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Changing Dynamics of Opioid Overdoses in West Virginia and Impact of Medication for Opioid Use Disorder and Recurrence of Overdose on Reducing Mortality among West Virginia Medicaid Beneficiaries

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Changing Dynamics of Opioid Overdoses in West Virginia and Impact of Medication for Opioid Use
Disorder and Recurrence of Overdose on Reducing Mortality among West Virginia Medicaid
Beneficiaries

Zheng Dai

Dissertation submitted to the School of Public Health at West Virginia University
in partial fulfillment of the requirements for the degree of

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ABSTRACT

Changing Dynamics of Opioid Overdoses in West Virginia and Impact of Medication for Opioid Use Disorder and Recurrence of Overdose on Reducing Mortality among West Virginia Medicaid Beneficiaries

Zheng Dai

Background

With increasing number of opioid overdoses in West Virginia (WV) in recent years and limited number of people receiving treatment, the dissertation study aims to better understand fatal overdose problems in WV and the impact of medication for opioid use disorder (MOUD) in preventing overdose deaths.

Method

WV drug-related deaths from 2005 to 2018 was used to describe the involvement of fentanyl and FAs. WV Medicaid claim data was analyzed to describe the recurrent opioid overdose and the changes in receipt of MOUD. Further, a Medicaid opioid overdose cohort was created to evaluate the effect of occurrence of recurrent overdose and receipt of MOUD on survival outcomes following a non-fatal overdose after 12 months.

Results

Fentanyl and FAs were drastically increasingly involved in WV fatal overdoses. Overall, only about 5-10% of people who experienced an opioid overdose received MOUD at any time. Compared with no MOUD, those who received MOUD were associated with non-significant increase of all-cause mortality (adjusted hazard ratio 1.14), and occurrence of recurrent overdose was associated with non-significant increase of all-cause mortality (adjusted hazard ratio 1.54).

Conclusion

Starting 2015, drug involvement in the deaths changed from predominantly prescription opioids to fentanyl and new identified FAs. MOUD is likely to be effective in lowering mortality risk in WV. However, small sample size and limited follow up period prevented us from reaching sufficient statistical power. Future research with more recent years' Medicaid data are needed to guide the timely receipt of MOUD for the patients in urgent need.

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Chapter 1

Chapter 1. Introduction

1.1 Background

Unintentional injuries, which is the third leading cause of death, have been increasing since 2014 despite the overall decreasing trend of other top causes of death ¹(Xu et al. 2016). The overall mortality rate for unintentional drug poisonings in the United States (US) grew exponentially in recent years ²(Jalal et al. 2018). There were an estimated 72,000 deaths due to drug poisoning in 2017 ³(Hedegaard et al. 2018), which exceeds those from motor vehicle crashes, gun violence and even HIV at the height of the 1990s HIV epidemic ⁴(Ciccarone 2019). Opioids are the main driver of drastically increasing drug overdose deaths over the last 20 years, accounting for over two-thirds of drug overdose death and resulting in a substantial public health burden of about five years of life lost per 1,000 people ⁵(Gomes et al. 2018). Further, an estimated over 2 million people aged over 12 were diagnosed as opioid use disorder (OUD) patients according to a Substance Abuse and Mental Health Services Administration (SAMHSA) report in 2017 ⁶(SAMHSA, 2017).

West Virginia (WV), which is a predominantly rural state in Appalachia, is at the epicenter of the US national opioid overdose crisis characterized by overdose and relapses ⁷(Wolf et al., 2020). WV leads the nation in drug overdose mortality with the highest mortality rate of 58 per 100,000 population as of 2017, almost 3 times the US average ⁸(Scholl et al., 2019). Across all states, WV had the third lowest median household income, third highest unemployment rate, seventh highest poverty rate, eighth highest prescribing rates for opioids, and tenth lowest rate for people who completed high school in 2017 ^{9,10}(CDC 2018; United States Census Bureau 2017). The current opioid crisis has strained the capacity of health care and social service resources and taken a significant toll on individuals, families, communities, and counties in WV ^{11,12}(Saloner et

al. 2019; Carre et al., 2017). In addition, West Virginia state law does not require overdose as a reportable condition and overdose reporting period is quarterly, making tracing overdose even hard (Davis et al., 2018)¹³.

1.1.1 Fentanyl Era

The substance use patterns have changed drastically over time. The US has gone through a triple wave epidemic of overdose deaths from three classes of opioids: 1) prescription opioids such as oxycodone, hydrocodone, methadone, etc., 2) heroin, and 3) synthetic opioids other than methadone, mainly fentanyl and fentanyl analogs ¹⁴(Ciccarone 2017). In the first wave, death rates for prescription drugs were greater among rural than urban populations. To curb the first wave of opioid epidemic, continuous efforts from national and state levels were committed, including restrictions on opioids prescriptions and establishment of PDMP nationwide. However, one study suggested that as prescription opioid use has waned, concurrent heroin abuse has increased, with distinct regional variations ¹⁵(Compton et al., 2016). The second and third wave predominantly affected the Northeast (including Mid-Atlantic) and the Midwest (including Appalachia) ²(Jalal et al. 2018). It is postulated that with greater difficulty obtaining prescription opioids, alongside widely available heroin supply, the drug users simply transmitted to heroin use and then leading to the increased illicitly manufactured fentanyl IMF use ¹⁶(Hempstead and Yildirim 2014). In summary, the current state of the opioid crisis is attributable to excessive prescribing behaviors, widespread availability of inexpensive heroin, and an increase in use of highly potent fentanyl and its analogs ^{17,18}(Armenian 2017; Suzuki and El-Haddad 2017).

Fentanyl and carfentanil, respectively, are approximately 50-100 and 10,000 times more potent than prescription morphine, and have been identified in adulterated prescription drugs, heroin, cocaine, and methamphetamine ^{9,19,20}(Arens 2016; Mars 2017; CDC 2018). Relative uncertainty

regarding purity of compounds has been largely ignored among illicit drug users, resulting in deaths due to misusing or abusing these substances ²¹(Frank and Pollack 2017). National data indicates that synthetic opioids, mostly fentanyl and FAs, were involved in more than half of opioid overdose deaths occurring in the 12-months ending November 2017 ⁹(CDC 2018).

It is postulated that the greater penetration of fentanyl is part of the reasons why higher overdose risk was observed in the Northeast and Midwest of the States, compared to the South ²²(Morgan et al. 2019). Fentanyl and FA-related deaths have increased dramatically with much of the fentanyl identified consisting of IMF ^{9,17,18}(Armenian et al. 2017; Suzuki and El-Haddad 2017; CDC 2018). Potent FAs such as carfentanil (veterinary drug) and furanyl fentanyl maintain fentanyl's pharmacologic effects while being difficult to detect with standard toxicological testing (Armenian et al. 2017; Suzuki and El-Haddad 2017). Fentanyl and carfentanil are such potent opioids or benzodiazepines that even a small amount of exposure can cause opioid overdose, coma, or death, which pose serious health threats to the public ^{17,18,23,24}(Armenian et al. 2017; Suzuki and El-Haddad 2017; Kuehn., 2010; Park et al., 2020). Combining IMF/FAs with other opioids increases the overdose risk by potentiating respiratory and central nervous system depression, often resulting in rapidly occurring death ^{25,26}(Fox et al. 2018; Slavova et al. 2017). To make matters worse, the “fentanyl high” lasts a much shorter time than heroin's does, suggesting injection drug users are more likely to inject more frequently, which makes them more susceptible to infectious diseases and overdose ^{17,18}(Armenian et al. 2017; Suzuki and El-Haddad 2017). The OUD population may fall into a potentially fatal drug use behavior with more mixed drug use and more injections.

1.1.2 West Virginia Medicaid Population

Medicaid programs effectively respond to the opioid crisis by expanding treatment coverage and reforming treatment delivery systems ²⁷(Barnes et al., 2020). Approximately 29% of the WV population are covered by Medicaid, and this makes WV rank highest in the nation in terms of proportion of population covered ²⁸(Kaiser Family Foundation 2018). According to West Virginia Department of Health and Human Resources Bureau (WVDHHR)²⁹, drug overdose decedents were much more likely to have Medicaid (71%) in the 12 months prior to their death as compared to West Virginia's adult population aged 19-64 (23%). Specifically, of those decedents with Medicaid, 81% utilized the benefit within 12 months prior to their date of death, excluding those decedents who only used the benefit within 48 hours before death²⁹. As for ED visits, 68% of decedents with Medicaid had at least one ED visit in the 12 months prior to death. Medicaid enrollees have an estimated 3-times higher risk of opioid overdose (Sharp and Melnik, 2015)³⁰ and has been identified as a high-risk population for fatal opioid overdose by Centers for Disease Control and Prevention (CDC) (Garg et al., 2017; Stoove et al., 2009)^{31,32}. In addition, the WV DHHR Bureau for Medical Services (BMS) gained approval in 2014 for a Medicaid Section 1115 waiver to develop a continuum of care for individuals with substance use issues. Expansion of Medicaid started in 2014, and served as an important step in increasing accessibility of MOUD for persons with substance abuse disorder ^{29,33}(WVDHHR 2017; Sharp et al. 2018).

Unfortunately, the need for care far exceeds the current treatment infrastructure in West Virginia, resulting in long waiting lists, and eventual overdose for many persons actively seeking treatment ³⁴(Pollini et al. 2006). Worse, patients are also suffering risks from many drug-related medical conditions, such as viral infections (HIV or hepatitis), suicide, alcohol use disorder, respiratory diseases, circulatory diseases and skin infections (Bohnert et al., 2012; Suffoletto and

Aeigler et al., 2020)^{35,36}. Private care facilities are a potential option, but often too expensive for persons living in West Virginia where the median annual family income is \$42, 644 ¹⁰(United States Census Bureau 2017) and the average cost of treatment can range from \$2,000 to \$15,682 ³⁷(Jones et al. 2009). Rural transportation also presents a difficult issue as over 50% of West Virginia's population is classified as rural ¹⁰(United States Census Bureau 2017), restricting state/city managed transportation services.

1.1.3 Medication for Opioid Use Disorder and Treatment Barriers

To address increasing opioid overdoses and cure increasing numbers of OUD patients, evidence-based and appropriate clinical interventions and treatment models to prevent opioid overdose mortality are urgently needed ³⁸(Wakeman 2019). Medication for opioid use disorder (MOUD) regimens utilizing three FDA approved medications (methadone, buprenorphine, and naltrexone) are promising treatment options in reducing drug use, compulsive drug seeking, substance use relapse, and overdose ^{33,39-46}(Sharp et al. 2018; Schwartz et al. 2013; Rudd 2016; Banta-Green et al. 2017; Zoorob 2019; Mancher and Leshner, 2019; Kimber et al., 2015; Volkow et al., 2014; Ma et al., 2018). Combined with behavioral therapy (e.g., cognitive-behavioral therapy or contingency management) and counseling or by itself, MOUD has proven to be effective in reducing drug-related outcomes, including ED visits, hospitalization and mortality ⁴⁷⁻⁵⁰(Alexandridis et al. 2018; Barnett 2009; Larochelle et al., 2018; Larochelle et al., 2016), as well as getting people back to productive functioning in the family and workplace. However, effective but not perfect, there haven't been systematic evaluation of MOUD effectiveness on WV population, which is quite different from other populations in the States, as we have explained previously.

For buprenorphine treatment, another reason why the timing of initiation of MOUD is critical is that patients must be in active opioid withdrawal to initiate the medication safely. The prognosis during or after the treatment would be better when induction is offered as soon as possible (Sigmon et al., 2016; Clausen et al., 2008)^{51,52}. However, many clinicians require the patients to meet certain criteria before offering them buprenorphine, such as active engagement in counseling, which may result in delays (Martin et al., 2018)⁵³. A study demonstrated the importance of the timing of initiation of methadone treatment by showing that the mortality risk for persons at waiting list is 10 times greater than for those who initiate treatment as soon as possible (Peles et al., 2013)⁵⁴. Similarly for naltrexone, patients need to go through a few days of opioid abstinence before the initiation of medication. The induction period is critically for a successful initiation of naltrexone, and many patients failed to pass the induction period which leads to early drop out and readily relapse (Lee et al., 2015; Gordon et al., 2015).^{55,56}

However, the massive “treatment gap” in accessing pharmacotherapy of OUD remains a challenge -- only one third of OUD patients identified from WV Medicaid received buprenorphine in early 2014 ⁵⁷(Koyawala et al., 2019). Nationally in 2017, only one out of nine SUD patients received MOUD⁵⁸. Among those receiving treatment, approximately one third of them dropped out within 90 days (suggesting limited effectiveness)⁵⁸⁻⁶¹.

According to the 2017 National Survey on Drug Use and Health⁶², for those underserved OUD populations who perceived a need for treatment but not receiving MOUD, some of them had difficulty accessing treatment resources (no health care coverage) and suffer from stigma towards drug-using (negative impression from neighbors, communities and health care providers). Additional barriers include shortage of providers who offer MOUD (long waiting list), limited health insurance coverage for OUD treatment (Methadone not covered in West

Virginia before 2018), and weak data on the quality of MOUD treatment evaluation⁶². Further, social and support care services that are necessary for a proper continuum of care are not widely available, resulting in poor treatment compliances, high drop out and readmission rates, and frequently happened relapses, leading to negative health outcomes including mortality⁵⁸.

1.1.4 Recurrent Opioid Overdose

In general, persons experiencing nonfatal overdose are at increased risk of overdose death (Coffin et al. 2007; Colledge et al., 2019; Thylstrup et al., 2020)⁶³⁻⁶⁵. This risk is further intensifying in states like West Virginia experiencing geographic isolation⁶⁶(Hall et al. 2008), massive opioid prescriptions (Okie, 2010; Paulozzi et al., 2011; Boyle et al., 2017)⁶⁷⁻⁶⁹, high rates of psychiatric conditions (Webster et al., 2017; Brady et al., 2017)^{70,71}, and having limited medical resources, resulting in gaps between need for sustainable treatment and the state's capacity to deliver these options (Jones et al. 2015)⁷². Therefore, it is of great public health importance to rapidly address the opioid overdose problem in WV. This study addressed the WV overdose problem through development of a series of studies focusing on drug-related deaths in Forensic Drug Data (FDD) and persons with opioid use disorder in Medicaid claims data.

An earlier estimation done over a decade ago suggested that on average an overdose decedent experienced 30 recurrent overdoses⁷³(Frazier et al. 2017). However, a recent study conducted in Kentucky demonstrated that fentanyl overdose has a strikingly low ratio of ED visits to deaths (Slavova et al. 2017)²⁶. Another study conducted in Massachusetts showed that the ratio of nonfatal to fatal overdoses has dropped to less than 12 in 2015 (Massachusetts Department of Public Health, 2017)⁷⁴. The study suggested that in the current fentanyl era, the nonfatal episode represents an important rescue window (Hasegawa et al., 2017)⁷⁵. Fentanyl overdoses occur much more rapidly than heroin or prescription opioids overdoses, resulting in death within

seconds (Dai et al., 2019)⁷⁶. A few minutes of oxygen deprivation, an overdose may lead to permanent brain damage or death (Zibbell et al. 2020)⁷⁷. Therefore, any presence of overdose is a potential opportunity for initiating treatment to reduce the chances of a recurrent overdose or even fatal overdose ⁷³(Frazier et al. 2017). People who have one overdose are more likely to have a following one (Olfson et al. 2018; Darke et al., 2007; Lowder et al., 2020; Havens et al., 2011)⁷⁸⁻⁸², and missing any chance for intervention would be potentially lethal for the overdose population, specifically when super-potent fentanyl or FAs are increasingly involved in overdoses.

1.2 Purpose Statement

This study is the first to comprehensively describe the current synthetic opioid problem, especially fentanyl and/or fentanyl analog-related death in WV. An in-depth description of characteristics of overdose and OUD patients among WV Medicaid population is very valuable for future policy making and treatment improvement. More importantly, another innovative aspect to the project is the application of survival methodologies alongside an in depth investigation of MOUD effectiveness in a West Virginia Medicaid population. In the case of treating OUD patients, the challenge is to provide the right treatment to the right patients at the right time. However, given there are long waiting list to receive MOUD due to limited treatment resources and low treatment retention rate, the survival outcome of OUD patients is of great concern. To date, no studies have incorporated comprehensive time-dependent MOUD information modelling to assess the patients' survival rates after the treatment. Cox proportional hazard models are appropriate to incorporate time-dependent MOUD and recorded non-fatal overdose information to identify the optimal time for effective intervention. Results from this study are expected to inform policy due to the fact that ~29% of WV's population are Medicaid

beneficiaries, and given the recent efforts by state agencies to expand MOUD access. The research group, including professional epidemiologists in drug overdose prevention, statisticians specialized in survival analysis and pharmacists with years' experience analyzing Medicaid data, is truly multidisciplinary.

