A Retrospective Study of the Opioid Epidemic and Fentanyl Related Overdose Fatality Cases in a Florida West Coast Medical Examiner District Population

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A Retrospective Study of the Opioid Epidemic and Fentanyl Related Overdose Fatality Cases in a Florida West Coast Medical Examiner District Population

by

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A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy Public Health with a concentration in Toxicology and Risk Assessment
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**ABSTRACT**

Opioids are scheduled by the propensity for misuse and abuse with a high rate of dependency and risk of fatal overdose. Opioids can be divided into different classes, including, natural, synthetic, and semi-synthetic. Opiates are naturally occurring and come directly from the opium poppy plant; whereas the semi-synthetics opioids are chemical modifications of the poppy plant. Synthetic opioids attach to the opioid receptor but contain no part of the poppy plant. The increased variety and frequency in opioid prescriptions contributed to an opioid epidemic in the United States which is still on going.

According to the CDC, the opioid epidemic has occurred in three waves. The first wave of the epidemic began in the 1990’s with the increase in opioid prescription pain medication overdoses. The second wave began around 2010 when heroin overdoses became more prevalent. This was followed by a sharp uptick in fentanyl deaths beginning around the year 2013, indicating the start of the third wave. The opioid epidemic has had a huge cost to society, not just due to deaths but also because of lost productivity, medical expenses and judicial system costs (Florence, Zhou, Luo, & Xu, 2016). To best design and implement strategies to combat this issue, an understanding of the population effected is needed. Since many public health policies are implemented at the regional level, knowing the characteristics and demographics of the epidemic at the local level is important.

This study evaluates trends in drug related death cases in the Florida District 6 Medical Examiner Office (MEO) from the calendar years 2011 through 2016.
Specifically, it focuses on opioids and the role of fentanyl in overdose related mortality. Additional attention is given to fentanyl and fentanyl analog related deaths. Fentanyl analogs present challenges from an analytical toxicology perspective. Fentanyl analogs can be difficult to detect. Two sets of data from each calendar year were obtained from the MEO. This data was collated, standardized and then statistically analyzed.

It was determined that there was not a significant difference in month of the year or the day of the week that drug related fatalities occurred. The time of day was statistically significant with more drug related mortalities occurring during the hours of 8:00am and 4:00pm. When assessing mortality rates, Pinellas and Pasco county demonstrated differences. Pasco county has higher overall mortality for opioid related deaths. Pinellas county has almost twice the number of the opioid, fentanyl, related overdose fatalities. Racial demographics, divided into White, Black, and Asian populations, demonstrated that the White population is disproportionally affected by fentanyl drug related mortality. Binary logistic regression showed that fentanyl and heroin tend to co-occur, and that ethanol, hydrocodone, methadone, morphine, and oxycodone do not usually co-occur with fentanyl in drug related fatalities.

These data help elucidate trends in the opioid epidemic at a regional level. There are differences between Pinellas and Pasco county; with the former having more fentanyl related drug deaths and the latter having more opioid related drug deaths over the six years analyzed. An interesting result is derived from the binary logistic regression. It is shown here that fentanyl and heroin tend to co-occur together. It is also shown that ethanol, hydrocodone, morphine, oxycodone, and
methadone do not co-occur with fentanyl related overdose cases. Notably, methadone has the strongest negative association with fentanyl related overdoses.
CHAPTER ONE: INTRODUCTION

Background

Opioid Use and Abuse

The National Institute on Drug Abuse (NIDA) has published that between 26.4 and 36 million people around the world abuse opioids. According to the CDC, one hundred and fifteen Americans die every single day due to an opioid overdose. Collectively, more than 630,000 people have died from drug overdoses from 1999-2016. The CDC estimates that in America the economic burden of opioid abuse costs $78.5 billion dollars per year; including lost productivity, judicial systems costs, and addiction treatment (Florence et al., 2016). America has a problem with opioid addiction (Clark & Schumacher, 2017). Notably at the state level, Florida has a statistically higher level of drug overdose than the national average.

Opiates are a class of drugs that are known for their analgesic properties; they are naturally occurring alkaloids derived from *Papaver somniferum*, the opium poppy plant (Kerrigan, 2010). Opioids can be divided into different categories including natural, semi-synthetic, and synthetic. Natural opiates are pharmacologically active compounds derived from the poppy plant (Loan et al., 1969). Semi-synthetic opioids are synthesized from natural opiates. Synthetic opioids are classified by their physiological effects, as they are similar to morphine. However, their chemical structures differ from the naturally occurring alkaloids found in the poppy plant (Kerrigan, 2010).
Production of natural and semi-synthetic opioids starts with naturally occurring alkaloids harvested from the seed pods of the poppy plant. The seed pods are scored causing raw opium to ooze out of the pods. This raw opium then dries on the outside of the seed pod. The raw opium is harvested by hand in a labor-intensive process in which it is scraped from each scored seed pod. After the opium is harvested it undergoes further purification to extract the natural analgesics - morphine, codeine, and thebaine (Holubek, Kudrnac, & Novak, 1958). These naturally occurring alkaloids are classified as opiates and act as central nervous system depressants. Opioids induce sleep, cause a reduction in sensitivity to pain, and induce a euphoric rush when administered. The euphoric rush is important in opioid addiction as users chase the euphoric high.

Natural opiates include morphine, codeine, and thebaine. Semi-synthetic and synthetic opioids include hydrocodone, oxycodone, hydromorphone, fentanyl, and heroin to name a few. Heroin and hydromorphone are made from morphine. Dihydrocodeine is made from codeine. Oxycodone and hydrocodone are made from thebaine. Therefore, they are semi-synthetics opioids. Natural, semi-synthetic, and synthetic varieties all function through the same mechanism acting on a set of opioid receptors. Synthetic opioids are structurally unrelated to morphine. There is a difference between opiates and opioids. Opiates are naturally occurring alkaloids and opioids are synthesized products. Oxycodone and hydrocodone are semi-synthetic opioids like heroin, and morphine is an opiate (Goldfrank, Bresnitz, & Weisman, 1983; Monwell, Bulow, & Gerdner, 2016; Monwell & Gerdner, 2019; Monwell, Johnson, & Gerdner, 2015). The words opiate and opioid are often used
interchangeably. In this study, when specific drugs were used in analyses they are listed.

Another main characteristic of opioid use is the high likelihood for developing physiological and psychological dependence that quickly leads to addiction. It is not known when the poppy plant was first cultivated for its natural analgesic properties, but it is estimated that it has been grown for these properties for more than 2000 years (Brownstein, 1993; Kerrigan, 2010; Spetea, 2013). However, the addictive power of opioids was known as early as the 1900s, and probably before that time (Skolnick, 2018). Defining the long history of opioid use is challenging given that archeological references can be vague making it difficult to determine what we knew historically about the addiction potential of opium and other opioids.

Morphine was isolated in 1806 and was used as the basis for the development of other semi-synthetic opioids (Kerrigan, 2010). Shortly after its discovery, morphine was used in medical procedures beginning in the 1850’s (Brownstein, 1993). It was quickly determined that patients could develop a tolerance to morphine and a need for the repeated administration of the drug. The addictive nature of morphine lead to explorations to find alternatives that were not as addictive. It was hoped that the new alternatives would offer the desired analgesic effects with reduced addiction potential (Brownstein, 1993; Kerrigan, 2010).

In 1898, the first semi-synthetic opioid, heroin, was synthesized and made available as a pharmaceutical preparation during the search for a less addictive substitute for morphine (Brownstein, 1993; Kerrigan, 2010; Tyers, 2018). Heroin has not been available in the United States as a pharmaceutical preparation since
the 1920’s. It was banned due the prevalence of addiction related problems and was associated with an increase in crime rates. America has struggled with illicit heroin use since that time (Huecker & Gossman, 2018). Widespread abuse has been documented in US since the 1970’s (Kerrigan, 2010). Drug trafficking has made illicit heroin readily available in America today (Burke, 2016). On the black market, heroin is cheaper than prescription opioids that have been diverted from medical sources (Burke, 2016; Meldrum, 2016). This makes heroin an economical but dangerous substitute for addicts whom have become addicted to prescription opioids. For this reason, readily available heroin has added fuel to the opioid epidemic.

Methadone is one of the most important synthetic opioid medications today due to its efficacy in combatting opioid addiction (Salsitz & Wiegand, 2016). It is a synthetic opioid that has a moderate long-lasting effect compared to other opioids (Kerrigan, 2010). Although methadone is not structurally related to morphine it binds to the opioid receptors and elicits effects through a generally similar mechanism (Martinez-Luna et al., 2018; Mravcik, Janikova, Drbohlavova, Popov, & Pirona, 2018). Methadone is often used to reduce opioid cravings in addicted individuals (Martinez-Luna et al., 2018; Woods & Joseph, 2018). When used for this purpose, addicted individuals are administered a dose of methadone in a strictly regulated clinical setting. It is used substantially in the detoxification process, after which patients are followed so that an appropriate maintenance dose can be developed (Kerrigan, 2010; Salsitz & Wiegand, 2016). An alternative to methadone is buprenorphine (Mravcik et al., 2018). Buprenorphine is a derivative of thebaine that produces long lasting analgesic effects (Cisewski, Santos, Koyfman, & Long,
This allows it to be used similar to methadone (Zhu et al., 2018). Individuals on methadone or buprenorphine can hold steady employment and lead relatively normal lives (Kerrigan, 2010; Salsitz & Wiegand, 2016).

