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A REVIEW OF OPIOID-RELATED DEATH TRENDS IN OKLAHOMA

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Abstract

Opioids are a popular analgesic compound that act at the opioid-receptors in the body to create effects of reduced pain and consciousness, euphoria, and dependence (Pathan, H. and Williams, J., 2012). The concept of pain as a fifth vital sign catalyzed the opioid epidemic through the over prescription of opioids. The opioid epidemic is characterized by three distinct waves beginning in the late 1990's consisting of prescription opioids, heroin, and fentanyl. The state of Oklahoma is lacking an encompassing model of the opioid epidemic within its borders. A variety of studies have been done in the United States and on an international scale that use spatio-temporal designs to evaluate demographic and geographic variables over time as they relate to the opioid crisis. The study herein presents a consolidated model of opioid-related deaths in Oklahoma from 2008-2022 using data from the Office of the Chief Medical Examiner. Summary statistics were performed centering on demographics, location, and drug categories for each year using Statistical Analysis Software (SAS). The results found that in Oklahoma overall opioid-related deaths were most common among Whites (86%), Males (57.8%), and people ages 25-44. There was an approximately 500% decrease in prescription opioid deaths from 2008-2022. Heroin deaths peaked in 2018 at 54 deaths. From 2008-2019 fentanyl deaths remained consistently low then saw an almost 7-fold increase from 2020-2022. Total opioid-related deaths were highest in Carter, Coal, Jefferson, Muskogee, Pawnee, and Pushmataha counties. Prescription opioids showed no geographic inclination while fentanyl deaths were concentrated in urban counties (Tulsa and Oklahoma). This study is the first of its kind in Oklahoma and its dissemination will inform both public and private entities on the use of funding, proactive resources, and treatment for opioid use and abuse. The datasets developed in this study will serve

as a resource for future substance abuse research that can bring greater specificity to demographic and geographic factors of deaths involving other prevalent drug classes.

Introduction

Beginning in the 1990's, there was an introduction of pain as a fifth vital sign[1] which catalyzed the over prescription of both natural and semi-synthetic opioids (DEA, 2021). The treatment of pain was pushed to raise awareness about the undertreatment of patients that were experiencing chronic pain (Mandell, B., 2016). Opioids quickly became the gold standard for pain treatment. These compounds act at the opioid-receptors that are dispersed throughout the central nervous system (CNS) in the body (Pathan, H. and Williams, J., 2012). When opioid-receptors are stimulated, they can create effects of reduced pain and consciousness, euphoria as well as dependence (Pathan, H., and Williams, J., 2012). The opioid epidemic is characterized by three distinct waves beginning in the late 1990's. The trends seen in the United States are similar to those seen across the globe with slight variations due to health-care practices and migration of pharmaceutical novelty. The first wave was characterized by the use and abuse of prescription opioids. The second wave began around 2010 with a shift towards heroin use as a result of the reformulation of the dominant opioid OxyContin (Beachler et al., 2022). That restriction was a reaction to the increased use of prescription opioids causing addiction and subsequent overdose. The adverse effect was the immediate shift towards a cheaper and more dangerous option of heroin which saw approximately 80% of heroin users admitting to previous abuse of prescription opioids (Liu et al., 2018). The third wave which currently plagues our nation is a result of the proliferation of illicitly manufactured fentanyl permeating the drug market through combination with the heroin, cocaine, and counterfeit pill supply. Since 2013, the third wave has progressed in a multivariate pattern due to geographical, pharmaceutical, legislative, demographic, age, and sex related factors.

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[1] Vital signs are measures used by medical professionals to assess basic functions of the body.

The opioid epidemic fulfills its definition as its effects extend well beyond the United States. The United Nations Office on Drugs and Crime (UNODC) performs an annual report that addresses global issues. The UNODC has worked to create a dashboard that contains information about Novel Psychoactive Substances (NPS). This resource makes tracking, exploring, and discovery of these substance trends uniform and readily available to the public. As of 2023, there are 1,240 NPS listed in the UNODC database (UNODC, 2023). Fentanyl analogs comprise 7% (total of 87 analogs) of those substances since NPS reporting began (UNODC, 2023). Synthetic opioids as a whole are the third largest group of reported substances (UNODC, 2023). Even after international control attempted to quench the proliferation of NPS in 2014, there were still 7 fentanyl precursors and 25 synthetic opioids added to the list (UNODC, 2023). These numbers reinforce that not only is the opioid crisis affecting Oklahoma but is rampant across the globe.

Public health agencies are also greatly invested in the opioid epidemic in terms of controlling the spread and stemming the effects of drug proliferation. In addition, public health entities operate on different funding systems and cooperation between agencies can bolster research and resource allocation. The main restricting factor in combating drug overdose is limited funding which in turn leads to limited testing and limited information about the picture of drug overdose problems in an area. Additional funding and joint cooperation can aid against this limiting factor. The opioid crisis has served as a catalyst for this type of joint work through programs such as the Overdose to Action or OD2A. This program began in 2018 and provides federal funding to 90 health departments across the nation to aid prevention tactics and collection of accurate data on drug overdoses (CDC, 2024). The primary purpose of this program is to transition from surveillance to prevention with accuracy and efficiency (CDC, 2024). The Oklahoma State Department of Health is a recipient of OD2A funding. One positive effect of this funding is the implementation of Naloxone Distribution Programs. Naloxone is a crucial opioid-antagonist that can be used to treat opioid-related overdose on site. While this funding has improved treatment plans in Oklahoma, there needs to be a precise model of overdose data across a range of variables to be able to accurately allocate resources.

Problem Statement

The state of Oklahoma is lacking an encompassing model of the opioid epidemic within its borders. There remains much to be uncovered about the patterns of opioid abuse that have developed over the past decade. Oklahoma governing bodies have taken several steps in response to the third wave of the opioid crisis to combat substance use and abuse. Among these efforts are the Anti-Drug Diversion Act, an updated guideline for prescribing practices, and pieces of legislation which seek to curb the number of opioid pills in circulation (Landmark Recovery, 2018). However, there have been no previous efforts to consolidate and analyze opioid-related deaths across the state of Oklahoma from the past 15 years. Outside of automated graphics from vital statistics and CDC using reported data from the state, there has only been one study which spanned 15 years from 2002-2017 using data from the Office of the Chief Medical Examiner (OCME) on opioid and methamphetamine related deaths. By covering a 15-year timeline, this study will seek to explore the opioid epidemic for Oklahoma as it has steadily increased throughout the third wave. This timeline will include the first wave of prescription opioids, the transition to heroin, and the beginnings of fentanyl to its currently dominating status in opioid-related deaths. This study will clearly represent the shift in the opioid epidemic from prescription to illicit substances.

Across the state of Oklahoma, methamphetamine has been the dominating source of drug overdose. Presently, the state has seen an increase in opioid deaths similar to the rest of the country. However, the trend has still not overcome the domination of methamphetamine. The previously mentioned study from Bonk et al. illustrates that trend from 2002-2017. Although there was a 62.9% contribution of opioids to total drug related deaths, there was a slight decrease overall from 2002-2017 (Bonk et al., 2020). In comparison, methamphetamine deaths sharply increased during that time by 402% (Bonk et al., 2020). A continuation of that study with a focus on opioid-related deaths has potential to determine any shifts in this trend given the nationwide increase in opioid death activity since the end of that study in 2017.

The OCME database is an advantageous resource for the analysis of the opioid epidemic in Oklahoma. The state is under one Medical Examiner's system and subsequently has a uniform set of cause and manner of death codes with reliable representation of a decedent's core attributes such as age, sex, race, and location of death. All other information pertinent to the decedent in question is also recorded in the database. Investigators, pathologists, and toxicologists all contribute data to a decedent's case. The database program has a feature that enables agency personnel to access datasets based on any number of selected variables of interest. For this study, data will be extracted from the OCME database in yearly groups based on the queried variables. The yearly datasets will be pulled into separate spreadsheets for further analysis.

Limitations to be aware of include the potential for confounding variables. For example, location of injury versus location of death, a full autopsy versus no autopsy substituted by case review, and inability to identify single ingestion versus co-ingestion of drug substances. The improvement of scientific methods over the course of this timeline is perhaps the greatest confounding variable given that as methods improve so does detection and thus reporting of cases with opioids in them. There will be resources to access the progression of OCME analytical methods that will inform patterns that may have resulted from the improvement of methods. While there is no cure for the opioid crisis, the trends depicted in this study will serve as a new and invaluable resource for combating drug abuse. The issue of drug addiction and abuse is not a foreign concept in Oklahoma. This is a multi-faceted problem containing demographic, geographic, and temporal variables that will all be covered in this study.

Purpose and Scope

The purpose of this study was to generate a consolidated understanding of the opioid epidemic in Oklahoma. This resource is needed for the state to be able to provide accurate resources for opioid treatment, awareness, prevention, response, and expansion of overdose reversal treatment. In order to evaluate all variables of interest, a spatio-temporal analysis and time-series design approach was used. This study remained within the scope of the following three research questions:

1. Is there a discernible difference between counties with regards to opioid death rates by year?
2. Is there a discernible difference over time with regards to age range, race, sex, and any other variables determined relevant while scoping the data?
3. Is there a discernible difference in opioid type death rates over time?

Significance

The most significant facet of this study is the fact that it will be the first of its kind in Oklahoma. In addition, it will serve as a resource to the OCME Agency as well as surrounding law enforcement and public health agencies concerned with combating the opioid epidemic. The publication of this information will not only inform state agencies, but also regional groups that are interested. The details extracted from the OCME database bring a detailed picture of the opioid crisis in Oklahoma that is not possible from generated reporting statistics. The datasets that were organized throughout this study also pose as a significant source for future research concerning statewide drug specific trends of interest. Furthermore, the standardized process of analyzing these datasets can be replicated for any future research. The opioid crisis escalated rapidly across time and space. The expectation is that this pattern will continue, and the data presented in this study will inform those trends as they progress. This study will serve as a resource for the state of Oklahoma in efforts to combat the voracious spread of drug related deaths.

Literature Review

The opioid epidemic has been studied by a variety of approaches. Among the most significant and applicable is a spatio-temporal study design. A study from the University of Washington describes their design as being "…used to examine patterns over space and time statistically to determine if there are significant patterns in where and when something is happening." (Washington ADAI, 2017). Spatio-temporal designs are able to answer multi-level questions and provide a visual representation of those answers. The primary reference for a study with that design is from Kline et al. in the state of Ohio concerning opioid-related death rates over a 12-year period. That study will be discussed in greater detail in the literature review. Figure 1 gives an overview of the demographic shift in opioid-related deaths that was elucidated by the work of Kline et al. It clearly illustrates the shift in opioid-related deaths between Whites and Blacks using a colorized scale. There is a high contrast between the maps in 2008 to more similarly colorized maps in 2018 which correlate to the similar death rates that developed over the course of that study.

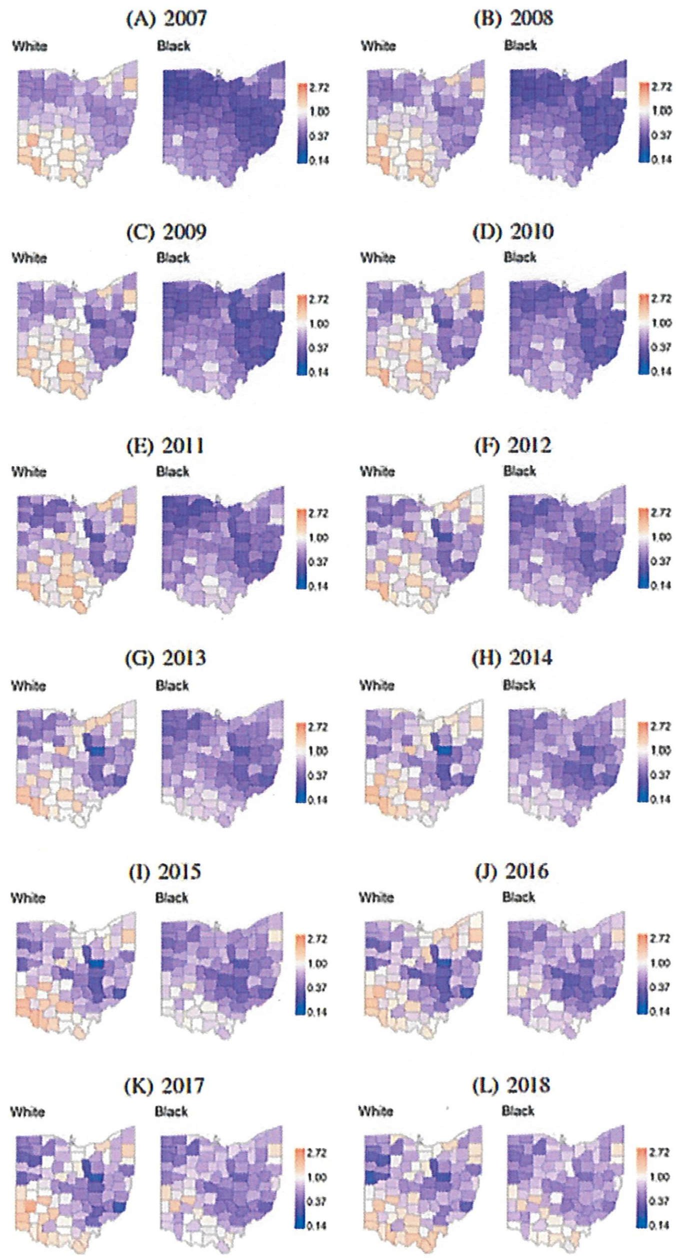

Figure 1:Opioid Mortality Rates by Race in Ohio, 2007-2018. (Kline et al., 2021).

The review of the literature contains four main sections involving topics pertinent to this thesis research. The first section covers previous drug-related studies that employed a mutually exclusive design. The second section illustrates the global opioid problem notating the similarities and differences seen outside of the United States. The third section includes geographic trends and their significance in drug-related trend research. The last section is comprised of previous spatio-temporal design studies which served as the primary model for this study.

Mutually Exclusive Design

There have been a variety of studies performed concerning patterns that have emerged throughout the opioid epidemic. The availability of different study designs will assist in scoping out experimental structures and limitations that will be relevant to this study. This review will cover multivariate pattern analysis and geographical analysis with a focus on a spatio-temporal design. The grip of opioid-related deaths was identified early on when Fernandez et al. performed a study of opioid-related fatal overdoses in Massachusetts beginning in 1990. Although that study only used public death files, it captured a trend that was also seen in several other states at the time. Across the 13-year timeline there was a 529% increase in opioid-related fatal overdoses (Fernandez et al., 2006). That trend agreed with significant increases also noted in New York City, Maine, Washington, Maryland, and Oregon. All of which experienced anywhere from a 38% increase to a 400% increase in opioid-related poisoning deaths (Fernandez et al., 2006). That overall alarming increase in opioid abuse can be broken down further when looking at those trends using mutually exclusive groups.

