in patients with repeat overdose history and should work to coordinate these patients with mental and physical health care as needed. Lastly, these findings suggest a need to address excess mortality risk among people with a history of non-fatal overdose. Findings from this project describe the magnitude of excess mortality among people with a history of a non-fatal overdose, especially causes of death related to substances; including drugs or alcohol.

5.2 Significance

In the United States, the opioid overdose death rate nearly doubled in four years between 2013 to 2017 (7.9 to 14.0 per 100,000), highlighting the urgent need to understand ways public health and clinical efforts can address rising morbidity and mortality associated with opioid abuse and misuse [4-9]. This study sought to identify the potential differences in risk for non-fatal, repeated and fatal overdose, which are all of growing concern. To date, little is known about the magnitude of repeat overdoses that occur within a clinical setting and the overdose event that is associated with the highest overdose mortality.

Understanding risk factors for fatal overdose and repeat overdose can inform public health and clinical efforts to combat the rise in mortality and morbidity associated with opioid overdoses.

The project specifically assessed the number of non-fatal overdoses and risk for mortality or repeated events. Results from this project parallel findings from previous research, which suggests the need for additional mental health programs and treatment for those who experience an opioid overdose. These findings also underscore the need to amplify primary prevention efforts targeted to those who may not have experienced a previous overdose, specifically those between the ages of 18 and 64 years.

This study was not without limitations. First, we were only able to examine opioid overdoses that were documented in VHA's clinical or mortality records. It is possible that the true number of opioid overdoses among this patient population was underestimated. Moreover, patients may have sought health services not associated with VHA, which could also bias results and limit consideration of associated characteristics. This study was conducted using data from veterans using VHA healthcare services, who often report a greater number of physical and mental health conditions compared to the general population [10, 11]. It is possible that patients with different physical and mental health comorbidities are associated with differential patterns of health care services and likelihood that overdose history is assessed and recorded. These analyses were conducted among patients seeking medical care which could lead to Berksonian bias, due to the difference in overall health among populations studied [12]. However, using comparison groups and stratifying by potential confounding features such as sex and age aided to reduce potential bias that may occur. Lastly, using clinical records with mortality files could have resulted in missed deaths resulting in an underestimate of true mortality. However, records were required to match fully on SSN and 80-90% on additional demographics such as name, date of birth, and sex [2, 13, 14]. Diagnostic codes in clinical records are not always a true representation the number of patients meeting diagnostic criteria. Clinical records are reliant on medical professionals

inputting them into the electronic health records therefore certain diagnostic codes, in particular the social codes, may be underutilized and lead to an underestimate in the patient population [15, 16].

Although this study used clinical records which have inherent limitations, to the best of our knowledge, this was the first study to explore multiple overdose outcomes and compare risk factors for category of overdose using a comprehensive list of potential medical and contextual characteristics including demographic, chronic pain diagnoses, mental health diagnoses, and social codes, which served as indicators of social determinants of health. Findings from this study could be useful in informing clinical tools developed by the VA, such as a clinical dashboard, which is used to identify patients at risk for an adverse event related to opioids, by integrating contextual factors that may increase a patients risk for experiencing an overdose [17-20].

5.3 Future research

These results indicate the need for additional research, specifically among those with co-occurring mental health and substance use disorders. While there are many public health interventions aimed at reducing the morbidity and mortality associated with overdoses, they have primarily focused on reducing the excess supply of prescription opioids. While some public health prevention efforts have demonstrated a reduction in overdose death, such as the implementation of prescription drug monitoring programs or the development of chronic pain guidelines, some researchers suggest this has pushed individuals to seek more potent non-prescription opioid options increasing risk for overdose morbidity and mortality [21-23]. Furthermore, public health and clinical interventions have been primarily developed to reduce the supply of opioids rather than reducing demand. Additional research is needed on initiation of

substance abuse and misuse and motivation for initial misuse. Findings from this study suggest that additional comorbidities, specifically mental health comorbidities, may be the underlying factors driving the current overdose crisis and in turn may be factors associated initial misuse or abuse. While safer prescribing practices are necessary to mitigate initial abuse or misuse, a high-level of stigma is present among people with an opioid use disorder (OUD) [24, 25]. Stigma-reduction is essential in supporting individuals with a history of substance abuse or dependence, including reducing the stigma surround seeking treatment for the disease [26]. Although there is a prolific amount of research showing the effectiveness of Medication-Assisted Treatment (MAT) for OUD, additional barriers often impede patients from receiving necessary treatment. Infrastructure barriers such as provider willingness and access to providers who can prescribe MAT often deter patients from receiving treatment [20, 26-28]. Given our findings, which show that mortality is highest for the first documented overdose, there is an urgent need to remove potential barriers that may impede patients from seeking medical resources needed.

