Patterns of Drug Poisoning and Adverse Cardiovascular Disease Event Mortality in Pennsylvania

by

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Abstract

Introduction: The objective of this essay was to identify the frequency and patterns of accidental drug poisoning and adverse cardiovascular disease event (ACVE) mortality in PA. Drug poisoning mortality has risen markedly over the last two decades. Several drugs involved in these deaths have known cardio-toxic effects. Yet, few reports have examined the trends in drug poisoning and ACVE in this time. This gap in knowledge needs to be further explored to examine patterns, trends, and risks.

Methods: A descriptive study was performed using data from CDC Wonder's Multiple Cause of Death (final), 1999-2020 Results report. ICD-10 codes X40-X44 were used for accidental drug poisoning, I11, I25, and I46 were used for ACVE and T40.0-T40.7 were used for drug type to explore patterns and trends of accidental drug poisoning and ACVE deaths across time, race, gender, and age. Counts and crude rates were used to show these patterns and trends. Graphs were made using GraphPad Prism.

Results: Accidental drug poisoning and ACVE mortality has been on the rise since 1999 with a spike in 2016. Most deaths from drug poisoning and ACVE were due to cocaine and other synthetic narcotics. Black/African American and those aged 35-59 experience drug poisoning and ACVE deaths most in Pennsylvania. Males had a crude rate of 2.1 per 100,000, Black/African Americans had a crude rate of 2.4 per 100,000, those aged 50-54 had the highest crude rate at 3.3 per 100,000.

Discussion: The burden of drug poisoning and ACVE deaths falls primarily among those aged 35-59 years, Black/African Americans, and males. Males might have a higher mortality due to risk-taking behaviors, cardiovascular outcomes, and drug misuse. Drug poisoning and ACVE deaths saw a spike around 2016 possibly due to the availability of fentanyl and other drugs in the state.

Conclusion: Research studies need to be implemented to further explore the relationship between accidental drug poisoning and ACVE. With upward trends seen in the results of the study there is a public health need to understand the relationship of accidental drug poisoning and ACVE and to increase prevention efforts.

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Preface

Thank you to Dr. Songer for mentoring and teaching me the importance of injury prevention/epidemiology and sparking my interest in understanding drug poisoning. Additional thanks to Dr. Glynn for her constant support during my time as a student at the University of Pittsburgh. Thank you Dr. Buchanich for your input and for offering your time to improve my essay. Lastly, thank you to the University of Pittsburgh and the School of Public Health for providing me the opportunity to learn and grow as a student.

1.0 Introduction

Adverse cardiovascular events (ACVE) as a suspected result of accidental drug poisoning deaths have been on the rise. These reports, however, have shown differing findings regarding the epidemiological outcomes as well as the pathophysiology of this interaction. Drug poisoning deaths have increased in the United States in the last 20 years and most of the research attention has fallen on how prescription opioids have been the cause. There has been less attention on other health outcomes due to opioids and other synthetic drugs such as cocaine and methamphetamine. These each can have toxic adverse effects on the heart. However, ACVE in this time of increasing drug poisoning deaths has not been studied greatly. Thus, this essay will focus on looking at previous literature on the topic and identifying patterns and trends of drug poisoning and ACVE comorbidity in Pennsylvania from 1999-2020 to understand the burden of disease.

1.1 Drug Poisoning in the United States and Pennsylvania

Drug poisoning deaths have become an important health issue in the United States. Meaningful recognition of this issue dates to the latter part of the 1990s, when there was a marked uptake in the use of opioids.[1] Drug related deaths increased from the 1990s to the 2010s from what is believed to be prescription opioids. Then, with stricter regulations for these drugs, heroin became the problem drug in street markets. In more recent years (2014 to present) illegal, synthetic drugs, most commonly fentanyl, became the primary drug of interest. Given its lethality, it is no surprise there has been a large spike in drug poisoning deaths.[2]

Many factors underlie the advent of this epidemic. Pressure from insurance companies, limited time for patient-provider interaction during visits, and relentless pharmaceutical marketing have also led to this increase in drug poisoning deaths.[3,4] In the 1990s and 2000s, many marketing materials advocated for stronger treatment of pain. Opioid treatment for pain was marketed as the best option and as one which would not lead to addiction. As a result, the use of prescription opioids increased markedly, and estimates show that around a third of those who use drugs wrongfully started with prescription opioids.[6] Subsequently, drug poisoning death rates increased exponentially.

In recent years, drugs attributed to accidental poisoning deaths have shifted from prescription opioids, to heroin, to fentanyl, and to combinations of opioids with psychotropic and other types of drugs. Mortality related to synthetic opioids, of which fentanyl and its analogs are the most common, have risen dramatically from 2014 to present.[6]

Distinct patterns in drug related mortality have been documented. Between 1999 and 2018 in the United States, rates of drug poisoning were higher for males than for females. The rate increased from 8.2 to 27.9 per 100,000 for men and 3.9 to 13.6 per 100,000 for women showing that males are disproportionality affected by drug poisoning. Previous research has observed that men tend to die more from drug poisoning, but the rate of women's drug poisoning mortality has been increasing. Men's mortality could be higher due to their exposure to drugs, using higher doses of the drugs, and being higher risk takers than females.[5]

In a NCHS Data Brief, ages 25-44 had the highest number of drug poisoning deaths and ages 45-64 were not far behind.[6] Right around age 25, individuals are starting to live on their own and are faced with challenges regarding jobs, relationships, home ownership, etc. They could be using drugs to cope with all the changes in their life, where hardships and challenges continue to increase with age.[7] In the United States from 1999-2008, White individuals and American Indian or Alaska Native (AI/AN) individuals had the highest change in age-adjusted death rates (White: 6.1 to 14.7, AI/AN: 6.0 to 15.6). Black/African American individuals reached an age-adjusted death rate of 10.9 in 2006.[6] In 2020 Black/African American males <65 years of age had an overdose rate seven times higher than White males of the same age range. Black/African American individuals 15-24 years old had the largest rate increase by 86% compared to other ages and races in 2019 and 2020.[8]

In 2018 Pennsylvania had the fourth highest age-adjusted drug poisoning death rate at 36.1 per 100,000 standard population, behind West Virginia, Delaware, and Maryland.[9] Understanding why rates are so high in Pennsylvania is crucial to combating this epidemic. Trends in Pennsylvania will be discussed in the results section.

1.2 Drug Poisoning ICD-10 Codes

Drug poisoning mortality as a cause of death is classified and used in administrative records with T, X and S codes from the International Classification of Diseases 10 (ICD-10). Codes S00-T88 classify injury, poisoning, and other consequences of external causes. They contain information about body regions affected and the nature of the injury.[10] X codes show the circumstance of the injury.[10] The X codes for accidental poisoning are X40 (accidental poisoning by and exposure to nonopioid analgesics, antipyretics and antirheumatics), X41 (accidental poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified), X42 (accidental poisoning by and exposure to narcotics and psychodysleptics [hallucinogens], not elsewhere classified), X43 (accidental poisoning by and exposure to other drugs acting on the autonomic and nervous system), and X44 (accidental poisoning by and exposure to other and unspecified drugs, medicaments and biological substances). X40 through X44 will be considered for the purposes of this essay.