Wave 2 of the opioid epidemic is characterized by an increase in heroin abuse. It is important to have this context to grasp the significance of the progressive shift toward synthetic opioids. This can be done by using a mutually exclusive group design. One study from Tuazon et al. explored the contribution of opioids and heroin to drug deaths in New York City prior to increases in fentanyl from 2000-2015. Much like this approach, that study pulls from postmortem toxicology records which allows for greater specificity of opioid type contributing to the deaths. Mutually exclusive groups were stratified by opioid analgesics without heroin, heroin without opioid analgesic, and the combination of both. The search limited opioid classification to include "…codeine without heroin, hydrocodone, oxycodone, fentanyl without heroin, and other narcotics including buprenorphine and tramadol." (Tuazon et al., 2019). Stratifying by these groups elucidated demographic shifts in opioid deaths as a result of "…the reformulation of oxycodone in 2010." (Tuazon et al., 2019). That change in legislation is thought to have affected prescription treatment and caused a transition to heroin specifically among the Black and Latino communities which receive less prescription opioids (Tuazon et al., 2019).

The same trend was seen in a 2017 study from O'Donnell et al. in the Northeast and Midwest regions of the United States. Identical stratified groups were used on a larger scale, and it was noted that increases in heroin deaths coincided with an increasingly potent heroin formulation that came at a "…relatively low price [and] might have made heroin a viable substitute…" (O'Donnell et al., 2017). This potency was a result of using fentanyl as the strengthening agent. O'Donnell et al. found the 77% increase in deaths involving heroin and synthetic opioids was driven by the rise of illicitly manufactured fentanyl. It was also noted by Tuazon et al. in 2019 that a decrease in exclusive heroin deaths was in line with an increase of heroin in combination with opioids. Both studies similarly identify the shift towards the synthetic opioid market early on in the third wave before synthetic fentanyl gained significant ground.

The study from O'Donnell et al. captured a glimpse of fentanyl beginnings from 2013 to 2015, noting almost triple overdose death rates in both the Northeast and Midwest as a result of heroin and synthetic opioid combinations. One limitation to consider when looking for this trend in Oklahoma is the inability to identify a co-ingestion case. Therefore, it cannot be confirmed that the synthetic opioid presence originated from the heroin supply or separately. Given what has been studied about the cutting of heroin supplies with fentanyl to increase potency it can be deduced, but not confirmed. O'Donnell et al. also pointed out a geographic nuance in the heroin supply across the country. Black tar heroin[2] dominates to the west of the Mississippi River and is more difficult to mix with fentanyl than white powder heroin to the east (O'Donnell et al., 2017). That correlates directly with the Northeast and Midwest regions that saw the largest increase in heroin and opioid combination deaths. The mutually exclusive design of that study allowed for the identification of that trend.

O'Donnell et al. also points out four limitations which are found to be a good indication of limitations that may be faced within this study. These include the underestimation of deaths due to minimal death certificate information, the categorization of an undetermined death might include a homicide or suicide as opposed to an accidental determination, testing methods for synthetic opioids have become more frequent and advanced within the last decade, and variations in reports due to jurisdictional differences. Expansion on the mitigation of these limitations will be made later. Most importantly these studies illustrate the effectiveness of a mutually exclusive design and its ability to accurately and proactively identify the transitions that have taken place throughout the opioid epidemic. Mutually exclusive studies influence the probability that an event will occur. This approach is beneficial because it can bring more specificity to the type of opioid causing the most harm as well as indicate opioid combinations that are on the rise. For instance, it has been shown that fentanyl is used as a cutting agent for other drugs, so by creating a category for fentanyl in combination with another drug of interest it is possible to identify a

[2] Black tar heroin is a less pure form of heroin that is just as potent. It has significantly lower solubility than white heroin making it more difficult to mix with fentanyl (Ciccarone, 2009).

present trend. A geographic focus across Oklahoma using mutually exclusive categories might elucidate drug trends with greater specificity.

Global Opioid Problem

The opioid epidemic is present not only in the United States, but plagues countries across the globe. Studying the opioid epidemic on a global scale can provide perspective on effects and contributing factors that may differ from the United States. A Norwegian study published in 2022 from Gjersing et al. focused on the issue of prescription opioid-related overdose from 2010-2018. That timeline illustrates the delayed pattern of the opioid issue across the globe and how factors such as policy and practice can affect these trends. It has been shown that policy directly affected the waves of prescription abuse and heroin use in the United States. While the prescription opioid pattern occurred in the United States beginning in the 1990's, Norway experienced that trend increase much later due to liberalization of prescribing practices in 2008. The liberalization of opioid prescribing practices also increased overdose deaths in Australia, Canada and the United States. but did not appear to have the same effect in England or Scotland (Gjersing & Amundsen, 2022). A 2017 study in Australia from Roxburgh et al. found that males accounted for 68% of the decedents differing from the Norwegian study which found that females were more likely to suffer from a prescription opioid overdose than males. However, one weakness found in the Norwegian study was the failure to look at other drugs present in the system, only the primary cause of death was considered. That shortcoming does affect statistical analysis because, as it was pointed out, the median number of drugs of any class found in drug-related deaths was four (Gjersing & Amundsen, 2022). In this study it will be possible to access all known drugs in the system at the time of death, but it will be most beneficial to narrow the scope in order to limit extraneous information.

Norway, Australia, and the United States exhibited the same pattern shift from prescription opioid to heroin abuse with the increase found to be statistically significant in Norway and Australia. In Norway, it was drastically lower than the rates seen in the United States with only a 1.0 per 100,000 increase from 2010-2018 (Gjersing & Amundsen, 2022). The main focus of that study was to notate "...PO [prescription opioids] as a function of place of death, sociodemographic characteristics, primary and secondary health care encounters, and criminal charges using multivariable (adjusted) logistic regression analyses" (Gjersing & Amundsen, 2022). The structure of the study from Roxburgh et al. was only concerned with opioid type, sex, gender, and intent (accidental or intentional). These factors were used to predict which groups were high risk for opioid-related drug overdose in order to alter treatment programs accordingly. The variety of variables considered in the Norwegian study could be extracted for use in a study across the state of Oklahoma. However, the limited scope as used in the study from Roxburgh et al. would be the most beneficial place to start. The Norwegian statistical approach could be taken into consideration as an extension of this study.

Canada is second only to the United States in opioid consumption. A study from Parai et al. focused on the Eastern region of Ontario over a 5-year period from 2011 to 2016. The smaller geographical area allowed for detailed access to death records and toxicology reports. Studying a smaller geographical area also identified regionally specific variables that might be at play. That geographic focus is beneficial when considering the demographic and socioeconomic variables that are present across the state of Oklahoma. A study from Fischer et al. looked at the prescribing practices of 10 Canadian provinces from 2011-2018. They found that there was a reduction in prescriptions across all 10 provinces, but 7 of the 10 still had increases in total opioid-related deaths (Fischer et al., 2020). For example, the Eastern region of Ontario has a lower opioid prescribing rate than the rest of the province which was thought to explain why its death rate of 3.5 per 100,000 is significantly lower than the province as a whole (Parai et al., 2019). However, the rise of illicit synthetic opioids is filling the supply gap and causing unintended consequences where there is dramatic decrease in prescription opioid practice (Fischer et al., 2020). It was found that the opioid-related death rate of Ontario in 2016 was half that of the United States at 6.2 per 100,000 whereas the United States was at 13.1 per 100,000 (Parai et al., 2019). That is interesting to note considering Canada is second in consumption of opioids, but still falls drastically behind in opioid deaths. That study illustrates the effectiveness of a geographical study in identifying regionally specific patterns that can be used to combat the opioid crisis.

Similar patterns of abuse are seen across the countries mentioned here as well as others. There is a consistent issue with poly-substance abuse, accidental overdose, decedents age 45-54 and a dominating presence of fentanyl in opioid-related deaths. It is seen that foreign nations are prominently concerned with legislative, socioeconomic, and prescription practices as a means to understand opioid abuse patterns. That is possible on a smaller scale in these countries where health care systems and populations are less varied than the United States. These factors, in addition to others, may be used at the state level where they are more manageable. Nonetheless, orienting the opioid epidemic status of our home front compared to the rest of the world may provide urgency to combat the issue through further study.

Geographic Study Design

Designing an approach that targets geographic patterns would extend the previous Oklahoma research from Bonk et al. Trends will differ at the county level from the state-wide trend. A study from Lippold et al. covering the opioid and synthetic opioid-related deaths from

2015-2017, found an increase in deaths across almost all racial and age groups studied. That time period, although short, took place when synthetic opioids were rising in popularity accounting for approximately 60% of opioid-related deaths at the time (Lippold et al., 2019). The geographical element focusing on large central metro, large fringe metro, and medium metro areas across the United States is especially beneficial when identifying weaknesses in treatment and resource distribution. There are two limitations of that study including a lack of mutual exclusivity for opioid type and suppressed data from certain ethnic groups. This will be overcome in a design that includes mutually exclusive groups by selected opioid type and a population adjusted analysis to ensure representation of smaller ethnic groups. A limitation pointed out by Lippold et al. that will be relevant in this study is the increase in testing for synthetic opioids over the past 15 years. The issue has been identified and resulted in an increasing number of methods that are able to identify a variety of synthetic opioids and subsequently results in an increase in synthetic opioid-related deaths that are reported. We know that synthetic opioids are shifting the demographics of opioid-related deaths as illicit fentanyl continues to infiltrate cocaine, methamphetamine, heroin, and counterfeit pill drug supplies. The issue has continued to evolve since the completion of that study in 2017 which is what we intend to illustrate in this research.

An ethnic population of particular interest in the state of Oklahoma is the prevalence of opioid overdose mortality among Native Americans. One serial cross-sectional study from Qeadan et al. in 2022 discusses the historically disproportionate effects of the opioid epidemic on the Native populations across the United States. The Native population experienced one of the highest increases in opioid-related death rates from 1999-2019, with a 519% increase among non-metro Natives and a 261% increase among metro populations (Qeadan et al., 2022). These trends are second only to the non-Hispanic white population in the United States. That paper points out the issue of polysubstance abuse of drugs with opioids. Specifically, among Native populations these substances include methamphetamine and heroin from 2008 – 2017 (Qeadan et al., 2022). That should be noted given the extensive abuse of methamphetamine in Oklahoma. Qeadan et al. also points out the systemic factors that could contribute to the disproportionate abuse among Natives such as "…diminished socioeconomic prospects, racism and historical trauma from colonization." While these factors were not statistically uncovered in that paper, they are to be considered when presented with these results. A study with a geographical design could illustrate this pattern given the Native Reservations present across the state.

Another serial cross-sectional design was used by Salazar et al. to determine premature mortality due to opioid overdose. The purpose of that study extends beyond this intended scope but serves as a potential model for assessing change over a large period of time at the state level. The cross-sections used in that study were age focused. This is an important variable to consider for this study with the addition of other variables such as sex, race, and geographic area. All of these variables combined would result in the desired spatio-temporal design which is an extension of the serial cross-sectional approach. Salazar et al. was able to identify that opioid overdose death rates increased from 3.8 to 8.2 per 100,000 people across the studied timeframe. Another important comparison was made to the national average showing that Texas has a lower death rate possibly due to a prescribing rate of 47.2 per 100 versus the national average of 51.4 per 100 (Salazar et al., 2022). This would be another viable area for extension on patterns found in Oklahoma.

We know that drugs do not appear everywhere all at once as indicated by O'Donnell et al. There are geographic shifts that happen over time and can be contributed to different variables. Studying county-level trends in Oklahoma can indicate if there are shifting patterns happening on a smaller scale within the state. In addition, studying demographic shifts is important for the assistance of treatment programs in areas where certain groups are more susceptible to overdose. Geographic centered studies mentioned here can indicate treatment shortages, premature death rates, and correlation between dispensing rates and death rates attributed to opioids.

Spatio-Temporal Study Design

As an extension to a serial cross-sectional focused design, the ideal approach is a spatio-temporal study. This design has been effectively implemented in a variety of studies concerning opioid-related deaths. The foremost article on this subject is one from Kline et al. in the state of Ohio. That research looked at the death rates of Blacks and Whites across Ohio counties from 2007-2018. Breaking down the rates by county allowed the rates to be differentiated from the statewide mortality patterns. Differences were largely attributed to the urban or rural status of a county (Kline et al., 2021). Appropriate adjustments were made to account for shared environment of Blacks and Whites and their dependence on space and time (Kline et al., 2021). The structure was designed to provide a more accurate representation than if the groups were analyzed individually. The results indicate that the death rates for Blacks began lower than that of Whites but increased at a faster rate such that by 2018 death rates for Whites and Blacks were similar (Kline et al., 2021). The study did not explore reasons for the disproportional increase in death rates. However, similar to other correlations we have previously seen, it was proposed that biased prescribing practices in combination with the rise of illicit fentanyl are contributing factors that need to be explored (Kline et al., 2021). While that study strictly focused on Blacks and Whites, it would be of interest in Oklahoma to consider the high Native American and

Hispanic populations as well as other variables of gender, age, and the socioeconomic status of the county.

Another study centered in Ohio determined 12 geographical hotspots of prescription opioid-related deaths over the course of 2010-2017 (Hernandez et al., 2020). That timeline captures the end of Wave 2 and the steady rise of Wave 3. The largest hotspot was located in the Southwest portion of Ohio around the Cincinnati metropolis which aligns with the patterns identified by Kline et al. The work from Hernandez et al. also agreed with the trends found by Kline et al. in that the White male population was most dominant in deaths, but the Black male death rate was close behind. However, by focusing on all races over space and time Hernandez et al. found great disparity between gender and racial groups. The authors contribute that to the overall temporal trend of the opioid epidemic following its three waves. Although both studies find that there is significant increase in overdose deaths, Hernandez et al. speculates that the underlying causes are different. While neither study statistically analyzes specific contributing factors, both have clearly defined where the problem is most prevalent in context of space and time. That is what we are intending to do with this work given there is no baseline for the status of the opioid epidemic in the state of Oklahoma.

Not only do these studies cover space in time, but they do so while considering multi-level questions. One study from Acharya et al. illustrates opioid overdose emergency visits in relation to the healthcare systems available in the area as well as the socioeconomic status of the county. That illustrated notable correlation between areas with better quality care and lower socioeconomic status as the best predictor for increased emergency visits (Acharya et al., 2022). It is expected that we would see variation at the county level. That trend was also clearly illustrated in a Connecticut study from Green et al. which found a difference in opioid type, particularly heroin, methadone, and prescription classifications, in counties due to the rural or urbanicity of such county. Both studies employ spatio-temporal design with multivariate levels that result in a clear representation of opioid-related deaths in their respective states.