Future studies should also examine the conditional probability of repeat overdose and identify the overdose event that is associated with highest mortality in other populations. Furthermore, additional research is needed to elucidate the relationship between psychiatric comorbidities and overdose risk. Mental health diagnosis and related conditions, including substance abuse or dependence, are suggested to be the driving factors for the rise in opioid overdoses. Because of this, additional research is also needed to understand the best treatment for individuals with co-occurring mental health diagnoses or a history of polysubstance use.

5.4. Conclusions

Understanding risk of experiencing a fatal overdose or repeated overdose is necessary in order to curb the current rise in fatal and non-fatal overdoses. These findings underscore the need for

amplified prevention efforts targeted to those without a history of overdose. Furthermore, these results suggest that healthcare systems should be ready for a rise in the number of patients seen for a repeat overdose. While these results suggest that patients with a repeat overdose may be in need of additional clinical services, coordinated health care is needed among those with a prior overdose. In order to tackle this multifaceted issue, additional primary care services are needed in conjunction with mental health care to address the potential comorbidities among those with a documented or suspected overdose. In conclusion, this study demonstrates that opioid overdoses remain a significant public health problem with additional research needed however, the current public health crisis is not driven solely by opioids, rather this appears to be mental health needs and associated crises. Health systems, clinical health providers, and others seeking to decrease deaths resulting from opioid overdose, are encouraged to systematically assess for and intervene on symptoms associated with mental health disorders.

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APPENDIX A

Diagnostic codes used for opioid overdoses recorded in the EHR		
Type of overdose	ICD-9	ICD-10
Opioid overdose hospitalization	965.00 (Opium) 965.01 (Heroin) 965.02 (Methadone) 965.09 (Other opiates/narcotics) OR E850.0 (Accidental: Heroin) E850.1 (Accidental: Methadone) E850.2 (Accidental: Other opiates)	T40.0X Opium T40.1X Heroin T40.2X Other opioids T40.3X Methadone T40.4X Synthetic narcotics T40.60X Unspecified narcotics T40.69X Other narcotics And a 6th character of 1,2,3,or 4
Opioid overdose mortality		Underlying cause of death code: X40-X44 (accidental), X60-X64 (intentional/self-harm), X85 (assault/homicide), Y10-Y14 (undetermined) And a contribution cause of death code T40.0-T40.4, T40.6

Abbreviations: ICD-9, *International Classification of Diseases, Ninth Revision*; ICD-10, *International Classification of Diseases, Tenth Revision*; EHR, electronic health record

APPENDIX B

Variables of interest among veterans with an opioid overdose		
Characteristic	Variable	Related ICD codes
Sex	Sex (1=male, 0=female)	Used last entered value
Age	Age (Continuous)	Age as of January 1, 2011
Date of visit	V_date (in SAS date9. format)	Time period 01/01/2011-12/31/2015
<i>Psychosocial & related mental health diagnoses</i>		
Any mental health diagnosis	mh_dx (1=yes, 0=no)	ICD-9: 290.00 to 319.99, excluding tobacco codes starting with 305 ICD-10: F00 to F99, excluding tobacco codes starting with F17
Anxiety	anx_dx (1=yes, 0=no)	ICD-9: 300 ICD-10: F40, F41
Depression	dep_dx (1=yes, 0=no)	ICD-9: 296.2, 296.3, 300.4, 311 ICD-10: F32, F33, F34.1
Bipolar	bip_dx (1=yes, 0=no)	ICD-9: 296.0, 296.1, 296.4, 296.5, 296.6, 296.7, 296.8 ICD-10: F31
PTSD	ptsd (1=yes, 0=no)	ICD-9: 309.81 ICD-10: F43.1
Adjustment disorder	adj_dx (1=yes, 0=no)	ICD-9: 309.0, 309.24, 309.28, 309.3, 309.4, 309.9 ICD-10: F43.20- F43.25
Schizophrenia or other psychotic disorders	sch_dx (1=yes, 0=no)	ICD-9: 295.90, 295.40, 295.70, 297.1, 297.3, 298.8, 293.81, 293.82, 298.9 ICD-10: F20.9, F20.81, F25.0, F25.1, F22, F24, F23, F06.2, F06.0, F29)
Traumatic stress	trst_dx (1=yes, 0=no)	ICD-9: 308.9, 309.89, 309.9 ICD-10: F43.0 F43.8, F43.9
Personality disorder	per_dx (1=yes, 0=no)	ICD-9: 301.83, 301.7, 301.81, 301.50, 301.4, 301.82, 301.6, 301.0, 301.20, 310.1 301.9 ICD-10: F60, F61
Opioid abuse/dependence	op_dx (1=yes, 0=no)	ICD-9 codes: 304.0, 304.7, 305.5 ICD-10 codes: F11
Alcohol abuse/dependence	alc_dx (1=yes, 0=no)	ICD-9: 303, 305.0 ICD-10: F10
Cannabis abuse/dependence	can_dx (1=yes, 0=no)	ICD-9: 304.3, 305.2 ICD-10: F12
Sedative, hypnotics, or anxiolytic abuse/dependence	sha_dx (1=yes, 0=no)	ICD-9: 304.1, 305.4 ICD-10: F13
Cocaine abuse/dependence	coc_dx (1=yes, 0=no)	ICD-9: 304.2, 305.6 ICD-10: F14
Other stimulant abuse/dependence	stm_dx (1=yes, 0=no)	ICD-9: 304.4, 305.7 ICD-10: F15

