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Describing at risk populations and emerging trends in opioid and stimulant co-occurrence in drug use, nonfatal overdoses, and fatal overdoses in the United States

PhD Dissertation Proposal

Herschel Smith IV, MPH
PhD Candidate, School of Public Health, Georgia State University, Atlanta, Georgia

Committee Members

Dr. Ruiyan Luo, PhD, MS, School of Public Health, Georgia State University, Committee Chair
Dr. Katherine Masyn, PhD, MA, School of Public Health, Georgia State University
Dr. Alana Vivolo-Kantor, PhD, MPH, National Center for Injury Prevention and Control, U.S. Centers for Disease Control and Prevention

Abstract (542 words)

Background

Drug overdose is one of the leading causes of injury death in the United States. Polysubstance use is the ingestion/injection of more than one substance at the same time, either intentionally or unknowingly, by the person using drugs. Studies indicate that polysubstance use and prescription drug misuse can enhance the potential for negative effects of each drug, leading to unpredictable consequences including nonfatal and fatal overdose. To examine polysubstance use and prescription drug misuse, the following studies will analyze urine drug test results, nonfatal overdoses and fatal overdoses involving multiple substances for trends and characteristics associated with increased risk of polysubstance use.

Methods

Chapter 1 describes background on drug use and overdose along with prevention strategies and data sources for drug use/overdose surveillance. Chapter 1 also discusses limitations to available research, statement of purpose, and implications of research findings.

Chapter 2 analyzes results from Millennium Health Urine Drug Test samples submitted between January 2022-June 2023 to assess positivity rates for combinations of fentanyl, methamphetamine and/or cocaine utilizing multinomial logistic regression.

Chapter 3 uses National Syndromic Surveillance Program (NSSP) data to analyze trends of nonfatal overdose emergency department (ED) visits involving opioids, stimulants, and both opioids and stimulants. Rates during January 2017-December 2022 were assessed using negative binomial regression. Differences in rates were assessed by calculating relative rates with confidence intervals, stratified by demographic characteristics. Overall trends were analyzed by assessing counts and rates over time.

Chapter 4 explores data from the State Unintentional Drug Overdose Reporting System (SUDORS) to analyze trends in fatal overdoses involving combinations of fentanyl and stimulants (i.e., methamphetamine and/or cocaine). Counts during January 2019-June 2022 were assessed using negative binomial regression. Differences in counts across covariates were assessed by calculating log of mean counts with confidence intervals, stratified by demographic characteristics. Overall trends were analyzed by assessing counts and rates over time.

Chapter 5 summarizes findings and discusses policy implications and future directions of research.

Results

Chapter 2 findings: Of specimens analyzed, urine drug tests from patients receiving substance use disorder treatment had greater odds of fentanyl-only, stimulant-only and co-positivity compared to patients receiving primary care.

Chapter 3 findings: Approximately 0.9% of all ED visits analyzed involved both opioids and stimulants. Nonfatal overdose rates varied by demographic characteristics and US Census region. Trend analyses showed increases in overall rates and counts for ED visits involving opioids, stimulants, and both opioids and stimulants during the study period with the 2020 COVID-19 pandemic and seasonality playing key factors.

Chapter 4 findings: Approximately 39% of all overdose deaths analyzed involved both fentanyl and a stimulant. Mean counts of fatal overdose varied by demographic characteristics and US Census region. Counts and percentages of overdose deaths involving both fentanyl and stimulants among all overdose deaths have increased over time.

Conclusion

Each of the three analyses investigated different aspects of the opioid overdose epidemic relating to polysubstance use. The findings from these studies expand upon present research by assessing associations and trends in opioid use, stimulant use and combined opioid and stimulant use. Healthcare providers, policy makers, and others can use the findings from these studies to develop programs, prevention strategies, and policies to reduce prescription drug misuse and overdose in communities. By understanding populations at greatest risk, available resources can be directed to improve health outcomes.

Describing at risk populations and emerging trends in opioid and stimulant co-occurrence in drug use, nonfatal overdoses, and fatal overdoses in the U.S.

by

Herschel Wellington Smith IV

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M.P.H., Georgia State University

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30303

APPROVAL PAGE

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by

Herschel Wellington Smith IV

Approved:

___Dr. Ruiyan Luo______
Committee Chair

__Dr. Katherine Masyn_____
Committee Member

__Dr. Alana Vivolo-Kantor_____
Committee Member

__07/22/2024_____________
Date

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Dr. Stephen Liu, PhD
Dr. Julie O’Donnell, PhD
B. Casey Lyons, MPH
Michael Sheppard, MS
Centers for Disease Control and Prevention, Division of Overdose Prevention
Millennium Health

Author's Statement Page

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Chapter 1: Literature Review and Statement of Purpose

Introduction

Drug overdose is one of the leading causes of injury death in the United States (Case, 2017). The opioid overdose epidemic has affected communities across the globe for several decades, commonly characterized by researchers in the U.S. in three waves: 1. Rise in prescription opioid overdose deaths in the late 1990s, 2. Rise in heroin overdose deaths in 2010, and 3. Rise in synthetic opioid (e.g., fentanyl) overdose deaths in 2013 (CDC, 2011; Rudd, 2014; Gladden, 2016; O'Donnell, 2017). Researchers in recent years have characterized a fourth wave of the overdose epidemic as characteristics of the health crisis continue to shift (Jenkins, 2021; Gray, 2022, Ciccarone, 2021). Recent data has identified increases in stimulant use, driven by methamphetamine and cocaine, and the combining of stimulants and opioids (Al-Tayyib, 2017; Ciccarone, 2021; Gray, 2022). Additionally, researchers have identified national increases in stimulant-involved overdose mortality between 2015 and 2018 (Cano, 2021). Moreover, researchers suggest that increases in stimulant use have introduced new complexities in terms of behavioral consequences (e.g., neurological deficits, suicidal ideation, psychosis, hostility, violence), available treatments, and engagement into drug use assistance services (Jenkins, 2021).

Alongside these findings, researchers investigating emerging trends in internet forums related to drug use and overdose have identified dramatic increases in internet forum mentions of both opioid and stimulant use between 2011 and 2020 (Sarker, 2022), with findings that suggest the total number of people who co-use[1] opioids and stimulants (PWCU), i.e., "who posted about opioids and/or opioid related medications and stimulants" (Sarker, 2022) has increased over time. Sarker et al. acknowledged some assumptions, for example,

[1] Co-use in biosurveillance and fatal overdoses can be defined as "instances where more than one illicit and/or licit substances have been identified by toxicology testing in a patient or decedent, either knowingly or unknowingly ingested". In other words, the confirmed presence of multiple substances used at the same time or in close enough proximity to be identified via toxicology report.

assuming current use may have resulted in overestimation, yet mentions of a substance reflect some degree of interest or consideration of a particular substance. Supportively, similar research aimed at detecting emerging drugs involved in overdose analyzing discussions on drug-related social media forums between 2011 and 2018 identified an increase in fentanyl-related internet chatter greater than 1 year earlier than other public health data systems started observing nonfatal, and subsequently fatal, overdoses (Wright, 2021), setting precedent for Sarker et al.'s findings. To continue to effectively combat this dynamic health crisis, we must further investigate changing drug use patterns and emerging trends in nonfatal and fatal overdoses involving both opioids and stimulants, particularly as the crisis compounds with other societal events/changes.

In 2020, another global health crisis - the COVID-19 pandemic - may have further inflamed the overdose epidemic. A study of US emergency department (ED) visits in mid-March through October 2020, during the COVID-19 pandemic, identified increases in visit rates for all drug and opioid overdoses compared to the same period in 2019, while overall ED visits decreased (Holland, 2021). Additionally, a Centers for Disease Control and Prevention (CDC) Health Alert Network Advisory in December 2020 described an acceleration in drug overdose deaths during the start of the pandemic (CDC HAN, 2020). In a 2021 National Centers for Health Statistics (NCHS) Data Brief, researchers detailed a 31% increase in age-adjusted drug overdose deaths from 2019 to 2020 (Hedegaard, 2021). In August 2022, researchers published a qualitative assessment on COVID-19-related themes identified among drug overdose deaths during the first half of 2020 (Tanz, 2022). They found several common themes that may have contributed to increases in overdose deaths including depression, stress, anxiety, job loss, financial strain, and altered living arrangements. Additionally, missed intervention opportunities included changes in treatment for substance use disorders and cancellation or postponement of other medical appointments. These factors, coupled with trends in drug-related internet chatter, increases in stimulant use and mortality, and behavioral consequences present numerous reasons to investigate emerging trends in co-use to inform preventive efforts.

Overdose Prevention and Intervention Strategies

CDC has presented evidence-based overdose prevention and intervention strategies to prevent drug use, morbidity and mortality to combat the opioid overdose epidemic (CDC Evidence-Based Strategies for Preventing Opioid Overdose: What's Working in the United States, 2018). Overdose prevention and intervention efforts have traditionally existed at several socio-ecological levels: individual-level (e.g., medications for opioid use disorder (MOUD)), community-level (e.g., distribution of naloxone and fentanyl test strips, prescription drug monitoring programs (PDMPs), behavioral health programs), and societal-level (e.g., Good Samaritan laws, eliminating prior-authorization requirements for medication for OUD, other drug overdose prevention policies) (CDC Evidence-Based Strategies for Preventing Opioid Overdose: What's Working in the United States, 2018).

Medication for opioid use disorder (MOUD) is an individual-level prevention strategy used to treat opioid use disorder through Food and Drug Administration (FDA) approved medications (NCIPC, 2018). The World Health Organization (WHO) has described MOUD as "one of the most effective types of pharmacological therapy for opioid dependence" (WHO, 2004). Opioid related programs have been effectively employed, providing methadone, buprenorphine, and naltrexone to combat opioid use disorder (OUD) (CDC NCIPC, 2018). Regarding stimulants, however, there are fewer available options for PWUD. Researchers address the current limitations of stimulant-focused interventions, as "no 'gold-standard' treatments exist for cocaine or methamphetamine use disorders" (Fischer, 2021). Current treatments for stimulant use disorders involve psychosocial interventions like twelve-step facilitation (TSF), cognitive behavioral therapy (CBT), and contingency management (CM) (Fleming, 2020). The long-term sustainability and efficacy of these programs have come into question, as effects diminish after the intervention is stopped (United Nations Office on Drugs and Crime [UNODC], 2019; Benishek, 2014). This highlights that there are remaining gaps in substance use disorder treatment programs, further emphasizing the need for effective surveillance strategies to inform prevention and intervention efforts.

Naloxone is an opioid antagonist that can immediately reverse the effects of an opioid overdose. CDC has emphasized targeted distribution programs to train and equip those who are most likely to witness an overdose with naloxone kits, particularly people who use drugs, first responders and harm reduction workers (CDC NCIPC, 2018). Naloxone presents no risk of addiction and does not generate a physical dependency. It also has no effect on persons who do not already have opioids in their system. Multiple systematic reviews have concluded that naloxone distribution programs are effective in reducing opioid-related mortality (Clark, 2014; Razaghizad, 2021; Cataife, 2021).

Fentanyl test strip (FTS) technology is a drug checking strategy to address the fentanyl crisis. Initially developed to screen urine samples for the presence of fentanyl, they have been effectively deployed by harm reduction organizations to help drug users detect fentanyl in other illicit drug solutions (Peiper, 2019). As a community-level prevention effort, distribution of FTS can be a powerful tool in changing drug use behavior and perceptions of overdose safety in persons who use drugs (PWUD) (Peiper, 2019). This could, in turn, help prevent overdoses and related harm.

State and local government policies such as 911 Good Samaritan Laws are societal-level prevention strategies that provide overdose victims and/or bystanders with limited immunity from drug-related criminal charges that may otherwise result from calling first responders to the scene (CDC NCIPC, 2018). The main aim of these laws is to defuse the potential conflict individuals might face, allowing overdose victims or bystanders to seek emergency care without putting themselves at risk of arrest (CDC NCIPC, 2018). Good Samaritan Laws, combined with naloxone access, have been associated with lower rates of overdose deaths in the United States (Hamilton, 2022).

Information gained from improved and continuous drug use and overdose surveillance can aid these and other prevention and intervention strategies. The importance of analyzing various data sources to direct drug use data and overdose data to action is clear.

Overdose Data to Action (OD2A)

CDC's Overdose Data to Action (OD2A) cooperative agreement supports jurisdictions across the U.S. in collecting high quality, timely, comprehensive nonfatal and fatal overdose data. This information is used to understand and track changes in the nature of the drug overdose epidemic and inform prevention and response efforts (CDC OD2A, 2021). Since its inception in 2019, OD2A has helped develop and implement innovative surveillance and prevention strategies at national, state, and local levels (CDC OD2A, 2021). Some of the data sources that inform OD2A are discussed further below.

Drug Use and Drug Overdose Surveillance: Data Sources

There are numerous data sources used to understand the shifting drug use patterns and trends in the U.S. overdose epidemic to inform prevention, intervention, and response efforts. For example, laboratory surveillance is a newer approach to public health surveillance of nonfatal overdoses relying on laboratory analysis of biospecimens, most often urine drug testing (UDT), from health care facilities. Lab surveillance data can be used to describe drug use patterns among PWUD to inform preventive strategies before adverse events related to drug use (i.e., overdose) occur. ED syndromic surveillance data are available in near real-time and can be used to rapidly detect nonfatal overdose spikes in communities by capturing experiences where PWUD had to seek immediate care after drug use. Mortality data includes informative coroner/medical examiner reports and toxicology results that can provide a more complete picture of drugs involved in a fatal overdose. However, mortality data are susceptible to substantially longer delays (e.g., 6-12 months) than lab surveillance or syndromic surveillance data. The following briefly describes these and other common drug use and drug overdose surveillance data sources employed in public health.

Laboratory Surveillance

Laboratory surveillance, sometimes characterized as biosurveillance, data is a relatively new tool for conducting drug overdose and drug use surveillance using specimens collected from public health, hospital, commercial, and forensic laboratories. Data that focuses solely on ED visits or fatalities can miss valuable details that could inform immediate and on-going public health crises or can arrive too late for preventive action. Studying drug use in laboratory surveillance data can fill in those gaps by providing details on drugs used in a specific region, common combinations of drugs, and drugs used commonly by persons seeking different types of health care, like substance use disorder treatment, behavioral health, or pain management. In 2019, the American Public Health League (APHL) convened the Opioids Biosurveillance Task Force to develop the role of public health laboratories in contributing analytical capabilities to public health surveillance systems (APHL, 2020).

The objectives of laboratory surveillance include rapidly identifying causes of overdoses, estimating the magnitude of the problem by tracking longitudinal trends between and within states, identifying high-risk areas and sub-groups, providing context to further evaluate intervention strategies, providing enhanced information for allocation prevention or treatment resources, and investigating novel exposure pathways (APHL, 2020). These objectives combine to enhance efforts to prevent future opioid overdoses.