Spatio-temporal studies have also proven effective in notating associations between policy changes and opioid-related deaths. One study from Cerda et al. studied 12 states where pain management clinics were enacted to affect opioid prescribing practices. The spatio-temporal model used in that study estimated "…relative rates of overdose and prevalence ratios of high-risk prescribing associated with any (prescription management clinic) PMC law…" (Cerda et al., 2021). The model found that unintended consequences of increased synthetic opioid and heroin deaths resulted from enacting laws with criminal penalty related to prescription opioids (Cerda et al., 2021). These changes resulted in a quick shift back to heroin and synthetic opioid dominating deaths. The attempts to limit the diversion of excess and potent opioid prescriptions to the street market led to the third wave. However, PMCs were found to be effective in reducing prescription opioid deaths by 16-27% in states that had criminal penalties (Cerda et al., 2021). This data will have future potential for research concerning the effectiveness of treatment legislation in Oklahoma. The state first needs a baseline for how the opioid epidemic has progressed over the past 15 years.

It is known that patterns are not uniform nor ubiquitous. Focusing on opioid deaths at the county level over the desired 15-year period will answer an array of questions. Such an approach will clarify demographic trends, spatial comparisons and possible shifts, trends in counties based on socio-economic status and opioid type if possible, and treatment implications. A spatio-temporal design affords the study the advantage of visualizing patterns of answered questions in a context that allows those answers to be extracted and utilized on a personalized scale.

Variations in resources across the state will determine treatment plans and response to opioid overdose. Analyzing the patterns of these deaths at the county level and more specifically answering questions concerning race, gender, and economic status will allow for such resources to be allocated appropriately.

This study will identify geographical hotspots of opioid-related deaths. This data would be useful for addressing weaknesses in drug assistant programs. One study from Sawyer et al. performed a vulnerability assessment over a one-year period to evaluate which counties were highest risk for opioid-related overdose. These findings were compared with treatment accessibility to address the weaknesses in the system (Sawyer et al., 2021). This type of extension would be highly valuable for regulating gaps in treatment assistance resources.

The opioid epidemic is a well-established issue not only in the United States, but across the globe. The state of Oklahoma has faced a progressing issue of opioid overdose deaths without sufficient documentation of the grip the epidemic has on its citizens. A comprehensive study is needed to establish a baseline of opioid use and abuse across the state. A spatio-temporal design covering the past 15 years would be representative of all three waves of the epidemic to present day.

Methods

The Office of the Chief Medical Examiner (OCME) performs postmortem examinations and toxicological testing in accordance with agency quality standard practices and procedures. Board certified Forensic Pathologists determine cause and manner of death based on their medical opinion and training. Toxicological testing is performed based on specimen availability and the opinion and training of the pathologist and toxicologists. Completed cases are stored in the agency database with all related information including identification, demographics, specific location of injury and death, cause and manner of death, toxicology results, the scene narrative, and relevant medical history pertaining to the decedent.

Case Selection

All deaths categorized as Accidental-Drugs and Poisons were pulled from the OCME database by year for the years 2008-2022. Excel spreadsheets containing the variables of interest were created for individual years. The raw data was deidentified to only include the assigned Medical Examiner's case number, demographics (age, race, sex), date and county of death, cause and manner of death, toxicology results, and subsequent immediate causes contributing to the death[3]. Efforts were made to populate columns with all drugs listed in the cause of death for accidental drugs and poisons deaths. A drug list was generated to assign drugs of interest into classes of Prescription Opioids, Benzodiazepines, Stimulants, and Other CNS Depressants. These designations were based on generally accepted drug classification and toxicologist expertise. All drugs classified under these categories are listed in Appendix A.

This study focused on demographics (age, race, and sex), location, and drug categories containing an opioid. Drug categories counted for each year were as follows: Prescription Opioids (Rx) only, Fentanyl only (including Fentanyl analogs), Heroin only, All Opioids (Rx or Fentanyl or Heroin), Rx with Heroin or Fentanyl, Rx with Benzodiazepines, Rx with Stimulants, Rx with Other CNS Depressants, Heroin with Benzodiazepines, Heroin with Stimulants, Heroin with Other CNS Depressants, Fentanyl with Benzodiazepines, Fentanyl with Stimulants, and Fentanyl with Other CNS Depressants.

[3] The IRB determined this study to not meet the definition for human subject research and permission was granted to proceed.

Statistical Analysis

Summary statistics were performed for demographics, location, and drug categories for each year using Statistical Analysis Software (SAS). Demographic summary statistics for age, race, and sex were only performed on cases that contained an opioid. Time series graphs were created for demographics and each drug category. All opioid-related death locations over the 15-year timeline were combined into one map and adjusted to the 2020 census population to visualize geographic patterns at the county level. Additional county level maps were created which indicate increased and decreased rates of prescription opioid and fentanyl related overdose deaths in 2008 and 2022.

Results

The opioid epidemic affects a variety of groups across space and time. This study covers a 15-year period from 2008-2022. During this time the population in Oklahoma was 3.7 million in 2010 and increased by 5.5% to approximately 3.9 million in 2020 (America Counts Staff, 2021). Urban areas comprised 65% of the population in 2010 (U. S. Census Bureau, 2012). Oklahoma, Tulsa, and Cleveland counties have the highest population density respectively (America Counts Staff, 2021). The average age in Oklahoma was 37 in 2020 (America Counts Staff, 2021). The ethnic group distribution is White (63.7%), Black or African American (6.99%), and American Indian and Alaska Native (7%) (America Counts Staff, 2021). The gender distribution is similar with females accounting for 50.4% of the population and males 49.6% (America Counts Staff, 2021).

Demographics

Demographic trends of opioid-related deaths experienced notable change over the 15-year period of this study. The White population comprised 86% of the total opioid-related deaths from 2008-2022 and was the highest race represented for each year. In addition, deaths among the Black population saw an 8-fold increase while all other Non-White races combined saw a 3-fold increase. As shown in Figure 2, a substantial increase in deaths across all races was noted from 2020-2022.

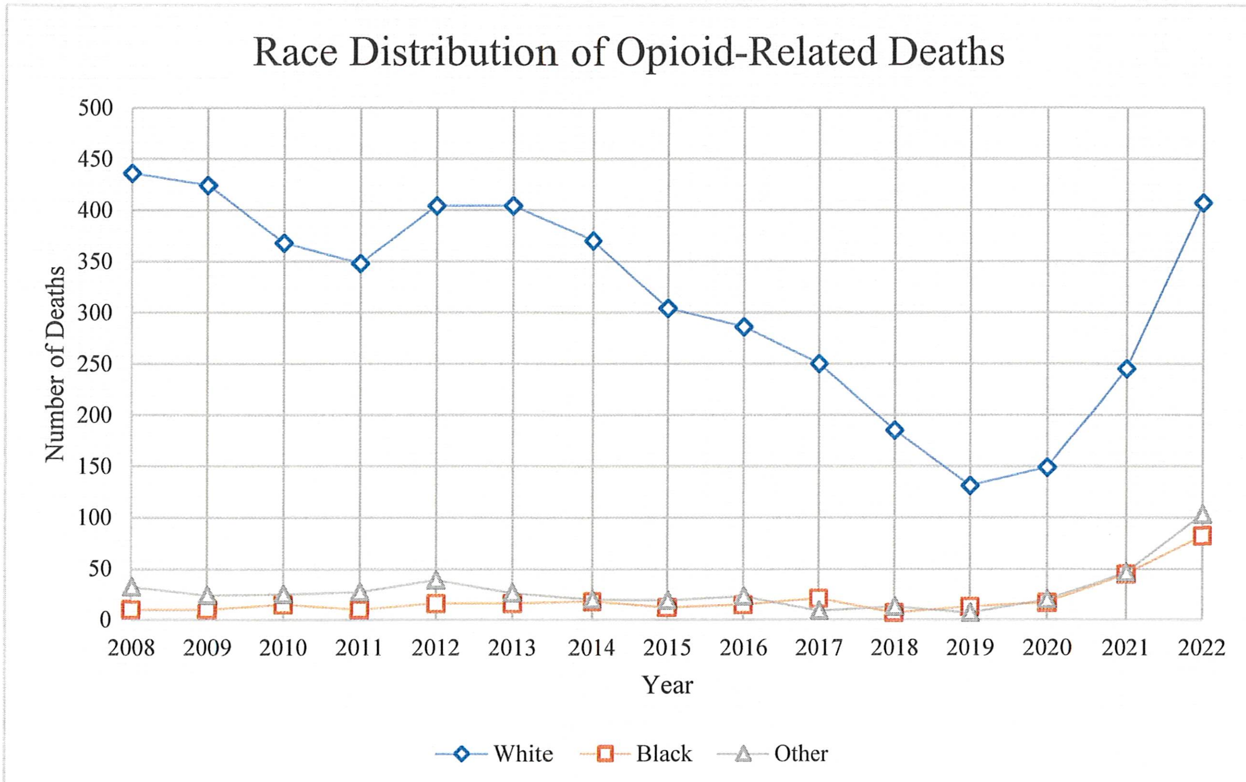

Figure 2: Total Opioid Deaths by Race in Oklahoma, 2008-2022.

Figures 3 and 4 illustrate age and sex trends for opioid deaths. The trends represented in Figure 3 depict opioid-type preferences across age groups. The 45-64 age range experienced the highest death rates from 2008-2018 during the height of prescription opioid abuse, decreasing drastically by 2019. The second highest age group in opioid-related deaths was 25-44 which saw an over 250% increase from 2020-2022 to become the leading age group, surpassing the 45-64 age group by nearly 200 deaths. The under 25 group remained consistent across time mimicking the dramatic decrease and increase in overall opioid deaths from 2017-2022. The 65 and over age group was noticeably lower than all other groups but illustrated the same overall trend across the

15 years. As shown in Figure 4 female and male deaths were almost identical to each other from 2012-2014 and saw divergence of nearly 2:1 male to female from 2020-2022. Altogether, males exhibited a slight preference for opioids comprising 57.8% of the total opioid deaths over 15 years. All demographic variables saw a decrease from approximately 2016-2020. This aligns with the overall decrease in opioid-related deaths during that same timeframe.

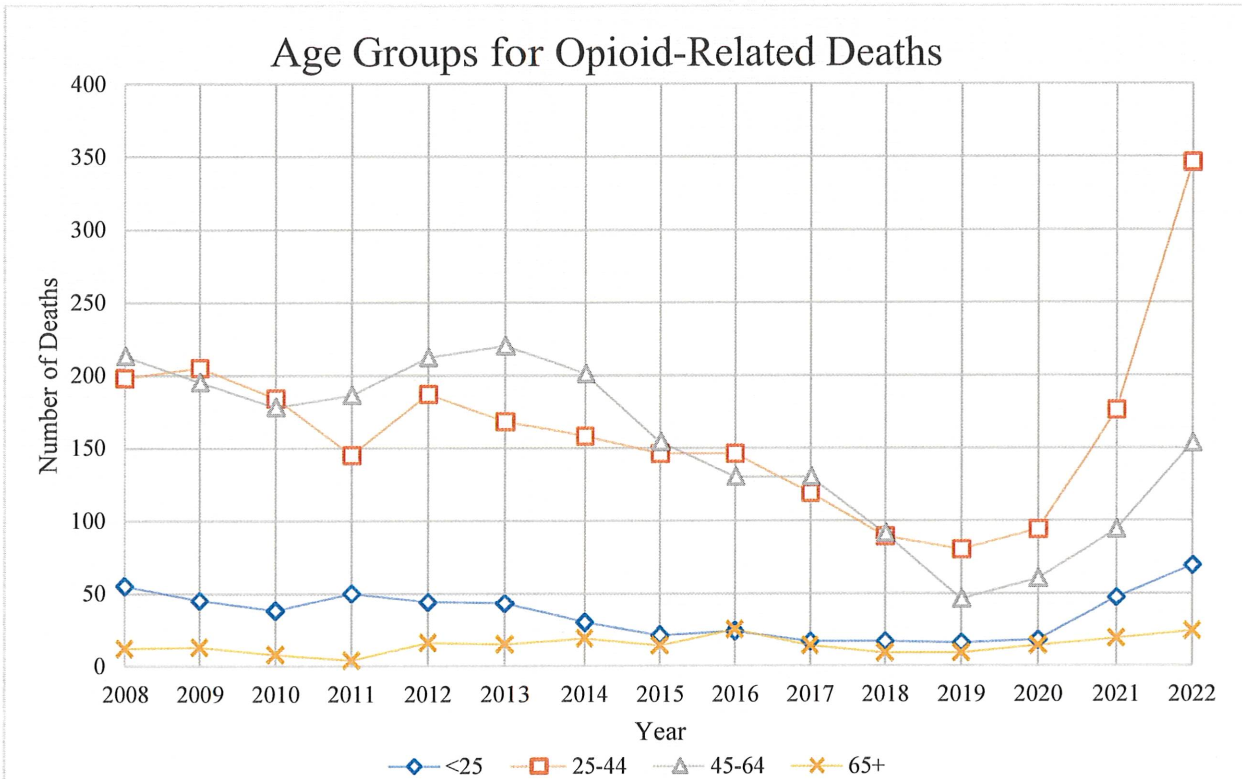

Figure 3: Total Opioid Deaths by Age Group in Oklahoma, 2008-2022.