There is a wide array of drugs that are classified under these X codes. One of the major drugs is opioids, which have been shown to help reduce pain and are often prescribed as painkillers after surgeries or injuries. Opioids consist of six natural alkaloids (drugs) which include morphine, noscapine, codeine, papaverine, thebaine, and narceine. The drugs naloxone, oxycodone, and buprenorphine are synthesized from thebaine.[11] Oxycodone was synthesized to treat moderate to severe pain from broken bones, pain associated with cancer and treatment, and is often given to patients after an operation.[12] Oxycodone is the fourth leading cause of drug poisoning deaths in the United States.[13]

Opioids are also synthesized into heroin from morphine. Heroin is typically injected, smoked, or snorted to create a “rush” in the body. This drug is highly addictive, and it can cause symptoms such as respiratory depression, nausea, among others.[14] Methadone is a drug that is often used for the management of opioid addiction because it acts against opioid receptors, however it too can be highly addictive.[15]

Until recently, the majority of fentanyl deaths were classified under the T40.4 code; a catch-all category for other synthetic narcotics. Fentanyl is 50 to 100 times more potent than morphine and is used to manage pain but is often abused illegally.[16] Recently drug dealers have been mixing fentanyl with other drugs like cocaine or heroin. Once fentanyl has been taken enough times, the brain begins to acclimate itself with the drug and craves more and more of it. This makes people susceptible to accidental drug poisoning mortality.

Stimulants are also responsible for drug poisoning deaths over the world. Two of the main types are methamphetamine and cocaine. Methamphetamine is derived from amphetamine and affects mental and physiological outputs of the body. It can generate euphoria by increasing monoamine levels in the synaptic cleft of the neuron.[17] Cocaine is also a very prevalent drug used worldwide. It is a highly addictive stimulant that is mostly used recreationally. Cocaine works by increasing dopamine levels in the brain, which prevents it from being recycled in the body for further use.[18]

1.3 Prevention Policies in Pennsylvania

Prevention policies have been put in place in Pennsylvania to fight the drug poisoning epidemic. Common prevention efforts include prescription pain treatment guidelines, prescription drug monitoring registries, increased availability of drugs that counteract opioids (e.g. naloxone), and other treatment oriented options. One such option is a non-opioid directive that allows patients receiving medical treatment to refuse opioid medications.[19] This directive permits a patient to seek alternative care and can "open a dialogue" between the patient and provider regarding drug misuse.[19] This can be beneficial for those in recovery for substance use disorders/opioid use disorders or those who believe they could become addicted to prescriptions.

The warm hand off was created in 2015 and is a policy where a patient's provider gives them an in-person introduction to a drug abuse specialist before the patient goes to treatment.[19] This allows patients to have a good relationship and build trust with the specialist which could improve their outcomes. The PA-SUN program, made in 2011, augments different treatments for those who abuse opioids. It increases access to FDA approved medication in the emergency room to treat opioid use disorders.[19] Lastly, there is naloxone (Narcan) available at all local pharmacies at no cost, which began in 2015.[19] Anyone can have access to Narcan which has the capability to stop drug poisoning for people of all socioeconomic statuses, races, and insurance levels. All prevention efforts have been put in place to diminish the burden and deaths from drug poisoning.

1.4 Drug Poisoning and Adverse Cardiovascular Events (ACVE)

In clinical settings, the impact of street drugs on the body is well known. Cocaine and methamphetamine have established adverse effects on the heart. Fentanyl in small amounts can lead to respiratory distress. Reports indicate an increase in the number of drug poisonings and adverse cardiovascular events (ACVE) comorbid deaths. However, little is known about the interaction between drug poisoning and these cardiovascular effects, particularly hypertensive heart disease (I11), ischemic heart disease (I25), and cardiac arrest (I46).

Hypertensive heart disease (I11) occurs from variations to the left ventricle, left atrium, and coronary arteries in the heart. These variations occur because of constant high blood pressure over a long period of time. Hypertension makes the heart work harder causing harm to the myocardium, which can lead to other complications including diastolic and/or systolic heart failure, acute coronary syndrome, and cardiac arrest.[20] Some professionals believe that opioids may help to lower blood pressure while others gravely disagree. It has been seen that morphine, a derivative of opioids, heightens hypertension through opiate receptors and noradrenergic neurons in the brain. In low doses, opioids have the ability to decrease blood pressure. However, those who use them frequently and for long periods of time may develop hypertension or complications from hypertension.[11]

Chronic ischemic heart disease (I25) is also known as coronary artery disease in literature. This disease occurs when blood circulation to the heart is blocked due to narrowed arteries throughout the body. Ischemic heart disease can lead to a myocardial infarction if the narrowed arteries are left untreated.[21] A study done by Jalali and their colleagues in 2021 found that opioid addiction is associated with cardiac events like ischemic heart disease and heart attack.[22]

Cardiac arrest (I46) occurs when the heart stops beating leading to decreased blood flow to the brain and body. Some symptoms include fatigue, dizziness, loss of breath, and chest pain. Cardiac arrest can be caused by arrhythmias, ventricular fibrillation, enlarged heart, and coronary artery disease.[23] Opioids hinder sodium and potassium channels in the heart. In turn, this can lead to longer action potentials and subsequent cardiac intervals which result in cardiac arrest. Long time use of opiates can lead to respiratory depression and cardiac toxicity leading to cardiac arrest.[24] Cocaine and methamphetamine, both stimulants, can initiate cardiac arrhythmias by producing electrical remodeling of ion channels. They can inhibit sodium channels, change the function of calcium channels, and disrupt binding of neurons.[25]

Despite the rapid rise in drug poisoning in the last 20 years, there are surprisingly few reports on the trends in ACVE and drug use. The following section outlines the available studies that focus on mortality and morbidity of drug poisoning and ACVE.