There are limitations to laboratory surveillance data. Specimens are de-identified to protect patient privacy and confidentiality, however, knowledge and context of other drug exposures such as pharmaceuticals used for routine therapeutic or medical purposes is lost. Researchers should not assume that all detected drugs and metabolites are associated with illicit use or contributors to overdose. Additionally, a 2020 systematic review (Martini, 2020) of drug detection in urine and oral fluid observed that detection windows vary across different drugs and specimen types, suggesting that recurrent testing of at-risk populations could be most useful in capturing trends.

Laboratory surveillance data related to drug use has been used in numerous recent publications including: Twillman et al.'s evaluation of trends of methamphetamine, cocaine, heroin and fentanyl positivity (Twillman, 2020); LaRue et al.'s analysis of fentanyl positivity rates among UDT result positive for cocaine or methamphetamine (LaRue, 2019); and Whitley et al.'s analysis of substance use disorder treatment practices and overdose mortality rates (Whitley, 2022).

Syndromic Surveillance Data (Morbidity data)

Syndromic surveillance data is a critical system for monitoring and analyzing a variety of public health threats in near real time. It uses timely data to track symptoms of patients in EDs before diagnoses are confirmed to detect unusual levels of illness providing an early warning system for public health officials. The two main systems using syndromic surveillance data to monitor nonfatal overdoses presenting in EDs are CDC's National Syndromic Surveillance Program (NSSP) and Drug Overdose Surveillance and Epidemiology (DOSE) systems.

NSSP is a collaboration of a Community of Practice including CDC, federal partners, state and local health departments, and academic and private sector partners. They collect, analyze and share patient encounter data received from health care facilities including EDs, urgent and ambulatory care centers, inpatient healthcare facilities, and laboratories (CDC NSSP, 2023). Data is available to NSSP for analysis within 24 hours of a patient's visit, and currently 78% of EDs in the U.S. contribute data (CDC NSSP, 2023).

Like NSSP, CDC's DOSE system was developed to analyze data from syndromic surveillance systems to rapidly identify public health outbreaks, specifically drug overdose-related ED visits at the local, state, and regional level. Supported by OD2A, DOSE uses ED syndromic data reported by health departments to gather aggregate data on suspected all drug, opioid, heroin, and all stimulant overdoses using standardized syndrome definitions for each. Syndrome definitions use diagnostic codes medical professionals use for clinical diagnosis and insurance billing purposes, specifically, International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes and Systematized Nomenclature of Medicine (SNOMED) codes (CDC DOSE, 2022). Additionally, syndrome definitions rely on "chief complaint" free text fields which medical professionals complete as the reason for a patient's ED visit (CDC DOSE, 2022). Generally, ED visits are classified as suspected overdoses when a chief complaint field includes: [1] both a drug term (e.g., opioid/heroin/fentanyl or common misspellings) and an overdose term (e.g., poisoning) and no terms indicating withdrawal, detoxication, seeking treatment, or other non-acute drug use terms; [2] and/or the discharge diagnosis field includes an ICD-10-CM or SNOMED code that indicates an acute unintentional or undetermined drug poisoning. Current syndrome definitions developed by the DOSE program include all drug, all opioid, heroin, all stimulants, fentanyl, cocaine, benzodiazepine and methamphetamine. There are currently 43 participating jurisdictions (42 states and the District of Columbia (DC)) with an average of over 90% of ED visits captured in syndromic surveillance data (CDC DOSE, 2022). One limitation of DOSE data is that comparisons should not be made between jurisdictions as variations in data quality, completeness and reporting across jurisdictions exist. Another limitation to syndromic data is that though data is very timely, there are normally not definitive toxicology tests available to confirm the presence of specific drugs (CDC DOSE, 2022).

Recent publications using ED syndromic surveillance data related to drug overdoses include: Vivolo-Kantor et al.'s comparison of syndromic surveillance and hospital discharge data for nonfatal drug overdose (Vivolo-Kantor, 2021); Holland et al.'s trends in ED visits for mental health, overdose and violence outcomes before and during the COVID-19 pandemic (Holland, 2021); Roehler et al.'s analysis of nonfatal overdoses among youth in the US (Roehler, 2021).

Mortality Data

There are multiple primary data sources for fatal overdose data. CDC's OD2A currently supports 47 states and Washington, DC to provide comprehensive overdose death data to the State Unintentional Drug Overdose Reporting System (SUDORS) (CDC SUDORS, 2022). SUDORS incorporates multiple data sources including death certificates, coroner/medical examiner (C/ME) reports, and postmortem toxicology reports to combine data elements like date and location of death, demographics information, cause-of-death, history of prior overdoses, all drugs detected and drugs contributing to death (CDC SUDORS, 2022). SUDORS data are much more comprehensive than other data sources, however, there is a significant lag in data availability as delays can be a year or more with complete data only available through 2021 from 32 jurisdictions (CDC SUDORS Dashboard, 2022).

The National Vital Statistics System (NVSS) collects and shares critical information on drug overdose deaths from all 50 states and DC, providing critical information on what substances were used and where deaths occurred (CDC NVSS, 2023). The system receives and analyzes data from death certificates, including cause of death information reported by coroners and medical examiners (CDC NVSS, 2023). These text descriptions are coded into ICD-10 codes for reporting. Reports of drug overdose deaths involving multiple drugs may be included in more than one overdose category. Online databases utilizing this data include CDC WONDER (Wide-ranging Online Data for Epidemiologic Research) and CDC Web-based Injury Statistics Query and Reporting System (WISQARS).

Recent examples of publications using drug overdose mortality data include Spencer et al.'s analysis of differences in urban-rural overdose death rates (Spencer, 2022a); Tanz et al.'s characterization of Buprenorphine-involved overdose deaths prior to and during Covid-19 pandemic (Tanz, 2023); and Spencer et al.'s analysis of drug overdose deaths in the U.S. between 2001 and 2021 (Spencer, 2022b).

Other data sources

There are numerous other data sources public health officials use to track trends related to drug use and overdoses. Some of these sources include drug prescribing and dispensing data, harm reduction data, linkage to care data, behavioral health data, and public safety data (CDC PDMP, 2021; Wallace, 2021; Fuller, 2022; Gummin, 2021; SAMSHA, 2023). Each data source could provide unique information on varying aspects of drug use and overdose. It is critical that strategists and policymakers utilize research from diverse data sources when developing and evaluating prevention and intervention plans.

Limitations of Available Research

As mentioned previously, the nature of the overdose epidemic is constantly changing, as emerging drugs and use patterns dictate prevention and intervention strategies. Currently available research has several limitations. At present, there are no nationally representative studies observing drug use patterns with lab surveillance data from 2021 or 2022. The use of timely lab surveillance and syndromic surveillance data can present early warning signs for changes in the overdose epidemic before those changes are reflected in fatal overdose data. Available laboratory surveillance research is also limited to the coverage of the laboratories testing specimens. New facilities are constantly being on-boarded and added to healthcare provider networks. Additionally, very few current studies assess co-use of opioids and stimulants at the national level. To our knowledge, zero studies have assessed opioid and stimulant co-use particularly stratifying by clinician type, as populations receiving different types of health care likely have very different drug use tendencies. Current syndromic surveillance research on drug overdose have not considered stimulant mentions in chief complaint text and discharge diagnosis codes in opioid-involved overdoses presenting to EDs. Finally, fatal overdose research has not yet explored polysubstance trends in opioids and stimulants in 2019-2021. Thus, we do not know how characteristics of drug use patterns and the overdose epidemic have continued to change.

Statement of purpose

Overall Aim

Analyze laboratory surveillance UDT, overdose morbidity, and overdose mortality data to inform drug use patterns, overdose prevention and intervention strategies in the U.S. Knowledge gained can help understand the shifting nature of the drug overdose epidemic and direct resources to more effective efforts, with the goal of reducing the economic and emotional burden drug overdoses impose on communities.

Study 1

This study seeks to describe current fentanyl and a stimulant co-positivity across populations receiving health care treatment related to substance use disorder compared to other populations receiving care.

Study 2

This study seeks to describe distributions and rates across demographics and identify trends between 2017-2022 in incidence of nonfatal drug overdoses presenting to EDs with chief complaints and discharge diagnosis describing both opioid and stimulant use at the time of overdose.

Study 3

This study seeks to describe distributions and rates across demographics and identify trends between 2019-2022 in fatal overdoses involving both fentanyl and stimulants.

Implications of Research Findings

The findings of this research can be used to inform implementation and evaluation of prevention and intervention strategies as well as drug-related policy. Investigation of UDT results in laboratory surveillance data will provide insights into current drug use patterns, informing how best to educate PWUD, PWCU, healthcare providers and other stakeholders on ways to reduce harm. Current laboratory surveillance data will be compared to co-positivity findings from previous years to assess changes in trends. Investigation of opioid/stimulant co-positivity in syndromic nonfatal overdose ED records will provide context for adverse outcomes related to co-use before incidence is reflected in lagged mortality data. Investigation of currently available mortality data for opioid/stimulant co-positivity will identify the current fatal burden. The combination of these analyses will paint a more complete picture of the current drug use and overdose landscape. Findings can also be used as a framework for future co-use analyses as poly-substance use and overdose continues to increase in prevalence, for example, in xylazine-involved fentanyl overdoses (Ciccarone, 2021; Friedman, 2022).

Chapter 2: Fentanyl and stimulant co-positivity among patients receiving substance use disorder treatment with urine drug testing in United States, January 2022–June 2023

Introduction

Characteristics of the opioid overdose epidemic have shifted over the past three decades, with the first wave of increases in prescription opioid overdose deaths occurring in the late 1990s, increases in heroin overdose deaths in the 2010s, and increases in synthetic opioid (e.g., fentanyl) overdose deaths in 2013 (Centers for Disease Control and Prevention [CDC], 2011; Rudd, 2014; Gladden, 2016; O'Donnell, 2017). Researchers have recently characterized a fourth wave spreading across the U.S. involving increases in overdoses involving opioids and stimulant, driven by co-use of fentanyl and methamphetamine or cocaine, further complicating the overdose crisis (Jenkins, 2021; Ciccarone, 2021; Gray, 2022). Two National Center for Health Statistics Data Briefs (Hedegard, 2021; Spencer 2023) highlighted not only increases in the co-involvement of opioids in drug overdose death rates involving cocaine and stimulants between 2011-2021, but also growing differences in overdose death rates involving opioids and cocaine or other stimulants compared to stimulant overdose death rates without opioids (Spencer, 2023). Identifying innovative ways to assess characteristics of drug use patterns is critical to curbing increasing rates of overdose.

The Substance Abuse and Mental Health Services Administration (SAMHSA) has characterized substance use disorders (SUDs) as impairment caused by the recurrent use of alcohol and/or other drugs and substance use treatment interventions intended to help people address problems associated with their use of alcohol or illicit drugs (SAMHSA, 2020). Studies have identified that individuals with SUD are particularly susceptible to overdoses; a recent meta-analysis reported that individuals with SUD were five times more likely to have a fatal drug overdose than those without SUD (Brady, 2017). Further, researchers have found that having a SUD with one substance increases susceptibility to developing physical dependence on additional substances (Crummy, 2020). Investigating current drug use patterns among individuals in the outpatient population receiving treatment for SUD is vital to informing and evaluating prevention and intervention strategies.

Medications for opioid use disorder (MOUD) programs treat substance use disorders using Food and Drug Administration (FDA) approved medications (CDC National Center for Injury Prevention and Control [NCIPC], 2018). The World Health Organization (WHO) has described MOUD as "one of the most effective types of pharmacological therapy for opioid dependence" (WHO, 2004). Opioid-related programs have been effectively employed, providing methadone, buprenorphine, and naltrexone to combat opioid use disorder (OUD) (CDC NCIPC, 2018). Regarding stimulants, however, there are fewer available treatment options for persons who use stimulants. Researchers address the current limitations of stimulant-focused interventions, as "no 'gold-standard' treatments exist for cocaine or methamphetamine use disorders" (Fischer, 2021). Current treatments for stimulant use disorders involve psychosocial interventions like twelve-step facilitation (TSF), cognitive behavioral therapy (CBT), and contingency management (CM) (Fleming, 2020). The long-term sustainability and efficacy of these programs have come into question, as effects diminish after the intervention is stopped (United Nations Office on Drugs and Crime [UNODC], 2019; Benishek, 2015). This highlights that there are remaining gaps in substance use disorder treatment programs, further emphasizing the need for innovative surveillance strategies to inform prevention and intervention efforts.

Laboratory data from public health, hospital, commercial, and forensic laboratories can fill gaps in surveillance from nonfatal ED data by specifying positivity and co-positivity of tested drugs, alongside demographic characteristics of patients providing samples, including type of health care received (APHL, 2018). Clinical testing data can help to identify problematic drug use patterns in a timely manner, providing opportunities for public health action to prevent overdose. By comparison, overdose mortality data, which includes postmortem toxicology testing, can be delayed by 12 months or more (CDC SUDORS Dashboard, 2022). Studying drug use patterns via drug testing among patients receiving SUD treatment can provide critical insights into how to improve treatment programs.

Millennium Health (MH) is a commercial clinical laboratory that provides drug testing services for patients receiving treatment for varying health care services. These drug test services help clinicians monitor prescription medication use, illicit drug use and effectiveness of treatment plans (Millennium Health, 2023). A recent publication of a cross-sectional study of MH data on one million urine drug test (UDT) results between January 2013 and September 2018 identified a 1955% increase in positivity rate for nonprescribed fentanyl in cocaine-positive specimens (0.9% of specimens in 2013 to 17.6% in 2018) and 877% in methamphetamine-positive specimens (0.9% of specimens to 7.9%) (LaRue, 2019). Additionally, a similar study of MH UDT results between January 2013 and October 2019 identified dramatic increases in co-occurring positivity rates among fentanyl positive results for methamphetamine (1280.45%), and cocaine (530.32%), and heroin (556.86%) (Twillman, 2020).

Polysubstance use is defined as "the ingestion of two or more substances in combination at the same time or in temporal proximity" (Martin, 2008; Hakkarainen, 2019). Researchers investigating patterns and motivations of polysubstance use were most often tied to desire to improve the experience based on expected effects of combinations, though a better understanding of reasons underlying polysubstance use is needed to limit the impact of the current overdose crisis (Boileau-Falardeau, 2022). Millennium Health's rigorous drug testing panel allows us to analyze a multitude of drug types from patients' individual samples. In this analysis, we investigate co-positivity rates in MH data as they relate to healthcare provider specialty. Presently, no studies have assessed fentanyl co-positivity with stimulants among individuals receiving SUD treatment compared to other types of healthcare in 2022-2023 data. Findings from this investigation can help inform current policies, prevention, and intervention strategies, and alert us to potential inequities co-positivity for fentanyl and stimulants.