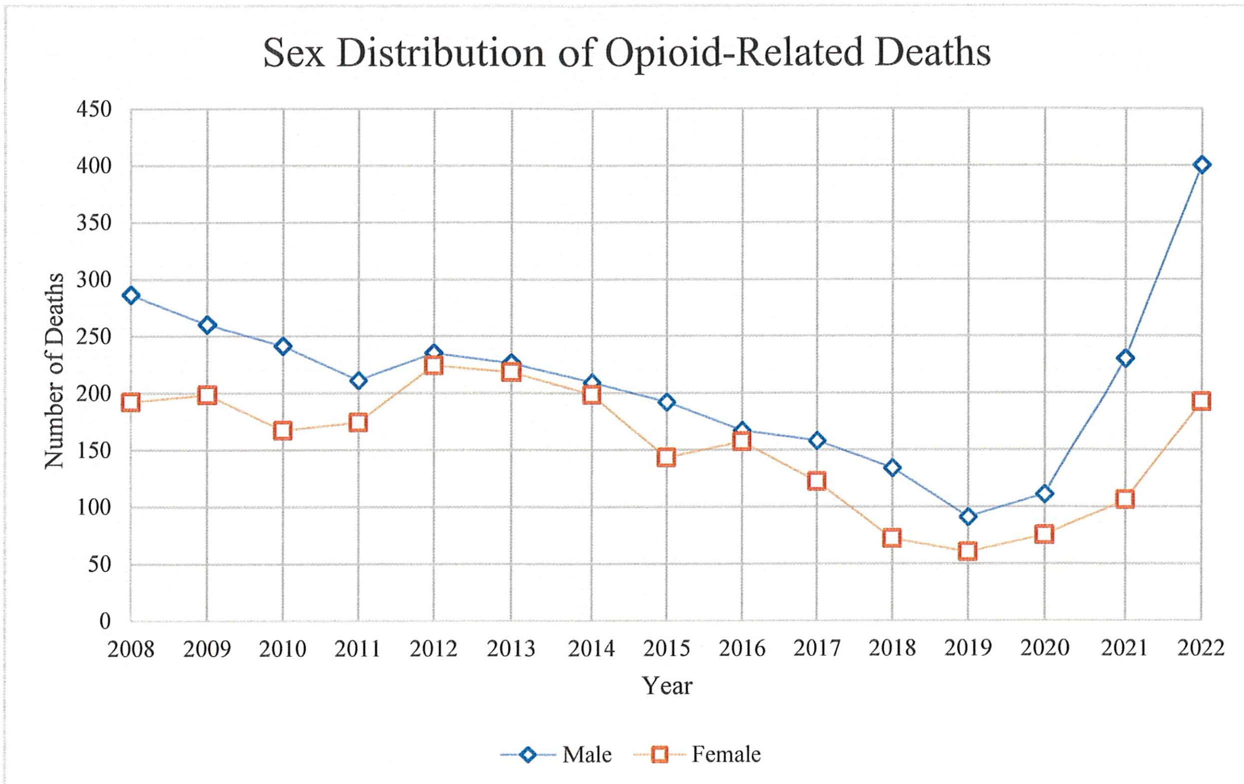

Figure 4: Total Opioid Deaths by Sex in Oklahoma, 2008-2022.

Opioids

Total accidental drugs and poisons deaths, shown in Figure 5, had a 103% increase over the 15-year timeline while the population only increased by approximately 5.5% during that same time. Opioids of all types accounted for 46.6% of those deaths. At their highest in 2008, opioids accounted for 75.4% of drug deaths and at the lowest in 2020 they accounted for just 22.5% of deaths.

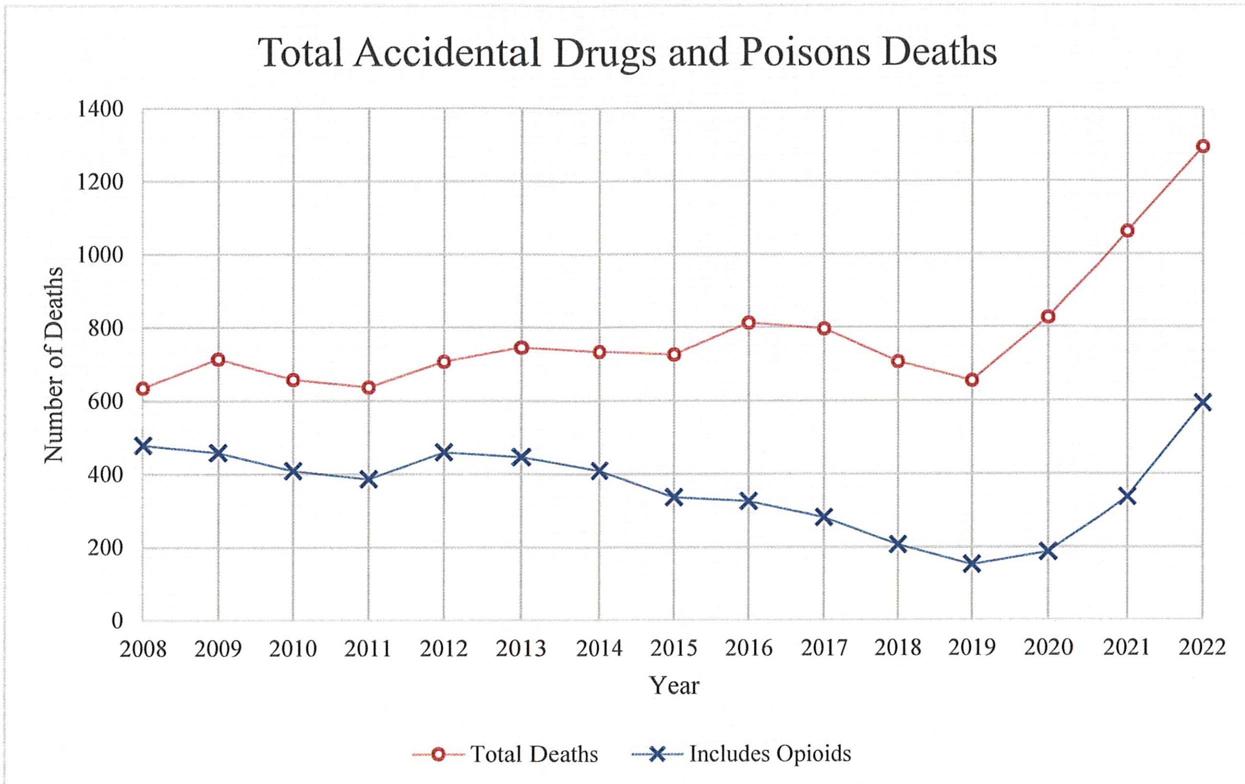

Figure 5: Total Accidental Drugs and Poisons Deaths in Oklahoma, 2008-2022.

Figure 6 shows opioid deaths by opioid type over the 15 years and clearly illustrates the three distinct waves of the opioid epidemic. Prescription opioid deaths steadily decreased over time starting at 429 deaths in 2008 and only 72 by 2022. This was replaced by fentanyl. There were only 61 fentanyl deaths in 2008 compared to 518 in 2022. This is approximately a 750% increase in deaths. Heroin is not a popular drug of abuse in Oklahoma, but still mimicked nationwide opioid patterns by increasing during the 2016-2020 period between the prescription opioid and fentanyl booms. At their highest, heroin accounted for a mere 26% of total opioid deaths in 2018. In 2018 and 2019 heroin deaths were higher than fentanyl deaths right before fentanyl saw a two-fold increase in just one year.

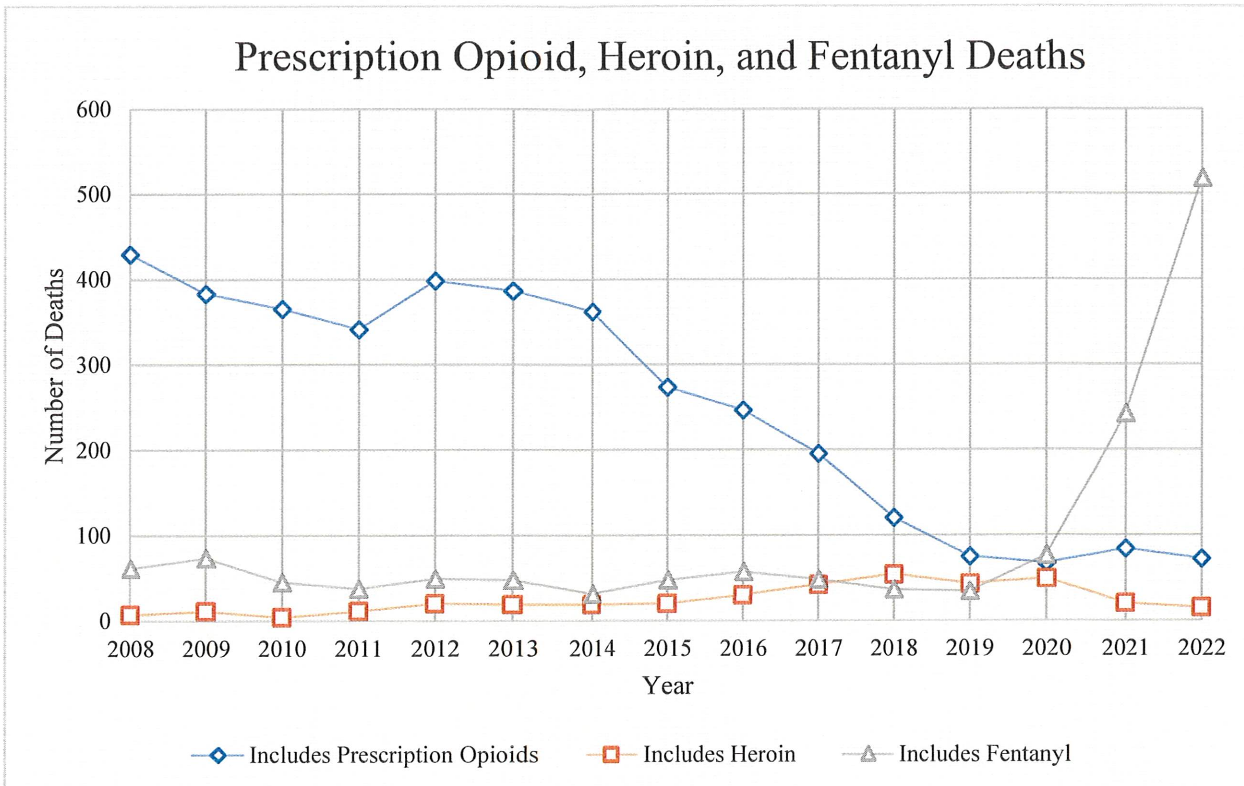

Figure 6: Total Deaths that included Prescription Opioids, Heroin, and Fentanyl in Oklahoma, 2008-2022.

Oftentimes opioids can be potent enough on their own to result in an overdose death. When looking at deaths that only contained a prescription opioid, heroin, or fentanyl in isolation in a single case there are interesting trends. Figure 7 illustrates that prescription opioid deaths, when found alone in a case, did not peak in 2008 like the trends noted in Figure 6. It was not until 2013 that isolated prescription opioid deaths peaked at 300 total deaths. In addition, heroin is not commonly found in combination with other drugs like prescription opioids and fentanyl. Over the 15-year period 80% of total heroin cases were heroin only deaths. Fentanyl only deaths remained consistent from 2008-2020 and experienced a drastic increase from 2020-2022. In

2008, there were 34 fentanyl only deaths and by 2022 that had increased nearly 13-fold to 435 deaths. This accounts for 84% of all fentanyl deaths in 2022.

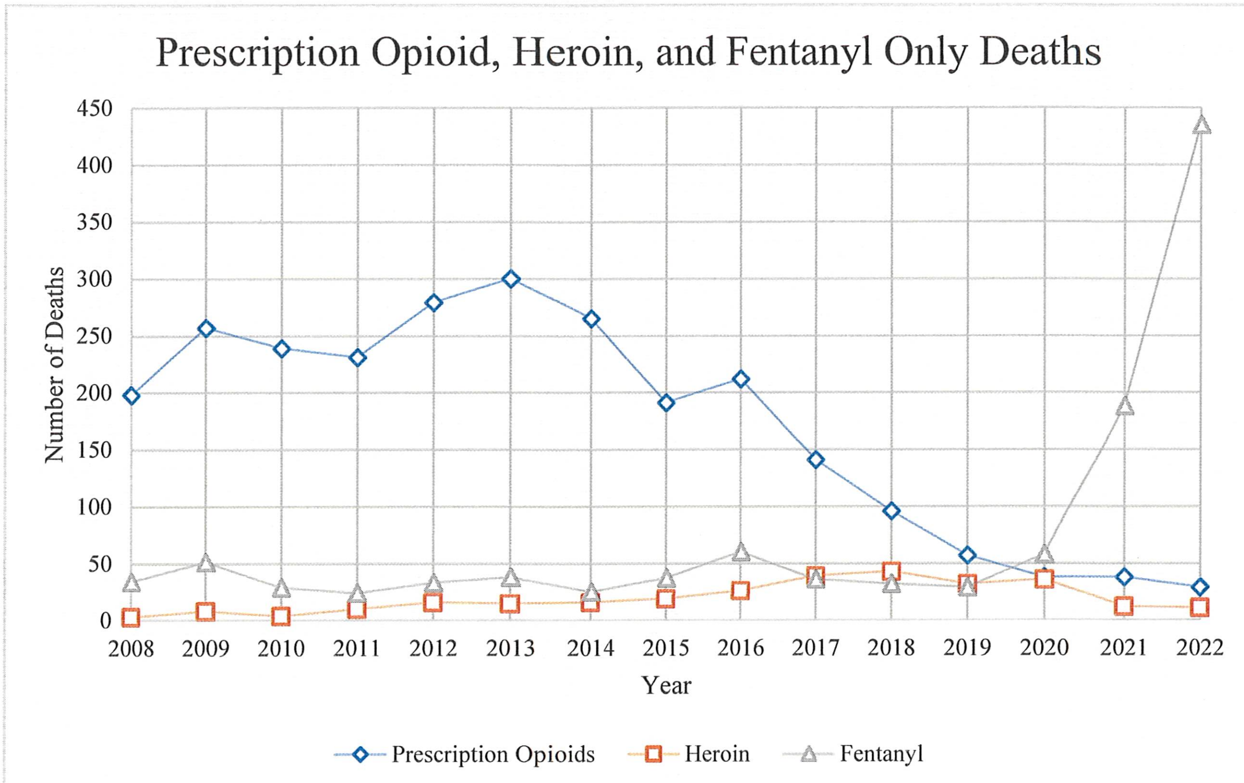

Figure 7: Total Deaths that only contained a Prescription Opioid, Heroin, or Fentanyl per case, 2008-2022.

Opioid Combinations

Opioid type was also studied in combination with other common drug classes of interest including benzodiazepines, stimulants, and other CNS depressants. Figure 8 illustrates the total number of cases that included each of these drug categories. There is a clear domination of opioid and stimulant cases which trade leading places between 2016 and 2017. The combination cases are represented in Figures 9, 10, and 11 respectively. During the height of prescription opioid-related deaths there was also a noteworthy presence of prescription opioid deaths that contained benzodiazepines. In 2008, 122 prescription opioid deaths also contained a benzodiazepine making up 28% of all prescription opioid death cases. The combination trend was mimicked through the transition to fentanyl with the 7-fold increase in fentanyl and benzodiazepine deaths from 2020 to 2022.