Results from this study will specifically add to the literature in the following three aspects:

1. Increase understanding of evolving poly-substance use patterns including fentanyl and fentanyl analogs among West Virginia drug use population.
2. Examine recurrent opioid overdose and how changes in receipt of MOUD following a non-fatal overdose influence risk of mortality among the WV Medicaid population.
3. Identify associations between time-dependent MOUD and mortality among a WV Medicaid overdose cohort, adjusting for recurrent overdose and other risk factors.

The long-term goal of the study is to provide evidence to inform treatment expansion and policy reform efforts in West Virginia to timely deliver MOUD to fulfill patients' urgent needs. The central hypothesis is that the differences in survival rates are time-dependent over the initiation of treatment, length of treatment, and recurrent overdose, controlling for patients' demographics, medical conditions, and drug use. To address the goals of our study, the following specific aims were formed as below.

1.3 Specific Aims

Sample design

For Aim 1, to describe fatal overdose problems in West Virginia and its relation to fentanyl and other opioids, data from forensic drug database (FDD) was analyzed to achieve the goal. FDD was created in 2005 in collaboration with the West Virginia Office of the Chief Medical

Examiner (WVOCME) to compile data from all WV drug-related deaths. West Virginia uses a centralized medical examiner system and the WVOCME maintains files for WV deaths. Drug-related death data used in this study was extracted from 2005 through June 2018. Deaths included those in which overdose was the immediate cause of death, or a transportation-related or other injury (e.g., motor vehicle, ATV, drowning, etc.) was the immediate cause of death but drugs were believed to be significant contributors to death. For example, fentanyl or FA-related deaths were defined as if one or more of these substances was found during postmortem toxicology testing and identified as a cause of or contributor to death in Parts I or II of the death certificate. All drug-related deaths in WV from 2005 to June 2018 were included into the analyses. West Virginia residence who died out of WV were not included. The deaths with substance identified but not ruled to cause or contribute to the death were excluded. For example, natural deaths from cardiovascular pathogen with marijuana identified and administered days ago were excluded.

For Aim 2 and 3, to identify association between time-dependent MOUD and recurrent overdose or all-cause mortality, a WV Medicaid overdose cohort was selected and analyzed for survival outcome. WV Medicaid created a Common Data Model (CDM) to incorporate an extensively cleaned subset of WV Medicaid data that was designed to study opioid-related measures. The CDM included WV Medicaid data from 2014 to 2016 for persons aged 18-64 and excluded about 20% of people who had dual-eligibility with Medicare, as Medicare is the primary payer and Medicaid does not include all claims from this group. An overdose cohort was then created from CDM by selecting continuously enrolled persons ages 18 to 64 with at least one nonfatal overdose event identified by ICD codes (Appendix A, ICD-9: 965.00-965.02, 965.09, E850.0-E850.2 or ICD-10: X40-X44, X60-X64, X85, Y10-Y14) from emergency department (ED) visits

or hospitalization. Multiple opioid overdoses that occurred during one hospitalization interval (admission and discharge date) were counted as one overdose event. Two overdoses recorded within two days were also accounted as one overdose event. Thus, a recurrent overdose event was defined as one occurring at least two days after the previous overdose (avoid potential carry-on effect from previous overdose). Among those who had at least 12 months length of observation overdose free, the first nonfatal overdose identified was marked as the index overdose. The retrospective cohort follow-up starts with the index overdose, and ends with death or with beneficiaries dropping out within 12 months after the index overdose. The cohort excluded those who died within 30 days of index overdose (make sure every subject had at least one-month follow up) and patients with any cancer diagnosis (avoid confounding effect from cancer) at any time of cohort. The ICD -9 and ICD-10 codes used to identify cancer were listed in Appendix A. Missing values were checked for age and gender and no one was excluded for this reason.

Predictors

For Aim 1, demographic characteristics, co-intoxicants as well as medical conditions were extracted from FDD directly. Each FDD case includes demographic information (e.g., age, sex, race, weight, height, date of death, zip code of residence), cause and manner of death, toxicology findings (e.g., drugs identified, concentrations, postmortem interval), whether a prescription was present within the past 30 days for controlled substances, autopsy findings, and medical history.

For Aim 2 and 3, demographic characteristics, including age, sex, race/ ethnicity and enrollment category, were extracted from the Medicaid enrollment files. Age was recorded at the time of index overdose. Start and end date of each overdose and any other diagnosis were extracted from inpatient and outpatient data files. Date and duration of each prescription were extracted from

pharmacy data files. For medication not applicable for prescription, including injectable naltrexone and implantable buprenorphine, the date and duration of each treatment episode were extracted from professional data files. In the Cox model, all medical conditions and prescriptions were extracted at the baseline (index overdose).

This study was reviewed and approved by the Institutional Review Board (protocol number: 1711862183A001) at the West Virginia University, Morgantown, WV.

Analysis Plan

For Aim 1, data management and analysis were conducted using SAS (version 9.4, SAS Institute, Cary, NC). For Aim 2 and 3, data management and analysis were conducted using Enterprise Grid software (version 5.1, SAS Institute, Cary, NC). Significance level was set to 0.05 for all tests unless otherwise specified.

Specific Aim 1: Describe fatal overdose problems in West Virginia and its relation to fentanyl and other opioids.

Hypothesis 1: Fentanyl or FAs-related deaths have different demographic and toxicological characteristics than those deaths with prescription opioids involved.

Descriptive analyses were used to characterize the drug-related deaths. T-tests and Chi-square tests were used for continuous and categorical data comparisons, respectively. Co-intoxicants in fentanyl and FA-related deaths are compared through the 2005–2014 and the 2015–2017 time periods because the number of fentanyl and FA-related deaths did not increase substantially until 2015. The number of drugs with a valid prescription (defined as a prescription present within 30 days prior to death) was determined through use of the WV CSMP. Comorbidities identified through autopsy reports and other information in decedents files are defined as follows:

cardiovascular (cardiomyopathy, cardiomegaly, hypertrophy, hypertensive cardiovascular disease, ischemic heart disease, atherosclerotic coronary artery disease, cardiac disease, heart failure, myocardial infarction), psychiatric other than substance abuse disorder (Alzheimer's disease, anxiety disorder, attention deficit hyperactivity disorder, bipolar affective disorder, chronic fatigue, delusional disorder, dementia, depression, mania, mental/behavioral disorders, obsessive-compulsive disorder, panic attacks, posttraumatic stress disorder, psychosis, schizophrenia, suicide attempts/ideation, self-mutilation behavior), pulmonary (asthma, sleep apnea, chronic obstructive pulmonary disease, pneumoconiosis), hepatic (hepatitis, cirrhosis, alcoholic/other liver disease, hepatic necrosis, hepatic failure), pain (ankylosing spondylitis, migraine/headache syndromes, arthritis/polyarthritis/rheumatoid arthritis/ osteoarthritis, systemic lupus, systemic sclerosis, neuropathy pain, acute pain, chronic pain, fibromyalgia, pancreatitis, systemic lupus, hip fracture), and history of substance abuse (drug, alcohol or other substance).

Specific Aim 2: Examine recurrent opioid overdose and the changes of receipt of Medication for Opioid Use Disorder (MOUD) following a non-fatal overdose among the West Virginia (WV) Medicaid population.

Hypothesis 2: Proportion of receipt of MOUD remains low even after a non-fatal overdose.

Sub aims include 1) characterizing overdose population among WV Medicaid beneficiaries, stratified by the number of overdoses and MOUD receipt; 2) examining occurrence of recurrent opioid overdose, change of receipt of MOUD and medication use before and after the index overdose.

The primary outcomes in this aim are recurrent overdose and receipt of MOUD. The receipt of MOUD was identified from both pharmacy datasets using National Drug Codes (NDC), and from inpatient and outpatient datasets using procedure codes. First, the descriptive statistical

analysis were performed to describe the opioid overdose cohort. Number and percentage were reported for categorical variables. Demographic characteristics including age, gender, and Medicaid eligibility category were analyzed. The number and frequency of overdose events, the monthly receipt of MOUD, the number and type of frequently present mental health conditions (including anxiety, bipolar, depression, alcohol use disorder, and substance use disorder) identified by ICD-9 or ICD-10 codes were also analyzed. Descriptive analyses compared medication (including opioid analgesics and benzodiazepines) use patterns before and after the index overdose.

Specific Aim 3: Identify associations between time-dependent MOUD and all-cause mortality/ opioid-specific mortality among a WV Medicaid overdose cohort, adjusting for recurrent overdose and other risk factors.

Hypothesis 3: Delay in initiation of MOUD after occurrence of first nonfatal overdose negatively affect patients' survival rates, which is also mediated by recurrent overdose events.

The primary outcome of interests in this aim are all-cause mortality and opioid-specific mortality in the 12-month follow up. The main exposures were receipt of MOUD and recurrent overdose. The first date of receipt of MOUD was identified and compared to the date of index overdose to determine the presence or absence of baseline status. Duration of MOUD was calculated as cumulative days in treatment and then dichotomized by the median value. The types of medication use were separated into three groups: buprenorphine use only, naltrexone use only, and mixed group.

Potential confounding variables were also examined. Patients' age and gender were obtained from Medicaid enrollment files. Age was categorized into 3 groups: 18 to 29 years, 30 to 44 years and 45 year or older. Post index overdose prescription of opioids and benzodiazepines

were also identified and dichotomized into presence or absence. Psychiatric diagnosis including anxiety, depression, bipolar, alcohol use disorder and other drug use disorder (stimulants, cannabis, etc. related disorder) were also identified.

Kaplan–Meier method was used to examine survival trends (all-cause mortality and opioid-specific mortality) by receipt of MOUD and number of overdoses. A log-rank test was used to assess the difference of time-to-events between subgroups.

Univariate and multivariable Cox proportional hazard models were applied to evaluate MOUD effectiveness on reducing both all-cause mortality and opioid-specific mortality, while adjusting for other important confounders, including presence of opioids, benzodiazepines, anxiety, depression, bipolar, alcohol use disorder, and other drug use disorder. Multivariable models were developed in a sequential approach, by first only modelling MOUD presence or absence, and then specifically modelling the subsets with MOUD presence. Timing of initiation of MOUD, duration of MOUD and recurrence of overdose were added into the subgroup Cox model to have a comprehensive evaluation of MOUD through survival approach.

We expect to determine an optimal intervention time and treatment plan through this analysis. The clinical significance of this aim is to evaluate patients' survival rates, taking into account comprehensive time-dependent MOUD and time-dependent recurrent overdose events. It is essential to identify patients who are in urgent need for MOUD, provide them priority for the right treatment, and maintain them in the treatment long enough to improve the long-term survival outcome.

Limitations

Although Medicaid claim data captures over 70% of West Virginia overdoses, a major limitation of data in the study time period (2014 – 2016) is that methadone was not covered by Medicaid. In other words, this study was unable to evaluate effectiveness of methadone in treating OUD patients and preventing deaths. However, few clinics offer methadone treatment in WV and most of them were paid out-of-pocket or covered by commercial insurance. Another limitation is the constrained power of survival analysis due to limited length of available data. Since we only had access to three years data, the identification of the first nonfatal overdose could be inaccurate, and the length of follow up (12 months) may be too short to capture the whole length of time staying in the treatment for some MOUD recipients, and to have a sufficient number of events (death) to reach a decent statistical power. However, the survival approach was able to justify the censored data and reduce bias. The methodology is sound and we will be able to reproduce the study with more years' data available. Lastly, the Medicaid data used in this study had excluded dual-eligible population in Medicare. Notwithstanding, this part only accounts for about 20% of overall Medicaid beneficiaries.

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Chapter 2

2.1 Abstract

Objective

To describe and analyze the involvement of fentanyl and fentanyl analogs (FAs) in drug-related deaths in West Virginia (WV), United States.

Methods

Retrospective analyses of all WV drug-related deaths from 2005 to 2017 were performed, including comparisons of demographic and toxicological characteristics among total deaths, deaths in which fentanyl/FAs were present, deaths in which they were absent, heroin-related deaths, and prescription opioid-related deaths.

Results

Most of the 8813 drug-related deaths were overdoses, with about 11% resulting from transportation/ other injuries in which drugs were contributors. Prescription opioid presence (without fentanyl) decreased by 75% from 2005–14 to 2015–17 (3545 deaths to 859 deaths, respectively), while fentanyl involvement in the deaths increased by 122% between these periods (487 to 1082 deaths). Ten FAs were identified (427 instances) after 2015. Alprazolam and ethanol were among the top five most frequently identified substances across years. Fentanyl, heroin and cocaine replaced oxycodone, diazepam and hydrocodone in the top five beginning in 2015. Few decedents had a prescription for fentanyl after 2015, with fewer prescriptions also present for other controlled substances identified.

Conclusions

Fentanyl, rapidly emerging FAs, and other illicit drugs in recent years pose a serious health threat even though prescription opioid-related deaths decreased over the same time period.

2.2 Introduction

Opioid-related deaths continue to increase in the United States, resulting in a substantial public health burden of about five years of life lost per 1000 population (Gomes et al., 2018)¹. Fentanyl and fentanyl analog (FA)-related deaths have increased dramatically with much of the fentanyl identified consisting of illicitly manufactured fentanyl (IMF) (Armenian et al., 2017; Suzuki and El-Haddad, 2017; Centers for Disease Control and Prevention CDC, 2018)²⁻⁵. Greater difficulty obtaining prescription opioids along with ready heroin availability may have contributed to increased IMF use (Hempstead and Yildirim, 2014)⁶. Potent FAs such as carfentanil (veterinary drug) and furanyl fentanyl maintain fentanyl's pharmacologic effects while being difficult to detect with standard toxicological testing (Armenian et al., 2017; Suzuki and El-Haddad, 2017)^{2,3}. Since fentanyl is about 50–100 times and carfentanil approximately 10,000 times more potent than morphine, they and other illicit FAs pose serious health threats (Armenian et al., 2017; Suzuki and El-Haddad, 2017)^{2,3}.

Fentanyl/FAs have been found in adulterated prescription drugs and in heroin, cocaine, and methamphetamine (Arens et al., 2016; Mars et al., 2017; McCall Jones et al., 2017; CDC, 2018)^{4,7-9}, resulting in deaths of individuals misusing or abusing these substances (Frank and Pollack, 2017)¹⁰. Combining IMF/FAs with other opioids increases the overdose danger by potentiating respiratory and central nervous system depression, often resulting in rapidly occurring death (Fox et al., 2018; Slavova et al., 2017)^{11,12}.

West Virginia (WV), which is predominantly rural, has the highest per capita drug overdose mortality in the United States (Hedegaard et al., 2017)¹³. Although heroin and synthetic opioids such as fentanyl contribute to an increasing number of drug-related deaths nationally (Rudd, 2016)¹⁴, studies have suggested that fentanyl overdoses might be more common in urban and

suburban areas (Marshall et al., 2017)¹⁵. The objective of this study was to compare fentanyl and FA-related deaths to drug-related deaths not involving fentanyl/FAs in West Virginia.

2.3 Methods

A forensic drug database (FDD) was created in 2005 in collaboration with the West Virginia Office of the Chief Medical Examiner (WVOCME) to compile data from all WV drug-related deaths. West Virginia uses a centralized medical examiner system and the WVOCME maintains files for WV deaths. Drug-related death data are available from 2005 through 2017 (a total of 78 [7%] of 2017 deaths were not available for entry at time of this manuscript). Each FDD case includes demographic information (e.g., age, sex, race, weight, height, date of death, zip code of residence), cause and manner of death, toxicology findings (e.g., drugs identified, concentrations, postmortem interval), whether a prescription was present within the past 30 days for controlled substances, autopsy findings, and medical history. Sources used by the OCME data entry personnel to compile the FDD data included the death certificate, autopsy report, external examination, investigator reports, medical records, police reports, toxicology reports, the West Virginia Controlled Substances Monitoring Program (WV CSMP), and any other relevant information in the decedent's file. Medical history information was obtained using a variety of sources, including county MEs, scene investigations, prescription records, autopsy reports, and medical records when available.

Deaths were defined as fentanyl or FA-related if one or more of these substances was found during postmortem toxicology testing and identified as a cause of or contributor to death in Parts I or II of the death certificate. Deaths included those in which overdose was the immediate cause of death, or a transportation-related or other injury (e.g., motor vehicle, ATV, drowning, etc.) was

the immediate cause of death but drugs were believed to be significant contributors to death(e.g., fentanyl and heroin present during confirmatory toxicology in vehicle operator's death).

Drug screening is routinely performed on all deaths investigated by the WV OCME, with confirmative toxicology tests conducted for most positive screens. Blood and/or tissue samples are screened for volatile compounds using gas chromatography with flame ionization detection and drugs of abuse using automated enzyme immunoassays. This latter test includes the following drugs/drug classes: amphetamines, barbiturates, benzodiazepines, buprenorphine, cocaine, fentanyl/fentanyl analogs, methadone, opiates (morphine, codeine, hydrocodone, hydromorphone, oxycodone, oxymorphone), and marijuana. In addition to the opiate immunoassay, a second immunoassay is specifically used to detect oxycodone and oxymorphone. Drugs or drug classes, including many therapeutic and nonprescription drugs, which screen positive undergo confirmation testing and quantitation. Fentanyl analogs were tested beginning in 2013 to coincide with national reports. Heroin was considered to have been used when the drug or its metabolite 6-monoacetylmorphine (6-MAM) was identified in any sample tested. Frequently 6-MAM is detectable in vitreous fluid or urine when no longer detectable in blood. The femoral or subclavian blood concentration ratio of morphine to codeine was also considered when heroin involvement in the death was suspected (Harruff et al., 2015)¹⁶. In a small number of cases, heroin was listed on the death certificate as a cause of or contributor to death on the basis of a compelling death scene investigation with toxicology reports identifying morphine (metabolite of 6-MAM) and small amounts to undetectable codeine.