A case control study of adverse cardiovascular event (ACVE) and suspected acute poisoning morbidity looked at 34 cases and 101 controls identified from a Poison Control Center. If an ACVE occurred, a copy of the patients' electrocardiogram was sent to a study investigator. All investigators were blinded to the hypothesis of the study and the cases. Other data was collected from a Poison Control Center's electronic record as well as patient notes and hospital medical records. For the 34 cases of ACVE in suspected drug poisoning, 15 of them had a cardiac arrest, 16 had a myocardial infarction, nine had dysrhythmias, and 19 had shock. The most common drug exposures in this study were benzodiazepines (17% of patients), opioids (16% of patients), and acetaminophen (15% of patients). Opioids were the only drugs greatly associated with the outcome of ACVE with an odds ratio of 3.0 (95% CI: 1.1-7.9, p=0.025). Those who had exposures to opioids had three times higher odds of experiencing an ACVE compared to the control group.[26]

A retrospective study of one million participants using the National EMS Information System (NEMSIS) was performed by Marissa Ritter and her colleagues. The aim of the study was to see if there was a connection between drug poisoning cardiac arrest morbidity during transport by EMS compared to those who did not have drug poisoning. In this study the explanatory variable was a dispatch reason of drug poisoning, and the outcome variable was cardiac arrest. Logistic regression was performed to explore this relationship. The study found 0.74% of participants had experienced a cardiac arrest. Results found overdose related dispatches had 65% greater odds of experiencing cardiac arrest (95% CI: 1.22-2.22). Males were 77% (OR=1.77, 95% CI: 1.67-1.88) more likely and Hawaiians were 56% (OR=1.56, 95% CI:) more likely to experience cardiac arrest after drug poisoning when compared to the reference category.[24]

Another study focused on drug poisoning cardiac arrests during the COVID-19 pandemic. Researchers performed a retrospective observational study using NEMSIS, similar to the article done by Ritter et al, however this focused on 2020 when social isolation, sickness, and diminished mental health was on a rise across the globe. Cardiac arrests as a result of drug poisoning rose from 40.1 people per 100,000 EMS activations in March at the start of the COVID-19 pandemic to a rate of 74.1 people per 100,000 EMS activations in May 2020 at the height of the COVID-19 pandemic. This number fell to 48.7 people per 100,000 in July and remained around 50.0 people per 100,000 through August, when the study ended.[27]

QT interval prolongation is an irregular heart rhythm that can be seen on an electrocardiogram (ECG). In a study by Perrin-Terrin and their colleagues, data was collected for patients receiving methadone in addiction centers using patient interviews and medical files. All patients were given an ECG and provided a blood sample to measure levels of methadone in their system. The median dose of methadone was 45mg and the median treatment length was three years. A univariate analysis was used to compare QT length and dispersion with different variables (gender, age, cardiac disease, drug use, and methadone use). A multiple linear regression was performed for QT length and dispersion with the variables to see which had significance. Results found that QT dispersion was longer in those who use QT prolonging drugs and have cardiac disease history with a β coefficient of 0.375 (95% CI: 0.273-0.477, $p<10^{-6}$).[28]

A prospective case control study looked at prescription opioid use for chronic pain with coronary heart disease and stroke.[29] Participants were from the REGARDS study, a national cohort study that examines stroke mortality in the United States. Data was collected from interviews, examinations, and samples of urine/blood. Participants had followed up telephone calls every six months. Cox proportional hazards were used to compute hazard ratios for coronary heart disease, stroke, and cardiovascular disease death. Use of prescription opioids was not associated with acute coronary heart disease for those who had the disease at baseline. Prescription opioid use was not associated with coronary heart disease (aHR=1.03, 95% CI: 0.83-1.26), but it was associated with cardiovascular disease death (aHR=1.24, 95% CI: 1.00-1.53). Coronary heart disease was higher for females that used prescription opioids compared to those who did not. Those who used oxycodone had an association with acute coronary heart disease (aHR=1.24, 95% CI: 0.81-1.90) and cardiovascular death (aHR=1.64, 95% CI: 1.07-2.52) compared to those who used hydrocodone. Taking prescription opioids and acetaminophen at the same time had the strongest association to cardiovascular death (aHR=1.41, 95% CI: 1.07-1.86).[29]

Manini and their colleagues performed a prospective cohort study on adult patients in the emergency department for acute drug poisoning over a 12-month period. Data regarding demographics, cardiovascular disease, blood and urine samples, and exposures were collected from medical charts. Patients were followed until their hospital discharge. Out of 274 patients that had an acute drug poisoning in the study, 12 had an adverse cardiovascular event including three cardiac arrests and two dysrhythmias. Results found no association between the drugs involved (opioids, benzodiazepines, sympathomimetics) and adverse cardiovascular events in this study.[30]

Table 1: Accidental Drug Poisoning and Adverse Cardiovasucular Event Literature Review Studies

Study	County/Area	N	Population	Study Type
Khodneva et al, 2016	United States	29,025	Participants of REGARDS study	Prospective Cohort Study
Perrin-Terrin et al, 2010	Toulouse, Montauban	42	Patients being treated with methadone for opiate maintenance	Prospective Cohort Study
Friedman et al, 2020	United States	25,900,000	NEMSIS data for overdose-related cardiac arrests and overdose-related EMC activations	Retrospective Observational Study
Ritter et al, 2022	United States	1,000,000	NEMSIS data	Retrospective Study
Manini et al, 2010	United States	135	Adults in 3 tertiary-care hospitals and one regional Poison Control Center	Prospective Case-Control Study
Manini et al, 2012	United States	274	Patients from the ER at Bellevue Hospital Center and NYU Medical Center	Prospective Cohort Study

1.5 Gaps in Knowledge

Based on the studies discussed, there are differing findings on the relationship between drug poisoning and ACVE. Understanding the pathophysiology and epidemiology of this interaction is important to decreasing the burden of disease. More research is needed to improve prevention efforts and ultimately reduce these deaths. Few studies have focused solely on the relationship between drug poisoning and ACVEs. Studies typically focus solely on drug poisoning or ACVEs, but the interaction is not well understood. Increasing knowledge and literature on this topic can only help the population.

1.6 Public Health Significance

Drug use can put a strain on any relationship and can decrease social support for an individual. Families can be dismantled, intimate relationships strained, and friendships ruined.[31,32] People all over the world are affected by drug use, making this topic extremely relevant.

According to the CDC, opioid poisoning deaths and opioid use disorders cost $1.02 trillion for the United States in 2017 alone.[33] This figure includes the cost attributed to health care treatment of the disorder, criminal charges, and loss of work production, including that from premature mortality. Cardiovascular disease costs around $219 billion annually in the United States.[34] Both estimates outline a substantial economic cost to the country. There is not, however, a report of how much drug poisoning and ACVE deaths combined cost in the United States. Therefore, further research to see the economic cost of drug poisoning and ACVE deaths together would be beneficial.

As shown above, there is preliminary evidence highlighting that drug misuse has several health effects to the individual (including ACVEs), and their families. Gaining a broader understanding of the frequency and patterns of ACVEs related to drug misuse can lead to evidence-based prevention efforts in the future and, ultimately, a reduction of deaths from this issue in the population.

2.0 Objectives

The purpose of this essay was to describe trends from 1999-2020 from accidental drug poisoning and adverse cardiovascular event (ACVE) deaths in Pennsylvania, which is the main objective of the study. Patterns of accidental drug poisoning and ACVE deaths by year and demographics (age, gender, race) in Pennsylvania will also be described. This essay will also propose strategies, based upon these patterns, to prevent accidental drug poisoning and ACVE deaths in the future.