Abstinence syndrome is the group of withdraw symptoms associated with the discontinuation of the administration of opioids (Dooley et al., 2018; Duceppe et al., 2018). These symptoms include but are not limited to anxiety, agitation, opioid cravings, and nausea (Grim, Harrison, & Wilder, 2013; Hall, Rice, Folger, & Wexelblatt, 2018). Abstinence syndrome symptoms can be severe and are felt within hours of the last dose. These symptoms lead the user to seek opioids again to stave off the negative impacts of abstinence syndrome.

As mentioned previously, some synthetic opioids act to help with abstinence syndrome for patients experiencing acute opioid withdraw (George et al., 2018; Lemon, Caritis, Venkataramanan, Platt, & Bodnar, 2018). The only opioids approved for this use are methadone and buprenorphine (Hall et al., 2018; Lemon et al., 2018; Walker, Logan, Chipley, & Miller, 2018; Woods & Joseph, 2018). The abstinence syndrome that is associated with the cessation of use of methadone is different than morphine; it is less intense, slower, and lasts longer than morphine’s abstinence syndrome (Brownstein, 1993). Users who have become addicted are seeking relief from abstinence syndrome.

The opioid epidemic is defined as the period in the United States and Canada where intentional and unintentional deaths attributed to opioids has escalated at an alarming rate (Clark & Schumacher, 2017; Kolodny et al., 2015; Tyers, 2018). The opioid epidemic began in the 1990’s and has escalated through the present (Cerda
et al., 2013). The spike in opioid related deaths in the United States has been dramatic and the financial burden has been profound (Florence et al., 2016). The start of the opioid epidemic is connected to an innocuous article from 1980 in the New England Journal of Medicine, which concluded that addiction was rare in hospitalized patients who received treatment for pain with opioids (Porter & Jick, 1980). Despite this publication doctors remained reluctant to prescribe opioids for the treatment of pain until the Joint Commission, formerly known as the Joint Commission on Accreditation of Healthcare Organizations, and the American Pain Society held a meeting that concluded that pain be treated not as a subjective medical problem, but as a fifth vital sign (Baker, 2017; Tormoehlen, Mowry, Bodle, & Rusyniak, 2011). This led to the practice of placing pain on a quantitative 1-10 scale (Baker, 2017; Phillips, 2000; Tormoehlen et al., 2011). “Excuses for inadequate pain control appear to have run their course and will no longer be accepted because poor pain control is unethical, clinically unsound, and economically wasteful.” (Phillips, 2000). This shift in the way American doctors prescribed opioids started the trend in increasing exposure to addictive pain medication among the population (Baker, 2017; Tormoehlen et al., 2011).

The four vital signs that had been measured before this point were blood pressure, respiration, temperature, and heart rate (Baker, 2017; Brownstein, 1993; Morone & Weiner, 2013). This paradigmatic shift in how health care providers assessed pain and prescribed opioids for the treatment of pain had a profound impact on patients (Herr & Titler, 2009). As healthcare providers prescribed more opioids, opioids began to be diverted and misused/abused (Van Zee, 2009). As the abuse of opioids rose, the opioid epidemic began. According to the CDC and
multiple scientific studies, there have been three waves within the opioid epidemic (Alexander, Kiang, & Barbieri, 2018; Ciccarone, 2019). The first wave of opioid overdoses is attributed to prescription opioids (Alexander et al., 2018). The second wave is attributed to the rise in heroin usage (Alexander et al., 2018; Ranapurwala, Naumann, Austin, Dasgupta, & Marshall, 2019). The third wave is due to overdoses from illicitly manufactured fentanyl (Ciccarone, 2019; Monwell & Gerdner, 2019).

Fentanyl is a noteworthy synthetic opioid that is a potent analgesic (Barry, 2018). A very small amount, as low as 3 nanograms per milliliter in whole blood in humans, of fentanyl is needed to cause fatal overdose (Figure 1.1). It is approximately 80 times stronger than morphine. Fentanyl was first manufactured in 1950’s and was used in the 1960’s in medical settings ("Fentanyl," 2018; Raffa et al., 2018). Fentanyl is manufactured as licit and illicit preparations. Licit pharmaceutical formulations are used in chronic pain management, break through pain in cancer and hospice patients, and in veterinary applications (Kerrigan, 2010; Raffa et al., 2018). These pharmaceutical preparations of fentanyl include a transdermal patch, a stick designed to melt slowly in the mouth for transmucosal absorption, and injectables used for the anesthesia of large animals by veterinarians. Illicitly manufactured fentanyl is produced with the intention to sell to opioid abusers and has also appeared in heroin.

According to the Drug Enforcement Agency (DEA), there have been twelve fentanyl analogs identified in addition to illicit fentanyl ("Fentanyl," 2018). These analogs include, but are not limited to, acetyl fentanyl, butyryl fentanyl, para-fluorobutyryl fentanyl, fluoroisobutyryl fentanyl, and methoxyacetyl fentanyl to name a few. Illicit fentanyl preparations effectively mimic illicit heroin except for
their overdose potential. Fentanyl analogs may be a hundred times more potent than illicit heroin ("Fentanyl," 2018).

**Opioid Receptors and Addiction**

While natural opioids have been known to man for a long time, it was not until the 1970’s that an understanding of how they work was established (Valentino & Volkow, 2018). Research from this time discovered that opioids act upon specific regions of the brain and that brain neurons produce their own opioid like compounds which act upon the same regions (Olson, Olson, Kastin, & Coy, 1979; Rhodes & Liebeskind, 1978). This led to the foundational understanding that opioids act as powerful mimetics upon the same opioid receptor systems as natural opioid-like compounds (Wang, 2018). All opioids work via these opioid receptors. This class of receptors is primarily located within the central nervous system and consists of three receptor subtypes - μ (Mu Opioid Receptor), κ (Kappa Opioid Receptor), and δ (Delta Opioid Receptor). Of these, agonism of the mu opioid receptor is most associated with the euphoric analgesia addicts seek (Lutz & Kieffer, 2013).

An individual that consumes opioid medication or illicit preparations can quickly become dependent on the substance. An individual user that experiences dependence will develop a tolerance for the drug and require higher doses to achieve the same effect. Withdrawal symptoms will occur when administration of the drug is discontinued (Concheiro, Chesser, Pardi, & Cooper, 2018; Finan, Remeniuk, & Dunn, 2018). It is possible to experience physical dependence without addiction. However, when dependence occurs addiction is likely to follow. Addiction
is characterized by biochemical changes in the brain that leads to altered behavior (Verdejo-Garcia, Chong, Stout, Yucel, & London, 2018). These changes from dependency to addiction include risk taking behavior and spending excessive resources to find and consume the drug, among other behaviors (Huecker & Gossman, 2018). Physical dependence leads to biochemical changes that lead to addiction (Mravcik et al., 2018).

**The Opioid Epidemic has Occurred in Three Waves**

The opioid epidemic in the United States began when opioid medications became widely prescribed leading to our current situation (G. Walker, 2018). In 2016, there was a new development in how opioids were to be prescribed. That year the Center for Disease Control described a new way to prescribe opioids limiting the scope of when opioids should be administered (Meldrum, 2016). Previous policy had caused over prescribing of opioids that lead to “dangerous pain control practices” (“Physicians for Responsible Opioid Prescribing,” 2016). Reversing the liberal prescription of opioids was the first step in reversing the policies that led to today’s current opioid epidemic (Baker, 2017).

According to the CDC, there have been three waves during the opioid epidemic. The first wave started in the 1990’s after physicians changed how they prescribed opioids. Once pain was considered as the fifth vital sign and opioids were widely prescribed, the addictive potential of this class of drugs was soon realized. The first wave of the opioid epidemic is characterized by massive rise in fatal prescription overdoses. This rise was driven in part by the massive marketing campaign of the extended release form of oxycodone known by the brand name
Oxycontin (Meldrum, 2016). Other major drug contributors to the opioid epidemic include hydrocodrone, hydromorphone, oxycontin/hydrocodone with acetaminophen additives. The first wave in the opioid epidemic was caused by the rise of overdoses due to prescription opioids (Figure 1.2).