Methods

Study Design and Variables:

This analysis is a cross-sectional study of Millennium Health UDT specimen data testing for over 100 drugs and metabolites including opioids, synthetic opioids, stimulants, benzodiazepines, synthetic cannabinoids, barbiturates, muscle relaxants, alcohol/alcohol metabolites and other drug categories. These UDT results are a convenience sample of UDT specimens submitted by healthcare facilities partnering with MH in 50 states and the District of Columbia, Puerto Rico, and the U.S. Virgin Islands. Our unit of analysis is individual unique patient UDT specimens with four possible outcomes: 1) only fentanyl positive, 2) only a stimulant (specifically illegal stimulants methamphetamine, cocaine or both) positive, 3) both fentanyl AND any stimulant positive [or co-positive], and 4) no positivity for fentanyl or a stimulant (i.e., methamphetamine or cocaine). Our independent variables include healthcare provider type (e.g., SUD treatment, pain management, or primary care), age group, sex, patient ZIP code matched rural-urban commuting area [RUCA] code, primary payer for the test (e.g., employer-sponsored insurance, private insurance, Medicaid, Medicare, or uninsured[2]), prescription for an opioid (e.g., fentanyl, hydrocodone, hydromorphone, oxycodone, oxymorphone, morphine, codeine or tramadol), and prescription for a medication for opioid use disorder (e.g., buprenorphine or methadone). RUCA codes, described below as rural-urban classification [RUC], are provided by the United States Department of Agriculture (USDA) Economic Research Service and were condensed to metropolitan, micropolitan, small town, and rural area classifications and reordered to improve interpretation (i.e., metro areas representing highest on a continuous scale with rural areas the lowest) (United States Food and Drug Administration [USDA], 2020).

We subset available specimens to an analytic dataset of specimens collected between January 1, 2022–June 30, 2023, from patients 15 years or older. Inclusion criteria included specimens that were tested for both fentanyl (or a metabolite) and a stimulant (cocaine or methamphetamine) and by health care provider types related to SUD treatment (including “addiction medicine”, “treatment center” and “behavioral health”), pain management, and primary care practices. Specimens received from multispecialty facilities, OBGYN, or “Other” were removed prior to analysis. Health care provider type was self-reported by health care practices ordering UDTs from MH. Additionally, specimens with unknown sex, “Other” primary payer type, and unknown patient

[2] Uninsured patients may include patients receiving services through safety net programs or block grant funded slots. A block grant is a noncompetitive, formula grant mandated by the U.S. Congress which grantees use to supplement Medicaid, Medicare, and private insurance services (SAMHSA, 2023).

county of residence or rural-urban identifier information for patients' ZIP code were removed. Finally, the first available specimen for each patient was selected for inclusion. This procedure is consistent with other analyses utilizing commercial laboratory UDT data to remove the need for a repeated measures analysis or another way of accounting for correlations associated with a patient (Saloner, 2023; Whitley, 2022).

Urine Drug Testing:

MH's UDT specimen analytic process employs liquid chromatography-tandem mass spectrometry (LC-MS/MS) to analyze specimens for drug positivity (Junger, 2023; Stanton, 2009). The LC–MS/MS testing method is an analytic chemistry technique that is commonly used in forensic and toxicology labs across the nation (Junger, 2023).

Analysis

We investigated the outcomes of interest by describing distributions across independent variables and building unadjusted and adjusted multinomial logistic regression models to report odds ratios (OR). Rates were calculated by percentage of the analytic dataset noted above. OR were calculated by exponentiating parameter coefficients.

All data analyses were performed with R statistical software (R 4.2.2 Project for Statistical Computing), specifically the 'nnet' package fitting multinomial logit models (Ripley, 2002). Statistical significance was identified with p-values less than 0.05 and Wald 95% confidence intervals (CIs) for OR that did not include 1.00.

Results

Demographic Characteristics & Positivity Rates

Of approximately 2.5 million specimens, the sample included 385,501 unique patient UDT results. The sample was evenly distributed between specimens from male and female patients (49.6% and 50.4%, respectively). The median age of patients in the sample was 46 years old with the middle 50% (interquartile) falling between 34 and 61 years. Most patients were receiving SUD treatment (53.3%), followed by care from pain management (28.3%) and a primary care practice (18.4%). Most patients' primary payer was Medicaid (45.2%), followed by Medicare (24.1%), employer-sponsored insurance (15.1%), and private insurance (9.0%)

with fewest patients being uninsured (6.7%). Most patients resided in a metropolitan area (71.9%), followed by micropolitan (16.9%), small town (7.0%), and rural areas (4.2%). Most patients did not have an opioid prescription (74.7%). Additionally, most patients did not have an MOUD prescription (85.8%). Less than 1% of patients had both an opioid prescription and an MOUD prescription (0.87%). Distributions of demographic characteristics and drug positivity are provided in Table 2.1.

From January 2022 through June 2023, crude positivity rates were 2.9% for fentanyl only, 5.3% for stimulant only, and 5.2% for co-positivity for both fentanyl and a stimulant.

Positivity Rates by Provider Type

Among patients receiving SUD treatment, 3.7% tested positive for fentanyl only, 8.8% for stimulants only, and 9.1% were co-positive. Among patients receiving pain management care, 2.1% tested positive for fentanyl only, 0.9% for stimulants only, and 0.2% were co-positive. Finally, among patients receiving primary care, 1.5% tested positive for fentanyl only, 2.2% for stimulants only, and 1.6% were co-positive.

Positivity Rates by Primary Payer

Among patients with employer-sponsored insurance, 2.1% tested positive for fentanyl only, 2.8% for stimulants only, and 1.6% were co-positive. Among patients with Medicaid, 3.8% tested positive for fentanyl only, 8.6% for stimulant only, and 9.8% were co-positive. Among patients with Medicare, 1.9% tested positive for fentanyl only, 1.6% for stimulants only, and 0.7% were co-positive. Among patients with private insurance, 2.1% tested positive for fentanyl only, 2.9% for stimulants only, and 1.7% were co-positive. Finally, among uninsured patients, 2.8% tested positive for fentanyl only, 5.3% for stimulants only, and 3.5% were co-positive.

Positivity Rates by Rural-Urban Classification

Among patients residing in rural areas, 2.0% tested positive for fentanyl only, 4.4% for stimulants only, and 3.4% were co-positive. Among patients in small towns, 1.8% tested positive for fentanyl only, 5.1% for stimulants only, and 3.0% were co-positive. Among patients in micropolitan areas, 2.2% tested positive for fentanyl only, 5.1 for stimulants only, and 4.4% were co-positive. Finally, among patients in metropolitan areas, 3.2% tested positive for fentanyl only, 5.4% for stimulant only, and 5.8% were co-positive.

Pearson Chi-square and Likelihood Ratio Tests:

Pearson Chi-square tests of marginal association between each independent variable and positivity outcome were statistically significant (p-values <0.001). Likewise, individual likelihood ratio tests of each covariate in the adjusted model containing all other covariates resulted in statistically significant associations (p-values <0.001) indicating a significantly better fit when including each variable. Based on these results, all proposed covariates were included in the final model. Pearson Chi-square and Likelihood Ratio test statistics and p-values were reported in Table 2.2.

Multinomial Logistic Regression Results:

Table 2.2 presents unadjusted and adjusted odds ratios and confidence intervals for fentanyl-only, stimulant-only, and co-positivity compared to no positivity. There was little difference between unadjusted and adjusted odds ratios by several of the independent variables discussed below. Table 2.3 presents conditional adjusted odds ratios and confidence intervals for fentanyl-only versus stimulant-only, fentanyl-only versus co-positivity and stimulant-only versus co-positivity.

Odds Ratios by Sex

Among males, adjusted odds of fentanyl-only positivity (aOR=1.17; CI: 1.13,1.22), stimulant-only positivity (aOR=1.09; CI: 1.06,1.12) and co-positivity (aOR=1.09; CI: 1.05,1.12) were higher compared to females for each positivity outcome versus no positivity. Adjusted odds of fentanyl-only positivity compared to stimulant-only positivity were higher among males compared to females (aOR=1.08; CI: 1.03,1.13) while adjusted odds of fentanyl-only positivity compared to co-positivity were lower (aOR=0.92; CI: 0.88,0.97). No statistically significant difference in adjusted odds by sex was observed between stimulant-only and co-positivity.

Odds Ratios by Age group

Within age group, 25-34 years old were treated as reference. Considering fentanyl-only positivity, 15-24 years old had approximately 22% greater adjusted odds of fentanyl-only positivity versus no positivity (aOR=1.22; CI: 1.14,1.31), while all other age-groups had significantly lower adjusted odds (aOR range: 0.39-0.60). Considering stimulant-only positivity versus no positivity, both 15-24 and 65+ age groups had approximately 50% lower adjusted odds (aOR range: 0.49-0.51) while 35-64 years old had significantly greater adjusted odds (aOR range: 1.06-1.29) of stimulant-only positivity than referenced 25-34 year-olds. Considering co-positivity versus no positivity, patients 25-34 years old had significantly greater adjusted odds than all other age-groups (aOR range: 0.21-0.83).

Meanwhile, 15-24 year olds had 2.5 times the adjusted odds of fentanyl-only positivity versus stimulant-only positivity compared to 25-34 year olds (aOR=2.50; CI: 2.28,2.74), while all other age groups had lower adjusted odds (aOR range: 0.37-0.78). Similarly, 15-24 year olds had 1.28 times the adjusted odds of co-positivity versus stimulant-only positivity compared to 25-34 year olds (aOR=1.28; CI: 1.18,1.40), while all other age groups had lower adjusted odds (aOR range: 0.37-0.67). Additionally, 15-24, 55-64 and 65+ year olds had lower adjusted odds of co-positivity versus fentanyl-only positivity compared to 25-34 year olds (aOR range: 0.51-0.89). The 35-44 and 45-54 year old age groups had higher adjusted odds of co-positivity versus fentanyl-only positivity compared to 25-34 year olds (aOR range: 1.24-1.38).

Odds Ratios by Provider Type

Across healthcare provider types with Primary Care Practice (PCP) as referent group, adjusted odds of fentanyl-only positivity were statistically significantly greater in patients receiving SUD treatment (aOR=2.57; CI: 2.39,2.78) and Pain Management (aOR=1.45; CI: 1.35,1.56). Odds of stimulant-only positivity were statistically significantly greater among patients receiving SUD treatment (aOR=2.77; CI: 2.62,2.94), and were lower among those in Pain Management (aOR=0.0.52; CI: 0.47,0.56). Similarly, adjusted odds of positivity for both fentanyl and stimulants were greater among SUD treatment (aOR=2.88; CI: 2.70,3.07), and lower among Pain Management (aOR=0.31; CI: 0.27,0.35).

Patients in Pain Management had higher adjusted odds of fentanyl-only versus stimulant only compared to PCP (aOR: 2.67; CI: 2.38,3.00) while no difference in odds was observed between SUD treatment and PCP. Regarding co-positivity versus fentanyl-only positivity, patients in SUD treatment had higher adjusted odds of co-positivity (aOR: 1.14; CI: 1.03,1.25) while Pain Management patients had lower odds of co-positivity (aOR: 0.23; CI: 0.19,0.27) compared to PCP. Similarly, regarding co-positivity versus stimulant-only positivity, patients in Pain Management patients had lower odds of co-positivity (aOR: 0.61; CI: 0.52,0.72) compared to PCP, while no significant difference in odds of patients in SUD treatment was observed.

Odds Ratios by Primary Payer

Unadjusted odds of positivity for patients with Medicare were approximately 0.9 (CI: 0.85,0.98) for fentanyl only, 0.6 (CI: 0.53,0.61) for stimulants only, and 0.4 (CI: 0.39,0.48) for co-positivity versus no positivity compared to patients with employer-sponsored insurance. In the adjusted model, fentanyl-only positivity was greater among patients receiving Medicaid and Medicare (aOR range: 1.33-1.64) compared to patients with employer-sponsored insurance. Adjusted odds of stimulant-only positivity were also greater among Medicaid, Medicare, and uninsured patients (aOR range: 1.31-2.30) than employer-sponsored insurance. Again, adjusted odds of positivity for both fentanyl and a stimulant were greater among patients receiving Medicaid, Medicare, and uninsured patients (aOR range: 1.33-3.75). Respective positivity odds among patients with private insurance were not statistically significant different from patients with employer-sponsored insurance.

Patients on Medicaid and those uninsured had lower adjusted odds of fentanyl-only positivity versus stimulant-only positivity compared to patients with employer-sponsored insurance (aOR range: 0.72-0.78). Meanwhile, patients on Medicaid and those uninsured had higher adjusted odds of co-positivity versus fentanyl-only positivity compared to patients with employer-sponsored insurance (aOR range: 1.20-2.28). Additionally, patients on Medicaid and Medicare had higher adjusted odds of co-positivity versus stimulant-only positivity compared to those with employer-sponsored insurance (aOR range: 1.16-1.63).

Odds Ratios by Rural Urban Classification

Adjusted odds of fentanyl-only positivity versus no positivity increased by approximately 30% with a one unit increase in RUC (aOR=1.30; CI: 1.26,1.34). Additionally, adjusted odds of stimulant-only positivity versus no positivity increased 4% (aOR=1.04; CI: 1.02,1.06). Odds of co-positivity versus no positivity increased 34% (aOR=1.34; CI: 1.31,1.37) with a one unit increase in RUC.

Regarding fentanyl-only versus stimulant-only positivity and co-positivity versus stimulant-only positivity, adjusted odds increased with a one unit increase in RUC (aOR range: 1.24-1.28). No difference in odds of positivity by RUC was observed in co-positivity versus fentanyl-only positivity.

Odds Ratios by Opioid Prescription Status

Unadjusted odds of fentanyl-only positivity were statistically significantly lower for patients with an opioid prescription (OR=0.63; CI: 0.60,0.66), however, adjusted odds of fentanyl-only positivity versus no positivity for patients with an opioid prescription were 2.13 times the corresponding odds for patients without opioid prescriptions (aOR=2.13; CI: 1.98,2.29). Adjusted odds of stimulant-only positivity among those prescribed opioids were 0.4 times the odds of those not prescribed opioids (aOR=0.37; CI: 0.34,0.40). Adjusted odds of co-positivity versus no positivity among patients with an opioid prescription were 0.3 times the odds of those without (aOR=0.28; CI: 0.24,0.32).

Adjusted odds of fentanyl-only versus stimulant-only positivity were 5.83 times higher among patients with opioid prescriptions compared to those without (aOR: 5.83; CI: 5.24,6.50). Meanwhile, adjusted odds were lower for patients with opioid prescriptions for fentanyl-only versus stimulant-only positivity (aOR: 0.13; CI: 0.11,0.15) and co-positivity versus stimulant-only positivity (aOR: 0.76; CI: 0.65,0.90). No difference in odds of positivity by opioid prescription status was observed in co-positivity versus fentanyl-only positivity.