3.0 Methods

A descriptive study was completed to see the trends and patterns of drug poisoning and adverse cardiovascular event deaths in Pennsylvania from 1999-2020. The main research question was to identify deaths due to ACVEs after accidental drug poisoning and to identify if there are any trends regarding time, age, gender, and race.

The study population for this research includes all deaths in Pennsylvania from 1999-2020 that met both of the following criteria;

- An underlying cause of death listed as due to accidental drug poisoning (defined by the presence of an ICD-10 code from X40-X44) Intentional and undetermined-intent drug poisoning deaths (ICD-10 codes: X60-X64, X85, and Y10-Y14) were not included in this assessment because of differing implications for prevention between these and accidental drug poisoning events.
- The presence of a multiple cause of death ICD-10 code related to hypertensive heart disease (I11), chronic ischemic heart disease (I25), or cardiac arrest (I46). These specific heart issues were chosen to characterize ACVEs because of their relationship and pathologically to drug use and they represented the highest number of heart-related deaths (compared to the rest of the circulatory diseases) in the available data.

By the structure of the death certificate and its rules for completion, these deaths would represent those where clinicians indicated that an ACVE was the immediate reason why the individual had died and that there was evidence that these heart related issues were due, directly, to drug poisoning as a precipitant (either in the short-term or long-term). When provided, the specific drugs involved in the drug poisoning were identified through the presence of ICD-10 codes T40.1-40.7 as a multiple cause of death code.

Data on related deaths for Pennsylvania were identified from CDC Wonder Multiple Cause of Death database.[35] CDC Wonder is a free public website used for pulling public health data including vital statistics such as births and deaths. Data was specifically identified from the Multiple Cause of Death (final), 1999-2020 Results report. Within this databased, patterns of ACVE and drug poisoning deaths were examined by 5-year age groups, gender (assigned at birth: male and female), and race (White and Black/African American).

In the results section for *Figure 1*, the results were abstracted from CDC Wonder by: state (Pennsylvania), year (1999-2020), and underlying cause of death (X40-X44). *Figure 2* was abstracted from CDC Wonder by: state (Pennsylvania), 5-year age group, and underlying cause of death (X40-X44). *Figure 3* was abstracted from CDC Wonder by: state (Pennsylvania), year (1999-2020), underlying cause of death (X40-X44), and multiple cause of death (I11+I25+I46). *Figure 4* was abstracted from CDC Wonder by: state (Pennsylvania), underlying cause of death (X40-X44), multiple cause of death (I11+I25+I46 in box 1 and T40.0-T40.7 in box 2). *Figure 5* was abstracted from CDC Wonder by: state (Pennsylvania), underlying cause of death (X40-X44), multiple cause of death (I11+I25+I46), and 5-year age group. *Figure 6* was abstracted from CDC Wonder by: state (Pennsylvania), underlying cause of death (X40-X44), multiple cause of death (I11+I25+I46) and gender (male and female). *Figure 7* was abstracted from CDC Wonder by: state (Pennsylvania), underlying cause of death (X40-X44), multiple cause of death (I11+I25+I46), and race.

To make the figures shown in the Results section, the software GraphPad Prism was used. Tables were made within Microsoft Word.

Some data was suppressed to prevent the presentation of the result of the database query; typically, when the query indicated that less than 10 deaths occurred. Data suppression in this report occurred for queries of events related to cardiac arrest alone, hypertensive CVD alone, for queries of ACVE related deaths by individual year, and for queries for race categories other than White and Black/African American. The purpose of this suppression was to protect the privacy of those individuals by limiting the potential to identify these persons because of their unique characteristics. A table listing the complete data that was suppressed is presented in Appendix A.

4.0 Results

From 1999-2020 there were 48,441 accidental drug poisoning deaths in Pennsylvania (Crude Rate=17.5 per 100,000). *Figure 1* shows the trend in accidental drug poisoning deaths (X40-X44) in Pennsylvania from 1999 to 2020, not taking ACVE into consideration. There was a steady increase in drug poisoning deaths from 1999 to 2010 and then there was a spike in 2016 with the largest peak in 2017, at 5,009 deaths. The rate of deaths reduced for two years and then rose again in 2020.

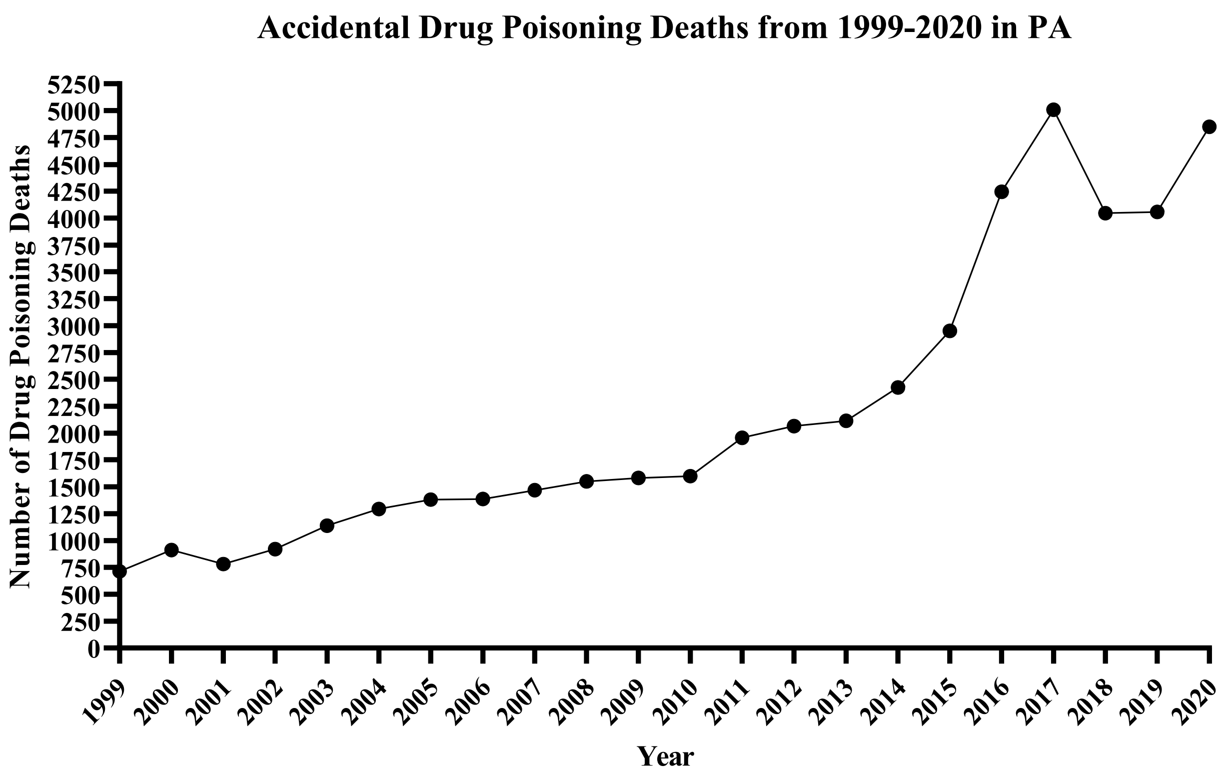

Figure 1: Accidental Drug Poisoning Deaths from 1999-2020 in PA.[35]

Figure 2 shows the crude rates of drug poisoning deaths by 5-year age groups from 1999-2020 in Pennsylvania. The age group 30-34 had the highest crude rate at 37.9 deaths per 100,000. The next highest age group was 35-39 at 35.5 deaths per 100,000.