Descriptive analyses were used to characterize the drug-related deaths. T-tests and Chi-square tests were used for continuous and categorical data comparisons, respectively. Co-intoxicants in fentanyl and FA-related deaths were compared between the 2005–2014 and the 2015–2017 time

periods because the number of fentanyl and FA-related deaths did not increase substantially until 2015. The number of drugs with a valid prescription (defined as a prescription present within 30 days prior to death) was determined through use of the WV CSMP. Comorbidities identified through autopsy reports and other information in decedents files were defined as follows: cardiovascular (cardiomyopathy, cardiomegaly, hypertrophy, hypertensive cardiovascular disease, ischemic heart disease, atherosclerotic coronary artery disease, cardiac disease, heart failure, myocardial infarction), psychiatric other than substance abuse disorder (Alzheimer's disease, anxiety disorder, attention deficit hyperactivity disorder, bipolar affective disorder, chronic fatigue, delusional disorder, dementia, depression, mania, mental/behavioral disorders, obsessive-compulsive disorder, panic attacks, posttraumatic stress disorder, psychosis, schizophrenia, suicide attempts/ideation, self-mutilation behavior), pulmonary (asthma, sleep apnea, chronic obstructive pulmonary disease, pneumoconiosis), hepatic (hepatitis, cirrhosis, alcoholic/other liver disease, hepatic necrosis, hepatic failure), pain (ankylosing spondylitis, migraine/headache syndromes, arthritis/polyarthritis/rheumatoid arthritis/osteoarthritis, systemic lupus, systemic sclerosis, neuropathy pain, acute pain, chronic pain, fibromyalgia, pancreatitis, systemic lupus, hip fracture), and history of substance abuse (drug, alcohol or other substance).

All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). A P value of less than 0.05 was considered statistically significant.

2.4 Results

A total of 8813 WV drug-related deaths from 2005 to 2017 were analyzed. Five data sources were reviewed on average per death, with toxicology, investigation and autopsy reports, and death certificates used most frequently. Of the 5924 drug-related deaths from 2005 to 2014, fentanyl was identified in 487 deaths (8.2%), most of which involved co-intoxicants with only

one FA found (Table 1). Of the 2889 drug-related deaths from 2015 to 2017, 1082 (37.5%) involved fentanyl and/or FAs. The mean decedent age in fentanyl and/or FA-related deaths was significantly lower (seven years) compared to deaths involving prescription opioids. Overall, most decedents were male, with about 87% of deaths classified by the OCME as unintentional. Body mass index (BMI) did not differ between fentanyl/FA-related and prescription opioid deaths from 2005 to 2014, although BMI was slightly but statistically significantly lower compared to prescription opioid deaths during 2015–2017. Drug overdose was the primary cause of death across years and was significantly higher in the fentanyl/FA-related cases (99%) compared to prescription opioid or total drug deaths. A transportation-related accident or other injury (e.g., impaired/intoxicated individual hit by vehicle or falling) was the primary cause of death in approximately 11%, with one or more drugs considered contributors.

Multiple drug use was common (77.5%) among drug-related deaths (Table 1). A slight but statistically significantly greater number of co-intoxicants was identified in prescription opioid-related deaths during 2015–2017 (mean=3.2) compared to fentanyl/FA-related deaths (mean=2.9). Females tended to have only a slightly higher average number of co-intoxicants present than males. Involvement of fentanyl/ FAs in the deaths increased dramatically during 2015–2017 (Fig. 1) while prescription opioid-related deaths, still a considerable problem, decreased (Table 1). From 2012 to 2017, the largest increases in the drugs identified were: fentanyl (1325%), methamphetamine (1375%), heroin (279%), and cocaine (171%), with most increases occurring from 2015 to 2017. Prescription opioids (not including fentanyl) were present in about 30% of 2015–2017 deaths compared to almost 60% of 2005–2014 deaths. Only age, manner of death, and cause of death were statistically significantly different between

fentanyl/FA-related deaths and prescription opioid deaths from 2005 to 2014, with all characteristics compared significantly different during 2015–2017 (Table 1).

Alprazolam, oxycodone, ethanol, diazepam, and hydrocodone comprised the top five identified substances in unintentional deaths from 2005 to 2014, while fentanyl, heroin, ethanol, alprazolam, and cocaine were the most common substances in 2015–2017 (Table 2). During 2015–2017, the most frequent co-intoxicants found together with fentanyl/FAs were heroin (36.3%), cocaine (19.9%), alprazolam (15.5%), ethanol (15.1%), and methamphetamine (14.7%). Only methamphetamine was found with similar frequency regardless of whether fentanyl/FAs were present or absent ($p = 0.6430$). Of the 1 196 unintentional heroin-related deaths from 2005 to 2017, 6-MAM was identified in 1061 cases (88.7%) and morphine was present in all remaining cases ($n = 135$). A morphine/codeine concentration ratio in femoral or subclavian blood could be calculated in 29 (21.5%) of these latter deaths; the ratio was greater than 1 in all cases and greater than 3 in 28 of the 29 cases (96.6%). Scene investigations also helped determine the likelihood of heroin involvement in these deaths.

Since 2015, fentanyl/FA deaths outpaced those of other prescription opioids identified in unintentional deaths. The number of fentanyl/FA related deaths exceeded those from other substances since 2016 and rose dramatically in 2017 (Fig. 1). Methamphetamine involvement has also rapidly increased from 2015 (7.6%) to 2017 (22.6%). Ethanol continues to maintain a significant presence in drug-related deaths each year (19.8% in 2017). Benzodiazepines were commonly found across years but decreased in 2017.

Ten different FAs were identified in any death from 2015 to 2017 (427 instances) (Table 3), with a single FA identified prior to 2015. The FAs identified include (in decreasing frequency): carfentanil, furanyl fentanyl, para-fluoro(iso)butyryl fentanyl, acetyl fentanyl, acryl fentanyl,

cyclopropyl fentanyl, butyryl fentanyl, 3-methyl fentanyl, methoxyacetyl fentanyl, and tetrahydrofuran fentanyl. They were often identified with co-intoxicant fentanyl, heroin, benzodiazepines, cocaine or other FAs. Fentanyl was a co-intoxicant in about 31–35% of deaths involving carfentanil and furanyl fentanyl, 87.5% of deaths involving acetyl fentanyl, and 61.3% of deaths involving para-fluoro(iso)butyryl fentanyl. Among a total of 317 cases with at least one FA present, heroin and benzodiazepines were identified in 121 (38.2%) and 87 (27.4%), respectively, with other prescription opioids less commonly found (81 cases; 25.6%).

The percentage of controlled substances for which decedents had a prescription decreased overall from 2005 to 2014 to 2015–2017, but the percentage steadily increased by age, from 9.8% of decedents aged 18–24 years to 42% of those 65 years and older. Fewer decedents had a prescription for hydrocodone (51.4% vs. 38.8%), oxycodone (39.3% vs. 37.3%), morphine (19.9% vs. 9.7%), alprazolam (44.5% vs. 34.5%), and diazepam (28.9% vs. 22.6%) during 2015–2017 compared to the earlier period. Very few decedents had a prescription for methamphetamine. For deaths involving methadone, commonly used in medication-assisted treatment for opioid abuse, a prescription was found with slightly higher frequency during 2015–2017 compared to earlier years (31.2% to 24.2%, respectively), although the number of methadone related deaths was much lower recently. Most notable was the recent decline in the percentage of decedents who had a prescription for identified fentanyl (23.9% to 1.7%).

Medical records were accessed for 25.6% (2259/8813) of all deaths (Table 4). Of these, a history of substance abuse (drugs and/or alcohol) was significantly higher in unintentional deaths involving fentanyl/FAs compared to deaths in which they were absent (87.6% vs. 67.8%), while co-morbid cardiovascular (41.1% vs. 50.3%) and pulmonary diseases (17.0% vs. 25.5%) were significantly less common in fentanyl/ FA-related deaths. There were no significant differences

in co-morbid psychiatric, pain, or hepatic conditions between deaths with or without fentanyl/FAs, with percentages in all groups relatively low (less than 20%).

2.5 Discussion

Drug-related deaths continue to rise in the United States (Armenian et al., 2017; Frank and Pollack, 2017; O'Donnell et al., 2017; Suzuki and El-Haddad, 2017; CDC, 2018)^{3,4,10,17,18}.

Fentanyl-related WV deaths have continued unabated since 2015, with a steep recent increase.

Drug involvement in the deaths has also changed, from predominantly prescription opioids to illicit drugs, generally with co-intoxicants. This recent shift from predominantly prescription opioids to illicit drugs suggests that programs to reduce prescription opioid deaths, e.g., prescription drug monitoring programs (PDMPs), are decreasing fatal intoxications from such opioids. However, when prescription opioids are less readily available, drug users often switch to cheaper, illicit substitutes (Alexander et al., 2016; Fink et al., 2018; Nam et al., 2017; Pergolizzi et al., 2018; Seth et al., 2018; Slavova et al., 2017)^{12,19-23}. Our finding of fewer decedents with prescriptions for identified controlled substances is consistent with these reports. Although a recent review found that PDMPs appeared to reduce overdose deaths, albeit based on low-strength evidence (Compton and Wargo, 2018)²⁴, they have continued to increase in WV. This increase might also be explained in part by geographical isolation, poverty, limited medical resources, heavy economic burdens, and social obstacles that could exacerbate the fentanyl problem in rural areas (Jozaghi and Marsh, 2017)²⁵.

Similar to other reports (Hayashi et al., 2018)²⁶, the mean decedent age was significantly younger in fentanyl/FA-related deaths compared to other drugs or those involving prescription opioids. Compared to non-fentanyl prescription opioids, fentanyl/FA-related deaths in 2015–2017 had a significantly greater proportion of males, lower BMI, and were more likely to be

unintentional in nature. Thus, it is important that efforts to reduce fentanyl abuse encompass the younger male population.

Characterizing the co-intoxicants involved in fentanyl-related deaths is important. Fentanyl or a FA was present as a single drug in a minority of deaths (12.9%), although to a significantly greater extent than single drug prescription opioids (9% of deaths). Co-intoxicants identified prior to 2015 were predominantly benzodiazepines and prescription opioids; more recently, they were likely to be illicit although benzodiazepine involvement continues to be high. Heroin, cocaine, and methamphetamine were present in 36.3%, 19.9%, and 14.7% of all unintentional fentanyl/FA-related deaths during 2015–2017, respectively, consistent with reports describing regular heroin and cocaine use as risks for fentanyl overdose (Baldwin et al., 2018; Hayashi et al., 2018; Mars et al., 2017; McCall Jones et al., 2017; Rubin, 2017)^{9,26-29}. Crystal methamphetamine use has been significantly associated with fentanyl identification (Amlani et al., 2015; Baldwin et al., 2018; Hayashi et al., 2018)^{26,27,30}, with fentanyl/FAs found to an increasing extent in confiscated methamphetamine (CDC, 2018)⁴. Methamphetamine was present to a similar extent in WV fentanyl/FAs present or absent deaths.

Fentanyl-related deaths with multiple co-intoxicants might partly result from the use of fentanyl-laced or counterfeit heroin, cocaine, opioids and benzodiazepines (CDC, 2016a; Marinetti and Ehlers, 2014; Unick and Ciccarone, 2017; CDC, 2018)^{4,31-33}. This could help explain the rapid rise in fentanyl-related deaths in WV, a state with traditionally high prescription opioid deaths. A prescription was present in a very small percentage of our recent fentanyl deaths, indicating predominantly IMF use or diversion.

Heroin was identified in over a third of fentanyl/FA-related deaths during 2015–2017 but can be difficult to detect due to its very rapid metabolism to 6-monoacetylmorphine, which has a

slightly longer but still relatively short half-life (Harruff et al., 2015)¹⁶. Thus, the morphine/codeine concentration ratio can assist in identifying heroin involvement in deaths. Codeine in small concentrations is often present in illicit heroin batches. A morphine/codeine ratio greater than three likely indicates that heroin use was the source of codeine present, while a ratio smaller than one typically indicates codeine ingestion (Harruff et al., 2015)¹⁶. In cases where 6-MAM was present in our study, all had a ratio greater than one, with most having a morphine/codeine ratio above three. Similar results were found in suspected heroin deaths in which 6-MAM was absent and a morphine/codeine ratio could be determined. Thus, only a relatively small number of 6-MAM-negative deaths might be falsely attributed to heroin, although some cases with heroin involvement could be missed.

The rapid increase in FA deaths represents an unprecedented public health threat (CDC, 2018)⁵, with prescription opioids and benzodiazepines still contributing to a significant number of deaths. Although relatively new to WV, FAs were identified for several years in other areas of the country (Hibbs et al., 1991)³⁴. A total of ten different FAs were identified in WV deaths during 2015–2017, usually with co-intoxicant fentanyl, heroin, benzodiazepines, cocaine or other FAs. Carfentanil and furanyl fentanyl were present most often, but new FAs continue to be identified.

Additional trends from the more recent drug-related deaths deserve special mention. Recent increases in methamphetamine involvement is of particular concern, particularly with the prevalence of cardiovascular disease in WV (CDC, 2016b)³¹. Heroin and cocaine were infrequently involved in WV deaths in past years but now constitute serious health threats. Alcohol should not be overlooked since it has consistently been among the top substances identified in WV drug-related deaths, present in almost a quarter of such deaths.

About 89% of WV drug deaths represented overdoses. Deaths were also included in which a transportation-related accident or other injury was the immediate cause of death, but drugs and/or alcohol were contributors. While not classified as overdoses, these deaths might have been avoided if the person was unimpaired. A total of 953 deaths between 2005 and 2017 fell into transportation or other injury categories (e.g., falling, drowning, choking/suffocating, being hit by trains or cars, ATV or other vehicular accidents) influenced by the presence of one or more substances. Of 321 such deaths from 2015 to 2017, fentanyl was found in 10 (3%) and prescription opioids were contributors in 70 (22%) (Table 1). By preventing overdose deaths, substance-related injury deaths might also be reduced. Further studies should explore trauma-related deaths directly or indirectly attributed to impairment.

Most study decedents had a history of drug and/or alcohol abuse, a known risk factor for opioid-related mortality (Webster, 2017)³⁵. This history was significantly more common in fentanyl/FA associated deaths, consistent with the illicit nature of FAs and the very low percentage of prescriptions present for fentanyl in the recent deaths. However, significantly lower rates of co-morbid cardiovascular and pulmonary conditions, also reported as risk factors for opioid-related death (Webster, 2017)³⁵, were found in WV decedents with fentanyl/FAs present. Existing diagnoses of psychiatric conditions and pain, reported to be risk factors for opioid mortality (Webster, 2017)³⁵, were found in about 20% and 11%, respectively, of our decedents' files. Since comprehensive medical histories were not available in most cases, these figures are likely incomplete. Further studies involving direct linkages with medical records are needed to examine the association of underlying medical conditions with drug mortality risk.

Most drug-related death reports have focused on overdoses based on ICD-10 codes (O'Donnell et al., 2017; Unick and Ciccarone, 2017)^{18,33}. A particular strength of this study is the use of

multiple data sources, including death certificates, autopsy reports, CSMP information, and toxicology analyses that allow individual opioids and drug combinations involved to be identified. A centralized medical examiner system in WV enables fairly complete decedent data to be compiled.

This study also has potential limitations. Accurately determining intent for manner of death (i.e., unintentional vs. suicide) is difficult postmortem. The WV OCME certifies deaths with the understanding that the potential for under-reporting suicides is substantial, and the number of suicides related to drug overdose deaths are likely underestimated (Rockett et al., 2018)³⁶.

Relevant data might be missing or incorrectly entered in the case file or FDD. However, data were checked for inconsistencies or missing values, with follow-up to the extent possible. Heroin can be difficult to identify in decedents due to rapid metabolism, so heroin in some cases might be missed. When fentanyl was found as a co-intoxicant, it cannot be determined whether the decedent used fentanyl in addition to heroin/other drugs or if heroin/ other drugs were taken that unknowingly contained fentanyl. Due to the frequency in which new FAs are appearing in the deaths, it is possible that as yet unknown analogs were not detected. A small number of drug-related deaths from 2017 were not yet entered into the FDD at the time of this study. However, preliminary review of these cases found that 31 (39.7%) had fentanyl present. Finally, West Virginia is a rural state with a high per capita drug overdose death rate. Although these findings might not be representative of other geographic areas, they are consistent with reports of increasing FA deaths in several states (CDC, 2018)⁵.