Oxycontin was marketed as a safe, long lasting analgesic. It was widely prescribed and addiction to oxycontin soon became rampant in the United States (Meldrum, 2016). As the medical community became aware of the issues associated with oxycontin, these prescriptions became harder to obtain. Addicts turned to the black market for prescription medications. Diverted oxycontin would sell on the street for as much as 40 dollars per pill (Meldrum, 2016). Simultaneously, illicit heroin was readily available and cheaper than pharmaceutical prescriptions. Drug addicted individuals turned to illicit heroin, because it was readily available and a cheap alternative to the difficult to obtain prescription opioids. These circumstances lead to the second wave of the opioid epidemic. The second wave in the opioid epidemic was characterized by a rise in overdose deaths involving illicit heroin (Figure 1.2).

The third wave is characterized by a sharp rise in overdoses involving synthetic opioids; specifically, illicitly manufactured fentanyl and fentanyl analogs (Barry, 2018; Raffa et al., 2018). According to the CDC, the third wave attributed to fentanyl and fentanyl analogs began in 2013 (Figure 1.2). Illicit fentanyl can be manufactured cheaply and is easy to obtain (Raffa et al., 2018). These fentanyl preparations are purchased and cut into heroin. It is believed that the end drug user is usually not aware of the presence of illicit fentanyl in their heroin (Brownstein, 1993; Meldrum, 2016; Raffa et al., 2018). Fentanyl contaminated
heroin poses an especially serious risk as the drug addict does not know the potency leading to a very high risk of fatal overdose.

**Data Origin**

**The Medical Examiner Office**

When a person expires under questionable circumstances, such as a potential drug overdose, the body is typically transported to the Medical Examiner Office. It is determined at the MEO if it was a drug overdose. It is the job of the Medical Examiner to determine the cause and manner of death (Meyers, 2018; Murray, 1966; Ryan, 1977). At that time, it is determined by the Medical Examiner if it is appropriate to perform an autopsy. In the majority of cases, an autopsy is performed, and biological samples are collected for toxicological analysis. These samples are submitted to a toxicology laboratory. The toxicology laboratory performs testing on the samples to determine if and what substances are present in the decedent (Hobbs, Jachimczyk, & Schloegel, 1980). A toxicology report is then prepared listing the substances found, typically controlled and non-controlled substances, and this report aids in determination of the cause and manner of death.

**Gas Chromatography-Mass Spectrometry**

One of the most useful analytical tools utilized by toxicologists in the laboratory is gas chromatography coupled with a mass spectrometer (GC-MS). Before GC-MS analysis, biological samples, like blood and urine, are subjected to techniques that allow compounds of interest, drugs, to be extracted from the
biological sample. Often solid phase extraction or liquid-liquid extractions are employed to create a biological extract that can be analyzed by GC-MS (Arbelaez, Borrull, Maria Marce, & Pocurull, 2014; Broich, Hoffman, Goldner, Andryauskas, & Umberger, 1971; Dowling & Regan, 2011; Lerch, Temme, & Daldrup, 2014; Ramirez Fernandez Mdel et al., 2014; Teng et al., 2015). Once a sample has been prepared through the extraction process, it is run through gas chromatography. The gas chromatograph acts as a sieve and separates the compounds in the extract based on the compound’s chemical characteristics with each compound eluting off of the GC at a specific time (Bjorkman & Stanski, 1988; Maruyama, Hosoya, & Nozaki, 1968; Szeitz, Riggs, & Harvey-Clark, 1996). The gas chromatograph generates a graph known as a total ion chromatogram (TIC). The TIC contains peaks for the compounds and drugs present in the biological extract. A gas chromatogram is obtained by running a compound, for example fentanyl, through a gas chromatograph. The compound will elute at predictable times if run under the same gas chromatographic parameters.

The gas chromatograph is attached to a detector, most commonly, a mass spectrometer. The mass spectrometer uses different ionization techniques and fragments the compounds separated by the gas chromatograph. These compounds are thus transformed into unique species that contains predictable mass to charge particles. These particles create a unique spectrum that is used to identify the compounds and drugs present in the original biological extract originating from the decedent. Figure 1.3 shows the mass spectrum generated by fentanyl. Fentanyl will look like this mass spectrum regardless of the extraction technique used in preparation of the biological specimen from the decedent. The combined
technologies offer a powerful tool for identification of biological specimens including temporal and chemical properties that lead to predictable elution times and mass spectrum generation.

GC-MS data is used in conjunction with other laboratory testing results to create a toxicology report. In addition to the toxicology reports, investigative reports are also prepared that provide social histories and background information on decedents. The toxicology reports, investigative reports, and autopsy reports are utilized by Medical Examiner to determine the cause and manner of death. The Medical Examiner then signs the death certificates certifying this information. The cause and manner of death are then collected for vital statistics by the local, state, and federal government.

**Gas Chromatography-Mass Spectrometry Data and Limits**

Each laboratory that performs testing on biological samples determines their own policies for how the testing is performed. Laboratory accrediting bodies work to help standardize toxicological practices, but variations in analytical approaches do exist. The origin of the data used in this study employs “full scan” GC-MS data. This means that all peaks present in a sample will be assessed to determine what substances are present. Many laboratories utilize an alternate approach to full scan analysis that specifically target compounds of interest. This approach is referred to as a utilization of a “drug panel”.

The compounds that are targeted in drug panels are decided upon during method development and validation. These drugs of interest are set, and the instrumental method does not allow for other non-targeted compounds to be
identified. This valid approach is helpful when you are targeting specific compounds. However, it can be problematic when new analogs, such as fentanyl analogs, are present in a sample. Fentanyl analogs that have not been identified before will not be seen on a drug panel. This leads to the potential problem of underreporting new illicit preparations of drugs. The full scan approach using GC-MS is better suited to identifying novel analogs because all compounds analyzed are included in the data and skilled analysts can determine new analogs based on their similarity to known compounds.

Although, GC-MS is a powerful diagnostic tool it does have limitations. Some of these limitations include the way the body metabolizes certain drugs. For example, heroin is almost immediately metabolized into 6-monoacetyl morphine (6MAM) and morphine in the body (Darke, Duflou, & Torok, 2010; Ruan, Chiravuri, & Kaye, 2016). This transformation happens so quickly that it can be difficult to detect heroin in biological specimens. This results in the potential overreporting of morphine and underreporting of heroin related fatalities.

**Intervention Strategies**

Curbing the opioid epidemic requires a multitude of approaches. Public policy approaches that deal with epidemics can be categorized as primary, secondary, and tertiary prevention strategies (Kolodny et al., 2015). These approaches all serve to mitigate and prevent opioid addiction and its harmful impacts (Baker, 2017). Primary prevention seeks to reduce the occurrence of the underlying problem, which in this case is opioid addiction (Kolodny et al., 2015). Secondary approaches aim to screen for the condition before serious problems occur (Kolodny et al.,
Tertiary strategies seek to prevent damage that occurs once the condition sets in (Kolodny et al., 2015). In the case of opioid addiction this includes prevention of medical complications and overdose deaths.

Locally within Pinellas County, a task force has been established to combat opioid overdoses. The Pinellas County Opioid Task Force was established in 2016 to create a coalition between law enforcement, the medical community, public health officials, and other community stakeholders (Pinellas County Opioid Task Force, 2017). The Opioid Task Force’s main goal is to reduce the societal and economic costs to Pinellas County due to the opioid epidemic (Pinellas County Opioid Task Force, 2017). The goals utilize intervention through primary, secondary, and tertiary approaches. Tertiary approaches are the most prevalent type of strategy employed by Pinellas County.

Collectively, Florida has requested fifty million dollars to dedicate to fighting the opioid epidemic which includes supporting the Pinellas County Opioid Task Force (Pinellas County Opioid Task Force, 2017). Twenty-seven million dollars is earmarked to fund medication treatment centers. 1.8 million dollars was requested to fund naloxone kits. Naloxone is a medication that blocks the action of opioids and temporarily reverses the drug’s effects. This will improve the efficacy of combating the local opioid epidemic through primary, secondary, and tertiary strategies.

**Statement of Problem**

It is known that the United States is experiencing an opioid epidemic (Baker, 2017; Kolodny et al., 2015; Meldrum, 2016). The impact of the epidemic has been
so profound that it has been suggested that it has lowered the overall life expectancy in the United States (Glenza, 2017). It has been shown that the opioid epidemic has occurred in three waves and the cause of the epidemic is not debated. Although we know that hundreds of Americans are dying every day from opioid drug overdoses, we have limited knowledge of the demographics in Pinellas and Pasco county that are affected by opioid overdose. National and State trends that have occurred during the opioid overdose have been published. These include, but are not limited to, medical workers suffering opioid overdose at higher rates than non-medical workers and the white population being more susceptible to opioid overdose. Regional data and an effective understanding of the opioid epidemic at a local level has yet to be elucidated.

**Purpose of the study and Research Questions**

The purpose of this study is to analyze the population of decedents in a Medical Examiner district in Florida to assess the opioid epidemic and fentanyl related overdose cases at a regional level. Additionally, this study will characterize the population to determine trends and look for correlations in multi-drug toxicity overdose related deaths. Multi-drug toxicity is when a decedent passes away with multiple different drug classes that contribute to their cause of death. This study encompasses the years 2011 through 2016. These years align with the end of the second wave of the opioid epidemic and include the third wave as published by the Center for Disease Control. This regional study will help elucidate if the regional opioid epidemic reflects the national opioid epidemic.
1. What does the typical overdose case look like in Pinellas and Pasco County?
   a. How are the counties different from each other?