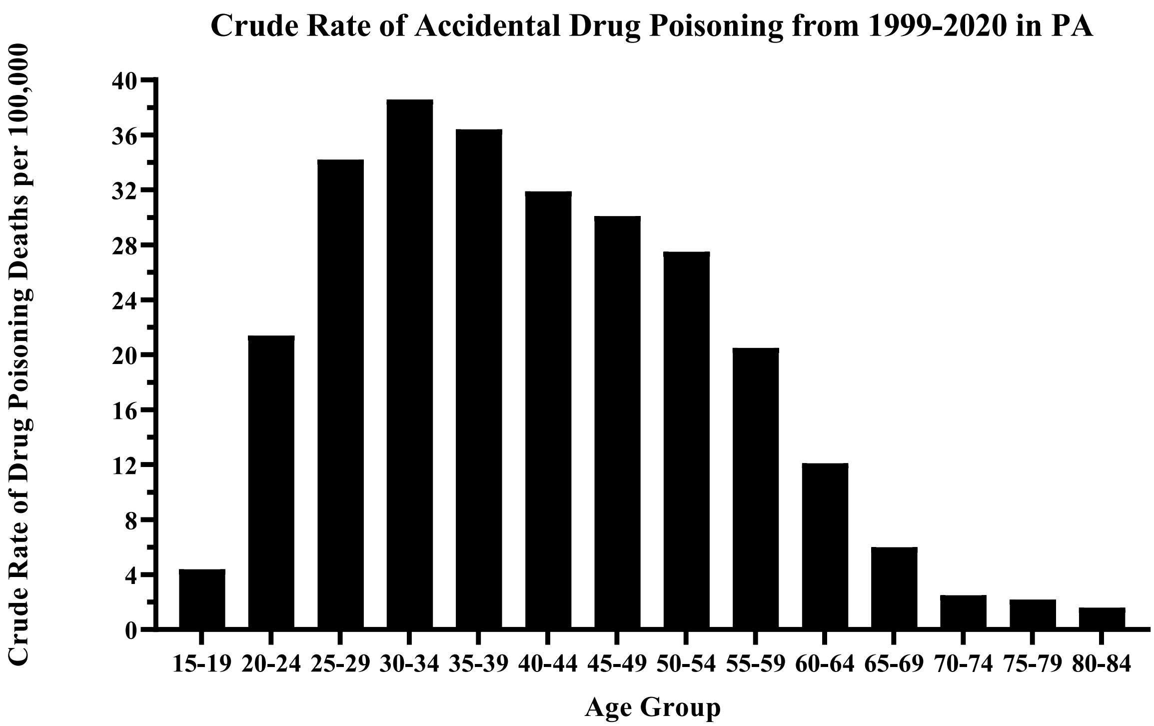

Figure 2: Accidental Drug Poisoning Death Crude Rates by 5-Year Age Group from 1999-2020 in PA.[35]

Figure 3 lists the frequency of identified ACVE deaths related to accidental drug poisoning from 1999-2020 in PA, a total of 3,872 ACVE deaths related to drug poisoning were identified. The number of drug poisoning and ACVE deaths steadily increased from 1999-2004. A peak in deaths occurred for a year in 2005 at 101 deaths. It then fell in 2006 and continued to rise until 2016 where it reached its largest peak at 408 deaths. The number then declined for two years down to 314 deaths and remained steady.

When looking at the crude rate per year, it remained between 0.4 and 0.8 from 1999 to 2008. It then rose to 1.3 in 2009 where it continued to rise and peak at 3.2 per 100,000 in 2016. The rate then declined to 2.9, 2.5, 2.6, and 2.4 for the years 2017, 2018, 2019, and 2020 respectively. The overall crude rate per 100,000 from 1999-2020 was 1.4.

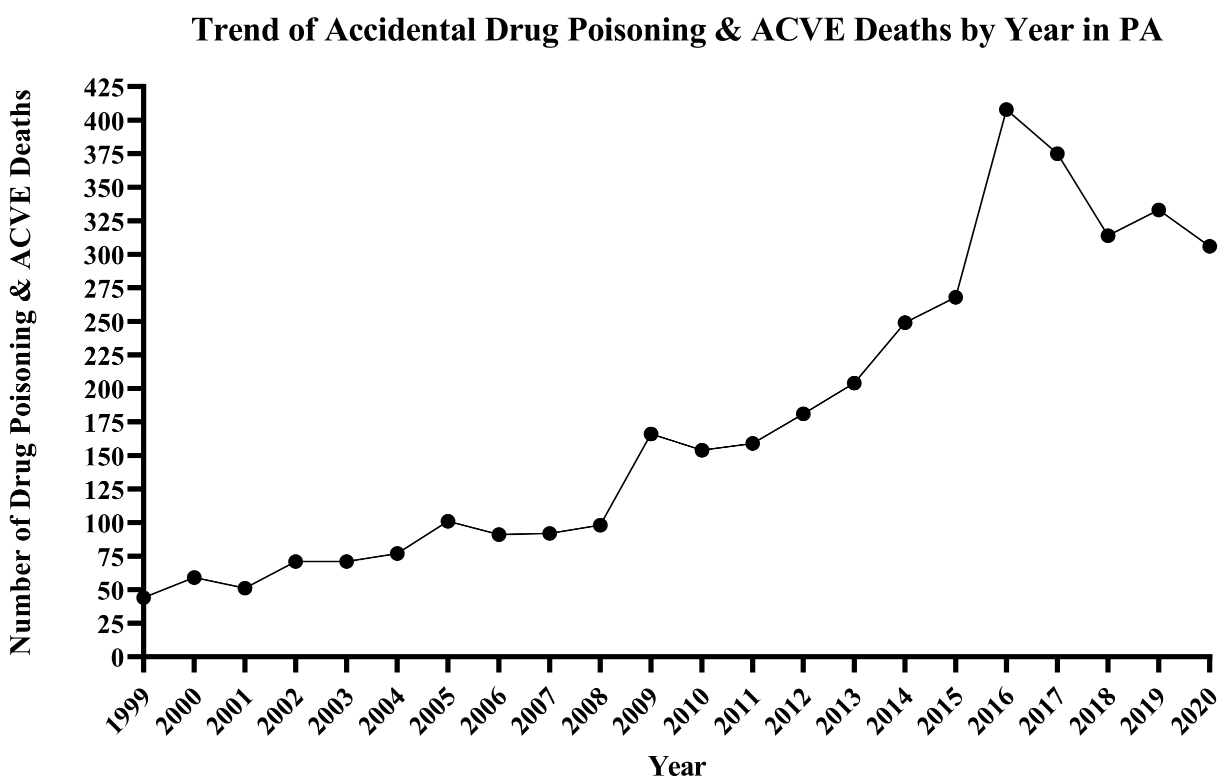

Figure 3: Trend in Accidental Drug Poisoning and All ACVE Deaths by Year in PA.[35]