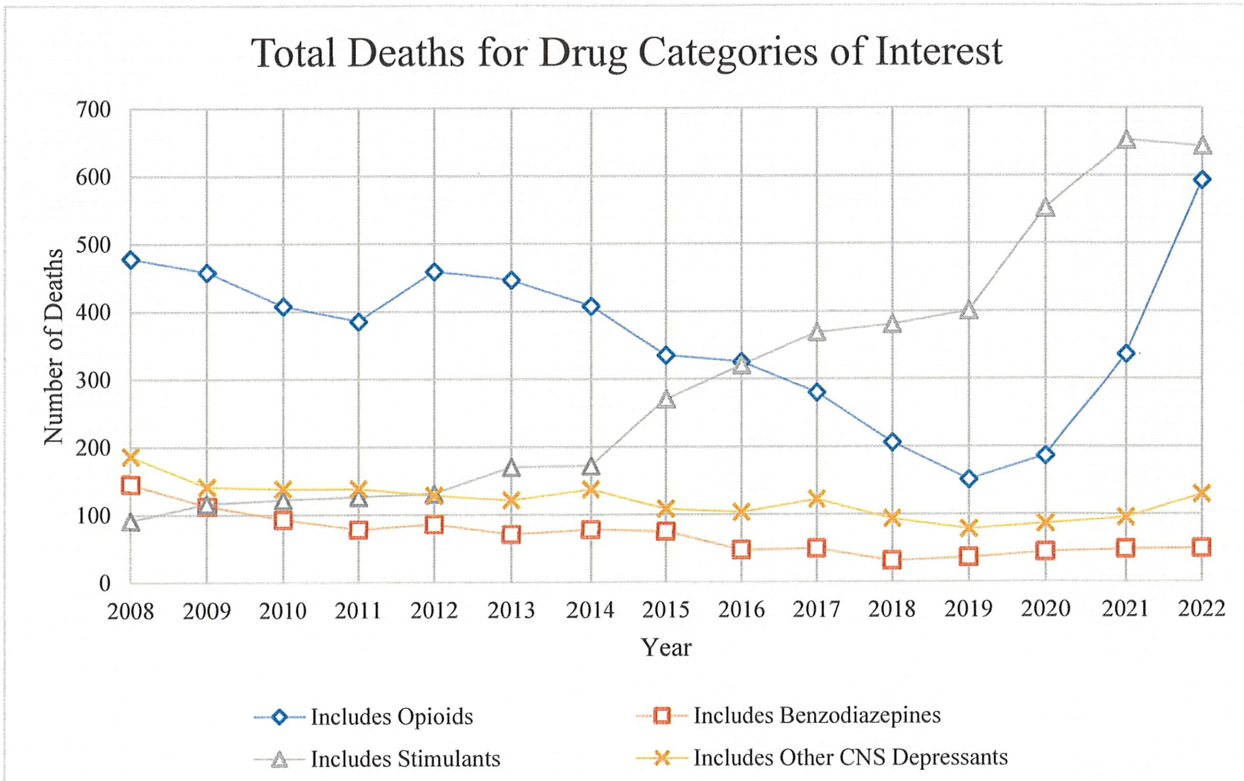

Figure 8: Total Deaths that Included Opioids, Benzodiazepines, Stimulants and Other CNS Depressants, 2008-2022.

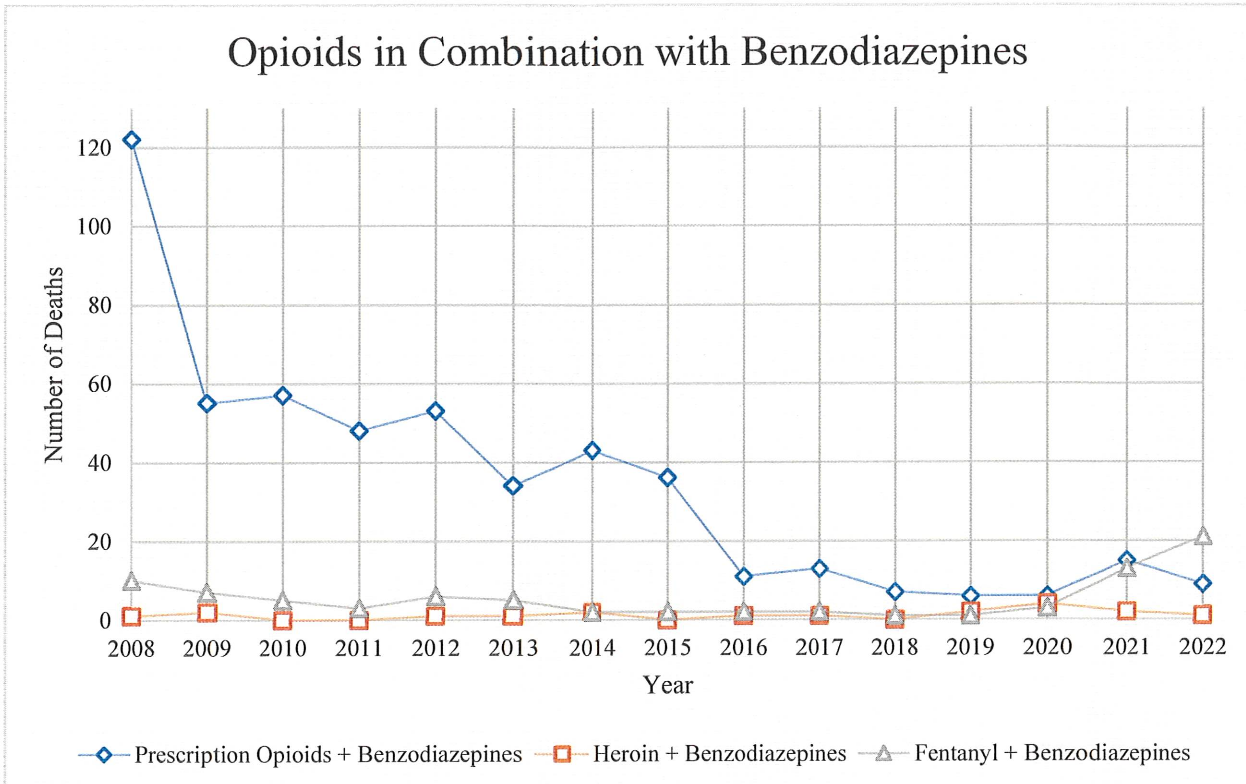

Figure 9: Total Deaths by Opioid Type in Combination with Benzodiazepines, 2008-2022.

Oklahoma is historically a methamphetamine abusing state. This is clearly visible when studying opioid trends in combination with stimulants represented in Figure 10. There does not appear to be an obvious trend among opioid type and stimulant use throughout the three waves. Prescription opioids with stimulants accounted for 34 of the 429 prescription opioid deaths in 2008. The frequency of this combination was cut in half by 2022, but experienced several increases and decreases over the 15 years. The anticipated fourth wave of the opioid epidemic is well represented by the 350% increase of fentanyl and stimulant deaths from 2020 to 2022. A trend that will likely continue. Heroin and stimulant combination deaths also increased from 2017 to 2020 during the height of heroin related deaths. This still only accounted for <5.0% of total opioid-related deaths.

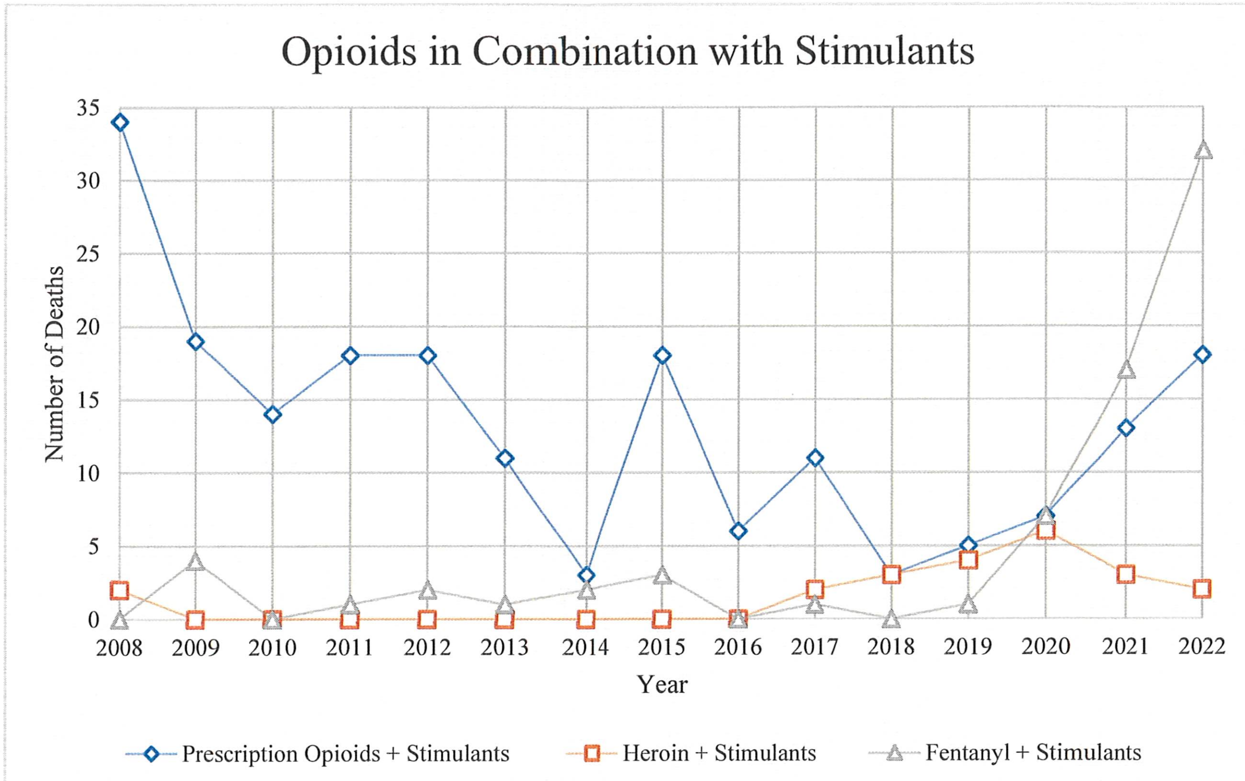

Figure 10: Total Deaths by Opioid Type in Combination with Stimulants, 2008-2022.

Opioids are also seen in combination with Other CNS Depressants as shown in Figure 11. This combination trend was highest in 2008 with prescription opioids and other CNS depressants together accounting for 24% of all opioid-related deaths. This combination decreased drastically across all opioid types and when combined only made up 6.9% of all opioid deaths in 2022. Heroin and fentanyl in combination with other CNS depressants remained consistently low over the 15-year timeline. However, fentanyl in combination with other CNS depressants saw a substantial upward trend (9-fold increase) starting in 2020. Results illustrated in Figures 2-11 are available in Appendix B.

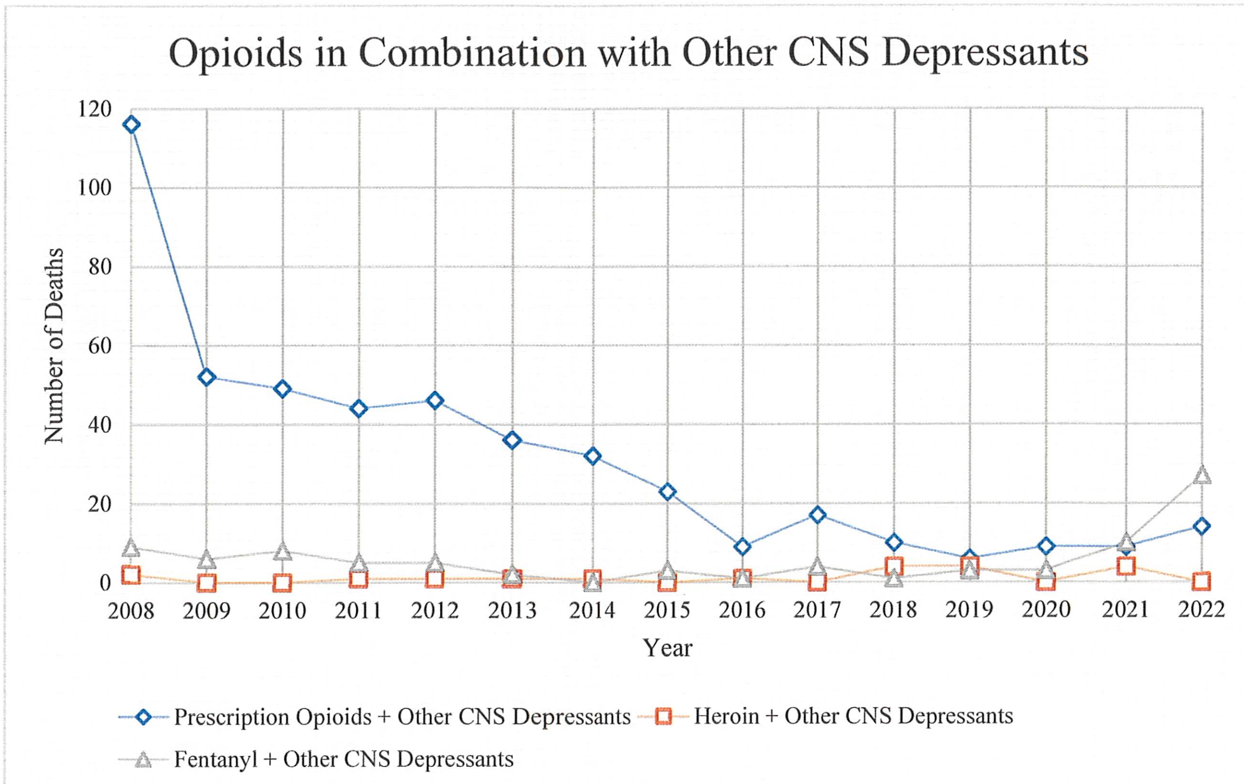

Figure 11: Total Deaths by Opioid Type in Combination with Other CNS Depressants, 2008-2022.

Geographic Patterns

Oklahoma has 77 counties, 6 of which had an opioid death rate between 20-29.99 deaths per 10,000 people adjusted to the 2020 Census. Those counties included: Carter, Coal, Jefferson, Muskogee, Pawnee, and Pushmataha. Figure 12 shows 27 counties with a death rate between 0-9.99 and 44 counties with a rate of 10-10.99 per 10,000. Large metropolitan counties did not have the highest rates due to population adjustment. The 6 highest counties were concentrated in the southern and eastern regions of the state.