Hallucinogen abuse/dependence	hal_dx (1=yes, 0=no)	ICD-9: 304.5, 305.3 ICD-10: F16
Any substance abuse/dependence	anysub_dx (1=yes, 0=no)	Any diagnosis for substance abuse/dependence
Polysubstance abuse/dependence	polysub_dx (1=yes, 0=no)	More than 1 diagnosis for substance abuse/dependence
TBI	tbi_dx (1=yes, 0=no)	ICD-9: 800.0-801.9, 803.0-804.9, 850.0-854.1, 950.1-950.3, 995.55, 959.01 ICD-10: S02.0, S02.1, S02.8, S02.91, S04.02, S04.03, S04.04, S06, S07.1, T74.4
Medication-Assisted Treatment (MAT)		
Record of MAT	MAT	Using stop code 523 (primary or secondary stop code) to identify MAT services
Chronic pain before index OD		
Back pain	b_pain (1=yes, 0=no)	ICD-9: 720.0-724.9 ICD-10: M45.9- M46.1, M46.90, M47.812, M47.12, M47.814, M47.817, M48.20, M48.10, M48.30, M48.9, M50.20, M51.9, M50.30, M51.34-M51.37, M48.02, M54.2, M53.0, M53.1, M54.12, M54.13, M43.6, M54.02, M67.88, M53.82, M54.6, M54.5, M54.30, M54.14-M54.17, M54.89-M54.9, M43.27, M43.28, M53.2X7, M53.3, M54.08, M43.8X9, M53.9
Arthritis	a_pain (1=yes, 0=no)	ICD-9: 710.0-739.9, excluding back pain codes ICD-10: M00-M02, M36.2, M36.3, M12, M35.3, M15, M16-M19, M05-M08, M1A, M10-M14
Migraines	m_pain (1=yes, 0=no)	ICD-9: 346.0-346.9 ICD-10: G43.0, G43.1, G43.4, G43.5, G43.6, G43.7, G43.8, G43.9, G43.A, G43.B, G43.C, G43.D
Headaches or tension headaches	h_pain (1=yes, 0=no)	ICD-9: 784.0 and 307.81 ICD-10: G44.1, R51, G44.209
Psychogenic	p_pain (1=yes, 0=no)	ICD-9: 307.80 and 307.89 ICD-10: F45.41, F45.42
Neuropathy	n_pain (1=yes, 0=no)	ICD-9: 355.0, 355.9, 356.0, 357.2, 357.9 ICD-10: G57.00, G58.9, G60, E08.42, E09.42, E10.42, E11.42, E13.42, G61.9
Fibromyalgia	f_pain (1=yes, 0=no)	ICD-9: 729.1 ICD-10: M60.9, M79.1, M79.7
Any chronic pain diagnosis	chr_dx (1=yes, 0=no)	Any of the diagnoses for chronic pain
Social determinants of health (SDoH) codes prior to index OD		
Problems related to housing and economic circumstances	Prob_econ (1=yes, 0=no)	ICD-9: V60.0, V60.1, V60.89, V60.6, V60.2, V60.9 ICD-10: Z59 (Z59.0-Z59.9)
Problems related to support group, including family and relationships	Prob_supp (1=yes, 0=no)	ICD-9: V61.0, V61.05, V61.8, V61.01, V61.06, V61.07, V61.08, V62.82, V61.03, V61.49, V61.02, V61.41, V61.3, V61.04, V61.09, V61.8, V61.9 ICD-10: Z63 (Z63.0-Z63.9)
Problems related to social environment	Prob_soenv (1=yes, 0=no)	ICD-9: V60.3, V62.4, V62.89 ICD-10: Z60.0, Z60.2, Z60.3, Z60.4, Z60.5, Z60.8, Z60.9