2. Are there predictors or indicators of synthetic opioid overdose death?

3. What is the average age, gender, and race of opioid overdose decedent?
   a. How does this compare to State and National Averages?
   b. Can certain counties be used as predictors for other regions of the country?
   c. Are there case history trends?

4. What other drugs are in the system and do they contribute to the cause of death?
   a. Are certain drug combinations more common?
   b. Do these drug combinations cycle or are there trends seen over time?

5. Are opioid overdoses under reported due to multidrug toxicity reports?

6. Are cases reported with opioids with other drug classes considered opioid deaths?

7. What drug combinations are most common when the cause of death is multidrug toxicity?
   a. How does this compare with State and National reports?

8. When, did fentanyl become prominent in cause and manner of death?
   a. When did fentanyl analogs begin showing up in death records?
   b. Can it be predicted when a fentanyl analog present in a county will change or “run its course”?
   c. Can it reliably be said that fentanyl is “contaminating” other drugs?
**Null hypothesis**

1. There are no significant trends in opioid overdose fatalities over 2011 through 2016 years in Pinellas and Pasco counties.

2. There are no significant differences in opioid overdose populations between Pinellas and Pasco counties.

3. There are no significant differences in opioid overdose populations between the national level and Pinellas and Pasco counties.

4. There are no significant changes in drug combinations in multidrug toxicities present in opioid overdose cases during 2011 through 2016 in Pinellas and Pasco counties.
Figure 1.1. Fentanyl dose needed to cause a fatal overdose. The penny is used to show the scale. The white powder is the amount of fentanyl needed to cause a fatal overdose. Reprinted from Fentanyl image 4 of 17. US DEA (https://www.dea.gov/)

Figure 1.2. The three waves of the opioid epidemic. Reprinted from Understanding the Epidemic with permission (Appendix C). CDC. (https://www.cdc.gov/drugoverdose/images/epidemic/png)
**Figure 1.3.** Mass spectrum of fentanyl. Spectrum was taken from fentanyl reference standard. The base peak is 245. The major ions include 146, 189, and 91. Fentanyl will always fragment in this unique pattern.
CHAPTER TWO: MATERIAL AND METHODS

Methodology and Data Collection

The data for this study was generated by the Florida District 6 Medical Examiner Office (MEO) in the general course of business. The MEO retrieves bodies of decedents and follows policies as prescribed by Florida Statute Chapter 406.11 and Florida Administrative Code Chapter 11G-2. First it is determined if there is jurisdiction. Once jurisdiction is ensured, the cause and manner of death are determined by employing multiple tools. These include investigative reports, autopsy reports, and toxicology reports. In some cases, DNA is involved to determine decedent identity. Autopsies are performed on decedents and biological specimens are collected and submitted to the forensic laboratory for toxicological analysis for a subset of cases. Toxicology reports are generated and submitted to the MEO. The MEO uses toxicology reports, autopsy reports, and investigative reports to determine the cause and manner of death. These data are submitted to the government for the compilation of vital statistics.

The process of MEO investigation, forensic testing, and reporting of the Medical Examiner findings undergo stringent quality control procedures. A strict chain of custody is maintained by the forensic laboratory for every biological specimen that enters the laboratory. Analytical data is reviewed through rigorous procedures with multiple experienced, well trained personnel agreeing on technical data before it is released. Both the Florida District 6 Medical Examiner and Pinellas
County Forensic Laboratory adhere to strict criteria and are accredited through appropriate accreditation bodies; National Association of Medical Examiner (NAME) and American National Standards Institute National Accreditation Board (ANAB) respectively. The data resides in databases maintained by the MEO and is public record which is available upon request.

An exemption was received from the Institutional Review Board for this study. After the exemption was granted a public records request was placed with the District 6 Medical Examiner Office requesting specific data categories, listed below in Table 2.1. All data requested in the public records request was received as deidentified data. All identifying information was redacted or exempt from the data that was obtained in the data sets from the public records request.

Two data sets for each year, 2011 through 2016, were obtained through the data request to the Florida District 6 Medical Examiner Office. The two data sets obtained for each year were named the Case Detail Report and FDLE Drug Stats - Drug Related Cause report. All data was deidentified. It should be noted that cases that involve homicides were redacted from the public records request and were not included in this study. The Case Detail Report contained approximately 1,800 to 2,000 cases for the years 2011, 2012, 2013, 2014, 2015, and 2016. The FDLE Drug Stats - Drug Related Cause report contained approximately 320 to 465 cases each year. Information from both data sets from all years was consolidated so all information for each drug related death case with toxicological data was combined into a single database. The database used for analysis contained 2,258 cases. This database was formatted so that qualitative and quantitative data was SAS compatible. The statistical software SAS University Edition was used for analysis.
An excerpt from the merged database is shown in Appendix A. The SAS code used for generation of data is found in Appendix B.

**Comparative Analysis**

In this study, statistical analysis of data sets from each year was performed to determine means and distributions of the quantitative data and frequency for the qualitative data. These data were compared year to year to assess for any significant differences using the nonparametric ANOVA test. Pinellas county and Pasco county data were compared to determine if any differences are present between two geographically close locations. It should be noted that there are demographic differences between Pinellas and Pasco county. These differences were compensated for before analysis was performed regarding race or per capita tests. Data for county population and demographics for 2011 through 2016 were derived from the United States Census Bureau. Pasco county’s population is approximately half that of Pinellas county (Table 2.2). Additionally, Pinellas county is more diverse with People of Color composing approximately 11% of the population with Caucasians composing 82.7%. People of Color make up approximately 8% of the population in Pasco county. Pinellas county’s population is slightly older than Pasco county with 24% and 22% of the population being over the age of 65 respectively.

Additionally, frequencies of specific drug classes present in opioid multi-drug toxicity overdoses were compared to frequencies of drugs within non-opioid overdoses to determine which drugs are associated with co-morbidity in opioid overdoses. Within the data obtained from the MEO, drugs were reported as present, cause of death, or absent. To create binary data, the toxicological data was
formatted so that all present and cause of death results were simply considered positive. Correlations between positive fentanyl results and the presence of other drugs was determined by binary logistic regression (Table 2.3 and 2.4). Only drugs that were found to be of statistically significant are reported. A cutoff value of 0.05 was used for the limit of statistical significance.

Furthermore, the data sets were evaluated to determine when fentanyl related overdose cases began to become more prevalent in District 6. The rise of fentanyl and fentanyl analogs was determined and compared between Pinellas and Pasco counties. Fentanyl positive cases were considered to be cases that contained fentanyl, fentanyl metabolites, or fentanyl analogs (see Table 2.3).

**Table 2.1** The data categories in the public record request.

<table>
<thead>
<tr>
<th>Data Type</th>
<th>Data Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantitative Data</td>
<td>Age, Date of Death</td>
</tr>
<tr>
<td>Qualitative Data</td>
<td>Sex, Race, Case Histories, 20 top Drug Panel, Cause of Death, Manner of death, County (Pinellas and Pasco)</td>
</tr>
</tbody>
</table>

**Table 2.2.** County populations from the United States Census Bureau.

<table>
<thead>
<tr>
<th></th>
<th>Pasco Population</th>
<th>Pinellas Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>466502</td>
<td>918565</td>
</tr>
<tr>
<td>2012</td>
<td>469905</td>
<td>922150</td>
</tr>
<tr>
<td>2013</td>
<td>474782</td>
<td>929214</td>
</tr>
<tr>
<td>2014</td>
<td>484048</td>
<td>937933</td>
</tr>
<tr>
<td>2015</td>
<td>495648</td>
<td>949321</td>
</tr>
<tr>
<td>2016</td>
<td>510561</td>
<td>962106</td>
</tr>
</tbody>
</table>
Table 2.3. Fentanyl, fentanyl analogs, and fentanyl metabolites.

<table>
<thead>
<tr>
<th>Fentanyl/Analogs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
</tr>
<tr>
<td>Acetyl Fentanyl</td>
</tr>
<tr>
<td>Butyryl Fentanyl</td>
</tr>
<tr>
<td>Despropionyl Fentanyl (4-ANPP)</td>
</tr>
<tr>
<td>Fluoroisobutyryl Fentanyl</td>
</tr>
<tr>
<td>Furanyl Fentanyl</td>
</tr>
<tr>
<td>Fluorofentanyl</td>
</tr>
<tr>
<td>Carfentanil</td>
</tr>
<tr>
<td>Fluorobutyryl Fentanyl</td>
</tr>
</tbody>
</table>

Table 2.4. The drugs that were analyzed in binary logistic regression.