2008-2022 Total Opioid Death Rates
2020 Population Adjusted (per 10,000)

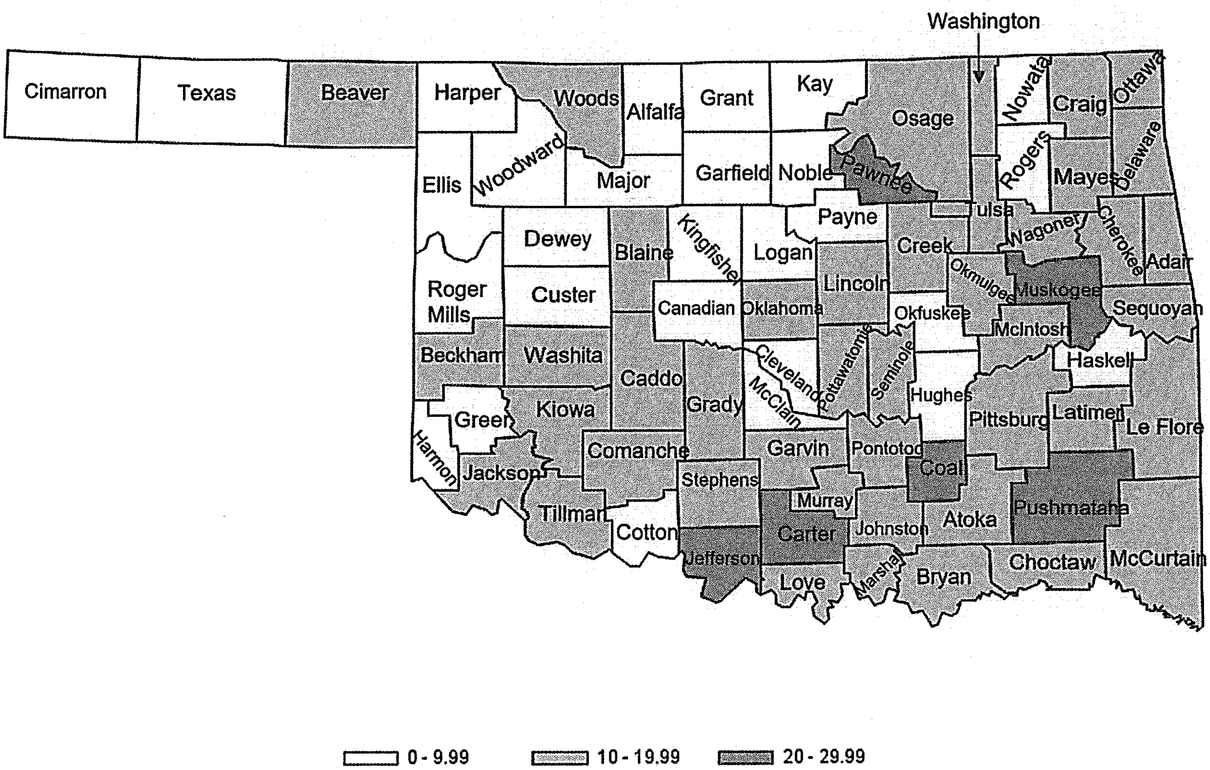

Figure 12:Total Opioid-Related Death Rates per 10,000 adjusted to the 2020 Oklahoma Census.

Figures 13-16 illustrate the drastic shift from prescription opioid to fentanyl abuse from 2008 to 2022. The widespread abuse of prescription opioids in 2008 is clearly shown in Figure 13 with a majority of counties having a death rate higher than 1 per 10,000 for the year. Then by 2022 prescription opioid deaths are almost non-existent with only one county having a death rate over 1 per 10,000 shown in Figure 14. The opposite trend is visible in Figures 15 and 16 for fentanyl related deaths. All 77 counties had a fentanyl death rate less than 1 per 10,000 in 2008. Figure 16 shows fentanyl death rates in 2022 where 16 counties had a rate higher than 1 per 10,000. Two of the three counties with the highest rate were Oklahoma and Tulsa counties. Prescription opioids did not exhibit a geographic predisposition for deaths, but fentanyl deaths were more concentrated in the Eastern region of the state.

2008 Prescription Opioid Death Rates
2010 Population Adjusted (per 10,000)

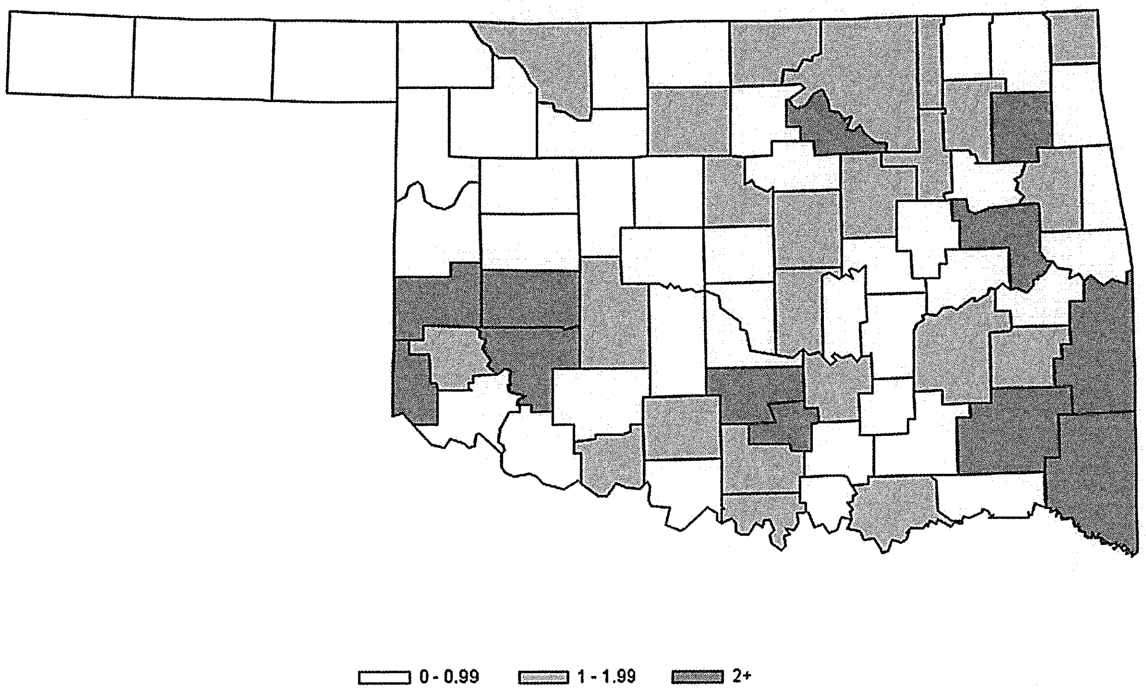

Figure 14:2008 Prescription Opioid Death Rates per 10,000 adjusted to the 2010 Oklahoma Census.

2022 Prescription Opioid Death Rates
2020 Population Adjusted (per 10,000)

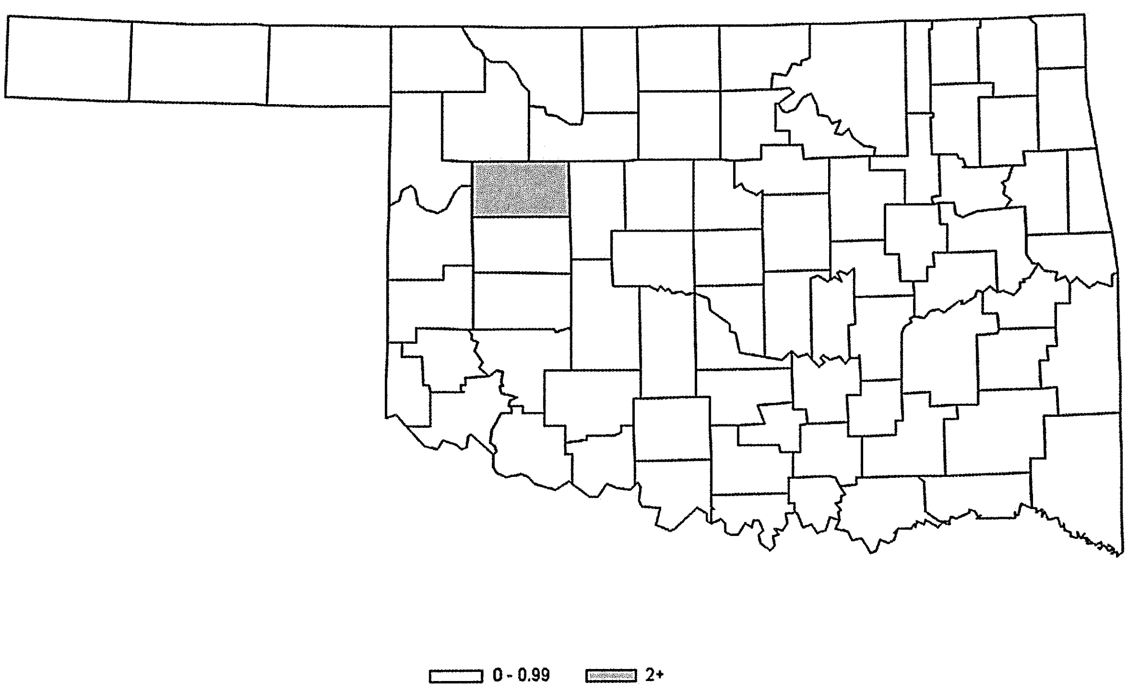

Figure 13: 2022 Prescription Opioid Death Rates per 10,000 adjusted to the 2020 Oklahoma Census.

2008 Fentanyl Death Rates

2010 Population Adjusted (per 10,000)

Figure 15: 2008 Fentanyl Death Rates per 10,000 adjusted to the 2010 Oklahoma Census.

2022 Fentanyl Death Rates

2020 Population Adjusted (per 10,000)

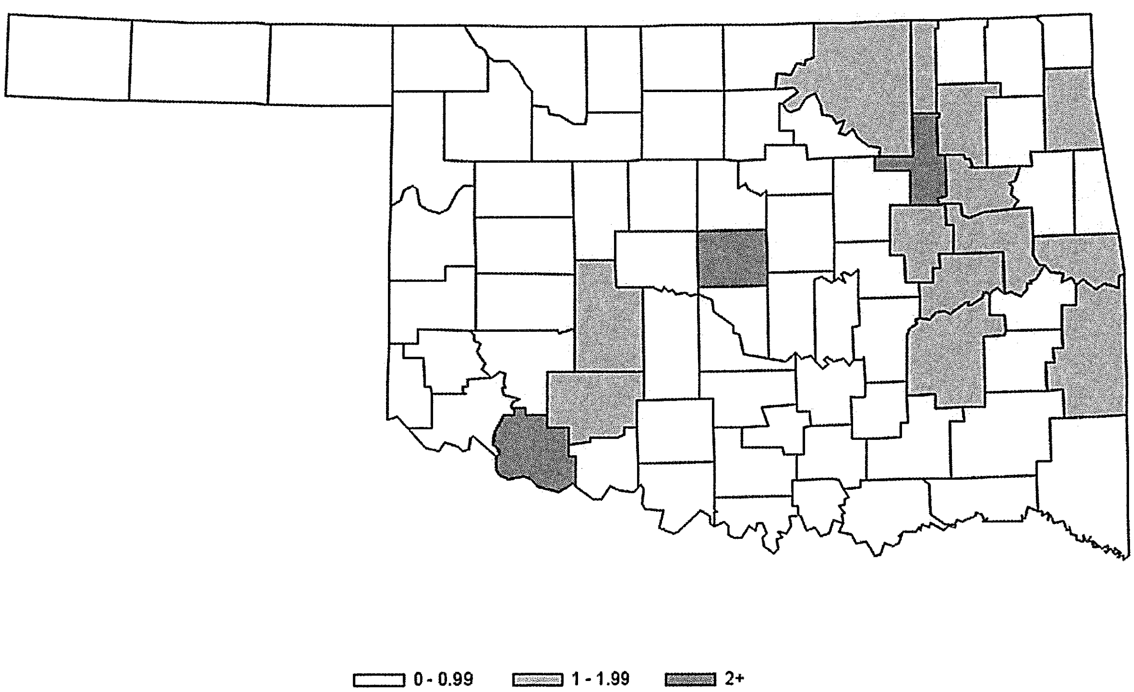

Figure 16: 2022 Fentanyl Death Rates per 10,000 adjusted to the 2020 Oklahoma Census.

Discussion

The results of this study illustrate the unique nature of the opioid epidemic as it has followed a distinct pattern in Oklahoma across all variables over the 15-year timeline. The accepted three wave design of the opioid epidemic from prescription opioid to heroin to fentanyl abuse was clearly visible in this study. However, the timeline of these trends in Oklahoma was several years delayed from national patterns. Additional similarities and differences were noted across all variables when compared to national and regional opioid overdose data.

Demographics

Demographic trends were only studied for opioid-related deaths. The demographic makeup of Oklahoma is predominantly White (63.7%) with a comparable male (49.6%) and female (50.4%) distribution (America Counts Staff, 2021). The race distribution is distinguishable in opioid trends as 86% of all opioid overdose deaths over the 15 years were White. This does not come as a surprise for Oklahoma based on the demographic makeup. However, national trends show that although Whites are among the highest odds of polysubstance abuse, the highest death rates were among Non-Hispanic Alaska Native American Indian and Non-Hispanic Black populations (Shover et al., 2022; Spencer et al., 2022). The Native American population in Oklahoma was not represented in this study due to limited numbers in these datasets compared to White and Black populations but would be an interesting area for further research.

Previous literature has shown racial bias in pain treatment and prescribing practices that has led to a disparate percentage of opioid-related death rates among Whites and Blacks during the height of the first wave (Alexander et al., 2018). While prescription laws such as the Anti-Drug Diversion Act in Oklahoma and the reformulation of OxyContin decreased prevalence of prescription opioids, it increased the presence of cheap and easily accessible heroin. This caused White populations to experience a slight decrease in opioid deaths. However, this easily accessible heroin infiltrated the illicit market and increased deaths nationwide among Blacks (Alexander et al., 2018). The variation in death rates among Whites and Non-Whites in Oklahoma may not only be a result of ethnic distribution, but also prescribing practices particularly during the height of prescription opioid abuse from 2008-2013. Deaths in Oklahoma among Non-White races (Blacks and Other) remained relatively steady through the first and second waves and did not see a notable increase until 2020. These racial trends in opioid death rates contrast with nationwide findings.

Other demographic factors such as age and sex show distinctive trends of opioid abuse. In Oklahoma, males and females exhibited similar opioid death rates at 57.8% and 42.2% over the 15 years. This is slightly lower than the national average which shows males make up 70% of opioid overdoses (NIDA, 2024). However, females have a tendency to advance from use to abuse of opioids faster than males (Back et al., 2011). This is due to the findings that females are more susceptible to chronic pain leading to misuse of prescription opioids (NIDA, 2022). In Oklahoma, the male and female opioid death distribution was closest from 2012-2014 during the height of total prescription opioid abuse indicating it as a driving factor. The highest disparity between males and females occurred from 2021-2022 during the illicit fentanyl boom. While females are 1.6 times more likely to abuse prescription opioids, males abuse heroin at a higher rate (Back et al., 2011). Males are more likely to abuse multiple substances and illicit substances (NIDA, 2022). These national gender trends are similar to those seen in Oklahoma.