Odds Ratios by MOUD Prescription Status

Among patients with MOUD prescriptions, adjusted odds of fentanyl-only positivity vs no positivity for patients with MOUD prescriptions were 3.1 times the odds for patients without an MOUD prescription (aOR=3.09; CI: 2.95,3.22). Adjusted odds of stimulant-only positivity were 0.6 times the odds of no positivity among those prescribed an MOUD compared to those without (aOR=0.57; CI: 0.55,0.60). Finally, adjusted odds of co-positivity among those prescribed an MOUD were 3.0 times those without (aOR=2.94; CI: 2.85,3.04).

Adjusted odds were higher for patients with opioid prescriptions for fentanyl-only versus stimulant-only positivity (aOR: 5.38; CI: 5.07,5.72) and co-positivity versus stimulant-only positivity (aOR: 5.13; CI: 4.87,5.41). No difference in odds of positivity by MOUD prescription status was observed in co-positivity versus fentanyl-only positivity.

Discussion

Summary of findings

This study aimed to describe fentanyl and stimulant co-positivity across populations receiving substance use disorder treatment compared to other types of care. Of specimens provided to Millennium Health between January 2022 and June 2023, this analysis found that patients receiving SUD treatment had more than twice the adjusted odds of fentanyl-only, stimulant-only and co-positivity versus no positivity compared to patients receiving primary care. Additionally, adjusted odds of co-positivity versus fentanyl-only positivity were 14% higher among patients receiving SUD treatment compared to those primary care. This aligns with a priori expectations as these patients are participating in SUD treatment programs, likely for illicit substance use or prescription drug misuse. Additionally, this study observed increased odds for fentanyl-only and co-positivity versus no positivity among patients with MOUD prescriptions, suggesting that many patients with opioid use disorder had ingested multiple substances during the UDT detection window. Similarly, odds of fentanyl-only versus stimulant-only and odds of co-positivity versus stimulant-only positivity were over 5 times higher among patients with MOUD prescriptions than those without. The present findings are consistent with a recent study of 2017-2021 UDT specimens assessing polysubstance use prevalence among patients on methadone medication treatment (Saloner, 2023), which identified increasing trends in positivity for fentanyl, methamphetamine, and cocaine during the study period (Saloner, 2023). These findings also align with the increasing prevalence of polysubstance use contributing to fatal opioid overdoses involving stimulants between 2013-2019 (Mattson, 2021). The present study's findings reiterate the need for healthcare providers developing SUD treatment programs to incorporate interventions that address polysubstance use.

Additionally, patients in pain management programs had increased odds of fentanyl-only positivity, but lower odds of stimulant-only positivity and co-positivity versus no positivity. Patients in pain management programs also had increased odds of fentanyl-only versus stimulant-only positivity. These findings align with recent findings from a similar analysis of UDT specimens of patients in pain management programs where positivity rates for cocaine, heroin, and methamphetamine were low (Guevara, 2022). The present study did not assess for positivity of specific prescribed substances. Future pain management specific analyses should consider positivity for prescribed substances versus alternatives.

This study saw adjusted odds ratios flip from below referent to above referent for each outcome among patients whose primary payer was Medicare. As Medicare primarily serves as a proxy for age, this finding suggests that older patients undergoing UDT display similar use patterns to other groups; care should be taken to ensure older PWUD have the same access to SUD treatment and other resources as younger populations. Past studies have identified disparities in patients receiving Medicare that have led to awareness there are other barriers to health care which are related to race, ethnicity, and socioeconomic status (Swift, 2002). As this is a convenience sample and we do not have access to race, ethnicity, or socioeconomic status data, investigating these interactions were not feasible. Future analyses should investigate this difference in odds of positivity more closely.

Adjusted odds of positivity versus no positivity among patients with Medicaid, Medicare and the uninsured types were greater than patients with employer-sponsored insurance for each positivity outcome.

Additionally, adjusted odds of co-positivity versus fentanyl-only positivity were greater among patients on Medicaid and those uninsured than those on employer-sponsored insurance. Similarly, adjusted odds of co-positivity versus stimulant-only positivity were greater among patients on Medicaid and Medicare than employer-sponsored insurance. Multiple studies of other health outcomes (i.e., major surgical operations, heart attack, total joint arthroplasty, kidney transplant) have identified increased risk of morbidity, mortality or waitlisting for a procedure among patients receiving Medicaid, Medicare, or those uninsured, suggesting that the vulnerability of these populations should be considered when developing targeted substance use disorder treatment programs (LaPar, 2010; Srivastava, 2023; Tirumala, 2022; Cron, 2023). The role of primary payer in relation to drug use and polysubstance use requires further investigation.

This study identified greater odds of positivity for fentanyl-only, stimulant-only, and co-positivity versus no positivity among males compared to females. Regarding polysubstance use, these findings are consistent with a scoping review of studies investigating differences in polysubstance use by sex where adult men were overall more likely to report polysubstance use than women (Goodwin, 2022). This study's findings observed females with lower adjusted odds of co-positivity versus fentanyl-only positivity compared to males. Goodwin and colleagues did encounter inconsistency and conflicting evidence when considering gender and sexuality, suggesting further investigation is necessary (Goodwin, 2022).

This study observed increased adjusted odds of positivity with increases in rural urban classification for each positivity outcome compared to no positivity. Similar findings were observed in fentanyl-only versus stimulant-only positivity and co-positivity versus stimulant only positivity. Since this is a convenience sample and the number of patients from rural areas was comparatively low, more investigation into rural-urban classification and drug positivity/co-positivity is warranted.

Limitations

There were some limitations to this analysis. First, the sample used in this analysis was a convenience sample, where healthcare providers partnering with Millennium Health submitted samples; thus, findings may not be generalizable to some patient populations. Second, this analysis had restricted access to UDT specimens that were submitted to Millennium Health between January 1, 2022–June30, 2023. The derived first available specimen may not have been the first specimen provided by a patient to a given provider. Additionally, this study had no way of determining the length of a patients' treatment program, number of UDTs required by their healthcare provider, or how long a patient had been receiving treatment prior to providing the specimen included in this analysis. This additional temporal information could provide more insights on patients' progress in treatment. Third, this study could not verify whether patients who tested positive for both fentanyl and a stimulant used both simultaneously; rather, UDT confirmed that both fentanyl and a stimulant were ingested within the UDT detection window. Detection windows differ for different substances, dosages, use patterns, and individuals' metabolism, but many researchers describe the standard window as up to four days (McNeil, 2023; Martini, 2020). Fourth, this analysis was restricted to patients who were tested for both fentanyl and a stimulant. Thus, patients not tested for substances analyzed in this study would not be included in the sample. Finally, as this is an observational study, causal relationships should not be inferred between drug positivity and any of the measured covariates.

Next Steps

This analysis found that patients receiving SUD treatment had increased odds of fentanyl-only positivity, stimulant-only positivity and co-positivity compared to patients receiving primary care. Additionally, patients receiving Pain Management treatment had increased odds of fentanyl only positivity. Public health officials should consider the implications of polysubstance use when developing substance use treatment recommendations/guidance. Clinicians should be aware of possible polysubstance use when developing treatment programs. Future UDT analyses should consider analytic techniques to investigate drug use patterns over time, as well as incorporating race/ethnicity and socioeconomic variables alongside variables included in this analysis.

Tables & Figures

Table 2.1 – Distribution of Drug Positivity∞ by Covariate Levels between Jan 1, 2022-June 30, 2023 (dataset pulled 7/20/2023)

Covariates N (%)	**Fentanyl only Positive** **N (%)**	**Stimulant only Positive** **N (%)**	**Co-Positivity** **N (%)**	**Neither** **N (%)**
Overall N = 386,501 (Covariate %)	12,254 (3.2)	35,601 (9.2)	20,220 (5.2)	318,426 (82.4)
Sex				
Male 191,621 (49.6)	6,030 (3.1)	11,844 (6.2)	11,424 (6.0)	162,323 (84.7)
Female 194,880 (50.4)	4,969 (2.5)	8,720 (4.5)	8,796 (4.5)	172,395 (88.5)
Age group				
Median age = 46				
15-24 27,226 (7.0)	1,325 (4.9)	1,120 (4.1)	1,579 (5.8)	23,202 (85.2)
25-34 74,456 (19.3)	3,382 (4.5)	5,544 (7.4)	7,960 (10.7)	57,570 (77.3)
35-44 83,723 (21.7)	2,426 (2.9)	6,782 (8.1)	6,890 (8.2)	67,625 (80.8)
45-54 63,048 (16.3)	1,364 (2.2)	4,094 (6.5)	2,516 (4)	55,074 (87.4)
55-64 66,630 (17.2)	1,307 (2.0)	2,417 (3.6)	1,072 (1.6)	61,834 (92.8)
65+ 71,418 (18.5)	1,195 (1.7)	607 (0.8)	203 (0.3)	69,413 (97.2)
Provider Type				
Primary Care Practice 71,212 (18.4)	1,031 (1.4)	1,541 (2.2)	1,165 (1.6)	67,475 (94.8)
Pain Management 109,362 (28.3)	2,340 (2.1)	945 (0.9)	250 (0.2)	105,827 (96.8)
SUD Treatment 205,927 (53.3)	7,628 (3.7)	18,078 (8.8)	18,805 (9.1)	161,416 (78.4)
Primary Payer				
Private Insurance 92,900 (24.0)	1,208 (2.1)	1,621 (2.8)	925 (1.6)	54,497 (93.6)
Medicaid 174,606 (45.2)	6,550 (3.8)	15,063 (8.6)	17,127 (9.8)	135,866 (77.8)

Medicare 93,235 (24.1)	1,810 (1.9)	1,497 (1.6)	656 (0.7)	89,272 (95.7)
Uninsured 25,760 (6.7)	719 (2.8)	1,368 (5.3)	912 (3.5)	22,761 (88.4)
Rural-Urban Classification				
Rural 16,229 (4.2)	325 (2.0)	722 (4.4)	544 (3.4)	14,638 (90.2)
Small Town 27,194 (7.0)	488 (1.8)	1,404 (5.2)	815 (3.0)	24,487 (90.0)
Micropolitan 65,297 (16. 9)	1,431 (2.2)	3,349 (5.1)	2,854 (4.4)	57,663 (88.3)
Metropolitan 277,781 (71.9)	8,755 (3.2)	15,089 (5.4)	16,007 (5.8)	237,930 (85.7)
Opioid[ε] Prescription Status				
No 275,008 (71.15)	8,465 (3.1)	19,688 (7.2)	19,996 (7.3)	226,859 (82.5)
Yes 111,493 (28.85)	2,534 (2.3)	876 (0.8)	224 (0.2)	107,859 (96.7)
MOUD[£] Prescription Status				
No 331,532 (85.78)	7,557 (2.3)	18,210 (5.5)	12,145 (3.7)	293,620 (88.6)
Yes 54,969 (14.22)	3,442 (6.3)	2,354 (4.3)	8,075 (14.7)	41,098 (74.8)

[∞] Positivity for fentanyl includes the following fentanyl analogs and metabolites: fentanyl, 4-ANPP, acetyl fentanyl, acryl fentanyl, carfentanil, and parafluorofentanyl. Stimulant positivity includes cocaine and methamphetamine.

[ε] Possible prescribed opioids include fentanyl, hydrocodone, hydromorphone, oxycodone, oxymorphone, morphine, codeine or tramadol.

[£] Possible medications for opioid use disorder include buprenorphine and methadone.

Table 2.2 – Unadjusted and Adjusted[ʔ] Multinomial Logistic Regression Results of Positivity[¤] Outcome (ref=neither positivity) across co-variates.

	Unadjusted Odds Ratios (95% CI)			Adjusted Odds Ratios (95% CI)		
Sex	p-value <0.001[¥]			p-value <0.001[€]		
	Fentanyl Only	**Stimulants Only**	**Both Fentanyl and a Stimulant**	**Fentanyl Only**	**Stimulants Only**	**Both Fentanyl and a Stimulant**
Female (ref)	-	-	-	-	-	-
Male	1.29 (1.24,1.34)	1.44 (1.40,1.48)	1.38 (1.34,1.42)	1.17 (1.13,1.22)	1.09 (1.06,1.12)	1.09 (1.05,1.12)
Age Group	p-value <0.001[¥]			p-value <0.001[€]		
	Fentanyl Only	**Stimulants Only**	**Both Fentanyl and a Stimulant**	**Fentanyl Only**	**Stimulants Only**	**Both Fentanyl and a Stimulant**
15 to 24 years	0.97 (0.91,1.04)	0.50 (0.47,0.54)	0.49 (0.47,0.52)	1.22 (1.14,1.30)	0.49 (0.46,0.52)	0.63 (0.59,0.66)
25 to 34 years (ref)	-	-	-	-	-	-
35 to 44 years	0.61 (0.58,0.64)	1.04 (1.00,1.08)	0.74 (0.71,0.76)	0.60 (0.57,0.64)	1.25 (1.20,1.30)	0.84 (0.81,0.87)
45 to 54 years	0.42 (0.40,0.45)	0.77 (0.74,0.8)	0.33 (0.32,0.35)	0.48 (0.45,0.51)	1.30 (1.24,1.36)	0.60 (0.57,0.63)
55 to 64 years	0.36 (0.34,0.38)	0.41 (0.39,0.43)	0.13 (0.12,0.13)	0.45 (0.42,0.49)	1.08 (1.02,1.14)	0.40 (0.38,0.43)
65+ years	0.29 (0.27,0.31)	0.09 (0.08,0.10)	0.02 (0.02,0.02)	0.40 (0.36,0.44)	0.51 (0.46,0.56)	0.22 (0.19,0.25)
Provider Type	p-value <0.001[¥]			p-value <0.001[€]		
	Fentanyl Only	**Stimulants Only**	**Both Fentanyl and a Stimulant**	**Fentanyl Only**	**Stimulants Only**	**Both Fentanyl and a Stimulant**
Primary Care (ref)	-	-	-	-	-	-
Pain Management	1.45 (1.34,1.56)	0.39 (0.36,0.42)	0.14 (0.12,0.16)	1.44 (1.33,1.56)	0.54 (0.49,0.59)	0.33 (0.29,0.38)
SUD Treatment	3.09 (2.90,3.30)	4.90 (4.65,5.17)	6.75 (6.36,7.16)	2.44 (2.26,2.63)	2.61 (2.46,2.76)	2.78 (2.61,2.96)
Primary Payer	p-value < 0.001[¥]			p-value <0.001[€]		