<table>
<thead>
<tr>
<th>Drugs in Logistic Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
</tr>
<tr>
<td>Amphetamine</td>
</tr>
<tr>
<td>Methamphetamine</td>
</tr>
<tr>
<td>Alprazolam</td>
</tr>
<tr>
<td>Clonazepam</td>
</tr>
<tr>
<td>Diazepam</td>
</tr>
<tr>
<td>Lorazepam</td>
</tr>
<tr>
<td>Midazolam</td>
</tr>
<tr>
<td>Nordiazepam</td>
</tr>
<tr>
<td>Oxazepam</td>
</tr>
<tr>
<td>Temazepam</td>
</tr>
<tr>
<td>Buprenorphine</td>
</tr>
<tr>
<td>Codeine</td>
</tr>
<tr>
<td>Fentanyl/Analogs/Metabolites</td>
</tr>
<tr>
<td>Heroin</td>
</tr>
<tr>
<td>Hydrocodone</td>
</tr>
<tr>
<td>Hydromorphone</td>
</tr>
<tr>
<td>Meperidine</td>
</tr>
<tr>
<td>Methadone</td>
</tr>
<tr>
<td>Morphine</td>
</tr>
<tr>
<td>Oxycodone</td>
</tr>
<tr>
<td>Oxymorphone</td>
</tr>
<tr>
<td>Tramadol</td>
</tr>
<tr>
<td>Cocaine</td>
</tr>
</tbody>
</table>
CHAPTER THREE: RESULTS

Month, Day, and Time of Day

The frequency of drug related deaths was assessed by month of the year. Means were calculated for each year and plotted on bar charts. For 2011, July had the most drug related fatalities. November had the fewest drug related fatalities. The mean was 36.5; this was the second highest mean across all years analyzed (Figure 3.1). For 2012, January had the most drug related fatalities. April had the fewest drug related fatalities. The mean was 32 (Figure 3.4). For 2013, the cases with toxicological data dropped with August and December tying for the highest number of cases. Like 2011, the year 2013 had the fewest fatalities in November; with a mean for the year of 26.7 (Figure 3.7). For 2014, the total number of deaths with toxicological data increased with a mean of 27.5 (Figure 3.10). The highest frequency of deaths occurred in December and the fewest occurred in July of 2014. For 2015, May and August had the highest number of deaths with toxicological data (Figure 3.13). The mean for 2015 was slightly lower than the previous year at 27.1. The year 2016 had the highest mean frequency at 38.5 (Figure 3.16). The most drug related deaths occurred in December and the least occurred in April.

The frequency of drug related deaths was assessed by day of the week. Means were calculated for each year and plotted on bar charts. For 2011, Saturday had the most drug related fatalities. Monday had the fewest drug related fatalities. The mean was 62.6 (Figure 3.2). For 2012, Wednesday had the most drug related
fatalities. Thursday had the fewest drug related fatalities. The mean was 54.9 (Figure 3.5). For 2013, the cases with toxicological data Sunday had the highest number of deaths. Tuesday had the fewest fatalities; with a mean for the year of 45.6 (Figure 3.8). For 2014, the total number of deaths with toxicological data increased with a mean of 47.1 (Figure 3.11). In 2014, the highest frequency of deaths occurred on Friday and the fewest occurred on Wednesday. For 2015, Saturday had the highest number of deaths with toxicological data and Wednesday had the fewest deaths (Figure 3.14). The mean for 2015 was slightly lower than the previous year at 46.4. The year 2016 had the highest mean frequency at 66 (Figure 3.17). The most drug related deaths occurred on Saturday and the least occurred on Tuesday.

The frequency of drug related deaths was assessed by time of day. Means were calculated for each year and frequencies were plotted on bar charts. For 2011, noon to 4:00pm had the most drug related fatalities. Four to eight in the morning had the fewest drug related fatalities. The mean was 73; this was the second highest mean across all years analyzed (Figure 3.3). For 2012, noon to 4:00pm had the most drug related fatalities. Midnight to 4:00am had the fewest drug related fatalities. The mean was 64 (Figure 3.6). For 2013, the most common time of death was 8:00am to noon. The fewest fatalities occur at 4:00am to 8:00am; with the lowest mean of all the years at 53.2 (Figure 3.9). For 2014, the total number of deaths with toxicological data increased with a mean of 55 (Figure 3.12). The highest frequency of deaths occurred during the hours of 8:00am to noon and the fewest occurred midnight to 4:00am. For 2015, noon to 4:00pm had the highest number of deaths with toxicological data (Figure 3.15). The fewest fatalities
occurred between midnight and 4:00am. The mean for 2015 was slightly lower than the previous year at 54.2. The year 2016 had the highest mean frequency at 77 (Figure 3.18). The most drug related deaths occurred between the hour’s noon to 4:00pm and the fewest occurred 4:00am to 8:00am.

To analyze trends from years 2011 through 2016 several methodologies were employed. Box plots were created to demonstrate difference from the mean in frequency of death by the month, day of the week, and time of the day. To determine trends in the data that regularly appear each year, the means, medians, 25th percentile and 75th percentile were determined and presented as box plots. These data in the box plots are presented as diamonds, lines, upper and lower whiskers respectively. The significance of trends across the years was assessed utilizing nonparametric one-way ANOVA. This test was used because of the limited number of years being compared and no assumptions about distribution were made.

Month to month variations in the difference from mean in number of deaths average between +/- 4 (Figure 3.19). These average monthly deviations were not significantly different between months based on nonparametric one-way ANOVA, as the Kruskal-Wallis probability was 0.737 (Figure 3.20). Day to day variations in the difference from mean in number of deaths average between -5 and +6 (Figure 3.21). Friday and Saturday tend to have slightly more deaths on average than other days. However, these deviations were not significantly different between days. This is based on the nonparametric one-way ANOVA Kruskal-Wallis probability of 0.286 (Figure 3.22). Variations in the difference of average number of deaths for each time bracket range from +28 to -22 (Figure 3.23). The time ranges of
midnight to 4:00am and 4:00am to 8:00am were found to have the lowest numbers of deaths compared to the yearly mean. Noon to 4:00pm and 8:00am to noon was determined to have the highest numbers of deaths compared to the mean. These deviations in the variance of number deaths for time ranges were determined to be significantly different based on nonparametric one-way ANOVA, as the Kruskal-Wallis probability was 0.0001 (Figure 3.23).

**Pinellas and Pasco County Compared**

To determine the morality rate data for each year by county, the number of deaths were calculated using population data obtained from the US Census Bureau (Table 2.2). This yielded death rates per 100,000 which allowed for direct comparison between counties.

The calculated rates for all drug related deaths in Pinellas and Pasco counties from 2011 through 2016 ranges between 21.6/100,000 and 33.4/100,000 (Figure 3.25). The rates for both counties for all drug related deaths were generally similar. However, Pasco had slightly higher rates in 2011, 2014, and 2015. Opioid related mortality death rates were similarly calculated in Figure 3.26. For this analysis opioids were defined as: codeine, heroin, hydrocodone, hydromorphone, morphine, oxycodone, and oxymorphone. Opioid deaths rates were highest in 2011. Pasco county has had a higher opioid related death rate for all six years analyzed (Figure 3.26). Fentanyl mortality rates have consistently risen in both counties between 2011 through 2016 (Figure 3.27). These rates were by far the highest in 2016. In the years 2015 and 2016, the fentanyl mortality rate in Pinellas county was almost twice that of Pasco county.
The age ranges of drug related deaths for each gender for the years 2011 through 2016 were determined and graphed as box plots. Among deaths positive for pharmaceuticals opioids, fentanyl, or heroin, there is no significant differences in ages between males and females (Figure 3.28). Additionally, these average ages do not significantly differ from the average age of 45.8 for all drug related deaths. The average ages for fentanyl or heroin related deaths was similarly graphed (Figure 3.29). While the average age trends down over consecutive years, the trend is not statistically significant. The average ages for fentanyl or fentanyl analog deaths for males and females from 2011 through 2016 was also determined (Figure 3.30). The age ranges of males and females with fentanyl related deaths was nearly identical to that of fentanyl and heroin deaths. Notably, 2016 is the only year the average age of fentanyl related deaths for both male and female is less than 40.