The substances involved in drug-related deaths must be closely monitored to ensure that appropriate harm reduction strategies are used. The frequency at which new FAs and IMF are appearing is particularly concerning since controlled substances monitoring programs cannot

track these substances. Routine toxicological detection of FAs is difficult, and clandestine laboratories can easily modify fentanyl and its derivatives. Expanded access to addiction treatment and ready availability of naloxone to treat acute opioid overdoses are needed (Frank and Pollack, 2017; Klebacher et al., 2017; Samet and Kertesz, 2018; Thomson et al., 2017; CDC, 2018)^{5,10,37-39}. Multifaceted fentanyl outbreak identification, prevention, harm reduction, and expanded treatment strategies that consider social, economic, and other contributing factors are needed to address the opioid and illicit drug crisis (Dasgupta et al., 2018; CDC, 2018)^{5,40}. Education and training of health providers, public health professionals, and health professions students are necessary to implement such strategies (Frank and Pollack, 2017; Samet and Kertesz, 2018; Thomson et al., 2017)^{10,38,39}. Public health, law enforcement, and other government agencies must work in collaboration to halt the production and supply of IMF, FAs and other illicit drugs.

2.6 Conclusions

Fentanyl involvement increased substantially over time in WV drug related deaths from 2005 to 2017, with ten different FAs identified since 2015. Prescription opioid presence decreased by about half with fentanyl, heroin, ethanol, alprazolam and cocaine constituting the top five identified drugs in these deaths since 2015. Alprazolam and ethanol were consistently among the top five drugs identified since 2005, with methamphetamine involvement increasing. In contrast, the presence of a prescription for most controlled substances identified in the deaths has been decreasing. Deaths involving fentanyl and newly identified FAs could represent the “tip of the iceberg” since fentanyl derivatives are often not readily detected.

Tables and Figures

Table 1 Changes in fentanyl, fentanyl analog, heroin, and non-fentanyl prescription opioid-related deaths in West Virginia, 2005-2017 (n = 8813).

2005 - 2014						2015 - 2017				
Characteristics	Total Drug-Related Deaths ^a n (%)	Fentanyl and/or Analogs ^b n (%)	Heroin ^c n (%)	Prescription Opioid(s) ^d n (%)	<i>p</i> - value ^e	Total Drug-Related Deaths ^a n (%)	Fentanyl and/or Analogs n (%)	Heroin ^c n (%)	Prescription Opioids(s) ^d n (%)	<i>p</i> - value ^e
Total ^f	5924 (NA)	487 (8.2)	508 (8.6)	3545 (59.8)	NA	2889 (NA)	1082 (37.5)	290 (10.0)	857 (29.7)	NA
Age (mean, SD)	41.6 (11.8)	39.7 (11.3)	36.1 (10.7)	41.3 (11.4)	0.0039	42.1 (12.3)	39.2 (11.2)	38.2 (11.2)	46.4 (11.4)	<0.0001
Male	3921 (66.2)	313 (64.3)	402 (79.1)	2240 (63.2)	0.6386	1952 (67.6)	766 (70.8)	202 (69.7)	515 (60.1)	<0.0001
BMI (mean, SD)	28.9 (7.6)	29.2 (6.9)	28.4 (6.6)	29.6 (7.9)	0.2544	28.4 (7.8)	28.1 (7.0)	28.9 (7.7)	29.3 (8.4)	0.0010
Number of drugs present										
Single drug	1320 (22.3)	48 (9.9)	97 (19.1)	366 (10.3)	0.8711	664 (23.0)	140 (12.9)	59 (20.3)	74 (8.6)	0.0018
2 drugs	1539 (26.0)	126 (25.9)	164 (32.3)	967 (27.3)		833 (28.8)	309 (28.6)	123 (42.4)	235 (27.4)	
3 drugs	1354 (22.9)	138 (28.3)	129 (25.4)	941 (26.6)		659 (22.8)	302 (27.9)	63 (21.7)	237 (27.7)	
4 drugs	895 (15.1)	97 (19.9)	66 (13.0)	651 (18.4)		409 (14.2)	202 (18.7)	24 (8.3)	161 (18.8)	
5 or more drugs	816 (13.8)	78 (16.0)	52 (10.2)	620 (17.5)		324 (11.2)	129 (11.9)	21 (7.2)	150 (17.5)	
Number of drugs present by sex (mean, SD)										
Female	3.2 (1.7)	3.3 (1.6)	3.1 (1.7)	3.5 (1.7)	0.2543	3.0 (1.6)	3.1 (1.4)	2.6 (1.5)	3.5 (1.7)	0.0013
Male	2.6 (1.4)	3.1 (1.3)	2.6 (1.4)	3.0 (1.4)	0.3451	2.5 (1.4)	2.9 (1.3)	2.4 (1.1)	3.0 (1.5)	0.0246

Total	2.8 (1.6)	3.2 (1.5)	2.7 (1.4)	3.2 (1.5)	0.8893	2.7 (1.5)	2.9 (1.3)	2.4 (1.3)	3.2 (1.6)	<0.0001
Manner of death										
Unintentional	4982 (84.1)	455 (93.4)	499 (98.2)	3141 (88.6)		2670 (92.4)	1068 (98.7)	284 (97.9)	762 (88.9)	
Suicide	517 (8.7)	8 (1.6)	8 (1.6)	175 (4.9)	0.0015	118 (4.1)	8 (0.7)	0 (0.0)	44 (5.1)	<0.0001
Other (Could not be determined, homicide)	425 (7.2)	24 (4.9)	1 (0.2)	229 (6.5)		101 (3.5)	6 (0.6)	6 (2.1)	51 (6.0)	
Cause of death by category										
Overdose	5292 (89.3)	480 (98.6)	506 (99.6)	3401 (95.9)		2568 (88.9)	1072 (99.1)	284 (97.9)	787 (91.8)	
Transportation (occupant, pedestrian, etc.)	197 (3.3)	2 (0.4)	1 (0.2)	40 (1.1)	0.0165	223 (7.7)	5 (0.5)	4 (1.4)	50 (5.8)	<0.0001
Other injuries (fall, firearm, drowning, etc.)	435 (7.3)	5 (1.0)	1 (0.2)	104 (2.9)		98 (3.4)	5 (0.5)	2 (0.7)	20 (2.3)	

NA: not applicable.

^a Includes deaths involving any drug or alcohol.

^b 2005-2014 included only 1 fentanyl analog identified in 1 death.

^c Any death involving heroin with no fentanyl and/or analogs.

^d Any death involving buprenorphine, codeine, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, diphenoxylate, propoxyphene, meperidine or tramadol; no fentanyl and/or analogs or heroin.

^e Comparison between fentanyl and/or analogs and prescription opioid(s).

^f Total drug-related deaths during time period.

Table 2

Drugs most frequently present in total, 2005-2014, and in total and fentanyl ± fentanyl analog-related unintentional deaths in West Virginia, 2015-2017 (n = 7652).

2005-2014 (n = 4982)			2015-2017 (n = 2670)			
Substance	Total ^a n (%)	Substance	Total ^a n (%)	F ± FA Present (n = 1068) n (%)	F ± FA Absent (n = 1602) n (%)	p - value ^b
Alprazolam	1551 (31.1)	Fentanyl	899 (33.7)	NA	NA	NA
Oxycodone	1430 (28.7)	Heroin	672 (25.2)	388 (36.3)	284 (17.7)	<0.0001
Ethanol	1262 (25.3)	Ethanol	593 (22.2)	161 (15.1)	432 (27.0)	<0.0001
Diazepam	1244 (25.0)	Alprazolam	495 (18.5)	166 (15.5)	329 (20.5)	0.0011
Hydrocodone	1029 (20.7)	Cocaine	457 (17.1)	213 (19.9)	244 (15.2)	0.0015
Methadone	783 (15.7)	Oxycodone	429 (16.1)	95 (8.9)	334 (20.8)	<0.0001
Cocaine	730 (14.7)	Methamphetamine	403 (15.1)	157 (14.7)	246 (15.4)	0.6430
Heroin	524 (10.5)	Diazepam	368 (13.8)	116 (10.9)	252 (15.7)	0.0003
Morphine	520 (10.4)	Hydrocodone	273 (10.2)	60 (5.6)	213 (13.3)	<0.0001
Fentanyl	454 (9.1)	Gabapentin	248 (9.3)	30 (2.8)	218 (13.6)	<0.0001
Oxymorphone	402 (8.1)	Clonazepam	217 (8.1)	63 (5.9)	154 (9.6)	0.0006
Clonazepam	358 (7.2)	Morphine	207 (7.8)	114 (10.7)	93 (5.8)	<0.0001
Citalopram	301 (6.0)	Buprenorphine	189 (7.1)	46 (4.3)	143 (8.9)	<0.0001
Diphenhydramine	299 (6.0)	Oxymorphone	145 (5.4)	20 (1.9)	125 (7.8)	<0.0001
Tramadol	214 (4.3)	Methadone	95 (3.6)	22 (2.1)	73 (4.6)	0.0006

NA: not applicable; F: fentanyl; FA: fentanyl analogs.

^a Total drug-related unintentional deaths during time period (excludes cases with other manners of death).

^b Comparison between deaths in which F and/or FA were present or absent.

Table 3 Fentanyl analogs identified in drug-related deaths in West Virginia, 2015 - 2017 (n = 2889).

Characteristic	Carfentanil (%)	Furanyl fentanyl (%)	Para-fluoro(isobutyryl) fentanyl (%)	Acetyl fentanyl (%)	Acryl fentanyl (%)	Cyclopropyl fentanyl (%)	Butyryl fentanyl (%)	3-Methyl fentanyl (%)	Methoxycetyl fentanyl (%)	Tetrahydrofuran fentanyl (%)
Total No. of cases	117	104	75	56	29	20	10	8	7	1
First identified date	2016/Aug	2015/Jan	2015/Jan	2013/Jan	2015/Jan	2017/Jun	2016/Dec	2016/Sept	2017/Sept	2017/April
Age (mean, SD)	38.8 (11.7)	40.1 (11.2)	40.9 (11.3)	37.4 (9.7)	35.0 (9.2)	39.6 (11.6)	44.1 (8.6)	33.6 (10.2)	43.4 (14.2)	26.0 (.)
Male	75 (64.1)	69 (66.3)	60 (80.0)	35 (62.5)	20 (69.0)	17 (85.0)	10 (100.0)	6 (75.0)	5 (71.4)	0 (.)
Number of drugs present (mean, SD)	3.2 (1.6)	3.9 (1.4)	4.1 (1.3)	3.8 (1.4)	3.5 (1.3)	3.2 (1.6)	4.7 (1.8)	2.4 (0.5)	4.4 (1.9)	4 (.)
Single drug	16 (13.7)	2 (1.9)	1 (1.3)	1 (1.8)	2 (6.9)	4 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2 drugs	27 (23.1)	14 (13.5)	9 (12.0)	8 (14.3)	5 (17.2)	3 (15.0)	1 (10.0)	5 (62.5)	1 (14.3)	0 (0.0)
3 drugs	28 (23.9)	26 (25.0)	12 (16.0)	17 (30.4)	9 (31.0)	5 (25.0)	2 (20.0)	3 (37.5)	1 (14.3)	0 (0.0)
4 drugs	24 (20.5)	32 (30.8)	29 (38.7)	17 (30.4)	7 (24.1)	4 (20.0)	2 (20.0)	0 (0.0)	2 (28.6)	1 (100.0)
5 or more drugs	22 (18.8)	30 (28.8)	24 (32.0)	13 (23.2)	6 (20.7)	4 (20.0)	5 (50.0)	0 (0.0)	3 (42.9)	0 (0.0)
Cases with concurrent										
Fentanyl	41 (35.0)	32 (30.8)	46 (61.3)	49 (87.5)	14 (48.3)	9 (45.0)	6 (60.0)	1 (12.5)	6 (85.7)	0 (0.0)

Other fentanyl analog(s)	28 (23.9)	31 (29.8)	41 (54.7)	1 (1.8)	15 (51.7)	5 (25.0)	5 (50.0)	2 (25.0)	3 (42.9)	1 (100.0)
Other prescription opioid(s)^a	28 (23.9)	25 (24.0)	14 (18.7)	20 (35.7)	3 (10.3)	2 (10.0)	3 (30.0)	2 (25.0)	2 (28.6)	1 (100.0)
Heroin	26 (22.2)	48 (46.2)	42 (56.0)	29 (51.8)	17 (58.6)	6 (30.0)	5 (50.0)	1 (12.5)	2 (28.6)	1 (100.0)
Benzodiazepine(s)^b	34 (29.1)	39 (37.5)	19 (25.3)	15 (26.8)	3 (10.3)	4 (20.0)	3 (30.0)	0 (0.0)	1 (14.3)	0 (0.0)
Ethanol	13 (11.1)	18 (17.3)	9 (12.0)	10 (17.9)	2 (6.9)	0 (0.0)	2 (20.0)	0 (0.0)	1 (14.3)	0 (0.0)
Methamphetamine	28 (23.9)	13 (12.5)	5 (6.7)	4 (7.1)	6 (20.7)	6 (30.0)	2 (20.0)	1 (12.5)	4 (57.1)	0 (0.0)
Cocaine	19 (16.2)	20 (19.2)	22 (29.3)	12 (21.4)	3 (10.3)	6 (30.0)	3 (30.0)	4 (50.0)	2 (28.6)	0 (0.0)
Most frequently occurring analog co-intoxicant	Furanyl fentanyl, 17 (14.5)	Para-fluoro(iso)butyryl /butyryl fentanyl, 32 (30.8)	Furanyl fentanyl, 32 (42.7)	Furanyl fentanyl, acryl fentanyl, para-fluoro(iso)b utyryl fentanyl, 1 (1.8)	Furan yl fentan yl, 13 (44.8)	Para-fluoro(iso)b utyryl fentanyl, Butyryl fentanyl, 2 (10.0)	Para-fluoro(iso)b utyryl fentanyl, 5 (50.0)	Carfent anil, Furanyl fentanyl, 1 (12.5)	Carfentani l, 2 (28.6)	Carfentanil, 1 (100.0)

^a Any death involving buprenorphine, codeine, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, diphenoxylate, propoxyphene, meperidine or tramadol; no fentanyl or heroin

^b Benzodiazepines include alprazolam, clonazepam, chlordiazepoxide, diazepam, lorazepam, oxazepam, temazepam.

Table 4**Comorbid medical conditions in unintentional drug-related deaths (n = 7652) - fentanyl + FAs vs. non-fentanyl + FAs in West Virginia, 2005-2017.**

Medical Conditions	Total Deaths n (%)	Fentanyl and/or Analogs Present n (%)	Fentanyl and/or Analogs Absent	<i>p</i> - value^b
			n (%)	
Total^a	6837	1420	5417	-
Cardiovascular	3306 (48.4)	584 (41.1)	2722 (50.3)	<0.0001
Psychiatric	1342 (19.6)	299 (21.1)	1043 (19.3)	0.128
Pulmonary	1622 (23.7)	241 (17.0)	1381 (25.5)	<0.0001
Hepatic	660 (9.7)	142 (10.0)	518 (9.6)	0.6192
Pain	738 (10.8)	154 (10.9)	584 (10.8)	0.9447
History of Abuse	4915 (71.9)	1244 (87.6)	3671 (67.8)	<0.0001

^aTotal cases with available medical history data; percentages calculated using total number as denominator.^bComparison between fentanyl and/or analogs present vs. fentanyl and/or analogs absent.

Fig. 1. Fentanyl ± fentanyl analogs and other drug involvement in unintentional deaths in West Virginia, 2012- 2017.

Solid line with solid square = Fentanyl and/or analogs, dotted line with hollow diamond = Benzodiazepines, solid line with solid triangle = Heroin, dotted line with hollow circle = Methamphetamine, solid line with solid diamond = Ethanol, dotted line with hollow square = Cocaine, solid line with solid circle = Oxycodone, dotted line with hollow triangle = Hydrocodone.

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Chapter 3

3.1 Abstract

Objective

The study aims to examine recurrent opioid overdose and how changes in receipt of Medication for Opioid Use Disorder (MOUD) following a non-fatal overdose influence risk of mortality among the West Virginia (WV) Medicaid population.

Methods

West Virginia Medicaid claims data was obtained from 2014 to 2016. People with an index non-fatal opioid overdose were identified as the first in the dataset using ICD codes and they were then followed up as a cohort for one year. Occurrence of recurrent opioid overdose and changes in receipt of MOUD and other medication use were examined.

Results

A total of 399,683 (77.8%) consecutively enrolled WV Medicaid beneficiaries from 2014 to 2016 were analyzed in the study. A total of 2995 people experienced 3525 documented overdoses and 389 (13.0%) of them had multiple overdoses (291 had two overdoses, 68 had three overdoses, and 30 had four to seven overdoses), resulting in an average of 1.18 overdoses per person in the 12-month follow up. Only 1140 (38.1%) of people were confirmed a diagnosis of OUD, and 431(25.3%) received MOUD at any time, of whom 273 (63.3%) received buprenorphine hydrochloride and/or Suboxone, 78 (18.1%) received naltrexone, and 80 (18.6%) received both medications. There were 125 patients who initiated MOUD after the index overdose. The median time staying in MOUD treatment was 88 days.