Problems related to upbringing	Prob_upbr (1=yes, 0=no)	ICD-9: V61.29, V61.8, V60.81 ICD-10: Z62.0, Z62.1, Z62.2, Z62.3, Z62.6, Z62.8
Problems related to environmental psychosocial circumstances	Prob_enpsych (1=yes, 0=no)	ICD-9: V62.5, V62.89, V62.81, V62.9 ICD-10: Z65.0, Z65.1, Z65.2, Z65.3, Z65.4, Z65.5, Z65.8, Z65.9
Problems related to abuse	Prob_abuse (1=yes, 0=no)	ICD-9: V61.21, V61.22, V62.83, V61.11, V61.12, V65.49 ICD-10: Z69.0, Z69.01, Z69.02, Z69.1, Z69.8
Counseling services	Prob_coun (1=yes, 0=no)	ICD-9: V65.49, V61.2, V61.1, V65.40, V65.9 ICD-10: Z71.81, Z71.89, Z71.9
Other problems related to mental and behavior	Prob_menbeh (1=yes, 0=no)	ICD-9: V40.0, V40.2, V40.3, V40.31, V40.39, V40.9 ICD-10: F48.9, F69
Any SDoH	any_sdoh (1=yes, 0=no)	Any of the above SDoH codes captured before index OD

Abbreviations: ICD, International Classification of Disease; ICD-9, International Classification of Disease, Ninth Edition; ICD-10, International Classification of Disease, Tenth Edition; PTSD, Post-traumatic stress disorder; TBI, Traumatic Brain Injury; MAT, Medication-Assisted Treatment; OD, overdose; SDoH, social determinant of health

APPENDIX C

Diagnostic codes used to classify indicators of social determinants of health		
Description	Description	ICD code
Problems related to housing and economic circumstances	<ul style="list-style-type: none"> • Homelessness • Inadequate housing • Discord with neighbors, lodgers and landlord • Problems related to living in residential institution • Lack of adequate food and safe drinking water • Extreme poverty • Low income • Insufficient social insurance and welfare support • Other problems related to housing and economic circumstances • Problem related to housing and economic circumstances, unspecified 	ICD-9: V60.0, V60.1, V60.89, V60.6, V60.2, V60.9 ICD-10: Z59 (Z59.0-Z59.9)
Problems related to support group, including family and relationships	<ul style="list-style-type: none"> • Problems in relationship with spouse or partner • Problems in relationship with in-laws • Absence of family member • Disappearance and death of family member • Disruption of family by separation and divorce • Dependent relative needing care at home • Other stressful life events affecting family and household • Other specified problems related to primary support group • Problems related to primary support group, unspecified 	ICD-9: V61.0, V61.05, V61.8, V61.01, V61.06, V61.07, V61.08, V62.82, V61.03, V61.49, V61.02, V61.41, V61.3, V61.04, V61.09, V61.8, V61.9 ICD-10: Z63 (Z63.0-Z63.9)
Problems related to social environment	<ul style="list-style-type: none"> • Problems of adjustment to life-cycle transitions • Problems related to living alone • Acculturation difficulty • Social exclusion and rejection • Target of (perceived) adverse discrimination and persecution • Other problems related to social environment • Problem related to social environment, unspecified 	ICD-9: V60.3, V62.4, V62.89 ICD-10: Z60.0, Z60.2, Z60.3, Z60.4, Z60.5, Z60.8, Z60.9