	Fentanyl Only	Stimulants Only	Both Fentanyl and a Stimulant	Fentanyl Only	Stimulants Only	Both Fentanyl and a Stimulant
Employer-sponsored (ref)	-	-	-	-	-	-
Medicaid	2.17 (2.04,2.31)	3.73 (3.54,3.93)	7.43 (6.95,7.94)	1.64 (1.54,1.75)	2.29 (2.17,2.42)	3.74 (3.50,4.01)
Medicare	0.91 (0.85,0.98)	0.56 (0.53,0.61)	0.43 (0.39,0.48)	1.36 (1.25,1.48)	1.32 (1.22,1.43)	1.52 (1.37,1.70)
Private Insurance	0.99 (0.90,1.09)	1.06 (0.97,1.14)	1.09 (0.99,1.21)	0.98 (0.89,1.07)	1.00 (0.93,1.09)	1.02 (0.92,1.13)
Uninsured	1.43 (1.30,1.56)	2.02 (1.88,2.17)	2.36 (2.15,2.59)	1.10 (1.00,1.22)	1.41 (1.31,1.52)	1.33 (1.21,1.46)
Rural-Urban Classification	p-value <0.001[¥]			p-value <0.001[€]		
	Fentanyl Only	**Stimulants Only**	**Both Fentanyl and a Stimulant**	**Fentanyl Only**	**Stimulants Only**	**Both Fentanyl and a Stimulant**
(continuous)	1.30 (1.26,1.34)	1.07 (1.06,1.09)	1.31 (1.29,1.34)	1.30 (1.26,1.34)	1.04 (1.02,1.06)	1.34 (1.31,1.37)
Opioid[§] Prescription	p-value <0.001[¥]			p-value <0.001[€]		
	Fentanyl Only	**Stimulants Only**	**Both Fentanyl and a Stimulant**	**Fentanyl Only**	**Stimulants Only**	**Both Fentanyl and a Stimulant**
No (ref)	-	-	-	-	-	-
Yes	0.63 (0.60,0.66)	0.09 (0.09,0.10)	0.02 (0.02,0.03)	2.13 (1.98,2.29)	0.37 (0.34,0.40)	0.28 (0.24,0.32)
MOUD[ɣ] Prescription	p-value <0.001[¥]			p-value <0.001[€]		
	Fentanyl Only	**Stimulants Only**	**Both Fentanyl and a Stimulant**	**Fentanyl Only**	**Stimulants Only**	**Both Fentanyl and a Stimulant**
No (ref)	-	-	-	-	-	-
Yes	3.25 (3.12,3.39)	0.92 (0.88,0.97)	4.75 (4.61,4.90)	3.09 (2.95,3.22)	0.57 (0.55,0.60)	2.94 (2.85,3.04)

[ʔ] Adjusted models include covariates: sex, age group, provider type, primary payer, rural-urban classification, opioid prescription status, and MOUD prescription status.

[¤] Positivity for fentanyl includes the following fentanyl analogs and metabolites: fentanyl, 4-ANPP, acetyl fentanyl, acryl fentanyl, carfentanil, and parafluorofentanyl. Stimulant positivity includes cocaine and methamphetamine.
[§] Possible prescribed opioids include fentanyl, hydrocodone, hydromorphone, oxycodone, oxymorphone, morphine, codeine, or tramadol.
[ȣ] Possible medications for opioid use disorder include buprenorphine and methadone.
[¥] Corresponding p-values are based on the Pearson Chi-square Test.
[€] Corresponding p-values are based on the Likelihood Ratio Test in adjusted models.

Table 2.3 – Adjusted[ʔ] Multinomial Logistic Regression Results with Alternative Positivity[¤] Reference Group across covariates.

	Adjusted Odds Ratios (95% CI)		
Sex	p-value <0.001[¥]		
	Fentanyl Only vs Stimulant Only (ref)	**Both Fentanyl and a Stimulant vs Fentanyl Only (ref)**	**Both Fentanyl and a Stimulant vs Stimulant Only (ref)**
Female (ref)	-	-	-
Male	1.08 (1.03,1.13)	0.92 (0.88,0.97)	1.00 (0.96,1.04)
Age Group	p-value <0.001[¥]		
	Fentanyl Only vs Stimulant Only (ref)	**Both Fentanyl and a Stimulant vs Fentanyl Only (ref)**	**Both Fentanyl and a Stimulant vs Stimulant Only (ref)**
15 to 24 years	2.50 (2.28,2.74)	0.51 (0.47,0.56)	1.28 (1.18,1.40)
25 to 34 years (ref)	-	-	-
35 to 44 years	0.48 (0.45,0.52)	1.38 (1.30,1.47)	0.67 (0.64,0.70)
45 to 54 years	0.37 (0.34,0.40)	1.24 (1.14,1.34)	0.46 (0.43,0.49)
55 to 64 years	0.42 (0.38,0.46)	0.89 (0.81,0.99)	0.37 (0.34,0.41)
65+ years	0.78 (0.68,0.89)	0.55 (0.46,0.65)	0.42 (0.35,0.51)
Provider Type	p-value <0.001[¥]		
	Fentanyl Only vs Stimulant Only (ref)	**Both Fentanyl and a Stimulant vs Fentanyl Only (ref)**	**Both Fentanyl and a Stimulant vs Stimulant Only (ref)**
Primary Care (ref)	-	-	-
Pain Management	2.67 (2.38,3.00)	0.23 (0.19,0.27)	0.61 (0.52,0.72)
SUD Treatment	0.93 (0.85,1.03)	1.14 (1.03,1.25)	1.06 (0.98,1.16)
Primary Payer	p-value <0.001[¥]		
	Fentanyl Only vs Stimulant Only (ref)	**Both Fentanyl and a Stimulant vs Fentanyl Only (ref)**	**Both Fentanyl and a Stimulant vs Stimulant Only (ref)**
Employer-sponsored (ref)	-	-	-
Medicaid	0.72 (0.66,0.78)	2.28 (2.08,2.50)	1.63 (1.50,1.78)
Medicare	1.03 (0.92,1.15)	1.12 (0.98,1.28)	1.16 (1.01,1.32)
Private Insurance	0.97 (0.86,1.10)	1.04 (0.91,1.20)	1.02 (0.89,1.16)
Uninsured	0.78 (0.69,0.88)	1.20 (1.06,1.37)	0.94 (0.84,1.06)

Rural-Urban Classification	p-value <0.001[¥]		
	Fentanyl Only vs Stimulant Only (ref)	**Both Fentanyl and a Stimulant vs Fentanyl Only (ref)**	**Both Fentanyl and a Stimulant vs Stimulant Only (ref)**
(continuous)	1.24 (1.20,1.29)	1.03 (0.99,1.07)	1.28 (1.24,1.32)
Opioid[§] Prescription	p-value <0.001[¥]		
	Fentanyl Only vs Stimulant Only (ref)	**Both Fentanyl and a Stimulant vs Fentanyl Only (ref)**	**Both Fentanyl and a Stimulant vs Stimulant Only (ref)**
No (ref)	-	-	-
Yes	5.83 (5.24,6.50)	0.13 (0.11,0.15)	0.76 (0.65,0.90)
MOUD[ȣ] Prescription	p-value <0.001[¥]		
	Fentanyl Only vs Stimulant Only (ref)	**Both Fentanyl and a Stimulant vs Fentanyl Only (ref)**	**Both Fentanyl and a Stimulant vs Stimulant Only (ref)**
No (ref)	-	-	-
Yes	5.38 (5.07,5.72)	0.95 (0.91,1.00)	5.13 (4.87,5.41)

[ʔ] Adjusted models include covariates: sex, age group, provider type, primary payer, rural-urban classification, opioid prescription status, and MOUD prescription status.

[¤] Positivity for fentanyl includes the following fentanyl analogs and metabolites: fentanyl, 4-ANPP, acetyl fentanyl, acryl fentanyl, carfentanil, and parafluorofentanyl. Stimulant positivity includes cocaine and methamphetamine.

[§] Possible prescribed opioids include fentanyl, hydrocodone, hydromorphone, oxycodone, oxymorphone, morphine, codeine, or tramadol.

[ȣ] Possible medications for opioid use disorder include buprenorphine and methadone.

[€] Corresponding p-values are based on the Likelihood Ratio Test in adjusted models.

Chapter 3: Describing the relationship between opioid-stimulant nonfatal overdoses and demographic characteristics and analyzing trends in EDs in the United States, 2017-2022

Introduction

Background:

Polysubstance use is defined as "the ingestion of two or more substances in combination at the same time or in temporal proximity" (Martin, 2008; Hakkarainen, 2019). Multiple researchers suggest polysubstance use involving opioids and stimulants is increasing among persons who use drugs (PWUD), potentially driven by changes in use behavior or due to the drug supply including adulterants or contaminants, which may lead to increases in drug-related morbidity and mortality (Ciccarone, 2017; Ciccarone, 2021; Compton, 2021). This can be extremely dangerous for PWUD as stimulant-related deaths are increasing (Ciccarone, 2021). Additionally, increases in internet forum mentions of both opioid and stimulant use between 2011 and 2020 indicate that use these substances simultaneously is becoming more prevalent (Sarker, 2022). Similar research of online posts in drug-related forums from 2011 and 2018 identified an increase in fentanyl-related internet chatter greater than 1 year earlier than other public health data systems (Wright, 2021), setting a precedent concern. To better understand the public health burden of trends identified in online postings, we must examine demographic distributions and trends in data systems that measure adverse outcomes due to opioid and stimulant use, specifically overdoses presenting to emergency departments (EDs).

Researchers have described varying demographic characteristics associated with elevated risk of nonfatal overdose. From January 1 to April 18, 2020, Rodda et al. (2020) observed greater opioid overdose ED visits and deaths in California among males compared to females, and among 25-34 and 35-44 year-olds compared to other age groups. Rodda and colleagues (2020) observed a dramatic increasing trend from the start of the year through April, noting that California pandemic mitigating measures were implemented on March 19th. Similarly, while analyzing trends in opioid overdose ED visits by patient characteristics between January 2018- March 2022, Casillas et al. (2022) observed highest rates males compared to females, among 25-34 year olds compared to other age groups, and non-Hispanic Whites. While investigating stimulant-related emergency medical records in Massachusetts between 2013-2020, Bettano et al. (2022) observed incidents more likely among males, adults between 25-44 years old, and non-Hispanic Whites.

Past research has described increasing trends in ED visits related to opioids (Vivolo-Kantor, 2018; Vivolo-Kantor, 2019; Rodda, 2020; Casillas, 2022), stimulants (Bettano, 2022), and opioids and stimulants (Suen, 2022), comparatively. Researchers have also examined prevalence of single- and polydrug-involved ED visits in 2018 (Pickens, 2022), but to our knowledge, minimal national research has been published investigating trends in overdose ED visits involving both opioids and stimulants over time, particularly following 2020.

Syndromic surveillance data is a critical system for monitoring and analyzing public health threats. It uses timely data to track symptoms of patients in EDs before diagnoses are confirmed to detect unusual levels of illness providing an early warning system for public health officials. In the United States, the two main systems using syndromic surveillance data to monitor nonfatal overdoses presenting in EDs are CDC's National Syndromic Surveillance Program (NSSP) and Drug Overdose Surveillance and Epidemiology (DOSE). NSSP is a collaboration of a Community of Practice including CDC, federal partners, state and local health departments, and academic and private sector partners. They collect, analyze and share patient encounter data received from health care facilities including EDs, urgent and ambulatory care centers, inpatient healthcare facilities, and laboratories (CDC NSSP, 2023). Data is available to NSSP for analysis within 24 hours of a patient's visit, and currently 78% of EDs in the U.S. contribute data (CDC NSSP, 2023). The goal of this study is to examine NSSP syndromic surveillance data to describe the relationships between ED visits involving both opioids and stimulants and demographic characteristics. Additionally, we aim to describe overall emerging nonfatal overdose trends to fill this knowledge gap.

Methods

Study Design:

This analysis studied nonfatal overdoses presenting to ED facilities sharing data to NSSP ESSENCE (Electronic Surveillance System for Early Notification of Community-Based Epidemics). Data from 33 jurisdictions[c] were collected between January 2017-December 2022 the overall trends of nonfatal overdose. Data quality filters were applied to restrict facilities in analysis consistent to criteria from other recent CDC Epidemiology and Surveillance Branch Morbidity publications: coefficient of variations ≤ 45 and average weekly discharge diagnosis informative ≥75%. These data quality filters were applied due to fluctuations in reporting due to onboarding of new facilities and lapses in reporting during and after the 2020 COVID-19 pandemic and are consistent with recommendations from NSSP (2023).

Demographic characteristic (sex, race and ethnicity) that were 'Unknown', 'Not Categorized', 'Other', 'Refused to answer' or 'Not Reported or Null' were removed from the analytic dataset. Analytic data were also limited to persons 15 years or older and to hospital facilities participating in the National Syndromic Surveillance Program in the contiguous United States (i.e., observations from Guam were omitted).

This study has three mutually exclusive outcomes: 1) ED visits meeting ONLY the syndrome definition for opioid overdose (CDC Opioid Overdose v4 Parsed) (also known as (aka) opioid-involved ED visits or opioid overdoses), 2) ED visits meeting ONLY the stimulant overdose (CDC Stimulant v4 Parsed)

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[c] Reporting jurisdictions include Alabama, Arizona, Arkansas, Colorado, Connecticut, Florida, Georgia, Kansas, Kentucky, Louisiana, Maine, Maryland, Mississippi, Missouri, Montana, Nebraska, Nevada, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oregon, Pennsylvania, Rhode Island, South Carolina, Tennessee, Utah, Virginia, Washington, West Virginia, and Wisconsin.

syndrome definition (aka stimulant-involved ED visits or stimulant overdoses), and 3) ED visits meeting both the opioid and stimulant overdose syndrome definitions (aka opioid- and stimulant-involved ED visits or opioid/stimulant overdoses) (NSSP ESSENCE, 2023). The specifics of the syndrome definitions applied can be found in the Appendix.

Analysis:

We will study the dependence of rates for each overdose outcome on covariates in the total time period and investigate the monthly trend of nonfatal overdose rates and counts over time.

To explore suspected opioid- and stimulant-involved nonfatal overdoses in EDs between January 2017-December 2022, we first report the rate of suspected overdose per 10,000 ED visits for each covariate category. Then, we fit negative binomial regression models to the overdose counts to estimate the relative rates of our three outcomes of interest across covariates with the log of total ED visits as an offset. We will report corresponding counts and rates as well as unadjusted and adjusted relative rates (RRs) across covariates (e.g., age, sex, race/ethnicity and U.S. Census region) to describe the relationship between nonfatal opioid and stimulant overdose and demographic characteristics with 95% Confidence Intervals (CI). Confidence intervals for RRs that do not include 1.00 were considered significant. Statistical analyses were performed in R programming language (R 4.2.2 Project for Statistical Computing), specifically using the glm.nb() function of the “MASS” package Negative Binomial Poisson regression (Ripley, 2002).