When looking at what drugs are responsible for the drug poisoning and ACVE in *Figure 4*, other synthetic narcotics (T40.4) and cocaine (T40.5) are highest. Cocaine is responsible for 745 deaths and other synthetic narcotics is at 650 deaths. Heroin (T40.1) and other opioids (T40.2) fall closely behind at 317 and 484 deaths respectively.

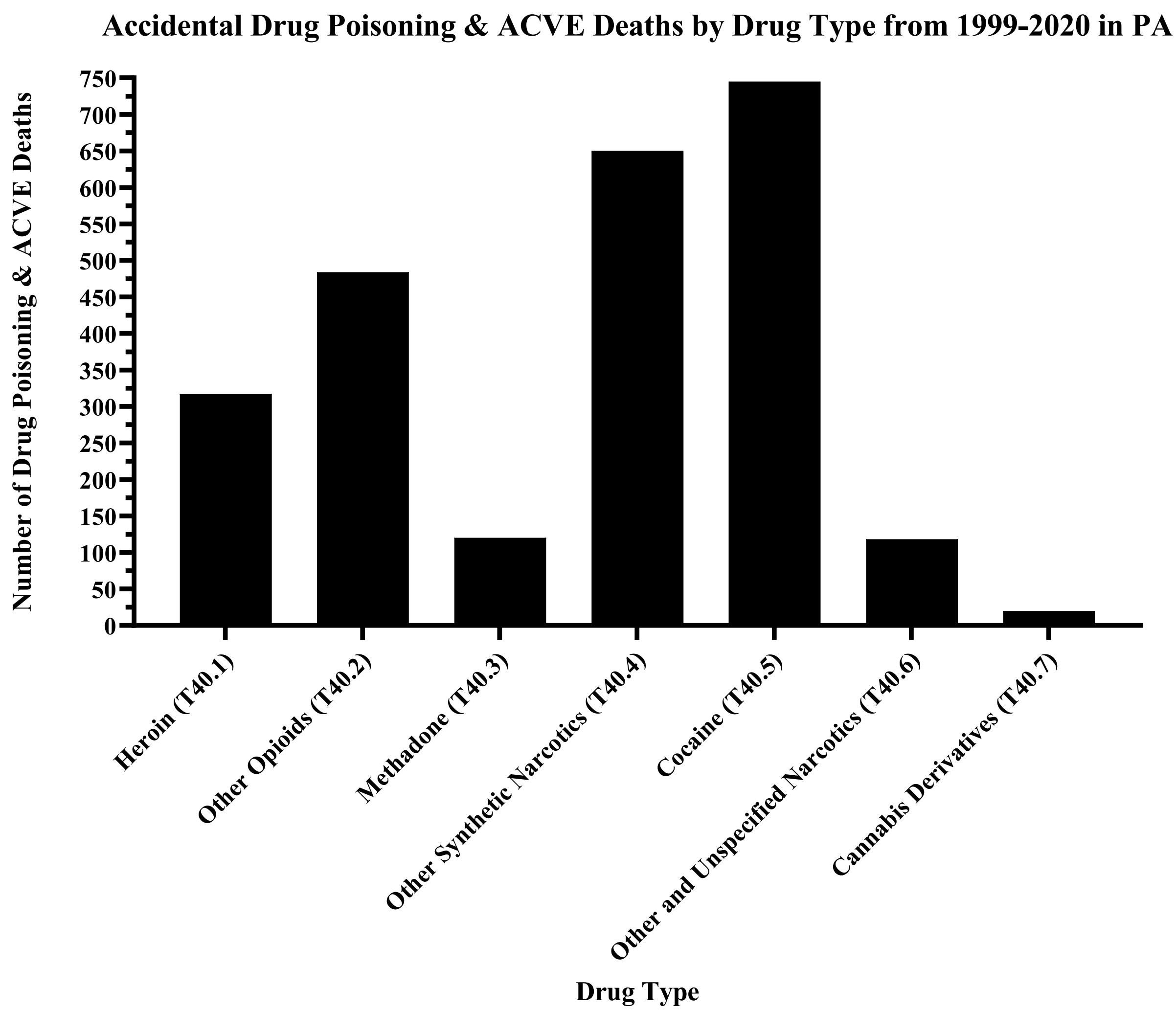

Figure 4: Accidental Drug Poisoning and ACVE Deaths by Drug Type from 1999-2020 in PA.[35]

The age group 50-54 had the highest crude rate due to accidental drug poisoning and ACVE, as seen in *Figure 5* at 3.3 per 100,000. The graph has a right skew to it with more deaths falling on the younger ages of the graph. The 5-year age group 55-59 had the second highest crude rate at 3.0 per 100,000 and ages 45-49 had the third largest crude rate at 2.8.