To understand how drug mortality affects different demographics in Pinellas and Pasco county, the mortality rate for each race listed in the database was determined using demographic statistics. Keeping in mind, that the original data sets were divided into three race categories; White, Black, or Asian. Demographic mortality rates are illustrated in Figure 3.31. There is a substantial difference, greater than 3-fold, between White versus Black and Asian populations. While this difference is evident in both counties, the difference between the Black and White race adjusted fatality rates is less pronounced in Pinellas county. When analyzing demographic differences in opioid and fentanyl related deaths the contrast is even more pronounced. It exceeds a 4-fold difference between White versus Black or Asian race categories.
**Probability of Co-Occurrence with Fentanyl**

Binary logistic regression was performed to assess which drugs occurred more often in the presence or absence of fentanyl, and whether these drugs tend to co-occur or be mutually exclusive. The drugs used in the analysis are listed in Table 2.4. A probability cutoff value of .05 was used. The fit statistics demonstrate that this model is a good fit (Table 3.1). The odds ratio point estimates represent the probability of co-occurrence divided by probability of exclusivity and are listed in Table 3.2. These values represent how many times more likely these outcomes (presence of certain drugs) occur concurrently compared to separately. Heroin has a point estimate 3.650. This means that the probability of heroin and fentanyl occurring are about 3:1. Ethanol has a point estimate of 0.531. Hydrocodone has a point estimate of 0.501. Methadone has a point estimate of 0.195. Morphine has a point estimate of 0.586. Oxycodone has a point estimate of 0.471. This means that ethanol, hydrocodone, methadone, morphine, and oxycodone will occur with fentanyl with approximate odds of less than .5 to 1, depending on the specific point estimate for each drug, relative to occurring separate from fentanyl. These data include the statistically significant drugs. Drugs from Table 2.4 that were found to be indeterminate by this test are not included in the listed odds ratios.
Figure 3.1. Total number of deaths with toxicology data by month for 2011. The month is on the X axis and the number of drug related fatalities is on the Y axis. The green line represents the arithmetic mean deaths per month.
Figure 3.2. Total number of deaths with toxicology data by day of the week for 2011. The day of the week is on the X axis and the frequency of drug related fatalities is on the Y axis. The green line represents the arithmetic mean deaths by day for the entire year.
Figure 3.3. Total number of deaths with toxicology data by time of day 2011. The time of day is on the X axis and the number of drug related fatalities is on the Y axis. The green line represents the arithmetic mean deaths by time of day for the whole year.
**Figure 3.4.** Total number of deaths with toxicology data by month for 2012. The month is on the X axis and the number of drug related fatalities is on the Y axis. The green line represents the arithmetic mean deaths per month over the course of the year.
Figure 3.5. Total number of deaths with toxicology data by day of the week for 2012. The day is on the X axis and the number of drug related fatalities is on the Y axis. The green line represents the arithmetic mean deaths by day over the course of the year.
Figure 3.6. Total number of deaths with toxicology data by time of day for 2012. The time of day is on the X axis and the number of drug related fatalities is on the Y axis. The green line represents the arithmetic mean deaths by time of day for the entire year.
Figure 3.7. Total number of deaths with toxicology data by month for 2013. The month is on the X axis and the number of drug related fatalities is on the Y axis. The green line represents the arithmetic mean deaths per month over the course of the year.
Figure 3.8. Total number of deaths with toxicology data by day of the week for 2013. The day is on the X axis and the number of drug related fatalities is on the Y axis. The green line represents the arithmetic mean deaths by day over the course of the year.
**Figure 3.9.** Total number of deaths with toxicology data by time of day for 2013. The time of day is on the X axis and the number of drug related fatalities is on the Y axis. The green line represents the arithmetic mean deaths by time of day for the entire year.
Figure 3.10. Total number of deaths with toxicology data by month for 2014. The month is on the X axis and the number of drug related fatalities is on the Y axis. The green line represents the arithmetic mean deaths per month over the course of the year.
Figure 3.11. Total number of deaths with toxicology data by day of the week for 2014. The day is on the X axis and the number of drug related fatalities is on the Y axis. The green line represents the arithmetic mean deaths by day over the course of the year.
Figure 3.12. Total number of deaths with toxicology data by time of day for 2014. The time of day is on the X axis and the number of drug related fatalities is on the Y axis. The green line represents the arithmetic mean deaths by time of day for the entire year.
Figure 3.13. Total number of deaths with toxicology data by month for 2015. The month is on the X axis and the number of drug related fatalities is on the Y axis. The green line represents the arithmetic mean deaths per month over the course of the year.
Figure 3.14. Total number of deaths with toxicology data by day of the week for 2015. The day is on the X axis and the number of drug related fatalities is on the Y axis. The green line represents the arithmetic mean deaths by day over the course of the year.
Figure 3.15. Total number of deaths with toxicology data by time of day for 2015. The time of day is on the X axis and the number of drug related fatalities is on the Y axis. The green line represents the arithmetic mean deaths by time of day for the entire year.
Figure 3.16. Total number of deaths with toxicology data by month for 2016. The month is on the X axis and the number of drug related fatalities is on the Y axis. The green line represents the arithmetic mean deaths per month over the course of the year.
**Figure 3.17.** Total number of deaths with toxicology data by day of the week for 2016. The day is on the X axis and the number of drug related fatalities is on the Y axis. The green line represents the arithmetic mean deaths by day over the course of the year.
Figure 3.18. Total number of deaths with toxicology data by time of day for 2016. The time of day is on the X axis and the number of drug related fatalities is on the Y axis. The green line represents the arithmetic mean deaths by time of day for the entire year.
**Cumulative Figures for 2011-2016**

![Box Plot](image)

**Figure 3.19.** A box plot including all year’s monthly data. The month is on the X axis and the difference from the yearly mean of monthly fatalities is on the Y axis. The boxes enclose the 25th - 75th percentile. Means are signified by diamonds and the medians by lines. Whiskers represent minimums and maximums.
Table 3.1. ANOVA Analysis of Monthly Deviation from Mean. These values correspond to the Figure 3.20.

<table>
<thead>
<tr>
<th>Month</th>
<th>N</th>
<th>Sum of Scores</th>
<th>Expected Under H0</th>
<th>Std Dev Under H0</th>
<th>Mean Score</th>
</tr>
</thead>
<tbody>
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<td>32.500000</td>
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</tr>
<tr>
<td>August</td>
<td>6</td>
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<td>219.0</td>
<td>49.047620</td>
<td>45.666667</td>
</tr>
<tr>
<td>September</td>
<td>6</td>
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<td>219.0</td>
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<td>38.000000</td>
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<td>6</td>
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<td>49.047620</td>
<td>32.666667</td>
</tr>
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</tbody>
</table>

Kruskal-Wallis Test

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>7.7325</td>
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<td>0.7370</td>
</tr>
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</table>
Figure 3.20. Nonparametric One-Way ANOVA results inclusive of all years for month of the year. The X axis is the month the Y axis is the Wilcoxon rank sum score. The boxes enclose the 25th - 75th percentile. Means are signified by diamonds and the medians by lines. Whiskers represent minimums and maximums.
**Figure 3.21.** A box plot of all year’s day of the week data. The day of the week is on the X axis and the difference from the mean by day of the week fatalities is on the Y axis. The boxes enclose the 25th - 75th percentile. Means are signified by diamonds and the medians by lines. Whiskers represent minimums and maximums.
Table 3.2. ANOVA Analysis of Daily Deviation from Mean. These values correspond to the Figure 3.22.

<table>
<thead>
<tr>
<th>Day</th>
<th>N</th>
<th>Sum of Scores</th>
<th>Expected Under H0</th>
<th>Std Dev Under H0</th>
<th>Mean Score</th>
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<tbody>
<tr>
<td>Sunday</td>
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<td>128.00</td>
<td>129.0</td>
<td>27.811837</td>
<td>21.333333</td>
</tr>
<tr>
<td>Monday</td>
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<td>126.00</td>
<td>129.0</td>
<td>27.811837</td>
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</tr>
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<td>Tuesday</td>
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<td>129.0</td>
<td>27.811837</td>
<td>15.916667</td>
</tr>
<tr>
<td>Wednesday</td>
<td>6</td>
<td>95.00</td>
<td>129.0</td>
<td>27.811837</td>
<td>15.833333</td>
</tr>
<tr>
<td>Thursday</td>
<td>6</td>
<td>111.00</td>
<td>129.0</td>
<td>27.811837</td>
<td>18.500000</td>
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<tr>
<td>Friday</td>
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<td>129.0</td>
<td>27.811837</td>
<td>28.083333</td>
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<tr>
<td>Saturday</td>
<td>6</td>
<td>179.00</td>
<td>129.0</td>
<td>27.811837</td>
<td>29.833333</td>
</tr>
</tbody>
</table>

Average scores were used for ties.

Kruskal-Wallis Test

<table>
<thead>
<tr>
<th>Chi-Square</th>
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<tbody>
<tr>
<td>7.3941</td>
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<td>0.2859</td>
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</table>
Figure 3.22. Nonparametric One-Way ANOVA results inclusive of all years for day of the week. The X axis is the day of the week and the Y axis is the Wilcoxon rank sum score. The boxes enclose the 25th - 75th percentile. Means are signified by diamonds and the medians by lines. Whiskers represent minimums and maximums.
Figure 3.23. A box plot of all years’ time of data. The time of day is on the X axis and the difference from the mean of monthly fatalities is on the Y axis. The boxes enclose the 25th - 75th percentile. Means are signified by diamonds and the medians by lines. Whiskers represent minimums and maximums.
**Table 3.3.** ANOVA Analysis of Time Range Deviation from Mean. These values correspond to the Figure 3.24.