To investigate the overall trends of nonfatal overdose rates and counts and to evaluate the effects of the occurrence of COVID-19 pandemic, we separately modeled monthly rates and counts via a continuous piecewise linear regression for each outcome of interest. In addition, to capture the periodic pattern observed in the data, we include the trigonometric functions, sine/cosine terms (also known as Fourier terms) with a 12-month seasonal period, in the model (Bhaskaran, 2013). Sine and cosine trigonometric functions have been used in many past public health studies assessing seasonal variation in time series analyses (Wojcik, 2023; Bhaskaran, 2013; Stolwijk, 1999; Barnett, 2010). Bhaskaran (2013) notes that pros of using this method include long-term patterns are modeled smoothly, using relatively few parameters. With this model, we simultaneously modeled the change in the trend and the seasonal pattern.

Model for the ED counts with a breakpoint at t_0 and a 12-month period have the form:

(1)

$$Y_{counts} = \beta_0 + \beta_1 t + \beta_2 (t - t_0)_+ + \beta_5 \cos\left(\frac{2\pi t}{12}\right) + \epsilon$$

Models for the ED rates additionally have an indicator for “beginning of pandemic mitigating measures” in April and May 2020, and a post May 2020 indicator:

(2)

$$Y_{rates} = \beta_0 + \beta_1 t + \beta_2 (t - t_0)_+ + \beta_3 I(t = April\ or\ May\ 2020\ ) + \beta_4 I(t > May\ 2020) + \beta_5 \cos\left(\frac{2\pi t}{12}\right) + \epsilon$$

In models (1) and (2), t represents time in months, t_0 denotes the breakpoint which is chosen as April 2020, the broad pandemic mitigating measures occurrence time of COVID-19 in the US, and $(t - t_0\ )_+$ represents the time since the breakpoint t_0 , which is $t - t_0$ if $t > t_0$ and is 0 if $t \leq t_0$ . . With these models, the parameter β_1 represents the slope of time before the breakpoint (ie, the changing rate of the mean of Y as t varies before the breakpoint), β_2 represents the change in the slope of time at the breakpoint (i.e., the difference of the changing rate of the mean of Y after and before the breakpoint). In the rate models, we use I(.) to represent the indicator function. Then β_3 and β_4 represent the additional effects of the pandemic on Y beyond the change of the slopes. The parameter β_5 represents the seasonal effect across a 12-month period. We explored the best fitting models by R-squared values for improvements in model fit, and report coefficients and 95% confidence intervals (CI), where intervals that do not include 0.00 are considered statistically significant. Residual plots were reviewed to identify any severe linear regression assumption violations. Trend analyses were performed using lm() function of the "stats" package in R (R 4.2.2 Project for Statistical Computing).

Results

Demographic Characteristics

Thirty-three jurisdictions reported 135,979,028 emergency department visits between January 2017-December 2022. Among these, 400,669 (29.5 per 10,000 ED visits) were overdoses involving opioids without stimulants, 69,231 (5.1) involved stimulants without opioids, and 12,007 (0.9) involved both opioids and stimulants between January 2017 and December 2022. Among males, rates of overdose ED visits involving opioids without stimulants (42.2), stimulants without opioids (8.0), and both opioids and stimulants (1.3) were higher relative to females (19.7, 2.9, and 0.5), respectively. Across age groups, rates of ED visits involving opioids without stimulants, stimulants without opioids, and both opioids and stimulants were highest among the 25-34 year-olds (49.0, 9.2, and 1.8, respectively). Across race/ethnicity, rates of overdose ED visits involving opioids without stimulants, stimulants without opioids, and both opioids and stimulants were highest among the American Indian or Alaska Native, non-Hispanic group (39.7, 12.0, and 1.3, respectively). Highest rates of overdose ED visits occurred in the West (opioids without stimulants: 32.3, stimulants without opioids: 9.0, both opioids and stimulants: 1.02). Full descriptive statistics by covariate are presented in Table 3.1. The following paragraphs will describe negative binomial regression results for each outcome.

Negative Binomial Regression Results:

All unadjusted and adjusted relative rates (aRR) and 95% CI are reported in Table 3.2 and Table 3.3, respectively. Adjusted models include all covariates analyzed.

Overdose ED visits involving Opioids without Stimulants

Unadjusted and adjusted rates of opioid-involved ED visits were lower among females compared to males [ref] (aRR: 0.50, 95% CI: 0.45,0.55).

Regarding age groups, adjusted rates were lower among 15-24, 35-44, 45-54, 55-64, 65-74, 75-84, and 85+ age groups compared to 25-34 (aRR range: 0.20-0.81).

Regarding race/ethnicity, adjusted rates of opioid overdose were lower among Asian, Native Hawaiian or other Pacific Islander (NHPI), and Hispanic patients compared to non-Hispanic Whites (aRR range: 0.31-0.72). Adjusted rates were higher among non-Hispanic American Indian or Alaska Natives (AIAN) (aRR: 1.20; 95% CI: 1.01,1.42).

Adjusted rates of opioid overdose were higher in the Northeast, South and West Census regions compared to the Midwest (aRR range: 1.52-2.43).

Overdose ED visits involving Stimulants without Opioids

Unadjusted and adjusted rates of stimulant-involved ED visits were lower among females compared to males [ref] (aRR: 0.34, 95% CI: 0.30,0.38).

Regarding age groups, adjusted rates of stimulant overdose were lower among 15-24, 45-54, 55-64, 65-74, 75-84, and 85+ age groups compared to 25-34 year-olds (aRR range: 0.20-0.81). The rate among the 35-44 age group was not significantly different from the 25-34 year-olds (aRR: 0.85; 95% CI: 0.70,1.04).

Regarding race/ethnicity, adjusted rates of stimulant overdose were lower among Asian non-Hispanic (NH), NHPI, and Multiracial NH patients compared to non-Hispanic Whites (aRR range: 0.31-0.72). Adjusted rates were higher among AIAN and Black patients (aRR range: 1.52-1.89).

Adjusted rates of stimulant overdose were higher in the South and West Census regions compared to the Midwest (aRR range: 1.23-2.71). Rates were lower in the Northeast compared to Midwest (aRR: 0.62; 95% CI: 0.51,0.76).

Overdose ED visits involving Opioids and Stimulants

Unadjusted and adjusted rates of ED visits involving opioids and stimulants were lower in females compared to males [ref] (aRR: 0.36, 95% CI: 0.31,0.43)

Unadjusted and adjusted rates of opioid- and stimulant-involved ED visits were lower among all age groups, except 35-44 year-olds, compared to 25-34 years [ref] (aRR range: 0.01-0.48). No statistically significant difference identified between 25-34 and 35-44 year-olds (aRR: 0.82; 95% CI: 0.64,1.05).

Compared to White [ref] patients, adjusted RRs for opioids and stimulants involved ED visits were lower for Asian NH, NHPI, and Hispanic patients (aRR range: 0.26-0.64). Of note, unadjusted rates for Hispanic patients were not significantly different from White patients. No significant differences in unadjusted or adjusted rates were identified between AIAN, Black, and Multiracial NH patients compared to Whites.

Adjusted rates of overdose ED visits involving opioids and stimulants were higher in the Northeast, South and West Census regions compared to the Midwest (aRR range: 1.68-4.82). The following paragraphs will describe overall trend analysis results.

Trend Results:

Trend analysis coefficient estimates (referred to as β) and 95% confidence intervals are reported in Table 3.4a. Plots of overall trends for rates and counts of mutually exclusive opioid-, stimulant- and both opioid and stimulant-involved ED visits are available in Figures 3.1a, 3.2a and 3.3a, respectively, with fitted curves imposed. Alternative ED visit rates model coefficients and plots are provided in

Supplemental Materials in the Appendix for comparison where outliers in April and May 2020 were omitted from analysis.

The opioid-involved ED visit rates without stimulants (per 10,000 ED visits) increased by 0.17 (95% CI: 0.13,0.21) units per month, meanwhile, opioid-involved ED visit counts without stimulants increased by 85.9 (95% CI: 75.46,96.29) per month on average prior to pandemic mitigation measures. Similarly, stimulant-involved ED visit rates without opioids increased by 0.05 (95% CI: 0.04,0.06) and counts increased by 13.39 (95% CI: 11.62,15.17) more visits were observed in that timeframe. Likewise, both opioid- and stimulant-involved ED visit rates (β : 0.01; 95% CI: 0.01,0.01) and counts (β : 3.05; 95% CI: 2.63,3.47) observed slight increasing trends pre-pandemic.

For all outcome variables, the coefficients for the amount of time since the April breakpoint are negative, implying that the slopes of time decrease after the breakpoint and the pandemic occurrence had a decreasing effect on the changing rates of the outcome variables regarding the ED visit rates and ED visit counts. Specifically, the changing rate of opioid-involved ED visit counts without stimulants decreases by 34 per month (β : -34.43; 95% CI: -55.55, -13.31) since the pandemic (i.e., on average, there are 34.43 less opioid-involved ED visits without stimulants per month since pandemic occurrence), leading to a slower increasing trend for the counts since the pandemic. The changing rate of opioid-involved ED visit rates without stimulants decreases by 0.47 units per month (β : -0.47; 95% CI: -0.55, -0.40) since the pandemic, leading to a small decreasing trend for the rates since the pandemic. Similarly, the changing rates of ED visit rates and counts involving only stimulants decreased after pandemic mitigation measures (Rates β: -0.13; 95% CI: -0.15, -0.12; Counts β: -21.02; 95% CI: -24.62, -17.41), leading to a small decreasing trend for the rate and a slow decreasing trend for the counts since the pandemic. Correspondingly, the changing rates of ED visit rates and counts involving both opioids and stimulants (Rates β: -0.02; 95% CI: -0.03, -0.02; Counts β: -2. 89; 95% CI: -3.75, -2.03) decreased after mitigation measures, leading to a small decreasing trend for the rate and a slow increasing trend for the counts since the pandemic.

The rates models included coefficients for the beginning of pandemic mitigating measures in the US in April/May 2020. These coefficients indicate a shocking effect on rates for all three outcomes where ED visits rates for opioids without stimulants were uplifted by 20.32 (95% CI: 17.71, 22.68) units in April and May 2020, stimulants without opioids increased by 1.66 (95% CI: 1.07, 2.19), and both opioids and stimulants increased by 0.52 (95% CI: 0.35,0.67) units, in addition to the linear trend and the periodic trend. This parameter was not included in models of counts.

The rates models also included coefficients for an indicator of time after May 2020. Coefficients for this indicator were positive for ED visit rates involving only opioids (β : 9.29; 95% CI: 7.70,10.88) and both opioids and stimulants (β : 0.10; 95% CI: 0.00,0.20), leading to an additional increase of the ED visit rates by 9.3 and 0.1 units every month, respectively, beyond the linear and periodic trends after May 2020. This coefficient was not statistically significant for stimulant-involved ED visit rates without opioids. This parameter was not included in models of counts.

Seasonality was a significant factor in rates and counts for all three outcomes of interest. See Table 3.4a for reported coefficient estimates and confidence intervals. Negative coefficients for the cosine terms described more opioid without stimulant, stimulant without opioid, and combined overdose ED visits in warmer months [May-August] than cooler [November-February], which can be seen in Figures 3.1a, 3.2a, and 3.3arespectively.

Discussion

Summary of findings

Between January 2017 and December 2022, approximately 30 in 10,000 ED visits involved opioids, 5 in 10,000 involved stimulants, and 1 in 10,000 involved both opioids and stimulants in the United States. Rates and counts of overdose outcomes varied by demographic characteristics. Rates of overdose for each outcome were consistently greater among males, 25-34 and 35-44 year olds, and patients in the West. These findings align with several studies of nonfatal and fatal overdoses in the US where overdose rates were greater among males and the 25-44 year age range (Rodda, 2020; Spencer, 2022). Additionally, Spencer et al. (2022) observed increased overdose deaths involving opioids and stimulants from 2020 to 2021, corroborating our findings.

For each outcome, rates varied by race/ethnicity. Compared to Whites, ED visit rates involving only opioids were higher among American Indian or Alaska Natives (AIAN). ED visit rates involving only stimulants were higher among AIAN and Black patients. ED visit rates involving both opioids and stimulants were lower among Asian, Native Hawaiian or other Pacific Islander (NHPI) and Hispanic patients, compared to Whites, while differences were not identified among other races. We did not identify any studies that investigated varying substance used by race, however, Spencer et al. (2022) similarly observed highest overdose death rates among AIAN and Black people, followed by Whites. Our findings align with additional evidence of racial/ethnic disparities in health that were magnified during the COVID-19 pandemic (Yancy, 2020; Dowling 2020; Galea, 2020; Khatri, 2021). Further investigation of polysubstance drug overdoses by race/ethnicity is necessary.

Despite relatively low percentages for stimulant-involved ED visits without opioids and ED visits involving both opioids and stimulants, trends in both counts and rates for all three outcomes changed dramatically during the study period. This analysis observed increasing overall trends in overdose ED visit rates and counts involving opioids without stimulants, stimulants without opioids AND both opioids and stimulants leading up to April 2020. Though statistically significant, increases in mutually exclusive opioid- and stimulant-involved overdose rates were not practically significant at 0.01 per 10,000 total ED visits prior to April 2020. Meanwhile, trends in counts increased approaching 2020, then leveled off, remaining elevated above 2017 observations through 2022 for all three outcomes. The differences in trend between rates and counts is likely due to denominator total ED visits dropping dramatically in

April and May of 2020 during mandated mitigation measures for the COVID-19 pandemic. This is consistent with multiple drug overdose studies analyzing ED visits before and during the pandemic (Khatri, 2021; Ochalek, 2020). The observed trends in nonfatal overdose also align with multiple studies of drug overdose deaths in the US prior to 2020 (Glick, 2018; Gladden, 2019; Jones, 2018; Al-Tayyib, 2017) and two studies which observed dramatic increases in 2020 (Ghose, 2022; Spencer, 2022). Considering our findings on polysubstance overdose trends, the Sarker et al. (2022) analysis of trends in internet forum posts co-mentioning stimulants and opioids observed steady increases in co-mentions of both opioids and/or opioid-related medications and stimulants between 2011-2020. Additionally, Gladden et al. (2019) observed increases in overdose deaths involving illicitly manufactured fentanyl (IMF) co-occurring with benzodiazepines, cocaine, and methamphetamine from July-December 2017 to January-June 2018. The present study follows-up on Gladden's work by extending the analyzed period, however, this analysis did not model trends by demographic characteristics, as Khatri et al. did for opioid overdoses. Differences in polysubstance overdose across demographics should be more closely examined in future studies.