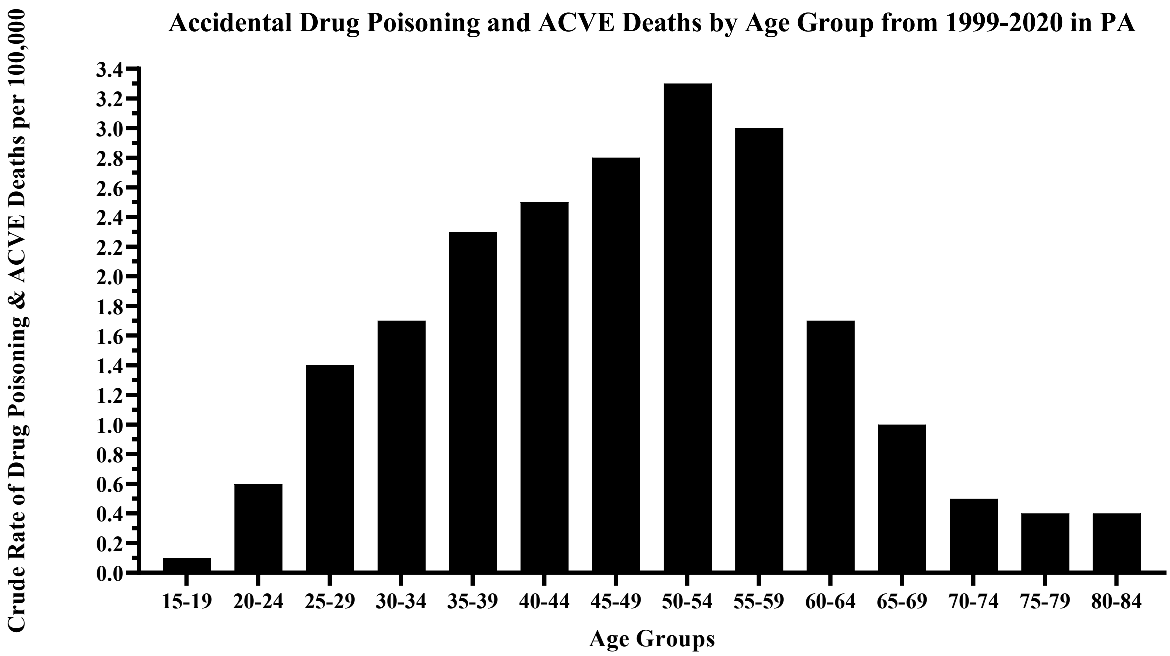

Figure 5: Accidental Drug Poisoning and ACVE Deaths by Age Group from 1999-2020 in PA.[35]

Figure 6 shows the crude rate drug poisoning and ACVE deaths by gender. Males overwhelmingly have more deaths. Males had the highest crude rate for accidental drug poisoning and ACVE deaths at 2.1 per 100,000. They had 2,845 deaths from accidental drug poisoning and ACVE from 1999-2020. Females had a crude rate of 0.7 per 100,000. They had 1,027 deaths from accidental drug poisoning and ACVE from 1999-2020.

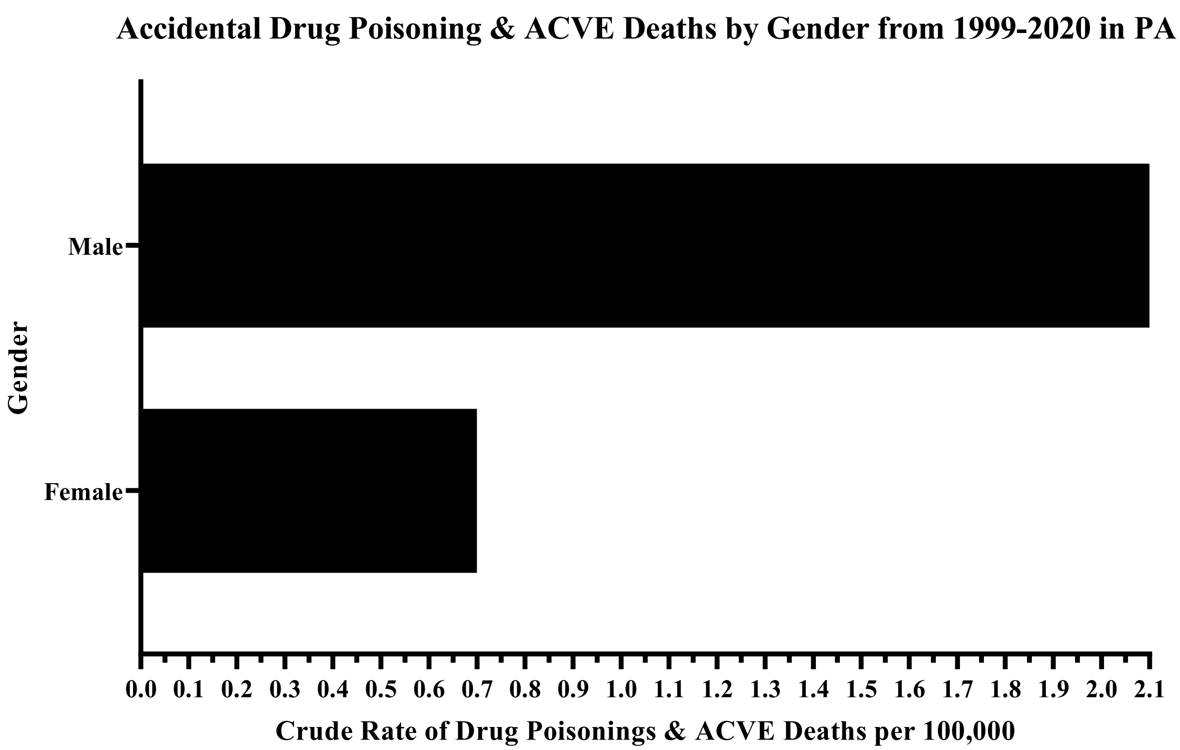

Figure 6: Accidental Drug Poisoning and ACVE Deaths by Gender from 1999-2020 in PA.[35]

Figure 7 shows the crude rate of drug poisoning and ACVE deaths by race. Black/African American and White individuals were the only two races that were not suppressed by CDC Wonder. Black/African American individuals had an overwhelmingly high crude rate per 100,000 for accidental drug poisoning and ACVE at 2.4. White individuals had a crude rate of 1.3 per 100,000.