**Wilcoxon Scores (Rank Sums) for Variable Difference_from_Yearly_Mean Classified by Variable Time_Range**

<table>
<thead>
<tr>
<th>Time_Range</th>
<th>N</th>
<th>Sum of Scores</th>
<th>Expected Under H0</th>
<th>Std Dev Under H0</th>
<th>Mean Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mdnt-4AM</td>
<td>6</td>
<td>44.0</td>
<td>111.0</td>
<td>23.547824</td>
<td>7.333333</td>
</tr>
<tr>
<td>4-8AM</td>
<td>6</td>
<td>44.0</td>
<td>111.0</td>
<td>23.547824</td>
<td>7.333333</td>
</tr>
<tr>
<td>8AM-Noon</td>
<td>6</td>
<td>173.0</td>
<td>111.0</td>
<td>23.547824</td>
<td>28.833333</td>
</tr>
<tr>
<td>Noon-4PM</td>
<td>6</td>
<td>179.0</td>
<td>111.0</td>
<td>23.547824</td>
<td>29.833333</td>
</tr>
<tr>
<td>4-8PM</td>
<td>6</td>
<td>136.0</td>
<td>111.0</td>
<td>23.547824</td>
<td>22.666667</td>
</tr>
<tr>
<td>8PM-Mdnt</td>
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<td>90.0</td>
<td>111.0</td>
<td>23.547824</td>
<td>15.000000</td>
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</table>

Average scores were used for ties.

**Kruskal-Wallis Test**

<table>
<thead>
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<th>Pr &gt; ChiSq</th>
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</thead>
<tbody>
<tr>
<td>27.8209</td>
<td>5</td>
<td>&lt;.0001</td>
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</table>
Figure 3.24. Nonparametric One-Way ANOVA results inclusive of all years for time of day. The X axis represents the time range of death and the Y axis is the Wilcoxon rank sum score. The boxes enclose the 25th - 75th percentile. Means are signified by diamonds and the medians by lines. Whiskers represent minimums and maximums. Medians are not statistically equal based on Kruskal-Wallis test.
Figure 3.25. Pinellas and Pasco County frequency of drug related deaths by year. The X axis is the year analyzed and the Y axis is the mortality rate for all drug related deaths included in the database. Data is broken down by county.
Figure 3.26. Pinellas and Pasco County frequency of opioid drug related deaths by year. The X axis is the year analyzed and the Y axis is the mortality rate for opioid related deaths included in the database. Data is broken down by county.
Figure 3.27. Pinellas and Pasco County frequency of fentanyl drug related deaths by year. The X axis is the year analyzed and the Y axis is the mortality rate for fentanyl related deaths included in the database. Data is broken down by county.
Figure 3.28. Box plot demonstrating gender and age of death with pharmaceutical opioids, fentanyl, or heroin present. The year analyzed is on the X axis and age is on the Y axis. Data is grouped by gender. The boxes enclose the 25th - 75th percentile. Means are signified by circles and the medians by lines. Whiskers represent minimums and maximums while dots represent outliers.
Figure 3.29. Box plot demonstrating gender and age of death fentanyl or heroin present. The year analyzed is on the X axis and age is on the Y axis. Data is grouped by gender. The boxes enclose the 25\textsuperscript{th} - 75\textsuperscript{th} percentile. Means are signified by circles and the medians by lines. Whiskers represent minimums and maximums while dots represent outliers.
Figure 3.30. Box plot demonstrating gender and age of death with fentanyl present. The year analyzed is on the X axis and age is on the Y axis. Data is grouped by gender. The boxes enclose the 25th - 75th percentile. Means are signified by circles and the medians by lines. Whiskers represent minimums and maximums while dots represent outliers.
Figure 3.31. Bar chart demonstrating total drug related deaths by race adjusted for percentage of population. The X axis the county with data subdivided by race and the Y axis is the mortality rate per capita. The mortality rate for all drug related deaths was calculated using the individual county demographics.
Figure 3.32. Bar chart demonstrating opioid and fentanyl drug related deaths by race adjusted for percentage of population. The X axis the county with data subdivided by race and the Y axis is the mortality rate for opioid and fentanyl related deaths. The mortality rate was calculated using the individual county demographics.
Model Convergence Status

Table 3.4. Model convergence status for binary logistic regression with fentanyl.

<table>
<thead>
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<th>Model Convergence Status</th>
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<tbody>
<tr>
<td>Convergence criterion (GCONV=1E-8) satisfied.</td>
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</table>

Fit Statistics

Table 3.5. Model fit statistics from binary logistic regression of fentanyl exposure in the total counties’ population from 2011-2016.

<table>
<thead>
<tr>
<th>Model Fit Statistics</th>
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<tbody>
<tr>
<td>Criterion</td>
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<td>AIC</td>
</tr>
<tr>
<td>SC</td>
</tr>
<tr>
<td>-2 Log L</td>
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Odds Ratios

Table 3.6 Odds ratio from binary logistic regression of fentanyl exposure in the total counties’ population from 2011-2016.

<table>
<thead>
<tr>
<th>Odds Ratio Estimates of Co-occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect</td>
</tr>
<tr>
<td>Ethanol &amp; Fentanyl</td>
</tr>
<tr>
<td>Heroin &amp; Fentanyl</td>
</tr>
<tr>
<td>Hydrocodone &amp; Fentanyl</td>
</tr>
<tr>
<td>Methadone &amp; Fentanyl</td>
</tr>
<tr>
<td>Morphine &amp; Fentanyl</td>
</tr>
<tr>
<td>Oxycodone &amp; Fentanyl</td>
</tr>
</tbody>
</table>
CHAPTER FOUR: DISCUSSION

Collectively, 2258 drug related death cases with toxicology data from the years 2011 through 2016 were studied. These drug related deaths occurred in District 6 in Florida. This district includes Pinellas and Pasco county. Pinellas and Pasco county are geographically close but have different demographics. Uncovering predictable patterns in drug mortality rates would allow the region to better allocate its resources in a way to more effectively and efficiently combat drug related deaths. The time range includes portions of the second and third wave of the opioid epidemic inclusive of the years 2011 through 2016. Opioids and the synthetic opioid fentanyl were the focus of this study. It should be noted, that the other major drug classes were considered when the probability of cooccurrence with fentanyl was assessed by binary logistic regression.

While there are differences in the average variance from the yearly mean in both the month and day of the week data, these differences are not statistically significant. It is interesting that the month and day of the week do not substantially change, because Florida is a tourist destination with predictable fluctuations in population demographics. These include tourists on Spring Break or winter season residents. Despite these demographic variations throughout the year, the population of drug related fatalities does not seem to be influenced by them. When looking at all drug related deaths by day of the week there do appear to be more deaths on Friday and Saturday. On average, the total number of drug related
deaths on Friday and Saturday are three and six deaths higher than the yearly average, respectively. However, these increased rates are not statistically significant. Looking at the time range data reveals that certain times of day have significantly different average number of deaths as compared to the yearly mean. This indicates that certain time frames contain higher or lower death rates. The most drug related mortality occurs during the daytime between the hours of 8:00am and 4:00pm. Fewer deaths occurred in the evening between the hours of 4:00pm to 8:00am. My preconceived notion was that overdoses would be highest late at night. These data show drug abusers seem to need their daily dose or “fix” during their normal day and are more prone to daytime drug related fatality. This carries through regardless of day of week or time of year for all the calendar years 2011 through 2016.

Although Pinellas and Pasco county are both serviced by the same Medical Examiner Officer, there was a difference in the impact of the opioid epidemic in each county when considering the drugs involved in multidrug toxicity overdose fatalities. Pasco county is more rural and is approximately half the population size compared to Pinellas County. Total drug related deaths, adjusted for population, demonstrated a similar overall profile for both counties. When the data was broken down by opioids, excluding the synthetic opioid fentanyl, versus fentanyl/fentanyl analog drug related deaths it was clear that there were consistent differences between the counties. The opioids analyzed in this test include codeine, heroin, hydrocodone, hydromorphone, morphine, oxycodone, and oxymorphone. Pasco county had consistently higher opioid related mortality across all years analyzed. Fentanyl was analyzed on its own without other opioids. Pinellas county had
significantly higher levels of fentanyl related deaths, almost double, in 2015 and 2016. Additionally, Pinellas county had a higher rate of fentanyl related fatalities over every year analyzed, 2011 through 2016. There is a surprising difference in specific opioid related death versus the opioid fentanyl related death rates given that the overall drug related death statistics match so well. Furthermore, it is interesting that Pinellas, which has a higher average income than Pasco, has a higher fentanyl related mortality rate. Fentanyl contaminated heroin is often used as a cheaper substitute for expensive prescription opioids. Pinellas and Pasco county had double the amount of fentanyl related overdose deaths from the years 2015 to 2016. These data track national trends (Scholl, Seth, Kariisa, Wilson, & Baldwin, 2018).