The most likely group to die from prescription opioids are females ages 45-54 (NIDA, 2022). This national trend aligns with the Oklahoma age and sex patterns exhibited from 2012-

2014 which accounted for 30% of total prescription opioid deaths. During this 3-year span, females and males had the most similar death rates at 49% and 51% respectively. In addition, the 45-64 age group was the leading age group for opioid deaths from 2008-2018 and was noticeably higher during this time. It was not until 2019 that the 25-44 age group surpassed the 45-64 age group. This aligns as the national leading age group for opioid deaths from 2020-2021 was 35-44 (Spencer et al., 2022). The under 25 and over 65 age groups were the two lowest age groups to experience opioid deaths over the 15 years. The under 25 age group would be considered opportunistic illicit users which tracks with the largest increase in deaths occurring during the illicit fentanyl spike from 2020-2022. In Oklahoma, the 25-44 and 45-64 age groups dominated the total opioid deaths due to high opioid prescription abuse amongst this pain experiencing demographic.

Pain as a fifth vital sign led to overprescribing practices that lasted from the 1990s to around 2010 (DEA, 2021). Oklahoma experienced the height of prescription abuse in 2013, slightly delayed compared to national trends that peaked in 2010 (DEA, 2021). There was a noticeable decrease in deaths after controls were placed on prescribing practices. These trends emphasize prescription opioids as the driving force behind the opioid epidemic during the first wave. Seemingly unchanged death rates among Non-White races from 2008-2019 is a different trend than seen across the country as previous literature has shown noteworthy increases in deaths among Black populations during the post-prescription opioid era (Alexander et al., 2022; Kline et al., 2021). In addition, the transition to illicit opioid abuse from heroin then fentanyl altered demographic trends seen in opioid deaths. The large increase in deaths among the 25-44 age group indicates a higher tendency towards illicit use among this age group as noted by national trends as well. In Oklahoma, there are clearly discernible differences in age, race, and gender opioid-related death patterns over the 15-year timeline.

Opioid Type

Oklahoma saw a 103% increase in total accidental drugs and poisons deaths from 2008-2022. The nation as a whole, saw a 5-fold increase in all overdose deaths from 2001-2021 and an 8-fold increase in opioid deaths since 1999 (Spencer et al., 2022; FCC, 2024). This drastic increase in opioid deaths is due to the proliferation of illicit fentanyl. A majority of this increase took place after 2017 when the issue was declared a national emergency under Section 319 of the Public Health Service Act (FCC, 2024). Oklahoma ranked 30th for overdose death rate in 2022 aligning with regional trends in Arkansas, Colorado, Kansas, and Texas (CDC, 2022). Louisiana and New Mexico had the highest death rates among bordering states (CDC, 2022). On a national level, the East Coast has a noticeably higher death rate with West Virginia, Washington D.C., Tennessee, and Delaware being the highest at greater than 55 deaths per 100,000 people (CDC, 2022). The dramatic increase in nationwide overdose deaths over the past 20 years is driven largely by the opioid crisis and is visible in this study of Oklahoma trends.

In Oklahoma in 2008, opioids accounted for 75.4% of drug deaths and in 2020 made up just 22.5% of deaths. One study shows nationwide prescription opioid decline beginning in 2011 (NIDA, 2024). Oklahoma total prescription opioid deaths peaked in 2008 and 2013 and then began a steep decline through 2018. The peak in 2013 was total cases that only included a prescription opioid in the cause and manner of death indicating that the peak in 2008 was due to polysubstance abuse. In particular, prescription opioids with benzodiazepines and other CNS depressants. The steep decline in prescription opioid deaths began after 2013 following legislation that resulted in the reformulation of OxyContin in 2010 and the Anti-Drug Diversion

Act amendment in Oklahoma in 2015 (Beachler et al., 2022; Landmark Recovery, 2018). During this decline of prescription opioid-related deaths, the nation saw an increase in heroin deaths from 2010 to 2016, but Oklahoma did not see a noteworthy increase (NIDA,2024). In Oklahoma in 2018, heroin peaked at 54 total deaths at which point prescription opioid deaths were still higher. This emphasizes the delay of drug use trends in Oklahoma relative to the nation as a whole. The low heroin death rates are largely due to the cheap and prevalent methamphetamine supply in Oklahoma that serves as the drug of choice.

There was a noticeable increase in stimulant related deaths in Oklahoma beginning in 2015 and surpassing opioid deaths in 2017. One study from 2013-2019 placed Oklahoma in the top 3 highest psychostimulant death rates with the West having the highest rate of psychostimulant deaths by region (Mattson et al., 2021). In 2020, Oklahoma opioid deaths once again dramatically increased with the proliferation of fentanyl. This increase was noted across the entire Western region. From 2018-2019 the Northeast had the highest percentage of synthetic opioid deaths at 71%, but the West experienced the largest increase in synthetic opioid deaths during this time (Mattson et al., 2021). The increased presence of both drugs indicates the possibility for polysubstance abuse. A trend that was also seen in Oklahoma by the 350% increase in fentanyl and stimulant combination deaths from 2020 to 2022. One study found that 60% of fentanyl cases contained methamphetamine ranking it above heroin and prescription opioids for the first time (Millenium Health, 2023). The fourth wave of the opioid epidemic is anticipated to be the combination of fentanyl with stimulants, both methamphetamine and cocaine (DEA, 2022; Shover et al., 2024). The fourth wave is already being seen in the West, while previous opioid trends began in the East. A trend that is mimicked in Oklahoma. This indicates the geographic nature of the spreading of drug abuse trends and the delayed arrival of drugs in certain regions.

The large increase in synthetic opioid deaths and dominating psychostimulant death trends in the West point to the distribution of methamphetamine and fentanyl from Mexico. This results from a couple of legislative and geographic factors that also affect trends in Oklahoma. The restriction of pseudoephedrine in the United States in 2005 resulted in Mexican cartels taking over the synthesis and distribution of methamphetamine (NIDA, 2021). The Mexican border provides easy access for distribution of the drug supply to the Western region of the United States. Following this restriction, stimulant deaths in Oklahoma were at the lowest from 2008 until an increase began in 2015.

Oklahoma saw an increase in synthetic opioid deaths beginning in 2020. This is largely due to the illicit fentanyl supply also being funded by foreign entities. Chemicals needed for the synthesis of fentanyl began with ANPP[4] and NPP[5] which were both scheduled in 2010 and 2007 (DOJ & DEA, 2020). This led to the development of a new precursor 4-ANPP[6] which has yet to be scheduled (DOJ & DEA,2020). There are now 38 domestic and 28 international suppliers of 4-ANPP with transactions noted in both the United States and Mexico (DOJ & DEA, 2020). In addition, beginning in 2020 a new adulterant, xylazine, was commonly found in the fentanyl drug supply. Xylazine is an animal tranquilizer not approved for use in humans that is added to the fentanyl supply to increase its effects (Smith, 2023). It is not controlled by The United States

[4] ANPP, also known as 4-anilino-N-phenethylpiperidine, is an immediate precursor needed for the organic synthesis of fentanyl using the Siegfried method (DOJ & DEA, 2020).
[5] NPP, also known as N-phenethyl-4-piperidone, is an intermediate chemical in the organic synthesis of fentanyl using the Siegfried method (DOJ & DEA, 2020).
[6] 4-ANPP, also known as 4-anilinopiperidine, was developed as a replacement for ANPP as an immediate precursor for fentanyl synthesis (DOJ & DEA, 2020).

Controlled Substances Act and is commercially available through both veterinary and generic pharmaceutical outlets (DEA, 2022). In addition, it can be purchased at a cheap rate from China, making the outsourcing of drug synthesis a common theme (DEA, 2022). Xylazine has been detected in 48 of the 50 states and had a 193% increase in detection in the South from 2020 to 2021 (DEA, 2022). This adulteration has led to a 1,127% increase in xylazine-fentanyl positive overdose deaths in the South making it the highest region by over 400% (DEA, 2022). In Oklahoma, the largest rise in total fentanyl deaths began in 2020 increasing by approximately 580% through 2022. The 13-fold increase in fentanyl only deaths in Oklahoma from 2008 to 2022 aligns with the national trends that point to adulteration of the fentanyl supply making it even more potent.

Xylazine is categorized as a CNS Depressant and has a different mechanism of action on the body than an opioid. If present in a high enough amount with fentanyl, xylazine can be deadly due to the compounding effects of both depressants (DEA, 2022). Approximately 80% of opioid-related overdoses nationwide involve polysubstance abuse with a non-opioid drug (Smith, 2023). In Oklahoma, fentanyl has proven to be deadly on its own indicated by fentanyl only deaths making up 79% of total fentanyl deaths over the 15 years. One tool to combat opioid overdose is the development and distribution of Naloxone. This mechanism is an opioid overdose reversal treatment that became commercially available in March of 2023. However, Naloxone was not readily available for the duration of this study. While this is an important step to combat opioid overdose, the adulteration of the already deadly fentanyl supply with non-opioid acting substances makes Naloxone treatment less effective.

Benzodiazepines and other CNS depressants were also studied in combination with opioids. Both of these drug categories exhibited a similar pattern when studied in combination with prescription opioids. The height of both combinations was in 2008 and steadily decreased through 2022. This indicates a correlation with a specific type of opioid that stimulants did not show a bias for. Stimulants in combination with opioids illustrated a more sporadic pattern than benzodiazepines and other CNS depressants. Minimal literature exists that have focused on benzodiazepines or other CNS depressants in combination with opioids to the same extent as stimulants. This is due to the prevalence of combinations of stimulants with fentanyl and the anticipation of the fourth wave of the opioid epidemic. However, the trends exhibited in Oklahoma with benzodiazepines and other CNS depressants illustrate patterns worth discussing.

At the beginning of the study timeline, a particularly popular drug cocktail was noted in the datasets which included a prescription opioid, alprazolam, and carisoprodol with meprobamate. This specific combination would treat chronic pain and anxiety. It further explains the height of prescription opioids in combination with benzodiazepines and other CNS depressants especially seen in 2008. One study found that co-prescription of benzodiazepines and opioids doubled from 2001 to 2013 (Sun et al., 2017). The same study found this combination increased risk for overdose nearly 10-fold although the definition of concurrent use varied from one day overlap to one year (Sun et al., 2017). Another study looked at benzodiazepine and opioid use populations and found characteristic predictors for this combination to be anxiety, chronic pain, depression, arthritis as well as region and race factors (Vadiei and Bhattacharjee, 2020). Prescribing practices appear to be the driving force behind benzodiazepine and opioid use. This aligns with findings from previous literature as well as the findings in this study. The height of prescription opioid deaths in Oklahoma occurred in 2008 as did the combination with benzodiazepines and other CNS depressants. Prescription opioids in combination with benzodiazepines made up 28% of prescription opioid deaths in 2008. An almost identical trend was seen for opioids in combination with other CNS depressants making up 24% of all opioid-related deaths in 2008. After 2008, both combinations steadily declined through 2022.

Benzodiazepines are also considered CNS depressants but were separated for this study due to different prescribing practices and general use of that class of drug compared to other CNS depressants. The other CNS depressants category primarily concerns drugs such as ethanol, muscle relaxants, and anticonvulsants among others. There is limited literature that focuses on opioids in combination with other CNS depressants due to the expansive definition of the category. The primary well-known issue with this combination is the increased depressant effects that lead to sedation, respiratory depression, coma, and even death (Lee et al., 2021). A 2021 case report from Lee et al. explores the problems faced from a pharmaceutical standpoint in treating patients with a variety of symptoms. Certain symptoms may necessitate concurrent use of CNS depressants such as opioid use disorder, mood disorder, and chronic pain (Lee et al., 2021). This leads to a need for careful consideration of dosage and regimentation of the pharmaceutical concoction that, when used improperly, can quickly lead to overdose whether fatal or non-fatal. These combinations also further complicate the effectiveness of opioid-reversal treatments like Naloxone.

One study indicates a nationwide increase in drug overdose deaths in lieu of the COVID-19 pandemic (FCC, 2024). There are indications of this in Oklahoma. During 2019 total drug overdose deaths were at the lowest point over the 15 years and in 2020 through 2022 there was a noticeable spike in deaths. The cause of this cannot be determined, but the timing is something to note. The distinct increase and decrease in total opioid deaths align with restrictive legislation and clearly illustrate the shifting opioid type that is the catalyst behind each wave of the opioid epidemic. In addition, opioids in combination with other drug classes have patterns that differ throughout the three waves. It has been shown that illicit substances enter through international borders. Due to Oklahoma's central location, the dissemination of drugs from border areas takes time and postpones the arrival of these substances. Each wave is distinctly represented in Oklahoma at a delayed rate compared to previous literature studying the opioid epidemic in the United States.

Geographic Patterns

Opioid-related death trends follow a noticeable geographic trend at the regional and national level as previously discussed. Interstate trends are also noted in terms of urban and rural areas as well as those related to socioeconomic factors and border proximity. The original scope of this study included creating a map of death rates per year, however, the data did not support noticeable difference in rates from year to year due to limited deaths in comparison to the population. Therefore, a single map was created for total opioid deaths over the 15 years. In addition, two sets of comparison maps were created to study the shift of the opioid epidemic from prescription opioids to fentanyl by comparing rates of both in 2008 and 2022. These two timepoints illustrated a clear and strong shift.

The six counties with the highest opioid-related death rates were Coal, Carter, Jefferson, Muskogee, Pawnee, and Pushmataha. All six are found in the Eastern and Southern regions of the state. These counties are 50-74.99% White and are on the lower end in terms of population density (America Counts Staff, 2021). Muskogee county ranks in the top 3 for diversity due to the Muscogee Reservation (America Counts Staff, 2021). In addition, median income, an important socioeconomic factor, was consistent across these counties. All six of the top counties in opioid death rates rank among the poorest counties in Oklahoma. Pushmataha is 73rd out of 77, Coal and Jefferson are close behind at 68 and 69, then Muskogee, Pawnee, and Carter rank slightly higher (NIMH, 2024). While the correlation between these factors was not scrutinized in this study, it is important to draw attention to the variables that may be at play. There exists minimal literature that draws strong conclusions regarding socioeconomic factors and drug abuse due to the multitude of variables. One study from UNODC draws some conclusions at the global level. The few studies done on middle to low-income groups found weak association with socioeconomic factors and drug use disorder (UNODC, 2020). When compared to more affluent groups however, the disadvantaged groups tend to have a higher level of risk of suffering from drug use disorder (UNODC, 2020). The exploration of these trends makes for an interesting focus for future research.