Conclusions

Only a quarter of people who experienced opioid overdose had received MOUD at any time and half of them stayed in the treatment less than 3 months, suggesting limited effectiveness. In addition of those overdosing only 38% had a diagnostic code for OUD in their record. Although a nonfatal overdose represents an opportunity to initiate MOUD, it was certainly under-utilized among WV overdose population.

3.2 Introduction

WV leads the nation in drug overdose mortality with the highest mortality rate of 58 per 100,000 as of 2017, almost 3 times the U.S. average (Wolf et al., 2020; Scholl et al., 2019)^{1,2}. The current opioid crisis has strained the capacity of health care and social service resources and taken a significant toll on individuals, families, communities, and counties in WV (Saloner et al. 2019)³. Medicaid programs have effectively respond to the opioid crisis by expanding treatment coverage and reforming treatment delivery systems (Barnes et al., 2020)⁴. Approximately 29% of the WV population are covered by Medicaid, and this makes WV rank highest in the nation in terms of proportion of population covered (KFF 2018)⁵. According to West Virginia Department of Health and Human Resources (WVDHHR)⁶, 71% of drug overdose decedents were enrolled in Medicaid in the 12 months prior to their death as compared to only 23% West Virginia's adult population aged 19-64. Specifically, of those decedents with Medicaid enrollment, 81% had medical claims within 12 months prior to their date of death, excluding those decedents who only used the benefit within 48 hours before death⁶. As for emergency department (ED) visits, 68% of decedents with Medicaid had at least one ED visit in the 12 months prior to death.

Expansion of Medicaid started in 2014, and served as an important step in increasing accessibility of medications for opioid use disorder (MOUD) for persons with substance abuse disorder (WVDHHR 2017; Sharp et al. 2018)^{5,7}. In 2017 the WV DHHR Bureau for Medical

Services (BMS) gained approval for a Medicaid Section 1115 waiver to develop a continuum of care for individuals with substance use issues starting in January 2018 which expanded the services offered for substance abuse treatment.

The three Food and Drug Administration (FDA) approved MOUD (methadone, buprenorphine, and naltrexone) have been shown to be effective treatment options in reducing drug use, compulsive drug seeking, substance use relapse, overdose, and lowering mortality (Sharp et al. 2018; Schwartz et al. 2013; Rudd 2016; Banta-Green et al. 2017; Zoorob 2019; Leshner and Mancher 2019)⁷⁻¹², yet they are infrequently provided to OUD patients (Larochelle et al., 2018; Frazier et al., 2017; Larochelle et al., 2016)¹³⁻¹⁵. Unfortunately, the need for care far exceeds the current treatment infrastructure in West Virginia, resulting in long waiting lists, and eventual overdoses for many persons actively seeking treatment (Pollini et al. 2006)¹⁶. In addition , patients are also suffering from many comorbid drug-related mental health conditions, such as anxiety, bipolar, depression, alcohol use disorder and other drug use disorders, which increase overdose risk (Bohnert et al., 2012; Suffoletto and Aeigler et al., 2020)^{17,18}.

Moreover, persons experiencing nonfatal overdose are at increased risk of overdose death (Coffin et al. 2007)¹⁹. This risk is further intensifying in states like West Virginia experiencing geographic isolation ²⁰(Hall et al. 2008) and having limited medical resources, resulting in gaps between need for sustainable treatment and the state's capacity to deliver these options ²¹(Jones et al. 2015). Given the fact that potent fentanyl and fentanyl analogs are increasingly involved in opioid overdoses, the number of non-fatal overdoses before mortality is decreasing ^{13,22,23}(Frazier et al. 2017; Slavova et al. 2017; Massachusetts Department of Public Health, 2017), suggesting urgency of starting treatment early to prevent deaths in OUD patients. Considering the substantial burden of the chronic nature of OUD, repeated overdose, and psychiatric

comorbidities among people who overdose, it is important to understand recurrent opioid overdose and changes of receipt of MOUD following a non-fatal overdose. Previous studies (Laroche et al., 2018; Suffoletto and Aegler et al., 2020)^{13,18} have shown that survival modelling approach could be used to determine whether recurrent opioid overdose was associated with increased risk of mortality, and receipt of MOUD was associated with decreased risk of mortality. Our study sought to examine recurrent opioid overdoses and how changes in receipt of Medication for Opioid Use Disorder (MOUD) following a non-fatal overdose among the West Virginia (WV) Medicaid population affect risk of subsequent mortality.

3.3 Methods

Sample design

West Virginia Medicaid claims data was obtained from WV Medicaid. They created a Common Data Model (CDM) to incorporate an extensively cleaned subset of WV Medicaid data that was designed to study opioid-related measures. The CDM included WV Medicaid data from 2014 to 2016 for persons aged 18-64 and excluded about 20% of people who had dual-eligibility with Medicare, as Medicare is the primary payer and Medicaid does not include all claims from this group. An overdose cohort was then created from CDM by selecting continuously enrolled persons ages 18 to 64 with at least one nonfatal overdose event identified by ICD codes (Appendix A, ICD-9: 965.00-965.02, 965.09, E850.0-E850.2 or ICD-10: X40-X44, X60-X64, X85, Y10-Y14) from emergency department (ED) visits or hospitalization. These ICD-9 codes have been validated with 81% positive predictive values for identifying fatal or nonfatal opioid overdose occurred before October, 2015 ²⁴(Green et al., 2017). Another study suggested that ICD-10 codes are able to capture more opioid-related hospitalizations that were otherwise missed by ICD-9 codes (Heslin et al., 2017)²⁵. Multiple opioid overdoses that occurred during one

hospitalization interval (admission and discharge date) were counted as one overdose event. Two overdoses recorded within two days were also accounted as one overdose event. Thus, a recurrent overdose event was defined as one occurring at least two days after the previous overdose (avoid potential carry-on effect from previous overdose). Among those who had at least 12 months length of observation overdose free, the first nonfatal overdose identified was marked as the index overdose. The retrospective cohort follow-up starts with the index overdose, and ends with death or with beneficiaries dropping out within 12 months after the index overdose. The cohort excluded those who died within 30 days of index overdose (make sure every subject had at least one-month follow up) and patients with any cancer diagnosis (avoid confounding effect from cancer) at any time of cohort. The ICD -9 and ICD-10 codes used to identify cancer were listed in Appendix A. Missing values were checked for age and gender and no one was excluded for this reason.

This study was reviewed and approved by the Institutional Review Board (protocol number: 1711862183A001) at the West Virginia University, Morgantown, WV.

Analysis Plan

The primary outcome of interests in this aim are recurrent overdose and relationship to receipt of MOUD. The receipt of MOUD was identified from both pharmacy datasets using NDC codes (Appendix B), and from inpatient and outpatient datasets using procedure code. First, the descriptive statistical analysis were performed to describe the opioid overdose cohort. Median was reported for continuous variables; number and percentage were reported for categorical variables. Demographic characteristics including age, gender, and Medicaid eligibility category were analyzed. The number and frequency of overdose events, the monthly receipt of MOUD, the number and type of frequently present mental health conditions (including anxiety, bipolar,

depression, alcohol use disorder, and substance use disorder) identified using ICD-9 or ICD-10 codes were also analyzed. Descriptive analyses comprise medication (including opioid analgesics and benzodiazepines) use patterns before and after the index overdose.

3.4 Results

A total of 513,707 Medicaid beneficiaries aged 18 to 64 were included in the CDM and 399,683 (77.8%) of them were continuously enrolled over the 3 years from 2014 to 2016 (Figure 1). No significant difference of demographic characteristics, including age, gender and race, between those continuously enrolled and non-continuously enrolled were identified. There were slight difference among eligibility categories among the two groups: young people were more likely to drop out of enrollment and non-disabled adults were less likely to drop out.

Of those continuous enrollees, there were 2,995 people (0.75%) who had experienced at least one opioid overdose over the 3-year period. The number of overdoses increased by 45% and 59% in 2015 and 2016 respectively, compared to the previous year (Table 1). The median period was 133 days between the first two overdoses, 74.5 days between the following two overdoses, and 69 days between the third and the fourth overdose.

There were initially 4472 overdoses documented among all 2995 continuously enrolled population. However, using 2 days as a cut-off (Olfson et al., 2018)²⁶ to distinguish distinct overdoses, 21% (n = 947) of overdose records were removed since they happened on the same day or the next day leaving a total of 3525 overdose related claims for the 2,995 individuals who had any overdose, of which 2606 (87%) had only 1 overdose and 389 (13%) had multiple overdose (number of overdose = 919), resulting in on average 1.18 overdose per person. Among people who had multiple overdoses, 291 had two overdoses, 68 had three overdose, 21 had four overdoses, and 9 had from five to seven overdoses. Compared with single overdose group,

multiple overdoses group shared similar demographic characteristics other than a significantly younger age (37.0 vs. 38.5, $p = 0.0129$) (Table 1). Frequency distribution of comorbid mental health conditions were similar, as the single overdose group and multiple overdoses group share similar proportion of anxiety diagnosis (10.6% vs. 10.5%), bipolar diagnosis (5.3% vs. 4.7%), alcohol use disorder (5.0% vs. 4.0%), other drug use disorder (36.2% vs. 37.7%), but only a higher rate of depression diagnosis (14.6% vs. 11.3%, $p = 0.0025$).

Additionally, among continuously enrolled beneficiaries who had at least one opioid overdose, 1140 (38.1%) of them had confirmed diagnosis of OUD. A total of 937 (82.2%) OUD patients died and 348 (37.1%) of them died of overdose. The median time interval between the first diagnosis of OUD and death is 494 days. Among those who died of overdose, the median time interval between the first diagnosis of OUD and death is 528.5 days. Among those who experienced an overdose, 272 (23.9%) were diagnosed after the index overdose with a median time interval of 119.5 days, 404 (35.4%) were diagnosed on the same date of index overdose, and remaining 464 (40.7%) were diagnosed prior to the index overdose with a median time interval of 269 days.

After excluding 1180 subjects with less than 12 months observation time period prior to the index overdose, 43 who died within 30 days of index overdose, and 69 with cancer diagnosis, the final survival cohort includes 1703 patients with 2001 records of overdoses (1.17 overdose per person on average), and 84 (4.9%) of them died within the following 12 months. Only 431 (25.3%) of patients who overdosed had ever received MOUD, among whom 273 (63.3%) received buprenorphine (buprenorphine hydrochloride and/or Suboxone), 78 (18.1%) received naltrexone, and 80 (18.6%) received both medications. Specifically, 125 (29%) initiated MOUD after the index overdose, 201 (46.6%) had initiated MOUD but dropped out before the index

overdose, and the remaining 105 (24.4%) initiated and continued the treatment through the index overdose. The median time staying in the MOUD treatment was 88 days, ranging from 2 to 1094 days. Notably, people who received any MOUD at any time had a higher rate of repeated overdose compare with people who never received any MOUD (13.5% vs. 9.8%, p -value = 0.03).

As unadjusted analysis of monthly receipt of medication shows (Figure 2) the proportion of people receiving opioid analgesics and benzodiazepines decreased from 21-22% by approximately 0.31% and 0.37% per month after the index overdose, respectively. Conversely, in the 12 months after an index overdose, the proportion of people receiving Suboxone increases by 0.19% per month, while the proportion of people receiving buprenorphine hydrochloride and naltrexone decreased to 0 and 0.3%, respectively.

3.5 Discussion

From 2014 to 2016, the number of overdoses occurred among WV Medicaid population increased around 50% for every year with a significant amount of people experiencing recurrent overdoses. In addition, the length of interval between two overdoses decreased as the number of recurrent overdoses increased, suggesting overdose occurred more frequently. Considering the drastically increased number of opioid overdoses every year, the task to curb opioid overdose remains challenging as the proportion of people receiving any type of MOUD after an index overdose is low. Despite overall observed increasing trend of receipt of MOUD at monthly level, still only about 5-10% of people received MOUD, which is far below the rates reported in Massachusetts (30% from 2012 to 2014) and Pennsylvania (33% from 2008 to 2013) (Larochelle et al., 2018; Frazier et al., 2017)^{13,14}. We may have much less accessibility to treatment. Another issue is the high rate of comorbid mental health conditions, especially given that almost a third of

the overdose population had other drug use disorders, including stimulants, cannabis related disorders (Appendix B). Currently we have MOUD to effectively treat OUD, however, we do not have any efficacious medications for stimulant use disorders (Ellis et al., 2018)²⁷. The high rates of SUD and OUD associated with high rates of prescription of opioid analgesics and benzodiazepines, which were at high risk of abuse and further worsen people's health.

The study also observed that people who received any MOUD at any time had a significantly higher rate of repeated overdose compared with people who never received any MOUD. The reason might be that the discontinuation of MOUD would elevate the risk of opioid overdose (Sordo et al., 2017; Davoli et al., 2007)^{28,29}, which deters many people who previously experienced overdose from receiving MOUD treatment. Almost 5% of this population died within 12 months (excluding cancer patients and those who died within 30 days of index overdose), which is close to the MA study (4.7%) (Larochelle et al., 2018)¹³, and over 10% experienced another overdose, resulting in high burden of opioid overdose which urgently needed any opportunity to initiate MOUD as soon as possible and keep the patients in the treatment long enough to have effective prognosis. Since over half of those deaths occurred among people aged 45 years or older, maybe elderly should be considered of high priority of referring for treatment. In addition, despite of an overall trend of decreasing prescription of opioids and benzodiazepines, there were clear drops after the index overdose. The monthly rate of prescription was still close to 20% after 12 month of index overdose. Although it is well known that opioid use or benzodiazepine use are risk factors leading to opioid overdose, how observed decreased prescription of opioids and benzodiazepines contributes to the next overdose or death was unclear among this population (Larochelle et al., 2016; Jones et al., 2015)^{15,21}.

Limitations of this study include inability to analyze receipt of methadone since methadone was not covered by WV Medicaid until January 1st, 2018, restriction to those continuously enrolled. However, few clinics offer methadone treatment in WV and most of them were paid out-of-pocket or covered by commercial insurance. The Medicaid data used in this study excluded dual-eligibility population with Medicare, which only accounts for 20% of overall Medicaid data. Due to only 1-year follow up, the study failed to capture the whole length of time staying in the treatment for some MOUD recipients. The study also did not analyze the effect of discontinuation of MOUD on recurrent overdose and mortality.

Considering the substantial burden of the chronic nature of OUD, repeated overdoses, psychiatric comorbidities, and relatively high prescription rates of opioids or benzodiazepines, it is important to gain a deeper understanding of the circumstances that influence fatal and nonfatal opioid overdoses. A further survival analysis is needed to evaluate MOUD effectiveness among this population while controlling for the previously discussed covariates, and expected to provide more details on how to curb opioid overdose.

Tables and Figures

Figure 1. Flow chart of case selection of opioid overdose cohort

Figure 2. Monthly receipt of opioid analgesic, benzodiazepines and medication for opioid use disorder

Table 1 Demographic and Medicaid-related Characteristics among Opioid Overdose Population (N = 2995)

	Overall^a	Single Overdose^b	Multiple Overdose^b
Number of people	2995	2606 (87.0%)	389 (13.0%)
Number of overdose	3525	2606 (73.9)	919 (26.1)
2014	743 (21.1) ^c	547 (73.6)	196 (26.4)
2015	1075 (30.5) ^c	807 (75.1)	268 (24.9)
2016	1707 (48.4) ^c	1252 (73.3)	455 (26.7)
Number of death	283 (9.5)	238 (84.1)	45 (15.9)
Age	38.3 ± 11.7	38.5 ± 11.8	37.0 ± 11.6
18 - 29	622 (20.8)	619 (84.8)	111 (15.2)
30 - 44	1294 (43.2)	1080 (86.4)	170 (13.6)
45 - 64	1079 (36.0)	907 (89.4)	108 (10.6)
Male	1511 (50.5)	1313 (86.9)	198 (13.1)
Race			
Non-Hispanic white	2655 (88.7)	2302 (86.7)	353 (13.3)
Non-Hispanic black	93 (3.1)	84 (90.3)	9 (9.7)
Hispanic	45 (1.5)	36 (80.0)	9 (20.0)
Others	202 (6.7)	184 (91.1)	18 (8.9)
Eligibility category ^d			
Pregnant Women	43 (1.4)	36 (83.7)	7 (16.3)
Children	88 (2.9)	75 (85.2)	13 (14.8)
Disabled Adults	152 (5.1)	131 (86.2)	21 (13.8)
Non-Disabled Adults	413 (13.8)	358 (86.7)	55 (13.3)
Expansion Adults	1251 (41.8)	1092 (87.3)	159 (12.7)
Psychiatric conditions			
Anxiety	317 (10.6)	233 (73.5)	84 (26.5)
Depression	413 (13.8)	310 (75.1)	103 (24.9)
Bipolar	153 (5.1)	111 (72.5)	42 (27.5)
Alcohol use disorder	141 (4.7)	105 (74.5)	36 (25.5)
Drug use disorder	1109 (37.0)	766 (69.1)	343 (30.9)

Note: ^a percentage was calculated by column;

^b percentage was calculated by row.