The COVID-19 pandemic had an impact on drug overdoses across the US. Though many states and the federal government pushed to facilitate telehealth services during 2020 (Drug Enforcement Administration & U.S. Department of Justice, 2020), overdose rates ballooned. A 2021 study describing trends in visits to substance use disorder treatment facilities noted that counties with higher COVID-19 rates had larger declines in weekly visits between March and August of 2020 (Cantor, 2021). Additionally, sources reported decreases in use (Palamar, 2020) and availability of select drugs during early months of the pandemic (United Nations Office of Drugs and Crime, 2020) while various studies identified increases in nonfatal and fatal overdoses in the same timeframe (Ochalek, 2020; Glober, 2020; Rodda, 2020; Slavova, 2020). None of the noted studies above investigated polysubstance use, which is where this analysis fills a knowledge gap.

Finally, seasonality was a key factor identified in trend analyses for all three outcomes of interest with peaks in rates and counts tending to occur in warmer months of the year. These findings agree with two prior CDC analyses that identified fluctuations in nonfatal overdose trends that correspond to quarterly (roughly seasonal) changes in the United States between 2016-2017 and 2017-2018 where greatest increases in trends were observed in transitions from winter to spring and (Vivolo-Kantor, 2018; Vivolo-Kantor, 2019). The present analysis adds to these findings by extending the analyzed period through 2022 and analyzing instances of nonfatal overdoses involving both opioids and stimulants.

Limitations

This analysis had at least two limitations. First, few nonfatal overdoses are captured alongside a confirmatory drug test to identify specific substances involved, making validation of polysubstance use difficult. Additionally, this analysis did not investigate whether other substances or circumstances were involved in the ED visit beyond the triggered opioid and/or stimulant overdose syndrome definition. Thus, overdoses involving both opioids and stimulants could be over- or underestimated as healthcare providers are limited to details provided by patients/bystanders. Second, findings in drug use and overdose relating to race/ethnicity are limited. Improvements in standardization of race/ethnicity data are necessary and work is currently being done in CDC's newest iteration of OD2A (CDC OD2A in States, 2023). In August of 2023, CDC launched Overdose Data to Action in States, funding 49 state health departments and the District of Columbia, requiring states to report community characteristics, including race and ethnicity data (CDC OD2A in States, 2023). These improvements in data collection can benefit analyses conducted to tailor more culturally relevant prevention and intervention strategies.

Next steps

This research describes populations with increased risk of nonfatal overdose and general nonfatal overdose trends involving opioids without stimulants, stimulants without opioids and both opioids and stimulants. Future analyses should consider incorporating descriptive and influential comparisons between opioid-involved ED visits and stimulant-involved ED visits compared to ED visits involving both opioids and stimulants and to each other. Trends in rates and counts of overdoses were increasing prior to the pandemic, and seasonality plays a key role. Future analyses should consider analyzing trends in opioid-involved ED visits, stimulant-involved ED visits, and ED visits involving both opioids and stimulants concurrently to better understand how the trends differ. Stakeholders must consider these factors when developing prevention and intervention strategies. Further investigation is warranted to better understand how trends are changing within at-risk populations.

Tables & Figures

Table 3.1 – Distribution of Opioid without Stimulants/Stimulant without Opioids/Both Nonfatal Overdose Emergency Department Visits by Covariate, January 2017-December 2022

Total ED visits N= 135,979,028 (Covariate %)	**Opioid Only Overdose ED Visits N= 400,669 (29.47 per 10,000 ED visits)**	**Stimulant Only Overdose ED Visits N= 69,231 (5.09 per 10,000 ED visits)**	**Both Opioid and Stimulant Overdose ED Visits N= 12,007 (0.88 per 10,000 ED visits)**
	Count (rate per 10,000 ED visits)		
Sex			
Female N = 76,680,927 (56%)	150,750 (19.66)	21,922 (2.86)	4,115 (0.54)
Male N = 59,298,101 (44%)	249,919 (42.15)	47,309 (7.98)	7,892 (1.33)
Age Group			
15-24 N = 17,739,207 (13%)	37,149 (20.94)	9,442 (5.32)	1,177 (0.66)
25-34 N = 22,802,177 (17%)	111,712 (48.99)	20,863 (9.15)	4,125 (1.81)
35-44 N = 19,652,749 (14%)	86,032 (43.78)	17,230 (8.77)	3,172 (1.61)
45-54 N = 18,609,311 (14%)	60,172 (32.33)	11,863 (6.37)	1,840 (0.99)
55-64 N = 19,985,373 (15%)	60,275 (30.16)	7,741 (3.87)	1,333 (0.67)
65-74 N = 17,202,222 (13%)	30,568 (17.77)	1,820 (1.06)	333 (0.19)
75-84 N = 12,821,636 (9%)	10,564 (8.24)	199 (0.16)	20 (0.02)
85+ N = 7,166,353 (5%)	4,197 (5.86)	73 (0.10)	7 (0.01)
Race/Ethnicity			
White, Non-Hispanic N = 89,563,827 (66%)	292,572 (32.67)	42,090 (4.70)	8,067 (0.9)
American Indian or Alaska Native, Non-Hispanic N = 1,265,880 (1%)	5,020 (39.66)	1,522 (12.02)	163 (1.29)
Asian, Non-Hispanic N = 1,883,941 (1%)	1,762 (9.35)	559 (2.97)	46 (0.24)

Black or African American, Non-Hispanic N = 31,634,739 (23%)	75,421 (23.84)	17,515 (5.54)	2,825 (0.89)
Hispanic or Latino N = 11,216,041 (8%)	24,794 (22.11)	7,372 (6.57)	880 (0.78)
Multiracial, Non-Hispanic N = 156,391 (0.1%)	607 (38.81)	73 (4.67)	12 (0.77)
Native Hawaiian or Other Pacific Islander, Non-Hispanic N = 258,209 (0.2%)	493 (19.09)	100 (3.87)	14 (0.54)
U.S. Census Region			
Midwest	16,242 (13.00)	4,081 (3.27)	285 (0.23)
Northeast	34,496 (28.55)	2,866 (2.37)	528 (0.44)
South	253,124 (31.07)	35,435 (4.35)	8,130 (1.00)
West	96,807 (32.34)	26,849 (8.97)	3,064 (1.02)

Table 3.2 – Unadjusted Relative Rates (RR) of Nonfatal Overdoses involving Opioids without Stimulants, Stimulants without Opioids and both Opioids and Stimulants [Negative Binomial Regression Results], January 2017-December 2022

	Opioids Only RR (95% CI)	**Stimulants Only RR (95% CI)**	**Both Opioids and Stimulants RR (95% CI)**
Sex			
Female	0.48 (0.41, 0.56)	0.39 (0.30, 0.50)	0.39 (0.29, 0.53)
Male (ref)	-	-	-
Age Groups (years)			
15-24	0.50 (0.38, 0.67)	0.67 (0.46, 0.96)	0.45 (0.29, 0.69)
25-34 (ref)	-	-	-
35-44	0.79 (0.59, 1.04)	0.91 (0.64, 1.31)	0.80 (0.52, 1.22)
45-54	0.59 (0.45, 0.79)	0.65 (0.45, 0.93)	0.47 (0.31, 0.73)
55-64	0.54 (0.41, 0.72)	0.38 (0.26, 0.55)	0.32 (0.21, 0.50)
65-74	0.38 (0.29, 0.51)	0.15 (0.10, 0.22)	0.15 (0.09, 0.24)
75-84	0.18 (0.14, 0.25)	0.03 (0.02, 0.04)	0.02 (0.01, 0.04)
85+	0.19 (0.14, 0.26)	0.02 (0.01, 0.03)	0.01 (0.00, 0.04)
Race/Ethnicity			
White (ref)	-	-	-
American Indian or Alaska Native, non-Hispanic	1.06 (0.80, 1.40)	1.38 (0.85, 2.22)	1.28 (0.75, 2.21)
Asian, non-Hispanic	0.30 (0.22, 0.39)	0.63 (0.39, 1.02)	0.34 (0.19, 0.60)
Black or African American, non-Hispanic	0.81 (0.61, 1.06)	1.31 (0.82, 2.09)	0.86 (0.53, 1.40)
Hispanic	0.70 (0.53, 0.92)	1.03 (0.64, 1.64)	0.73 (0.44, 1.18)
Multiracial, non-Hispanic	1.12 (0.83, 1.51)	0.84 (0.48, 1.47)	0.98 (0.43, 2.12)
Native Hawaiian or Other Pacific Islander, non-Hispanic	0.57 (0.42, 0.78)	0.65 (0.38, 1.13)	0.78 (0.35, 1.66)
U.S. Census Region			
Midwest (ref)	-	-	-
Northeast	1.68 (1.31, 2.14)	0.53 (0.36, 0.79)	1.37 (0.81, 2.29)
South	1.67 (1.32, 2.12)	1.05 (0.72, 1.51)	3.29 (2.02, 5.31)
West	2.14 (1.69, 2.72)	2.30 (1.60, 3.30)	3.83 (2.37, 6.13)

Table 3.3 – Adjusted§ Relative Rates (RR) Nonfatal Overdoses involving Opioids, Stimulants and both Opioids and Stimulants [Negative Binomial Regression Results], January 2017-December 2022

	Opioids Only RR (95% CI)	**Stimulants Only RR (95% CI)**	**Both Opioids and Stimulants RR (95% CI)**

Sex			
Female	0.50 (0.45, 0.55)	0.34 (0.30, 0.38)	0.36 (0.31, 0.43)
Male (ref)	-	-	-
Age Groups (years)			
15-24	0.51 (0.42, 0.61)	0.67 (0.55, 0.82)	0.40 (0.31, 0.52)
25-34 (ref)	-	-	-
35-44	0.81 (0.67, 0.97)	0.85 (0.70, 1.04)	0.82 (0.64, 1.05)
45-54	0.61 (0.50, 0.73)	0.59 (0.48, 0.72)	0.48 (0.37, 0.62)
55-64	0.55 (0.45, 0.66)	0.33 (0.26, 0.40)	0.32 (0.24, 0.42)
65-74	0.38 (0.32, 0.46)	0.11 (0.08, 0.13)	0.11 (0.08, 0.16)
75-84	0.20 (0.16, 0.24)	0.02 (0.01, 0.03)	0.01 (0.01, 0.02)
85+	0.20 (0.16, 0.25)	0.01 (0.01, 0.02)	0.01 (0.00, 0.02)
Race/Ethnicity			
White (ref)	-	-	-
American Indian or Alaska Native, non-Hispanic	1.20 (1.01, 1.42)	1.52 (1.24, 1.87)	1.06 (0.78, 1.43)
Asian, non-Hispanic	0.31 (0.26, 0.37)	0.56 (0.46, 0.70)	0.26 (0.18, 0.38)
Black or African American, non-Hispanic	1.01 (0.86, 1.19)	1.89 (1.58, 2.25)	0.97 (0.79, 1.19)
Hispanic	0.72 (0.61, 0.84)	0.93 (0.78, 1.11)	0.64 (0.51, 0.80)
Multiracial, non-Hispanic	1.07 (0.87, 1.31)	0.67 (0.48, 0.94)	0.67 (0.34, 1.21)
Native Hawaiian or Other Pacific Islander, non-Hispanic	0.56 (0.45, 0.69)	0.53 (0.38, 0.72)	0.47 (0.25, 0.82)
U.S. Census Region			
Midwest (ref)	-	-	-
Northeast	1.52 (1.30, 1.77)	0.62 (0.51, 0.76)	1.68 (1.26, 2.24)
South	1.63 (1.40, 1.89)	1.23 (1.03, 1.47)	4.24 (3.25, 5.54)
West	2.43 (2.09, 2.81)	2.71 (2.28, 3.22)	4.82 (3.69, 6.31)

§ Adjusted models include the following covariates: sex, age group, race/ethnicity, and U.S. Census region.

Table 3.4a – Trend Analysis[!] of Counts and Rates of Nonfatal Overdoses involving Opioids, Stimulants and both Opioids and Stimulants [Continuous Piecewise Linear Regression Results]

	Overall Trend	
Parameters	**Estimates⁺ (95% Confidence Intervals)**	
Opioids w/o Stimulants	**Rates** R^2 = 0.93	**Counts** R^2 = 0.92
Time	0.17 (0.13, 0.21)	85.87 (75.46, 96.29)
Time passed since April 2020 Breakpoint	-0.47 (-0.55, -0.40)	-34.43 (-55.55, -13.31)
Beginning Pandemic Mitigating Measures (April and May 2020)	20.32 (17.83, 22.8)	---
After May 2020	9.29 (7.70, 10.88)	---
Seasonality Variable (Cosine)	-1.38 (-1.92, -0.85)	-423.68 (-576.78, -270.58)
Stimulants w/o Opioids	**Rates** R^2 = 0.88	**Counts** R^2 = 0.79
Time	0.05 (0.04, 0.06)	13.39 (11.62, 15.17)
Time passed since April 2020 Breakpoint	-0.13 (-0.15, -0.12)	-21.02 (-24.62, -17.41)
Beginning Pandemic Mitigating Measures (April and May 2020)	1.66 (1.10, 2.22)	---
After May 2020	-0.22 (-0.58, 0.13)	---
Seasonality Variable (Cosine)	-0.36 (-0.48, -0.24)	-75.15 (-101.27, -49.02)
Both Opioids and Stimulants	**Rates** R^2 = 0.78	**Counts** R^2 = 0.85
Time	0.01 (0.01, 0.01)	3.05 (2.63, 3.47)
Time passed since April 2020 Breakpoint	-0.02 (-0.03, -0.02)	-2.89 (-3.75, -2.03)
Beginning Pandemic Mitigating Measures (April and May 2020)	0.52 (0.36, 0.68)	---
After May 2020	0.10 (0.00, 0.20)	---
Seasonality Variable (Cosine)	-0.08 (-0.12, -0.05)	-18.28 (-24.5, -12.07)

[!] Linear models of outcome including parameters for time in months, pandemic mitigating measures applied in April and May 2020, after May 2020, time passed since April 2020, and seasonality.

⁺ Parameter estimates represent how the slope of overdose rates over time change.