Problems related to upbringing	<ul style="list-style-type: none"> • Inadequate parental supervision and control • Parental overprotection • Upbringing away from parents • Hostility towards and scapegoating of child • Inappropriate (excessive) parental pressure • Other specified problems related to upbringing 	ICD-9: V61.29, V61.8, V60.81 ICD-10: Z62.0, Z62.1, Z62.2, Z62.3, Z62.6, Z62.8
Problems related to environmental psychosocial circumstances	<ul style="list-style-type: none"> • Conviction in civil and criminal proceedings without imprisonment • Imprisonment and other incarceration • Problems related to release from prison • Problems related to other legal circumstances • Victim of crime and terrorism • Exposure to disaster, war and other hostilities • Other specified problems related to psychosocial circumstances • Problem related to unspecified psychosocial circumstances 	ICD-9: V62.5, V62.89, V62.81, V62.9 ICD-10: Z65.0, Z65.1, Z65.2, Z65.3, Z65.4, Z65.5, Z65.8, Z65.9
Problems related to abuse	<ul style="list-style-type: none"> • Encounter for mental health services for child abuse problems • Encounter for mental health services for parental child abuse • Encounter for mental health services for non-parental child abuse • Encounter for mental health services for spousal or partner abuse problems • Encounter for mental health services for victim or perpetrator of other abuse 	ICD-9: V61.21, V61.22, V62.83, V61.11, V61.12, V65.49 ICD-10: Z69.0, Z69.01, Z69.02, Z69.1, Z69.8
Counseling services	<ul style="list-style-type: none"> • Spiritual or religious counseling • Other specified counseling • Counseling, unspecified 	ICD-9: V65.49, V61.2, V61.1, V65.40, V65.9 ICD-10: Z71.81, Z71.89, Z71.9
Other problems related to mental and behavior	<ul style="list-style-type: none"> • Nonpsychotic mental disorder, unspecified • Unspecified disorder of adult personality and behavior 	ICD-9: V40.0, V40.2, V40.3, V40.31, V40.39, V40.9 ICD-10: F48.9, F69
Any SDoH	Any of the above SDoH codes captured before index OD	

Abbreviations: ICD, International Classification of Disease; ICD-9, International Classification of Disease, Ninth Edition; ICD-10, International Classification of Disease, Tenth Edition; SDoH, social determinant of health

APPENDIX D

Underlying cause of death codes used for cause-specific mortality

Cause of death	ICD-10 Codes Associated With Underlying Cause of Death
Opioid overdose	X40-X44, X60-X64, X85, Y10-Y14 with secondary axis codes T40.0-T40.4, T40.6
External Cause of death	X60-X84, Y87.0, X85-Y09, Y87.1, V01-X39, X46-X59, Y85-Y86
<i>Suicide</i>	X60-X84, Y87.0
<i>Homicide</i>	X85-Y09, Y87.1
<i>Accidents</i>	V01-X39, X46-X59, Y85-Y86
Substance-related	F11.0-F11.5, F11.7-F11.9, F12.0-F12.5, F12.7-F12.9, F13.0-F13.5, F13.7-F13.9, F14.0-F14.4, F14.7-F14.9, F15.0-F15.5, F15.7-F15.9, F16.0-F16.5, F16.7-F16.9, F17.0, F17.3-F17.5, F17.7-F17.9, F18.0-F18.5, F18.7-F18.9, F19.0-F19.5, F19.7-F19.9, X40-X44, Y10-Y14, F10, G31.2, G62.1, I42.6, K29.2, K70, R78.0, X45, Y15
<i>Drug-related</i>	F11.0-F11.5, F11.7-F11.9, F12.0-F12.5, F12.7-F12.9, F13.0-F13.5, F13.7-F13.9, F14.0-F14.4, F14.7-F14.9, F15.0-F15.5, F15.7-F15.9, F16.0-F16.5, F16.7-F16.9, F17.0, F17.3-F17.5, F17.7-F17.9, F18.0-F18.5, F18.7-F18.9, F19.0-F19.5, F19.7-F19.9, X40-X44, Y10-Y14
<i>Alcohol-related</i>	F10, G31.2, G62.1, I42.6, K29.2, K70, R78.0, X45, Y15
Infectious	A00-B99
<i>Viral hepatitis</i>	B15-B19
<i>HIV</i>	B20-B24
Circulatory system	I00-I99
Respiratory system	J00-J98
<i>Influenza & pneumonia</i>	J09-J18
<i>Chronic respiratory disease</i>	J40-J47
Digestive system	K00-K92
<i>Cirrhosis & alcoholic liver disease</i>	K70, K73-74
Cancer	C00-D48
<i>Lung & bronchus</i>	C34
<i>Liver & intrahepatic bile duct</i>	C22
<i>Digestive system</i>	C15-C21, C23-C26
<i>Lymphoma & leukemia</i>	C82-C85, C91-C95
<i>Other cancers</i>	C00-C14, C27-C33, C35-C81, C86-C90, C96-D48

Abbreviations: ICD-10, International Classification of Diseases, Tenth Edition; HIV, human immunodeficiency virus