^c percentage was calculated by the number of overdose.

^d 1048 (35%) had missing eligibility category.

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Chapter 4

4.1 Abstract

Objective

The study aims to identify associations between the time of initiation of medication for opioid use disorder (MOUD) and risk of mortality for 1 year following a medically treated nonfatal overdose among a West Virginia (WV) Medicaid enrollee, adjusting for recurrent overdose and other risk factors.

Methods

A retrospective cohort including 1703 WV Medicaid beneficiaries ages 18-64 were followed after a nonfatal opioid overdose starting January 1, 2014 and until December 31, 2016, death, or 12 months after the index overdose, whichever came first. All-cause mortality and opioid-specific mortality data were extracted from West Virginia Vital Statistics and linked with WV Medicaid claim data. The effects of timing of initiation of MOUD, duration of MOUD treatment and occurrence of recurrent overdose on patients' survival rates were examined by Kaplan-Meier curves, and evaluated through Cox proportional hazard models in a sequential process, while accounting for other covariates, including age, gender, other drug use disorder (stimulants, cannabis, etc.), opioid use, and benzodiazepine use.

Results

In the 12-month follow up after the index overdose, 182 (10.7%) experienced at least one recurrent overdose, 84 (4.9%) died, of which 45 died of opioid poisoning. A total of 431 people (25.3%) received MOUD (buprenorphine, naltrexone or both) at any time and only 125 of them initiated MOUD after the index overdose. Compared with no MOUD, those who received MOUD were associated with non-significant increased all-cause mortality (adjusted hazard ratio

[AHR], 1.14 [CI 0.66, 1.96]) and opioid-specific mortality (AHR, 1.53 [CI 0.79, 2.95]).

Occurrence of recurrent overdose was associated with non-significant increased all-cause mortality (AHR, 1.54 [CI 0.83, 2.86]) and opioid-specific mortality (AHR, 1.80 [CI 0.83, 3.89]). Compared to those under age 30, older age groups had significantly higher all-cause mortality (age between 30-44, AHR, 2.77 [CI 1.21, 6.31]; age at or over 45, AHR, 5.68 [CI 2.52, 12.80]) and diagnosis of other drug use disorder (AHR, 1.54 [CI 0.99, 2.38]). Benzodiazepine use (based on filled prescriptions only) post index overdose was significantly associated with increased opioid-specific mortality (AHR, 1.89, [CI 0.99, 3.59]). Among people who received any MOUD, initiation of MOUD before index overdose was associated with non-significant decreased all-cause mortality (AHR, 0.62 [CI 0.20, 1.93]) and opioid-specific mortality (AHR, 0.83 [0.22, 3.11]); duration of treatment over 3 months was associated with non-significant decreased all-cause mortality (AHR, 0.34 [CI 0.10, 1.22]) and opioid-specific mortality (AHR, 0.46 [0.12, 1.74]).

Conclusions

Our study found that people who had had an overdose and then received any types of MOUD post overdose had higher all-cause mortality rates and opioid-specific mortality rates than those who did not. This is in contrast with other studies, which may be due to the fact that in a state with poor access to services, and those receiving MOUD had OUD of a higher severity.

However, among people who received any MOUD at any time, those who initiated MOUD early and those who stayed in the MOUD for over three months had better survival outcomes. Older age was significantly associated with high all-cause mortality rate but low MOUD receipt rates. Benzodiazepine use and comorbid other drug use disorder increased risk of mortality. In order to

prevent future mortality among people who experience an opioid overdose, it is critical to provide them access to MOUD in time and make sure they stay in treatment.

4.2 Introduction

West Virginia (WV) is in the midst of an opioid overdose crisis with a nationally leading overdose mortality rate of 58 per 100,000 as of 2017, almost 3 times the U.S. average (Scholl et al., 2019)¹. Since 2015, potent fentanyl and fentanyl analogs were greatly involved and drove a sharp increase in the WV fatal opioid overdose (Dai et al., 2019)². However, tracing non-fatal overdose is more difficult as until recently under West Virginia state law overdose was not a reportable condition and only required overdose reporting quarterly (Davis et al., 2018)³. In order to curb the opioid crisis, WV preceded the Affordable Care Act (ACA) and expanded Medicaid coverage starting on January 2014 (Saloner et al., 2019)⁴. The expansion mainly provided health insurance to non-disabled adults with incomes below 138% of the federal poverty level—a population with an elevated risk of opioid overdose. By the time of early 2016, over 50% of newly enrolled WV Medicaid beneficiaries were of expansion eligibility, compared to the pre-ACA monthly Medicaid average (KFF 2016; KFF 2018)^{5,6}. Medicaid enrollees have an estimated 3-times higher risk of opioid overdose (Sharp and Melnik, 2015)⁷, and has been identified as a high-risk population for fatal opioid overdose by Centers for Disease Control and Prevention (CDC) (Garg et al., 2017; Stoope et al., 2009)^{8,9}. In 2017, approximately 29% of the WV population were covered by Medicaid, but overdose decedents were more likely to be enrolled in Medicaid (71%) in the 12 months prior to their death (KFF 2018; WVDHHR 2016)^{5,10}, which makes WV Medicaid an excellent setting to evaluate the effectiveness of MOUD on addressing opioid overdose. However, data on the association between MOUD

treatment and mortality after a nonfatal overdose have not been evaluated in WV, which is a predominately rural state with a lower social-economic status compared to Pennsylvania and Massachusetts, where MOUD has been shown effectively in reducing mortality (Laroche et al., 2018; Suffoletto and Zeigler, 2020)^{11,12}.

Three Medications for OUD (MOUD) are proven treatment options (based on randomized controlled trials) in reducing drug use, compulsive drug seeking, substance use relapse, overdose and mortality (Sharp et al. 2018; Schwartz et al. 2013; Rudd 2016; Banta-Green et al. 2017; Zoorob 2019; Leshner and Mancher 2019)¹³⁻¹⁸. Buprenorphine is thought to be safer than methadone, a full opioid agonist, since a partial agonist is less likely to induce respiratory depression (Kimber et al., 2015)¹⁹. Naltrexone, an opioid antagonist, blocks the action of opioids and thus prevents patients from dying of respiratory depression (Volkow et al., 2014)²⁰. One recent systematic review and meta-analysis of 30 observational cohort studies identified a significant protective effect in reducing all-cause and overdose mortality among people who received any types of MOUD, especially during the time receiving MOUD (Ma et al., 2018)²¹. However, the mortality rate after opioid substitution treatment with buprenorphine was significantly higher, and the mortality rate after naltrexone treatment was significantly lower. However, another systematic review and meta-analysis of 19 observational cohort studies showed quite the opposite conclusion (Sordo et al., 2017)²², as substantial reductions in all-cause and overdose mortality for buprenorphine was identified, and the effect of naltrexone on mortality was unclear (Lincoln et al., 2018; Lee et al., 2017; Kelty and Hulse, 2012; Gibson and Degenhardt, 2007)²³⁻²⁶. Both reviews confirmed that with longer retention time in MOUD treatment, the mortality rate gets lower (Ma et al., 2018; Sordo et al., 2017)^{21,22}.

However, those studies failed to account the effect of repeated overdose on mortality. Persons experiencing nonfatal overdose are at increased risk of overdose death (Coffin et al. 2007)²⁷. A most recent systematic review and meta-analysis included 75 studies, suggesting a weak but positive relationship between non-fatal overdose and drug-related deaths (Colledge et al., 2019)²⁸, and this relationship was further quantified by a cohort study with over 10,000 patients, suggesting that a history of non-fatal overdose increased the risk of subsequent non-fatal overdose (1.57, 95% CI 1.42-1.73) and fatal overdose (1.43, 95%CI 1.12-1.82) (Thylstrup et al., 2020)²⁹.

Many studies, including systematic reviews with meta-analysis have determined risk factors associated with drug-related deaths. Commercially insurance claim data suggested that over 90% of people received opioids even after an overdose (Larochelle et al., 2016)³⁰, and continuous receipt of opioid after overdose is associated with high risk for recurrent overdose (Okie, 2010; Paulozzi et al., 2011)^{31,32}. As a known risk factor leading to opioid overdose, benzodiazepines use was common among opioid users, and increasingly involved in opioid analgesic overdose deaths from 18% in 2004 to 31% in 2011 (Thylstrup et al., 2020; Garg et al., 2017; Olfson et al., 2018; Jones et al., 2015)^{8,29,33,34}. Psychiatric conditions including anxiety, bipolar, depression, alcohol use disorder and other drug use disorders (stimulants, cannabis related) were prevalent among opioid users and were strongly associated with opioid-related mortality (Suffoletto and Zeigler, 2020; Olfson et al., 2018; Bohnert et al., 2012; Webster et al., 2017; Brady et al., 2017)^{12, 35-38}. Medicaid data from 45 states showed that over a third of decedents experienced a non-fatal overdose were diagnosed with drug use disorders, a fifth were diagnosed with anxiety, almost a quarter were diagnosed with depression, and about an eighth were diagnosed with bipolar and alcohol use disorder in the last 12 months of life (Olfson et al., 2018)³³.

Considering the substantial burden of the chronic nature of OUD, repeated overdoses and psychiatric comorbidities among people who had overdosed, it is important to gain a deeper understanding of the circumstances that influence fatal and nonfatal opioid overdoses. Previous studies (Larochelle et al., 2018; Suffoletto and Aegler et al., 2020)^{11,12} have shown that survival modelling approach could be used to examine recurrent opioid overdoses and how changes in receipt of MOUD following a non-fatal overdose among the WV Medicaid population affect risk of mortality. To achieve the goal, a survival cohort was established and identified from people who experienced an opioid overdose, and any receipts of MOUD and recurrent overdose associated with the cohort were described. The ultimate goal was to determine whether time-dependent MOUD, including initiation and duration of MOUD, and recurrent overdose were associated with reduced risk for all-cause mortality and opioid-related mortality.

4.3 Methods

Study Design and Data Source

A WV Medicaid overdose cohort was selected and analyzed for survival outcome as described in Chapter 3. A Common Data Model (CDM) was created by WV Medicaid to incorporate an extensively cleaned subset of WV Medicaid data that was designed to study opioid-related measures. The CDM included WV Medicaid data from 2014 to 2016 and excluded about 20% of people who had dual-eligibility with Medicare, as Medicare is the primary payer and Medicaid does not include all claims from this group. An overdose cohort was then created from CDM by selecting continuously enrolled persons ages 18 to 64 with at least one nonfatal overdose event. The first identified nonfatal overdose was selected from emergency department (ED) visits or hospitalization after a 12-month observation, and recorded as the index overdose using ICD-9 (965.00-965.02, 965.09, E850.0-E850.2) or ICD-10 (X40-X44, X60-X64, X85,

Y10-Y14) (Appendix A). The retrospective cohort follow-up starts with the index overdose, and ends with death or 12 months after the index (Figure 1).

Mortality data was obtained from WV Vital Statistics from 2014 to 2019, and West Virginia Medicaid claims data was obtained from WV Medicaid. The two datasets were linked by unique person identification number. For each death, the mortality data include date of death, manner of death, ICD-10 coded underlying cause of death and immediate causes of death. The ICD-10 codes used to identify opioid-specific deaths are listed in Appendix A (Olfson et al., 2018)³³. These ICD-9 codes were validated with 81% positive predictive values for identifying fatal or nonfatal opioid overdose occurred before October, 2015 (Green et al., 2017)³⁹. Another study suggested that ICD-10 codes are able to capture more opioid-related hospitalizations that were otherwise missed by ICD-9 codes (Heslin et al., 2017)⁴⁰. Multiple opioid overdoses that occurred during one hospitalization interval (admission and discharge date) were counted as one overdose event. Two overdoses recorded within two days were also accounted as one overdose event. Thus, a recurrent overdose event was defined as one occurring at least two days after the previous overdose (avoid potential carry-on effect from previous overdose). The cohort further excluded those who died within 30 days of index overdose (make sure every subject had at least one-month follow up) and patients with any cancer diagnosis (avoid confounding effect from cancer) at any time of cohort. The ICD -9 and ICD-10 codes used to identify cancer were listed in Appendix A. Missing values were checked for age and gender and no one was excluded for this reason.

This study was reviewed and approved by the Institutional Review Board (protocol number: 1711862183A001) at the West Virginia University, Morgantown, WV.

Key Variables

The primary outcomes of interest in this study were all-cause mortality and opioid-specific mortality in the 12-month follow up. The main exposures were receipt of MOUD and occurrence of recurrent overdose. The receipt of MOUD was identified from both pharmacy datasets using National Drug Codes (NDC), and from inpatient and outpatient datasets using the Healthcare Common Procedure Coding System (HCPCS) codes. The first date of receipt of MOUD was identified and compared to the date of index overdose to determine the presence or absence of baseline status. Duration of MOUD was calculated as cumulative days in treatment and then dichotomized by median value. The types of medication use were separated into three groups: buprenorphine use only, naltrexone use only and mixed group.

Potential confounding variables were also examined. Patients' age and gender were obtained from Medicaid enrollment files. Age was categorized into 3 groups: 18 to 29 years, 30 to 44 years and 45 year or older. Post index overdose prescription of opioids and benzodiazepines were also identified and dichotomized into presence or absence. Psychiatric diagnosis including anxiety, depression, bipolar, alcohol use disorder and other drug use disorder (stimulants, cannabis, etc) were also identified.

Statistical Analysis

Kaplan–Meier method was used to examine survival trends of all-cause mortality by receipt of MOUD and number of overdoses. A log-rank test was used to assess the difference of time-to-events between subgroups.

Univariate and multivariable Cox proportional hazard models were applied to evaluate MOUD effectiveness on reducing both all-cause mortality and opioid-specific mortality, while adjusting for other potential confounders, including the prescription of opioids and benzodiazepines post index overdose, presence of anxiety, depression, bipolar, alcohol use disorder, and other drug use

disorder. Multivariable models were developed in a sequential approach, by first only modelling MOUD presence or absence, and then specifically modelling the subgroup with any MOUD presence. Timing of initiation of MOUD, duration of MOUD and recurrence of overdose were added into the subgroup Cox model to have a comprehensive evaluation of MOUD through survival approach. To have a better understanding of model results, in-depth investigations into the subgroup analyses were carried out.

4.4 Results

The study identified a survival cohort after an index overdose with 1703 subjects, who had 2001 records of overdoses (1.17 overdose per person on average) in the 12-month follow up. For people in the cohort (Table 1), 47% were male, 42% aged between 29 to 44, 32% aged at or over 45, and 59% were enrolled as Medicaid expansion category. As for comorbid mental health conditions, 177 (10.4%) were diagnosed with anxiety, 213 (12.5%) had depression, 76 (4.5%) had bipolar, 72 (4.2%) had alcohol use disorder, and 524 (30.8%) had other drug use disorder. A total of 182 (10.7%) patients experienced at least one repeated overdose in the 12-month follow up; of whom 23 patients had two repeated overdoses, 8 patients had three repeated overdoses, and 4 patients had four repeated overdoses. During the one-year follow up, 84 (4.9%) persons died of whom 45 of them were died from opioid (Table 2). Further, among those deaths, 45 (53.6%) were unintentional, 33 (39.3%) were natural, 5 (6.0%) were suicide and 1 (1.2%) was undetermined. People who died within 12-month follow up were older than those who were alive, were more likely to be enrolled in disabled and expansion category, and had higher rates of psychiatric conditions. In addition, 21 (46.7%) of those who died from opioids had OUD diagnosis, compared to 605 (37.4%) of those who were alive after 1-year follow up had diagnosed OUD.

Only 431 (25.3%) patients had ever received MOUD either before or after the overdose, among whom 273 (63.3%) received buprenorphine (hydrochloride and/or Suboxone), 78 (18.1%) received naltrexone, and 80 (18.6%) received both medications. There were 251 (58.2%) persons with 733 OUD diagnosis among those who had ever received MOUD, and 418 (32.9%) persons with 989 OUD diagnosis among those who had never received any MOUD. The OUD diagnosis rate is significantly higher among people who received any MOUD ($p < 0.0001$). In addition, the average number of OUD diagnosis records among MOUD recipients was 2.9, which is 21% higher than 2.4 among non-MOUD population.