The prescription opioid death rates exhibited in Figure 13 are widespread and highest in three of the top six counties for total opioid deaths. This illustrates a consistent pattern about drug use in these counties. There was approximately a 6-fold decrease in prescription opioid deaths from 2008 to 2022 clearly illustrated from Figure 13 and 14. An interesting pattern exists when studying the transition from prescription opioids to fentanyl. The counties with the highest death rates among prescription opioids in 2008 do not overlap with the highest counties for fentanyl. Fentanyl deaths are highest in metropolitan areas of Tulsa and Oklahoma counties with the exception of Tillman County along the Texas border. In addition, prescription opioid deaths were widespread across the state with no visible tendencies. However, fentanyl deaths were concentrated mostly along the Eastern region of the state. There exists a slight difference in drug overdose death rates in urban and rural communities at 28.6 and 26.2 per 100,000 respectively at the national level (Spencer et al., 2022). This same study found fentanyl death rates to be higher in urban communities which aligns with trends seen in Oklahoma (Spencer et al., 2022).

Contrary to this, natural and semi-synthetic opioids which make up the prescription opioid class tend to have a higher death rate in rural areas which also aligns with trends in Oklahoma (Spencer et al., 2022).

Geographic patterns provide insight for areas that are more susceptible to opioid-related deaths. There are other variables that contribute to these patterns that should be expounded on in future research. The patterns shown in this study can inform the use of resources that should be concentrated in areas of higher death rates to attempt to stem the effects of the opioid crisis in Oklahoma. While no correlation conclusions can be made from the data in this study, the socioeconomic level of the leading counties by opioid death rate should be considered when looking at the resources available in those areas.

Limitations

There are inherent limitations in this study that are indicative of the ever-changing nature of the opioid epidemic. Analytical testing has to advance as the illicit drug market continues to distribute designer drugs. This causes an increase in the types of drugs being detected and may indicate a disproportionate presence of a novel drug as new methods are put in place. One example of this within our study is the presence of fentanyl analogs beginning in 2016 which were not detected before due to a new method validation that allowed the lab to detect it. However, the number of cases that contained a fentanyl analog did not skew the data and was aligned with the rise of total fentanyl cases. In addition, our methods cannot determine whether a drug was obtained illicitly or by prescription beyond what is listed in the medical history. This also pertains to fentanyl which can be abused by prescription or illicitly. The rise of illicit fentanyl may contain adulterants such as xylazine or 4-ANPP which can be indicative of the country of origin. Not all fentanyl cases contain these adulterants, and the source of the drug cannot be determined with OCME analytical procedures.

An area of detection that may be considered a limitation is the inability to identify co-ingestion. Co-ingestion is relevant to this study due to the focus on drug combinations including opioids. While this study identified compelling trends in opioid drug combinations, no conclusions can be drawn regarding the source of these combinations. Both drugs could be present due to separate use over time, adulterated batches of illicit drugs, or purposeful simultaneous ingestion. The method of ingestion would be helpful to identify types of drugs that are more prone to adulteration. In addition, it might reveal the rise and fall of the 'speedball' trend which initially included heroin in combination with a stimulant such as cocaine. With the anticipated fourth wave of the opioid epidemic being the combination of opioids with stimulants it would be possible to see the new 'speedball' being methamphetamine and fentanyl, especially in Oklahoma.

It should also be noted that the medical opinion of Forensic Pathologists differs due to education and training but is standardized to agency and accreditation guidelines. This may influence what drugs and how many are listed as contributing to the cause and manner of death. In addition, variations occur on a case-by-case basis due to specimen availability. In these instances, testing is prioritized based on the toxicologist's expertise and preliminary screening tests. This may limit the number of drugs that are detected as specimens are consumed during the testing process.

Future Perspectives

The data that was organized to make this study possible will serve as an invaluable resource for similar studies in the future. A wide array of variables are collected during the death investigation process and thus offer a unique area for research because of the endless possibilities. The foundation that was laid during this research will continue to be built on in coming years. There is a very systematic way of organizing data that will allow information in the future to be added to the datasets that are already available. This will prevent the undertaking of organizing data retroactively. In addition, this study focused on a general overview of opioid-related deaths, but more specificity can be brought to opioid deaths. For example, in the future a more detailed focus could be made on any of the demographic or location variables. There is specific interest for a focus on drug deaths among the Native American population in Oklahoma. The occurrence of drug combinations would also be a valuable area for expansion by choosing a certain drug class to study in combination with opioids. This would be of interest as illicit fentanyl continues to adulterate the drug market. In the future, a concentration could be made on benzodiazepines or stimulants in a similar way that opioid trends were studied here. As the information from this study is disseminated, it would be possible to study effects of opioid resources in areas of allocation. Most importantly, it has been noted that improved methods lead to an increase in testing and detection of novel substances. This phenomenon will continue to influence the drugs that are being reported and at what rate. Attention could be brought to the implementation of new methods and their effects on reporting.

Conclusion

The results of this 15-year study produced a distinct encompassing model of how the opioid epidemic has played out in Oklahoma. There exists clear age, race, and sex related differences in opioid use across the state. Opioid-related deaths are most common among the 45-64 age group during the height of prescription abuse. The 25-44 age group became the leader in 2020 at the beginning of the fentanyl increase. These age trends support those seen nationwide.

Males have a slightly higher opioid death rate than females. Although nationwide data shows a greater difference in gender for opioid deaths than seen in Oklahoma. The race distribution in Oklahoma is predominantly White and is proportionally represented by making up 86% of all opioid-related deaths. The demographic tendencies depicted here can inform treatment plans and information dissemination across the state. There remains much to be uncovered about correlation between these demographic variables and opioid use.

The opioid epidemic has followed a distinct three wave pattern progressing from prescription opioid use to heroin and now fentanyl. These waves have appeared at similar times across the globe as well as in Oklahoma. Prescription opioid deaths were the leading opioid category in Oklahoma from 2008 to 2019. The generally accepted timeline of the first wave was from the late 1990's to around 2010. Oklahoma prescription opioid deaths fall well within this timeline and peaked slightly later than national trends indicate. The height of prescription opioid deaths coincided with the height of opioid deaths in combination with benzodiazepines and other CNS depressants. The progression to heroin use was not well-represented in Oklahoma due to the prevalence of methamphetamine during that time. However, the peak of heroin deaths in 2018 falls slightly behind the nationwide peak in 2016. The proliferation of illicit fentanyl became a national crisis in 2017 but did not begin to increase deaths in Oklahoma until 2020. Fentanyl and stimulant combination deaths also noticeably increased beginning in 2020. This pattern further emphasizes the delay of drug abuse trends seen in Oklahoma compared to the rest of the United States. Factors related to this delay can be inferred from previous literature as well as the findings in this study but cannot be confirmed without more specific analysis.

The study of geographic trends of opioid-related deaths in Oklahoma can greatly improve the allocation of resources in areas that are disproportionately affected. This 15-year study uncovered that prescription opioid-related deaths were widespread across the state, varying by county location, population, and socioeconomic factors. Whereas fentanyl related deaths were concentrated in the two urban centers of Oklahoma. Overall opioid-related deaths were robust in counties with lower socioeconomic status. Further research would need to be done to elucidate the correlation of these variables.

While this study can make no conclusions on the cause of the trends noted here, the illustration of trends at all is a profound advancement for the status of the opioid epidemic in Oklahoma. This foundation can be used to begin looking at cause and correlation studies that were beyond the scope of this research. The three research questions proposed at the beginning of this study were clearly and completely answered by the data presented here. The opioid epidemic continues to plague the globe and shows no sign of abating. It is crucial that the Oklahoma State Department of Health and officials apart of the Community Task Force on Substance Abuse understand the nuances of this crisis within state borders. These agencies, along with the Oklahoma Bureau of Narcotics and Dangerous Drugs, Department of Mental Health and Substance Abuse Services, and the Oklahoma State Bureau of Investigation will receive a copy of this information. This study provides a foundational picture of the opioid crisis in Oklahoma and will serve as a resource for agencies concerned with allocating resources for opioid treatment, awareness, and prevention.

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Appendix A: Drug Class List

Benzodiazepines

Alprazolam	Oxazepam	8-aminoclonazolam	Flubromazepam
Chlorazepate	Temazepam	Adinazolam	Flubromazolam
Chlordiazepoxide	Triazolam	Bromazepam	Flunitrazepam
Clonazepam	Benzodiazepines	Bromazolam	Loprazolam
Diazepam	Flualprazolam	Clobazam	Meclonazepam
Flurazepam	Etizolam	Clonazolam	Metizolam
Lorazepam	7-aminoclonazepam	Delorazepam	Midazolam
Nordiazepam	7-aminoflunitrazepam	Desalkylflurazepam	Phenazepam
		Diclazepam	4-chlorodeschloroalprazolam

Prescription Opioids

Alfentanil	Meperidine	Norpropoxyphene	Sufentanil
Codeine	Methadone	Oxycodone	Tramadol
Dihydrocodeine	Morphine	Oxymorphone	Opiates
Hydrocodone	Nalorphine	Pentazocine	Buprenorphine
Hydromorphone	Normeperidine	Propoxyphene	Norbuprenorphine
			Tapentadol

Stimulants

Amphetamine	Dimethoxyamphetamine	Methylenedioxymethyl-amphetamine	Pseudoephedrine
Benzoylecgonine	Mephentermine	Methylphenidate	Fenfluramine
Benzphetamine	Methamphetamine	Phendimetrazine	Methylone
Caffeine	Methyldimethoxy-amphetamine	Phenmetrazine	Alpha-pvp
Cocaine	Methylenedioxy-amphetamine	Phentermine	Alpha pyrrolidinovalerophenone
Diethylopropion	Methylenedioxyethyl-amphetamine	Phenylpropanolamine	Benzylpiperazine

Other CNS Depressants

Amobarbital	Dextromethorphan	Lamotrigine	Phenytoin
Amyl nitrate	Difluoroethane	Loperamide	Pregabalin
Baclofen	Dimenhydrinate	Meclizine	Primidone
Butabarbital	Diphenhydramine	Mephenesin	Promethazine
Butalbital	Doxylamine	Mephenytoin	Propofol
Butyl nitrate	Ethanol	Mephobarbital	Secobarbital
Carbamazepine	Ethchlorvynol	Meprobamate	Thiamylal
Carbinoxamine	Ethinamate	Metaxalone	Thiopental
Carbromal	Ethosuximide	Methaqualone	Tizanidine
Carisoprodol	Ethylene glycol	Methocarbamol	Topiramate
Chloral hydrate	Gabapentin	Methsuximide	Trichloroethanol
Chlorpheniramine	Gamma-hydroxybutyrate	Methyprylon	Tripelennamine
Chlorzoxazone	Glutethimide	Mitragynine	Triprolidine
Cyclizine	Hydroxyzine	Orphenadrine	U-47700
Cyclobenzaprine	Isotonitazene	Pentobarbital	Xylazine
		Phenobarbital	Zolpidem

Appendix B: Data Tables

Table 1: Race Distribution of Opioid-Related Deaths in Oklahoma.

	White	Black	Other
2008	436	10	32
2009	424	10	24
2010	368	15	25
2011	348	10	27
2012	404	16	39
2013	404	16	26
2014	370	18	20
2015	304	12	19
2016	286	15	23
2017	250	21	9
2018	185	7	13
2019	131	13	7
2020	149	17	20
2021	245	45	46
2022	407	82	103

Table 2: Age Distribution of Opioid-Related Deaths in Oklahoma.

	<25	25-44	45-64	65+
2008	55	198	213	12
2009	45	205	195	13
2010	38	184	178	8
2011	50	145	186	4
2012	44	187	212	16
2013	43	168	220	15
2014	30	158	201	19
2015	21	146	154	14
2016	24	146	130	25
2017	17	119	130	14
2018	17	89	91	9
2019	16	80	46	9
2020	18	94	60	14
2021	47	176	94	19
2022	69	346	153	24

Table 3: Sex Distribution of Opioid-Related Deaths in Oklahoma.

	Male	Female
2008	286	192
2009	260	198
2010	241	167
2011	211	174
2012	235	224
2013	226	218
2014	209	198
2015	192	143
2016	167	157
2017	158	122
2018	134	72
2019	91	60
2020	111	75
2021	230	106
2022	400	192

Table 4: Total Accidental Drugs and Poisons Deaths by Drug Category.

	Includes Opioids	Includes Benzodiazepines	Includes Stimulants	Includes Other CNS Depressants	Total Accidental Drug Deaths
2008	478	145	91	186	634
2009	458	113	116	141	713
2010	408	93	122	138	657
2011	385	78	126	138	636
2012	459	86	131	128	706
2013	446	71	170	121	744
2014	408	78	172	137	733
2015	335	75	270	108	725
2016	325	47	320	103	812
2017	280	49	368	122	795
2018	206	31	380	93	705
2019	151	36	400	78	653
2020	186	44	551	86	826
2021	336	48	652	95	1061
2022	592	49	643	129	1292

Table 5: Deaths by Opioid-Type.

	Prescription Opioids		Heroin		Fentanyl	
	Total	Only	Total	Only	Total	Only
2008	429	198	7	3	61	34
2009	383	257	11	8	73	51
2010	365	239	4	4	45	29
2011	341	231	11	10	37	24
2012	398	279	20	16	49	33
2013	386	300	19	15	47	38
2014	362	265	19	16	31	25
2015	273	191	20	19	47	37
2016	246	212	30	26	57	60
2017	195	141	42	39	48	36
2018	120	96	54	43	36	32
2019	75	57	43	32	34	29
2020	67	38	49	36	76	58
2021	84	38	20	12	242	188
2022	72	29	15	11	518	435

Note. Total refers to all deaths that included that opioid-type. Only refers to deaths that had that opioid-type in isolation.

Table 6: Deaths by Opioid-Type in Combination with Drug Classes of Interest.

	Prescription Opioids			Heroin			Fentanyl		
	Benzos	Stim	CNS	Benzos	Stim	CNS	Benzos	Stim	CNS
2008	122	34	116	1	2	2	10	0	9
2009	55	19	52	2	0	0	7	4	6
2010	57	14	49	0	0	0	5	0	8
2011	48	18	44	0	0	1	3	1	5
2012	53	18	46	1	0	1	6	2	5
2013	34	11	36	1	0	1	5	1	2
2014	43	3	32	2	0	1	2	2	0
2015	36	18	23	0	0	0	2	3	3
2016	11	6	9	1	0	1	2	0	1
2017	13	11	17	1	2	0	2	1	4
2018	7	3	10	0	3	4	1	0	1
2019	6	5	6	2	4	4	1	1	3
2020	6	7	9	4	6	0	3	7	3
2021	15	13	9	2	3	4	13	17	10
2022	9	18	14	1	2	0	21	32	27

Note. Benzos = Benzodiazepines. Stim = Stimulants.
CNS = Other CNS Depressants.