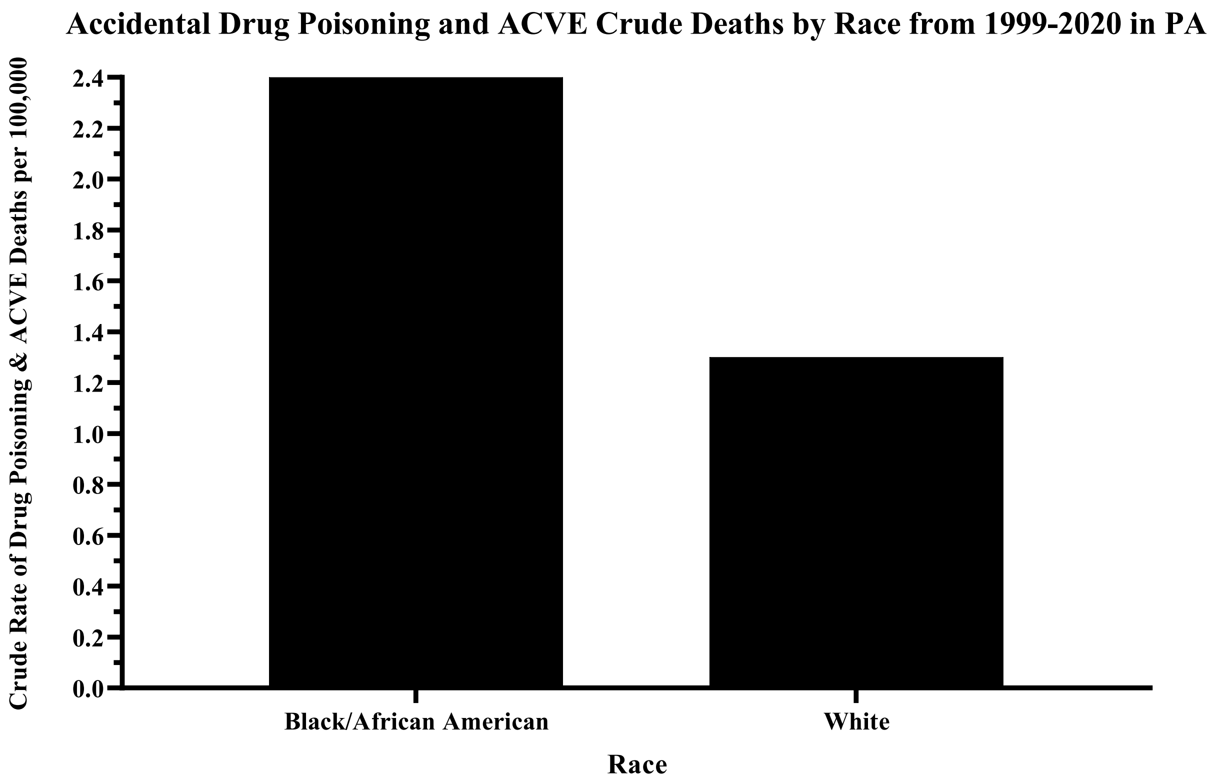

Figure 7: Accidental Drug Poisoning and ACVE Deaths by Race from 1999-2020 in PA.[35]

5.0 Discussion and Conclusion

It can be observed that in recent years there was an upward trend of ACVE deaths related to drug poisonings in Pennsylvania. These findings address a notable gap in the literature and provide evidence that this association needs to be studied further. These findings appear to follow the increase in accidental drug poisoning deaths overall in the state. Most deaths were associated with the drug Cocaine (T40.5) or Other Synthetic Narcotics (T40.4), which includes fentanyl. The spike in *Figure 1* and *Figure 3* from 2016 occurred at the same time that fentanyl become more prevalent in the population, arousing suspicion that the ACVE deaths could be a function of fentanyl availability.

Certain demographic groups were identified as having higher levels of drug poisoning and ACVE deaths, including males, those aged 35 to 59, and Black/African American individuals in Pennsylvania. This could be due to higher rates of drug misuse in males, or because males tend to be risk-takers, but they also typically tend to experience cardiovascular diseases more than women. From 1999-2020, only 11.7% of the population in Pennsylvania identified as Black/African American and 85% identified as White. The other 3.3% identified as American Indian or Alaska Native and Asian or Pacific Islander. In *Figure 8* most deaths occur in Black/African American individuals compared to White individuals. When looking at the *Figure 6* of age, those aged 50-54 had the highest number of drug poisoning and adverse cardiovascular event deaths as well as highest crude death rate.

These results are similar to results in previous literature. Previous studies have found a relationship or interaction between drug poisoning and ACVE.[24,26,29] Manini et al saw that out of 34 cases of ACVE after suspected drug poisoning 15 were cardiac arrest.[26] Ritter et al saw that those who had drug poisoning dispatches had 65% greater odds of having a cardiac arrest. They also saw that males were 77% more likely to experience these cardiac arrests.[24] Khodneva et al saw that prescription opioid use was associated with cardiovascular disease death.[29] This research focused on accidental drug poisoning rather than intentional as well as mortality rather than morbidity data. Although there is little research on this topic, results have been largely consistent across available studies.

The studies previously discussed in the introduction are mainly observational or descriptive. Three out of the five studies previously mentioned had a small sample size which can make the power and reliability of the study decrease as well. Ensuring larger sample sizes in future studies could help increase the reliability and validity of the study.

Based on previous literature and results identified in this analysis, different drugs can result in different ACVEs after drug poisoning.[24,27–30] Based on this research, cocaine, and other synthetic narcotics (including fentanyl) were most responsible for drug poisoning and ACVE deaths. This could be due to how the cardiovascular system reacts to the drug or how severe the drug poisoning level was. Initially it could be hypothesized that drug poisoning and ACVE deaths would be higher in older population due to the fact that the elderly tend to have more cardiovascular complications, however this was not the case within Pennsylvania where most of the data was found in those middle-aged. This follows a pattern seen for drug poisoning mortality overall.[35]

5.1 Future Recommendations

This examination represents a preliminary look at possible heart-related effects of drug poisoning/misuse. Further research should be undertaken to learn more about this interaction, including the distinction between ACVE deaths from acute drug poisoning and ACVE deaths related to chronic drug misuse. Once data for the years 2021 and 2022 are released, the availability of information including fentanyl drug involvement (identified from a new ICD-10 code) should be observed to more fully understand the possible burden of this drug. It could also be beneficial to see how Pennsylvania differs from other states in their drug poisoning and ACVE death rates. Looking into the pathophysiology of drug poisoning and ACVE could also be helpful. Once this is done, research can be done to analyze prevention efforts that were implemented in low mortality states that succeeded to see if they can be used in Pennsylvania.

5.2 Strengths and Limitations

Strengths of this study include the source of the data. CDC Wonder identifies information from all death certificates submitted to state health departments. Classification of drug poisoning and ACVE was based upon ICD-10 codes; a standard applied worldwide and a common case definition. This descriptive study also allows for more hypotheses and quantitative data to form for future research. Without a baseline understanding of the patterns and trends of drug poisoning and ACVE, it can be difficult to perform quantitative analyses.

Limitations within this paper include the suppression of data within CDC Wonder. Data with less than 10 cases were suppressed to keep the identity of those patients private. This phenomenon prevented more subgroup analyses to distinguish, for example, if the drug involved in the individual's death changed over time. Fentanyl was classified under "other synthetic narcotics" for the ICD-10 T codes during this time frame along with other drugs. This does not allow us to see the real burden that fentanyl had on the population individually. Lastly, it was not possible to identify if the drug involvement in the death represented a short-term, acute event, such as drug overdose, or if it pertained to more chronic misuse of drugs arising from a drug use or opioid use disorder.

5.3 Conclusion

There is a public health importance to understand why there has been a large spike in drug poisoning and adverse cardiovascular event deaths so additional prevention efforts can be implemented. More studies need to be done to see the interaction of drug poisoning and ACVE specifically in high-risk populations including those who are male, 35-59 years of age, and Black/African American. Understanding how drug poisoning and ACVE effects different populations is the first step to combatting this disease and prolonging life.

Appendix A

Appendix Table 1: Suppression of Data Within CDC Wonder

Figure Number	Suppressed Data (<10 Deaths in Code)
Figure 1	No Suppression.
Figure 2	Suppression ages <1-14 and 85-100+.
Figure 3	No Suppression.
Figure 4	Suppression of T Codes T40.8 and T40.9.
Figure 5	Suppression of ages <1-14 and 85-100+.
Figure 6	No Suppression.
Figure 7	All American Indian/Alaska Native data were suppressed. Crude rates for Asian/Pacific Islander were suppressed.

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