MOUD and non-MOUD groups

The Kaplan-Meier survival curve in Figure 2 shows that people who did not receive any MOUD had a higher decreased survival rates, compared with people who received MOUD at any time (0.948 vs. 0.958). In the unadjusted Cox model, compared with no MOUD, receipt of MOUD was associated with non-significant decrease in all-cause mortality (adjusted hazard ratio [AHR], 0.80 [CI 0.48, 1.35]) and non-significant increase in opioid-specific mortality (AHR, 1.33 [CI 0.71, 2.50]). In the adjusted multivariable Cox model (Table 3), compared with no MOUD, receipt of MOUD was associated with non-significant increase in all-cause mortality (AHR, 1.14 [CI 0.66, 1.96]) and opioid-specific mortality (AHR, 1.53 [CI 0.79, 2.95]). Further in the subgroup analyses, among people who received any MOUD (Table 4), initiation of MOUD before index overdose was associated with non-significant decrease in all-cause mortality (AHR, 0.62 [CI 0.20, 1.93]) and opioid-specific mortality (AHR, 0.83 [0.22, 3.11]); duration in the treatment over 3 month was associated with non-significant decrease in all-cause mortality (AHR, 0.34 [CI 0.10, 1.22]) and opioid-specific mortality (AHR, 0.46 [0.12, 1.74]). In another subgroup analysis, the study subjects were separated into four mutually exclusive groups: no

MOUD, MOUD initiated after index overdose, MOUD initiated and ended before the index overdose, and MOUD initiated and lasted through index overdose. Compared with the first three groups, the last group had non-significantly decrease in all-cause mortality (AHR, 0.59 [CI 0.14, 2.49]) and non-significant increase in opioid-specific mortality (AHR, 0.94 [CI 0.22, 4.08]).

Single vs. Multiple overdose groups

The Kaplan-Meier survival curve in Figure 3 shows that people who experienced a recurrent overdose had a more rapid decreased survival rate, compared with people who only experienced one overdose (0.934 vs. 0.953). In the unadjusted Cox model, occurrence of a recurrent overdose was associated with non-significant increase in all-cause mortality (AHR, 1.40 [CI 0.76, 2.58]) and opioid-specific mortality (AHR, 1.81 [CI 0.85, 3.89]). In the adjusted multivariable Cox model (Table 3), occurrence of recurrent overdose was associated with non-significant increase in all-cause mortality (AHR, 1.54 [CI 0.83, 2.86]) and opioid-specific mortality (AHR, 1.80 [CI 0.83, 3.89]). The receipt of MOUD was significantly associated with occurrence of recurrent overdose ($p = 0.0377$), with 58 (13.5%) had another overdose in the MOUD group, compared with 124 (9.7%) had another overdose in the no MOUD group. In unadjusted Cox model with occurrence of recurrent overdose as outcome event, compared with no MOUD, receipt of MOUD had significantly increased hazard ratio at 1.42 [CI 1.04, 1.93]. In the subgroup analysis, among those who received any MOUD, solely received buprenorphine was significantly associated with occurrence of recurrent overdose (HR, 1.43 [CI 0.99, 2.06]).

Among the covariates, older age (age between 30- 44, AHR, 2.77 [CI 1.21, 6.31]; age at or over 45, AHR, 5.68 [CI 2.52, 12.80]) and diagnosis of other drug use disorder (AHR, 1.54 [CI 0.99, 2.38]) were significantly associated with increased all-cause mortality. Diagnosis of other drug use disorder (AHR, 1.69, [CI 0.93, 3.07]) and being male (AHR, 1.69, [CI 0.93, 3.07]) were

associated with marginally significantly increased opioid-specific mortality. Benzodiazepine prescription post index overdose was associated with marginally significantly increased all-cause mortality (AHR, 1.55 [CI 0.96, 2.53]) and significantly increased opioid-specific mortality (AHR, 1.89, [CI 0.99, 3.59]).

4.5 Discussion

In a cohort of 1703 persons who had a nonfatal opioid overdose between 2015 and 2016 in West Virginia, the rate of all-cause mortality at 12 months following overdose was 4.9% and the rate of opioid-specific mortality was 2.6%. A total of 431 (25.3%) persons received MOUD (buprenorphine, naltrexone or both). Specifically, 125 (29%) initiated MOUD after the index overdose. Compared with no MOUD, those who received MOUD at any time was associated with non-significant increased all-cause mortality (adjusted hazard ratio [AHR], 1.14 [CI 0.66, 1.96]) and opioid-specific mortality (AHR, 1.53 [CI 0.79, 2.95]).

To the best of our knowledge, this is the first West Virginia based study to use a survival approach to examine the association between MOUD and mortality after a nonfatal opioid overdose in the Medicaid setting, and taking recurrent overdose into consideration. Our finding that the use of MOUD actually increased mortality although not significantly is in conflict with other studies that found a protective effect of using MOUD (Laroche et al., 2018; Kelty and Hulse et al., 2016; Frazier et al., 2017)^{12,25,41}, one possible explanation is that receipt of MOUD is an indicator for those identified with higher severity of OUD. In addition, WV has much less access to treatment and this effect will be investigated further. Additionally, the short length of study follow-up period and small sample size in survival analyses also limited the statistical power to reach a significant level. The all-cause mortality rate in our study is very close to another study analyzing the Massachusetts population who survived a non-fatal overdose (4.9 vs.

our 4.7), with 10 times larger sample size around similar study period (from 2012 to 2014) (Laroche et al., 2018)¹². In comparison with the WV Medicaid population, both the MA cohort (Laroche et al., 2018)¹² and a Pennsylvania Medicaid cohort (Frazier et al., 2017)⁴¹ had a much larger proportion of people who received any MOUD both prior to (26% or 29% vs. our 18%) or after the index overdose (30% or 33% vs. our 7%), which is a huge difference. Notably, the data in our study period is 2014-2016 which is after WV Medicaid expansion started January 2014 when in theory MOUD therapy should be more accessible; whereas the data analyzed in MA was between 2012 and 2014. The huge difference of proportion of people receiving MOUD might well explained why the MA study demonstrated significant association between the use of buprenorphine or methadone and reductions in all-cause and opioid-specific mortality, while in WV only those with the most severe or recognizable OUD received treatment. In addition, those who died from opioids did have a higher rates of OUD diagnosis and significantly higher number of OUD diagnosis records, suggesting that receipt of MOUD is an indicator for those identified with higher severity of OUD.

In this study, 10.7% of those having their index overdose had a recurrent overdose within 12 months following an index overdose. The rate of recurrent overdose varies across different studies. The Pennsylvania study found that 14.9% of patients who experienced a non-fatal overdose had a recurrent overdose in 12 months (Suffoletto and Zeigler et al., 2020)¹². An Indiana study suggested that the prevalence of repeated nonfatal overdose resulting in emergency department (ED) visits increased almost four-fold between 9% in 2012 to 35% in 2017, and on average 10.9% between 2014 and 2017 (Lowder et al., 2020)⁴². ED data from two other states suggested that 10.0% of drug-related ED visits led to near-fatal events (Hasegawa et al., 2014)⁴³. In a national study among 2848 commercially insured patients, the rate of repeated overdose

after an index overdose was 7% in a year, and 17% in two years for patients receiving high dosages of opioids (Larochelle et al., 2016)³⁰. Medicaid data from 45 states found that during the 12 months after an initial nonfatal overdose, the rate of subsequent overdose was 29.5 per 100 person-years and that of fatal opioid overdose was 1.15 per 100 person-years (Olfson et al., 2018)³³. The reason why the rate of recurrent overdose is relatively low among WV Medicaid population might be that claim data was not able to capture all overdose. Due to spatial isolation and limited medical resources, many opioid overdose might not result in medical care seeking attempts, and end up with either death or rescued in the community by naloxone (Saloner et al., 2018)⁴. The lack of reported overdose is not unique in WV, though (Larochelle et al., 2018)¹².

Strengths and limitations

MOUD has shown to be effective in reducing mortality in other states, and our study was the first West Virginia based study to evaluate MOUD effectiveness among overdose population in the WV Medicaid setting. The study also examined the effect of risk factors on mortality among overdose population, including exposure to prescription opioids, benzodiazepines and psychiatric diagnosis. The limitations of the current study, especially the small sample size and limited follow up period, indicate the need for more research to have a better understanding of how time-dependent MOUD and repeated overdoses affect people's survival outcomes in West Virginia. First the generalizability of the study was largely constrained because of the short length of study follow-up period, which only followed the cohort for 1 year as this was used in recently published studies (Larochelle et al., 2018; Suffoletto and Zeigler et al., 2020)^{11,12}. Studies applying survival approaches usually have a follow up period over three years to reach a decent sample size and statistical power, therefore, another two to three years data are needed for a comprehensive study in WV as the state only had a small number of overdoses over the study

period: 1703 compared to 17568 in the Massachusetts study (Laroche et al., 2018)¹¹. Second, the study was unable to evaluate the effect of methadone on survival rates since methadone was not covered by WV Medicaid until recently in January 1, 2018. A third limitation is that the Medicaid data in the CDM we used does not include all patients in Medicaid as it already excluded persons with dual-eligibility with Medicare, which accounts for about 20% of overall Medicaid population.

Conclusions

In conclusion, while this study found that in some groups receiving MOUD that it is likely to be effective in lowering mortality risk in West Virginia, the fact that MOUD recipients were more likely to have OUD with a higher severity and that less of the population received treatment likely hampered the effectiveness of treatment. In addition, limited sample size prevented us from reaching sufficient statistical power. The findings from this study confirmed the contribution of continuous efforts by state agencies to expand Medicaid eligibility and MOUD access. Additional data and future research are needed to guide the timely receipt of MOUD for the patients in urgent need. The state agencies should consider necessary policy change to continue to expand treatment access, Medicaid eligibility, and also provide people who had opioid overdoses to receive comprehensive and effective treatments and supports.

Tables and Figures

Figure 1. Flow chart of case selection of opioid overdose cohort

Figure 2. Kaplan-Meier Survival Curve among receipt of MOUD group and no MOUD groups (N = 1703)

Figure 3. Kaplan-Meier Survival Curve among single overdose group and multiple overdose groups (N = 1703)

Table 1 Demographic and Medicaid-related Characteristics among Opioid Overdose Cohort Comparing those Alive and Dead at end of 1 year (N = 1703)

	Overall	Alive	Dead
Number of people	1703	1619 (95.1) ^a	84 (4.9) ^a
Number of overdose	2001	1905 (95.2) ^a	96 (4.8) ^a
2015	729	693 (36.4) ^b	36 (37.5) ^b
2016	1272	1212 (63.6) ^b	60 (62.5) ^b
Age (mean ± std)	38.2 ± 11.6	37.9 ± 11.5	45.4 ± 10.5
18 - 29	459 (27.0)	452 (27.9)	7 (8.3)
30 - 44	708 (41.6)	677 (41.8)	31 (36.9)
45 - 64	536 (31.5)	490 (30.3)	46 (54.8)
Male	802 (47.1)	763 (47.1)	39 (46.4)
Race			
Non-Hispanic white	1506 (88.4)	1433 (88.5)	73 (86.9)
Non-Hispanic black	60 (3.5)	56 (3.5)	4 (4.8)
Hispanic	28 (1.6)	28 (1.7)	0 (0.0)
Others	109 (6.4)	102 (6.3)	7 (8.3)
Eligibility category			
Pregnant Women	31 (3.0)	30 (3.0)	1 (2.9)
Children	46 (4.5)	45 (4.5)	1 (2.9)
Disabled Adults	95 (9.2)	92 (9.2)	6 (17.7)
Non-Disabled Adults	248 (24.0)	240 (24.0)	3 (8.8)
Expansion Adults	614 (59.4)	594 (59.4)	23 (67.7)
Psychiatric conditions			
Anxiety	177 (10.4)	164 (10.1)	13 (15.5)
Depression	213 (12.5)	198 (12.2)	15 (17.9)
Bipolar	76 (4.5)	72 (4.5)	4 (4.8)
Alcohol use disorder	72 (4.2)	66 (4.1)	6 (7.1)
Drug use disorder	524 (30.8)	488 (30.1)	36 (42.9)

Note: ^a percentage was calculated by row;

^b percentage was calculated by number of overdose.

Table 2. Cause of death among the analytical cohort (N = 84)

ICD10	Underlying cause of death	Count	Percent
A310	Pulmonary mycobacterial infection	1	1.19
B182	Chronic viral hepatitis C	1	1.19
B24	Unspecified human immunodeficiency virus [HIV] disease	1	1.19
C959	Leukemia	1	1.19
E109	Insulin-dependent diabetes mellitus	1	1.19
E115	Non-insulin dependent diabetes mellitus	1	1.19
E119	Non-insulin dependent diabetes mellitus	1	1.19
E141	Unspecified diabetes mellitus	1	1.19
E149	Unspecified diabetes mellitus	1	1.19
E668	Other obesity	1	1.19
G35	Multiple sclerosis	1	1.19
G931	Anoxic brain damage, not elsewhere classified	1	1.19
I119	Hypertensive heart disease without (congestive) heart failure	1	1.19
I219	Acute myocardial infarction, unspecified	1	1.19
I250	Atherosclerotic cardiovascular disease, so described	1	1.19
I251	Arteriosclerotic heart disease	1	1.19
I259	Chronic ischaemic heart disease, unspecified	1	1.19
I429	Cardiomyopathy, unspecified	1	1.19
I499	Cardiac arrhythmia, unspecified	1	1.19
I500	Congestive heart failure	1	1.19
I709	Generalized and unspecified atherosclerosis	1	1.19
J440	Chronic obstructive pulmonary disease with acute lower respiratory infection	1	1.19
J449	COPD	2	2.38
K559	Vascular disorder of intestine, unspecified	1	1.19
K565	Intestinal adhesions [bands] with obstruction	1	1.19
K703	Alcoholic cirrhosis of liver	1	1.19
K746	Other and unspecified cirrhosis of liver	1	1.19
K769	Liver disease, unspecified	1	1.19
K861	Other chronic pancreatitis	1	1.19
N179	Acute renal failure, unspecified	1	1.19
N390	Urinary tract infection, site not specified	1	1.19
R99	Other ill-defined and unspecified causes of mortality	1	1.19
V059	Pedestrian injured in collision with railway train or railway vehicle	1	1.19
V892	Person injured in unspecified motor-vehicle accident, traffic	1	1.19
X41	Accidental poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified	1	1.19
X42	Accidental poisoning by and exposure to narcotics and psychodysleptics [hallucinogens], not elsewhere classified	6	7.14
X44	Accidental poisoning by and exposure to other and unspecified drugs, medicaments and biological substances	35	41.67
X61	Intentional self-poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified	1	1.19
X62	Intentional self-poisoning by and exposure to narcotics and psychodysleptics [hallucinogens], not elsewhere classified	1	1.19
X70	Intentional self-harm by hanging, strangulation and suffocation	1	1.19
X72	Intentional self-harm by handgun discharge	2	2.38
Y14	Poisoning by and exposure to other and unspecified drugs, medicaments and biological substances, undetermined intent	1	1.19
Y850	Sequelae of motor-vehicle accident	1	1.19

Table 3 Multivariable Cox proportional hazards analyses for all-cause and opioid-specific mortality by receipt of medications for opioid use disorder (MOUD) in 12 months following index nonfatal opioid overdose (N = 1703).

Predictor	All-cause Mortality				Opioid-specific Mortality			
	Hazard Ratio	95% Confidence Interval of Hazard Ratio		P-value	Hazard Ratio	95% Confidence Interval of Hazard Ratio		P-value
MOUD	1.14	0.66	1.96	0.64	1.53	0.79	2.95	0.21
Recurrent overdose	1.54	0.83	2.86	0.17	1.80	0.83	3.89	0.14
Opioid prescription	0.67	0.42	1.08	0.10	0.63	0.33	1.20	0.16
Benzodiazepine prescription	1.55	0.96	2.53	0.08	1.89	0.99	3.59	0.05
Other drug use disorder	1.54	0.99	2.38	0.05	1.69	0.93	3.07	0.08
Age between 30 to 44	2.76	1.21	6.31	0.02	1.90	0.80	4.48	0.14
Age at or over 45	5.68	2.52	12.80	<0.01	2.09	0.84	5.24	0.12
Male	1.01	0.66	1.55	0.96	1.69	0.93	3.07	0.09

Table 4 Multivariable Cox proportional hazards analyses for all-cause and opioid-specific mortality among recipients of medications for opioid use disorder (MOUD) in 12 months following index nonfatal opioid overdose (N = 431).