It has been reported that the life expectancy in the United States has decreased beginning in the year 2015 (Xu, Murphy, Kochanek, & Arias, 2016). It has also been shown that the number of opioid related deaths increased while concurrently the age of death decreased (Hedegaard, Warner, & Minino, 2017). Furthermore, male drug related overdose deaths per capita were significantly higher as of 2016 compared to female drug related deaths (Hedegaard et al., 2017). When contrasting data in this study to the national data it is shown that Florida District 6 does not totally correspond with national trends. The age of death shifts lower for 2016 but the change is not statistically significant. It is possible that more recent data that included 2017 and 2018 could demonstrate a continued trend toward younger opioid drug related deaths. Additionally, contrary to national statistics there were not significant differences when gender was analyzed in opioid
drug related deaths for any of years analyzed. Both Pinellas and Pasco county had comparable opioid gender mortality rates over all years.

The data sets originally obtained in the public records request contained broad race categories; White, Black, and Asian. The data from each county was adjusted for population and racial diversity. Mortality rates for different populations were then determined. It was found that White people were disproportionately affected by drug related deaths and opioid, including fentanyl, related deaths in Pinellas and Pasco county compared to other racial categories. The mortality rate for opioid related drug deaths is ten times higher for the White population than for the Black or Asian population in Pasco county. The mortality rate for opioid related drug deaths is almost five times higher for the White population than for the Black or Asian population in Pinellas county. These data are supported by published data which characterize the opioid epidemic as impacting lower income white communities (Friedman et al., 2019; Johnson, 2016). The cause of these racial disparities are not known, but may be attributed to limited access to healthcare by minorities, or doctor’s prescribing fewer opioid medications to minorities groups (Johnson, 2016; Pletcher, Kertesz, Kohn, & Gonzales, 2008).

Binary logistic regression was used to determine which drugs are most or least likely to be present in drug related deaths at the same time as fentanyl. Convergence and model fit analysis indicated that the model was an adequate fit. Of the drugs that were calculated to have statistically significant explanatory factors, only heroin had a positive odds ratio point estimate. The heroin odds ratio of 3.650 indicates that the probability of co-occurrence is much higher than exclusivity. This means that heroin is about three times as likely to occur when
fentanyl or a fentanyl analog is present in an overdose fatality in this region during the years studied compared to drug related fatality cases that do not contain fentanyl or fentanyl analogs. This result could be explained by drug users consuming fentanyl contaminated heroin, or drug users specifically seeking out illicit fentanyl. Additionally, heroin is often cut or adulterated with fentanyl which would result in cooccurrence.

Binary logistic regression also elucidated five drugs with odds ratios less than one. This indicates these drugs are used exclusive from fentanyl or fentanyl analogs in fatal overdose cases in Pinellas and Pasco county for the years 2011 through 2016. The drugs that do not appear to co-occur with fatal fentanyl overdoses include morphine, ethanol, hydrocodone, oxycodone, and methadone in order of diminishing odds ratios. Finding that some opioids negatively correlate with fatal fentanyl overdose was not expected. Given that these drugs can be used in lieu of fentanyl by opioid addicted individuals, it was thought that they would co-occur in drug overdose related fatalities. The explanatory variable with lowest significant odds ratio was methadone, with the odds ratio of 0.195. Interestingly, this suggests that methadone, a common treatment for opioid addiction, is not present in fatal fentanyl overdoses. This conclusion is drawn because fentanyl and methadone occur together less than expected based on probability.

These data demonstrate that in Pinellas and Pasco county, the populations that have overdose related fatalities on illicit preparations are different than the populations that overdose on licit preparations. This suggests that people on methadone may be a reachable population from a public health perspective that is not probable to be predisposed to fentanyl overdose related mortality.
REFERENCES


Dowling, G., & Regan, L. (2011). A new mixed mode solid phase extraction strategy for opioids, cocaines, amphetamines and adulterants in human blood with hybrid liquid chromatography tandem mass


Dependence and Risk of Neonatal Abstinence Syndrome. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Epidemiology, 29*(2), 261-268. doi: 10.1097/EDE.0000000000000780


Monwell, B., Bulow, P., & Gerdner, A. (2016). Type of opioid dependence among patients seeking opioid substitution treatment: are there


## APPENDIX A: EXCERPT FROM DATABASE

<table>
<thead>
<tr>
<th>Case #</th>
<th>Date</th>
<th>Year</th>
<th>Month</th>
<th>Day</th>
<th>Time</th>
<th>Time Range</th>
<th>Age</th>
<th>Cause</th>
<th>Manner</th>
</tr>
</thead>
<tbody>
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<td>Ethanol Toxicity</td>
<td>Accident</td>
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<td>January</td>
<td>Saturday</td>
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<td>Oxydodone Toxicity</td>
<td>Accident</td>
</tr>
<tr>
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<td>January</td>
<td>Saturday</td>
<td>18:20:00</td>
<td>4-8PM</td>
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<td>Multidrug Toxicity</td>
<td>Accident</td>
</tr>
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<td>January</td>
<td>Wednesday</td>
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<td>Wednesday</td>
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<td>January</td>
<td>Wednesday</td>
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<td>January</td>
<td>Saturday</td>
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<td>Drowning</td>
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<td>January</td>
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<td>January</td>
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<td>Accident</td>
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<td>January</td>
<td>Wednesday</td>
<td>9:00:00</td>
<td>8AM-noon</td>
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<td>Accident</td>
</tr>
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<td>January</td>
<td>Wednesday</td>
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<td>January</td>
<td>Saturday</td>
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<td>Saturday</td>
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<td>Oxydodone Toxicity</td>
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<td>5110101</td>
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<td>January</td>
<td>Monday</td>
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<td>4-8PM</td>
<td>56</td>
<td>Acute and Chronic Ethanolism</td>
<td>Accident</td>
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<td>January</td>
<td>Tuesday</td>
<td>10:18:00</td>
<td>8AM-noon</td>
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<td>Accident</td>
</tr>
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<td>January</td>
<td>Wednesday</td>
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<td>Noon-4PM</td>
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### APPENDIX A: EXCERPT FROM DATABASE

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<td>W</td>
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</table>
APPENDIX B: SAS CODE

Time frequency analysis
proc sgplot data=WORK.'2011'n;
   vbar Time_Range / datalabel categoryorder=respdesc;
   xaxis ;
   yaxis grid;
   refline 73 / axis=y lineattrs=(thickness=2 color=green) label
           labelattrs=(color=green);
run;

Month frequency analysis
proc sgplot data=WORK.'2011'n;
   vbar Month / datalabel;
   xaxis discreteorder=data;
   yaxis grid;
   refline 36.5 / axis=y lineattrs=(thickness=2 color=green) label
           labelattrs=(color=green);
run;

Day frequency analysis
proc sgplot data=WORK.'2011'n;
   vbar Day / datalabel categoryorder=respdesc;
   xaxis ;
   yaxis grid;
   refline 62.6 / axis=y lineattrs=(thickness=2 color=green) label


APPENDIX B: SAS CODE

labelattrs=(color=green);
run;

Example nonparametric one-way ANOVA

proc npar1way data=WORK.IMPORT wilcoxon plots(only)=(wilcoxonboxplot);
   class Day;
   var Difference_from_Yearly_Mean;
run;

Population corrected analysis

proc sgplot data=WORK.POPCOMPRACEOP;
   vbar County / response=Opiate___Fentanyl_Related_Deaths group=Race
groupdisplay=cluster datalabel;
   xaxis discreteorder=data;
   yaxis grid;
run;

Binary logistic regression

proc logistic data=WORK.IMPORT;
   class Ethanol Heroin Hydrocodone Methadone Morphine Oxycodone /
param=ref ref=first ;
   model Fentanyl(event='Y')=Ethanol Heroin Hydrocodone Methadone
Morphine Oxycodone / link=logit lackfit technique=fisher;
run;
APPENDIX C: IRB EXEMPTION LETTER & PERMISSIONS

10/25/2017

Anne Powell
Environmental and Occupational Health
11733 Lipsey Rd
Tampa, FL 33618

RE: Not Human Subjects Research Determination
IRB#: Pro00032603
Title: Characterization of persons at high risk of fentanyl overdose death in fentanyl related overdoses a Medical Examiner district in Florida.

Dear Mrs. Powell:

The Institutional Review Board (IRB) has reviewed your application. The activities presented in the application involve methods of program evaluation, quality improvement, and/or needs analysis. While potentially informative to others outside of the university community, study results would not appear to contribute to generalizable knowledge. As such, the activities do not meet the definition of human subject research under USF IRB policy, and USF IRB approval and oversight are therefore not required.

While not requiring USF IRB approval and oversight, your study activities should be conducted in a manner that is consistent with the ethical principles of your profession. If the scope of your project changes in the future, please contact the IRB for further guidance.

If you will be obtaining consent to conduct your study activities, please remove any references to "research" and do not include the assigned Protocol Number or USF IRB contact information.

If your study activities involve collection or use of health information, please note that there may be requirements under the HIPAA Privacy Rule that apply. For further information, please contact a HIPAA Program administrator at (813) 974-5638.

Sincerely,

V. Jorgensen, MD

E. Verena Jorgensen, M.D., Chairperson
USF Institutional Review Board
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