Predictor	All-cause Mortality				Opioid-specific Mortality			
	Hazard Ratio	95% Confidence Interval of Hazard Ratio		P-value	Hazard Ratio	95% Confidence Interval of Hazard Ratio		P-value
Receipt of MOUD at baseline	0.62	0.20	1.93	0.41	0.83	0.22	3.11	0.79
Duration in MOUD over 88 days	0.34	0.10	1.22	0.10	0.46	0.12	1.74	0.25
Recurrent overdose	1.36	0.44	4.24	0.60	2.09	0.64	6.87	0.22
Opioid prescription	0.37	0.12	1.12	0.08	0.36	0.10	1.28	0.12
Benzodiazepine prescription	2.05	0.74	5.70	0.17	1.81	0.56	5.89	0.32
Other drug use disorder	2.34	0.87	6.33	0.09	1.84	0.59	5.78	0.30
Age between 30 to 44	1.31	0.37	4.65	0.67	1.19	0.32	4.40	0.79
Age at or over 45	3.65	1.03	12.94	0.04	2.28	0.55	9.53	0.26
Male	0.97	0.38	2.50	0.95	0.87	0.30	2.55	0.80

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Chapter 5

5.1 Summary

This dissertation study consists of three parts each of which are separate papers. The first paper described the impact substance abuse has on mortality in West Virginia (WV) and analyzed the involvement of fentanyl and fentanyl analogs (FAs) in drug-related deaths in WV from 2005 to 2017. A WV forensic drug data (FDD) was used to compile all WV drug-related deaths, and the results of analyzing the cause of those deaths showed that most of the 8813 drug-related deaths were overdoses, with about 11% resulting from transportation/ other injuries in which drugs were contributors. Prescription opioid presence (without fentanyl) decreased by 75% from 2005–14 to 2015–17 (3545 deaths to 859 deaths, respectively), while fentanyl involvement in the deaths increased by 122% between these periods (487 to 1082 deaths). Ten FAs were identified (427 instances) beginning 2015. Alprazolam and ethanol were among the top five most frequently identified substances across years. Fentanyl, heroin and cocaine replaced oxycodone, diazepam and hydrocodone in the top five drugs found beginning in 2015. When the West Virginia Controlled Substance Monitoring Program (WV CSMP) was checked for each decedent, few decedents had a prescription recorded for fentanyl after 2015, with fewer prescriptions also present for other controlled substances identified. In conclusion, fentanyl involvement increased substantially over time in WV drug related deaths from 2005 to 2017, with ten different FAs identified since 2015. Prescription opioid presence decreased by about half with fentanyl, heroin, ethanol, alprazolam and cocaine constituting the top five identified drugs in these deaths since 2015. Alprazolam and ethanol were consistently among the top five drugs identified since 2005, with increasing methamphetamine involvement. In contrast, the presence of a prescription for most controlled substances identified in the deaths has been decreasing, suggesting more involvement of illegal drugs in those deaths. Death involving fentanyl and newly identified FAs

could represent the “tip of the iceberg” since fentanyl derivatives are often not readily detected, since many of them were newly synthesized compounds with unknown chemical structure.

The second paper involved analysis of the WV Medicaid data and explored the change of recurrent opioid overdose and receipt of Medication for Opioid Use Disorder (MOUD) following a non-fatal overdose among persons enrolled in West Virginia (WV) Medicaid. Among 513,707 WV Medicaid beneficiaries from 2014 to 2016, a total of 399,683 (77.8%) were continuously enrolled and analyzed in the study. An overdose cohort was created by selecting any people who experienced an opioid overdose after a 12-month overdose free period, and removing those who died within 30 days of index overdose, or with cancer diagnosis. After removing multiple overdose records occurred on the same day or the following day, the final analytical cohort included 1703 subjects and 182 (10.7%) experienced at least one recurrent overdose in the 12-month follow up. Only 431(25.3%) subjects received any MOUD, of whom 273 (63.3%) received buprenorphine (hydrochloride and/or Suboxone), 78 (18.1%) received naltrexone, and 80 (18.6%) received both medications. There were 125 patients who initiated MOUD after the index overdose. The median time staying in MOUD treatment was 88 days (range from 2 to 1094 days). In conclusion, only a quarter of people who experienced an opioid overdose received MOUD and half of them stayed in the treatment less than 3 months, suggesting limited effectiveness. Although a nonfatal overdose represents an opportunity to initiate MOUD, it was certainly under-utilized among WV overdose population.

The third paper identified associations between time-dependent MOUD and mortality among a WV Medicaid overdose cohort, adjusting for recurrent overdose and other risk factors. All-cause mortality and opioid-specific mortality data were extracted from West Virginia Vital Statistics and linked with WV Medicaid claim data. In the 12-month follow up after the index overdose,

182 (10.7%) experienced at least one recurrent overdose, 84 (4.9%) died and 45(53.6%) of these died of opioid poisoning. A total of 431 (25.3%) received MOUD (buprenorphine, naltrexone or both), and only 125 of them initiated MOUD after the index overdose. Compared with no MOUD, MOUD was associated with non-significant increased all-cause mortality (adjusted hazard ratio [AHR], 1.14 [CI 0.66, 1.96]) and opioid-specific mortality (AHR, 1.53 [CI 0.79, 2.95]). Occurrence of recurrent overdose was associated with non-significant increased all-cause mortality (AHR, 1.54 [CI 0.83, 2.86]) and opioid-specific mortality (AHR, 1.80 [CI 0.83, 3.89]). Older age (age between 30-44, AHR, 2.77 [CI 1.21, 6.31]; age at or over 45, AHR, 5.68 [CI 2.52, 12.80]) and diagnosis of other drug use disorder, including stimulant, cannabis, sedative related disorders (AHR, 1.54 [CI 0.99, 2.38]) were significantly associated with increased all-cause mortality. A filled prescription for benzodiazepine post index overdose was also significantly associated with increased opioid-specific mortality (AHR, 1.89, [CI 0.99, 3.59]). Among people who received any MOUD, those who initiated MOUD before index overdose had a non-significant decreased all-cause mortality compared to those who initiated MOUD after index overdose (AHR, 0.62 [CI 0.20, 1.93]) and opioid-specific mortality (AHR, 0.83 [0.22, 3.11]); duration of treatment over 3 months was associated with non-significant decreased all-cause mortality (AHR, 0.34 [CI 0.10, 1.22]) and opioid-specific mortality (AHR, 0.46 [0.12, 1.74]). In conclusion, people who received any type of MOUD had non-significant higher all-cause mortality rates and opioid-specific mortality rates, possibly because receipt of MOUD is an indicator for those identified with higher severity of OUD. However those who initiated MOUD early and people who stayed in the MOUD for over three months had better survival outcomes than others receiving MOUD. Benzodiazepine use and comorbid other drug use disorder increased risk of mortality. Age over 44 was also significantly associated with high all-cause

mortality but low rate of MOUD receipt. In order to prevent future mortality among people who experience an opioid overdose, it is critical to provide them access to MOUD and make sure they stay in treatment.

5.2 Significance

The overall mortality rate for unintentional drug poisonings in the United States (US) grew exponentially in recent years (Jalal et al. 2018)¹. There are estimated 72,000 deaths due to drug poisoning in 2017 (Hedegaard et al. 2018)², and opioids are the main driver of the drastically increasing drug overdose deaths over the last 20 years, with evolving substance use patterns changed drastically over time. WV leads the nation in drug overdose mortality with the highest per capita drug overdose mortality rate of 57.8 per 100,000 population as of 2017, almost 3 times the US average (Scholl et al. 2018; Hedegaard et al. 2018)^{2,3}. The current state of the opioid crisis is attributable to earlier excessive prescribing behaviors, widespread availability of inexpensive heroin, and an increase in use of highly potent fentanyl and its analogs (Armenian 2017; Suzuki and El-Haddad 2017)^{4,5}. The current opioid crisis has strained the capacity of health care and social service resources and taken a major toll on individuals, families, communities, and counties in WV (Saloner et al. 2019)⁶. In general, persons experiencing nonfatal overdose are at increased risk of overdose death (Coffin et al. 2007)⁷. This risk is further intensifying in states like West Virginia experiencing geographic isolation (Hall et al. 2008)⁸ and having limited medical resources, resulting in tremendous gaps between the need for sustainable treatment and the state's capacity to deliver these options (Jones et al. 2015)⁹. Therefore, it is of great public health importance to rapidly address the opioid overdose problem in WV.

This study addressed the WV overdose problem through developing a series of studies focusing on drug-related deaths using the Forensic Drug Data (FDD) and persons with opioid use disorder

in Medicaid claims data. To establish effective strategies to address WV opioid overdose problem, the first step is to have a comprehensive understanding of current opioid crisis. Secondly, since we do have evidence-based and appropriate clinical interventions and treatment models to prevent opioid overdose mortality (Wakeman 2019)¹⁰, MOUD, effective but not perfect, has not been systematically evaluated its effectiveness on WV population, the characteristics of which is quite different from other populations in the States. Lastly, there are some significant barriers existing in both scientific evidence gaps and medical resources gaps that keep West Virginia OUD patients from being treated. To answer the question that whether MOUD can be effective in reducing mortality, a survival approach was applied to quantitatively assess the association between time-dependent MOUD, recurrent non-fatal overdose events and the patients' survival outcome, after controlling for patients' demographics, comorbidities and prescriptions. To the best of our knowledge, the study is the first to comprehensively describe the current synthetic opioid problem, especially fentanyl and/or fentanyl analog-related death in WV. The study shed lights on profiling a full description of characteristics of overdose and OUD patients among WV Medicaid population, which is very valuable for future policy making and treatment improvement, along with the application of survival methodologies alongside an in depth investigation of MOUD effectiveness in a West Virginia Medicaid population.

5.3 Future research

The limitations of the current study, especially the small sample size and limited follow up period, indicate the need for more research to have a better understanding of how time-dependent MOUD and repeated overdoses affect people's survival outcomes in West Virginia. First the generalizability of the study was largely constrained because of the short length of study follow-up period, which only followed the cohort for 1 year as this was used in recently published

studies (Larochelle et al., 2018; Suffoletto and Zeigler et al., 2020)^{11,13} and we only had 3 years of data and more years of data has only recently become available. Studies applying survival approaches usually have a follow up period over three years to reach a decent sample size and statistical power, therefore, another two to three years data are needed for a comprehensive study in WV as the state only had a small number of overdoses over the study period: 1703 compared to 17568 in the Massachusetts study (Larochelle et al., 2018)¹¹. Moreover, with more years of Medicaid data available, we would be able to assess not just the one-year mortality rate but maybe three-year or five-year mortality rates, to evaluate the long-run survival outcome. Second, the study was unable to evaluate the effect of methadone on survival rates since methadone was not covered by WV Medicaid until recently in January 1, 2018. This is another essential reason why we need more recent years' data to have a full evaluation of MOUD effectiveness.

Methadone has been shown to be an effective treatment for OUD although some studies have shown varying effects on lowering patients' mortality rates in study settings, with some demonstrating a significant decreased all-cause mortality as well as opioid-specific mortality (Larochelle et al., 2018; Sordo et al., 2017; Ahmadi et al., 2003)^{11,14,15}. However some studies found that methadone was not as effective as buprenorphine and naltrexone (Larochelle et al., 2016; Kelty and Hulse)^{16,17}. It is of great importance to include this medication in the analysis to achieve a better understanding of the treatment effectiveness of all three medications in West Virginia. A third limitation is that the Medicaid data in the CDM we used does not include all patients in Medicaid as it already excluded persons with dual-eligibility with Medicare, which accounts for about 20% of overall Medicaid population. People with dual-eligibility include those aged under 65 with disabilities, and people of any age with End-Stage Renal Disease. When dual eligible beneficiaries have claims, Medicare pays first and Medicaid pays last so only

limited claims data are available in Medicaid for these people. According to the findings from our study, older age (over 44) population were at elevated risk of all-cause mortality. Additional data linkage with Medicare to have access to the claim data would be a necessary step to have full evaluation of overall WV Medicaid population. The elderly population in West Virginia were believed to have higher rates of opioid prescriptions and benzodiazepine prescriptions, which lead to other drug-related comorbidities or psychiatric conditions (Peirce et al., 2012)¹⁸.

To curb the opioid overdose from a larger scope and advancing with the times, poly-substance use and poly-substance induced overdose are key factors that needed for additional studies.

There were emerging methamphetamine-related deaths in West Virginia and many of them were mixed using with opioids (Kariisa et al., 2019)¹⁹. Additional studies should focus on developing the treatment tailored for increasing numbers of mixed opioid and stimulant users (Ellis et al., 2018)²⁰.

5.4 Conclusions

With drastically increasing numbers of both non-fatal overdoses and fatal overdoses, understanding the risk of repeated overdose and the value of receiving appropriate MOUD in time is essential to prevent deaths. The findings from this study confirmed the contribution of continuous efforts by state agencies to expand Medicaid eligibility and MOUD access. That being said, the state is facing an increasingly critical opioid overdose situation, as well as opportunities to initiate treatment to curb the rise in fatal and non-fatal overdoses. Moreover, the findings of this study underscore the need for good compliance of patients staying in the treatment rather than in and out intermittently, leading to increased risk of relapse and mortality. The study results inform necessary policy change to guarantee that any patients who are receiving MOUD are able to finish the treatment regardless the change of eligibility status.

Furthermore, in order to reach a better treatment effect, additional primary care services to address comorbidities along with social support are needed to prevent relapse, which would otherwise waste all the previous efforts.

In conclusion, this study suggests that MOUD is likely to be effective in lowering mortality risk in West Virginia, however, limited sample size prevented us from reaching sufficient statistical power. The new data has just become available, and with more recent years' data, we are planning to expand the study years to determine how effective MOUD is in lowering both all-cause mortality and opioid-specific mortality and evaluate the impact of poor compliance to the treatment, resulting in compromised treatment effectiveness. More future research are needed to guide the timely receipt of MOUD for the patients in urgent need. The state agencies should consider necessary policy change to expand treatment access, Medicaid eligibility, and also provide people who had opioid overdoses to receive comprehensive and effective treatments and supports.

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APPENDIX A DIAGNOSTIC CODES USED IN ANALYSIS

Diagnostic codes used for opioid overdoses recorded in the West Virginia Medicaid		
Type of overdose	ICD-9	ICD-10
	965.00 (Opium)	T40.0X Opium
	965.01 (Heroin)	T40.1X Heroin
	965.02 (Methadone)	T40.2X Other opioids
	965.09 (Other opiates/narcotics)	T40.3X Methadone
	E850.0 (Accidental: Heroin)	T40.4X Synthetic narcotics
Opioid overdose	E850.1 (Accidental: Methadone)	T40.60X Unspecified narcotics
hospitalization	E850.2 (Accidental: Other opiates)	T40.69X Other narcotics
		X40-X44 (accidental)
		X60-X64 (intentional/self-harm)
		X85 (assault/homicide)
		Y10-Y14 (undetermined)
Opioid overdose		With a contribution cause of
mortality		death code T40.0-T40.4, T40.6
	304.0 Opioid dependence	F11.1 Opioid abuse
	305.5 Opioid abuse	F11.2 Opioid dependence
Opioid use disorder		F11.9 Opioid use

Cancer Diagnosis Codes

Subjects were categorized as having cancer in the Medicaid data if they had one or more claims in calendar years 2014-2016 with one of the following ICD-9 or ICD-10 diagnosis codes:

- ICD-9 Codes: 140.X-165.X, 170.X-172.X, 174.X-175.X, 179-203.X, 238.6, 273.3, V10.X
- ICD-10 Codes: C00.X-C26.X, C30.X-C34.X, C37.X-C41.X, C43.X, C47.8, C48.X-C58, C60.XC73, C75.X-C85.X, C88.X, C90.X, C96.X, D03.X, D47.Z9, Z85.X

Appendix B Variables of Interest

Characteristics	Variables	Values or Related codes
Age	Age groups; categorical	1: 18-29; 2: 30-44; 3: >= 45.
Gender	Sex; categorical	1: Male; 2: Female.
Eligibility category	Eligibility category; categorical	1: Pregnant Women; 2: Children; 3: Disabled Adults; 4: Non-Disabled Adults; 5: Expansion Adults.
Race	Race, categorical	1: Non-Hispanic white; 2: Non-Hispanic black; 3: Hispanic; 4: Others.
Psychiatric conditions		
Anxiety	anx (1=yes, 0=no)	ICD*-9: 300; ICD-10: F40, F41 ICD-9: 296.2, 296.3, 300.4, 311;I
Depression	dep (1=yes, 0=no)	ICD-10: F32, F33, F34.1 ICD-9: 296.0, 296.1, 296.4, 296.5, 296.6, 296.7, 296.8;
Bipolar	bip (1=yes, 0=no)	ICD-10: F31 ICD-9: 303;
Alcohol use disorder	alc (1=yes, 0=no)	ICD-10: F10 ICD-9: 292, 304, 305;
Drug use disorder	dru (1=yes, 0=no)	ICD-10: F12-F19 ICD-9 codes: 304.0, 304.7, 305.5;
Opioid use disorder	oud (1=yes, 0=no)	ICD-10 codes: F11
Medication for opioid use disorder (MOUD)		
Any receipt of MOUD	moud (1=yes, 0=no)	
Receipt of MOUD at baseline	moudbaseline (1=yes, 0=no)	
Duration in MOUD over 88 days	duration (1=yes, 0=no)	
Naltrexone		The Healthcare Common Procedure Coding System (HCPCS): J2315; National Drug Code (NDC):

	00406117001, 00406117003, 16729008101, 16729008110, 47335032683, 47335032688, 51224020630, 51224020650, 68084029121, 68094085362
	HCPCS: J0592; NDC: 00054017613, 00054017713, 00054018813, 00054018913, 00228315303, 00228315473, 00228315573, 00228315603, 00378092393, 00378092493, 50383028793, 50383092493, 50383093093, 65162041503, 65162041603
Buprenorphine Hydrochloride	HCPCS: J0571-0575; NDC: 12496120201, 12496120203, 12496120401, 12496120403, 12496120801, 12496120803, 12496121201, 12496121203
Suboxone	