Figure 3.1a:

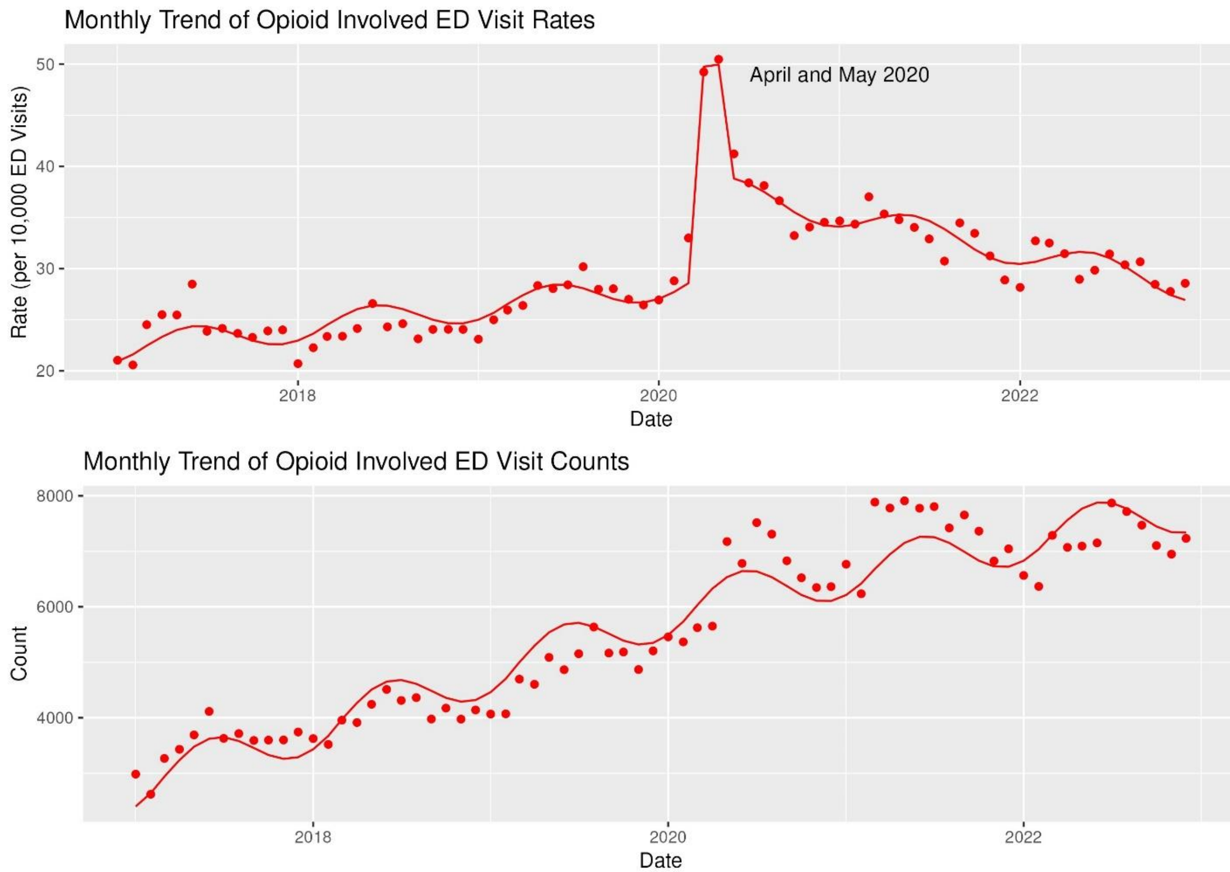
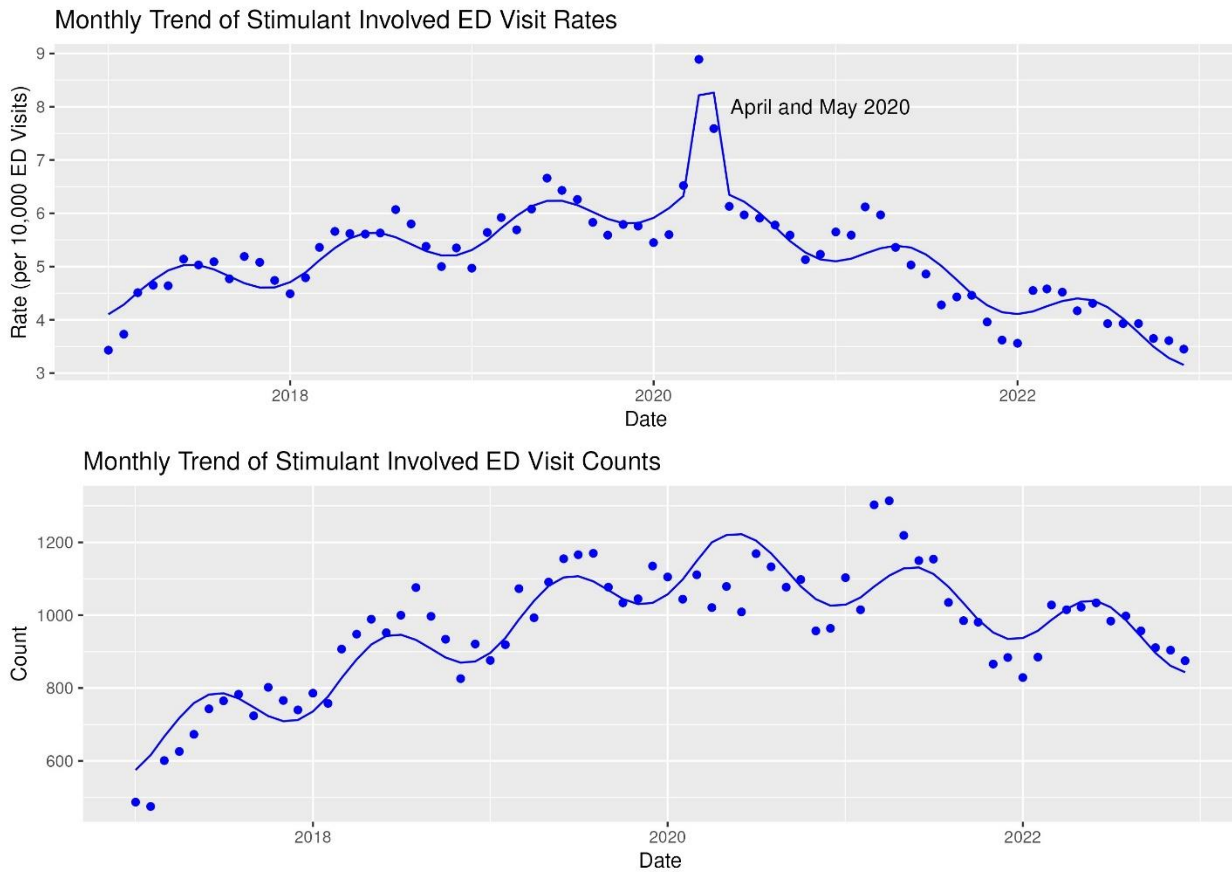
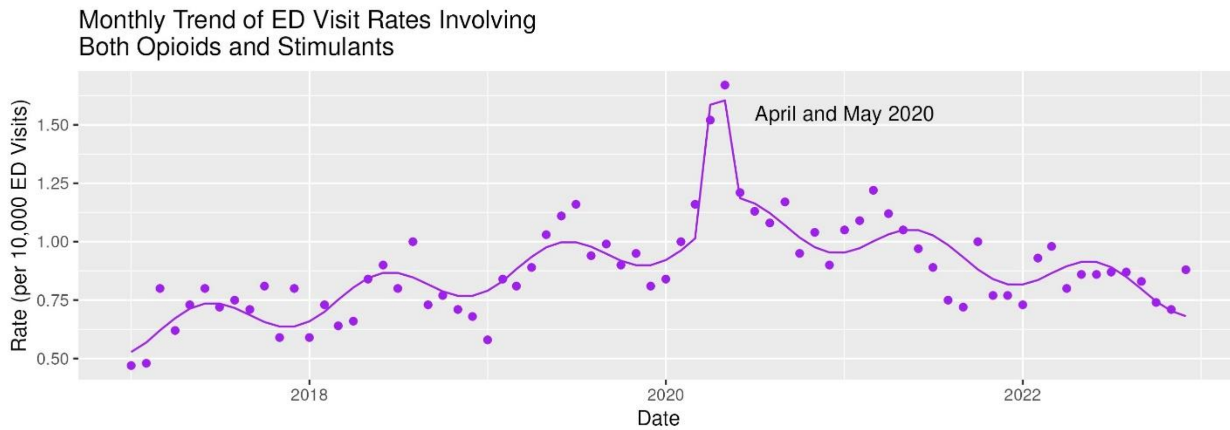

Monthly Trend of Opioid Involved ED Visit Rates
April and May 2020
Rate (per 10,000 ED Visits)
50
40
30
20
2018
2020
2022
Date
Monthly Trend of Opioid Involved ED Visit Counts
Count
8000
6000
4000
2018
2020
2022
Date

Figure 3.2a:

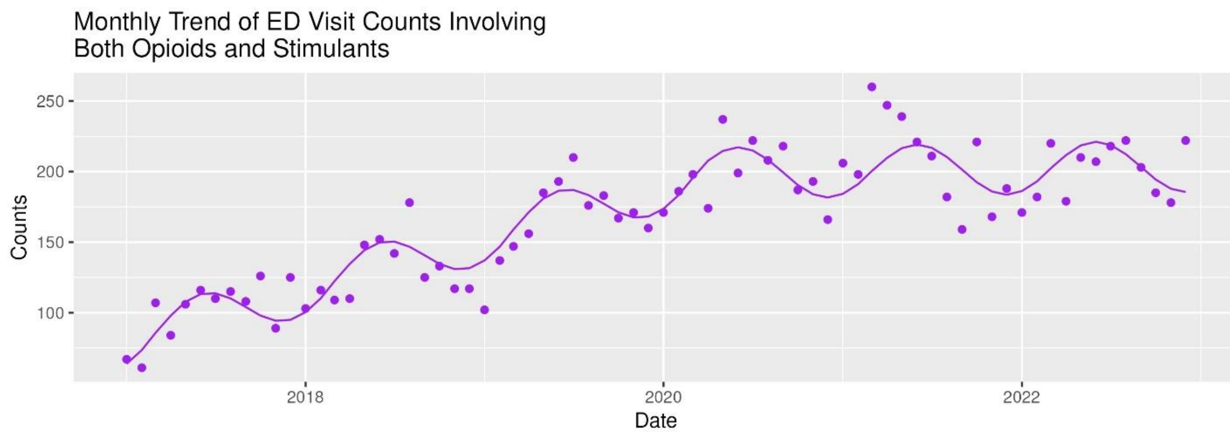


Monthly Trend of Stimulant Involved ED Visit Rates
Rate (per 10,000 ED Visits)
April and May 2020
Date
2018
2020
2022
9
8
7
6
5
4
3
Monthly Trend of Stimulant Involved ED Visit Counts
Count
1200
1000
800
600
Date

Figure 3.3a:



Monthly Trend of ED Visit Rates Involving
Both Opioids and Stimulants
April and May 2020
Rate (per 10,000 ED Visits)
1.50
1.25
1.00
0.75
0.50
2018
2020
2022
Date



Monthly Trend of ED Visit Counts Involving
Both Opioids and Stimulants
Counts
250
200
150
100
2018
2020
2022
Date

Chapter 4: Comparing trends in overdose deaths involving fentanyl with stimulants in the US, January 2019-June 2022

Introduction

Background:

The U.S. overdose crisis continues to evolve as emerging substances and combinations of substances lead to increases in morbidity and mortality (Compton, 2021). O'Donnell et al. (2017) describe the rate of deaths involving heroin substantially increasing nationally and across all US census regions between 2006-2015. The study also observed a dramatic uptick in the rate of synthetic opioid overdose deaths between 2013-2015 (O'Donnell, 2017). Additional overdose mortality research has described increases in opioid-involved overdoses and presence of other substances (including benzodiazepines, cocaine, and methamphetamine (commonly shortened to "meth")) between 2016 and 2017 (Kariisa, 2019) and increases between 2017 and 2018 (Gladden, 2019). Authors describe a limitation of prior analysis as "patterns in drugs involved in opioid deaths might vary across states and demographic groups". These increasing trends paralleled a study of polysubstance use poisoning deaths in Canada between 2014 and 2017, where polysubstance deaths had an average annual percent change of 23% across the study timeframe (Konefal, 2022). The overdose crisis has continued to change since these studies were published, warranting investigations into newly available data.

Many researchers have chronicled demographic characteristics associated with overdose morbidity and mortality across the 2010s. Unick et al.'s (2017) study of national drug overdose hospitalizations between 2000 and 2014 observed regional and demographic differences rates of prescription opioid overdose (POD) and heroin overdose (HOD) hospitalizations. Unick (2017) found that non-Hispanic Whites had statistically significantly higher increases in rates of hospitalization compared to other categories. In more recent years, a study of drug overdose deaths in 2017-2018 observed deaths involving synthetic opioids increased among males and females, persons aged >= 25 years, and in the Northeast, South, and West census regions (Wilson, 2020). Likewise, Spencer et al. (2022) observed higher overdose death rates in 2021 than in 2020 for all age groups 25 and over and for all race and Hispanic-origin groups except non-Hispanic Asian people. Further, numerous studies have found evidence of racial/ethnic disparities in health that were magnified during the COVID-19 pandemic, including within the overdose epidemic (Yancy, 2020; Dowling 2020; Galea, 2020; Khatri, 2021; Slavova, 2023). It is critical to understand how drug overdose deaths differ across demographic characteristics with most recently available data.

CDC's OD2A currently supports 47 states and Washington, DC to provide comprehensive overdose death data to the State Unintentional Drug Overdose Reporting System (SUDORS) (CDC SUDORS, 2022). SUDORS incorporates multiple data sources including death certificates, coroner/medical examiner (C/ME) reports, and postmortem toxicology reports to combine data elements like date and location of death, demographics information, cause-of-death, history of prior overdoses, all drugs detected and drugs contributing to death (CDC SUDORS, 2022). SUDORS data are much more comprehensive than other data sources, however, there is a significant lag in data availability as delays can be a year or more with complete data only available through 2022 from 32 jurisdictions (CDC SUDORS Dashboard, 2022).

The goal of this analysis is to investigate demographic factors associated with and overall trends in overdose deaths involving both fentanyl and a stimulant (i.e., methamphetamine and/or cocaine). We intend to fill knowledge gaps in past research by exploring overall trends, expanding the number of U.S. jurisdictions included, and exploring newly available drug overdose death data. The SUDORS surveillance system has expanded from 33 jurisdictions in 2017 to 48 jurisdictions in 2019 (CDC SUDORS, 2022). Additionally, in 2019, SUDORS expanded from including only opioid-involved deaths to including all drug overdose deaths to better understand drug combination deaths and identify emerging threats (Gladden, 2019). In this analysis, we will describe fatal overdose trends among decedents where fentanyl and/or a stimulant were identified in toxicology reporting and noted as contributing to death. To be considered for contribution to death, a drug must first be identified in toxicology report results.

Methods

Study Design:

This is an analysis examining associations between overdose deaths and demographic characteristics and trends in monthly fatal overdoses in national SUDORS data between January 2019 – June 2022. For this analysis, we will examine three mutually exclusive outcomes: 1) deaths with fentanyl identified as cause of death (COD) with no positivity for stimulants (i.e., methamphetamine or cocaine), 2) deaths with stimulants as COD with no positivity for fentanyl (or fentanyl metabolites), and 3) deaths involving both fentanyl and a stimulant where either or both were deemed COD. Deaths with fentanyl include the following fentanyl metabolites: norfentanyl, despropionylfentanyl, hydroxyfentanyl, and hydroxynorfentanyl (Feierman, 1996). Deaths with stimulants include methamphetamine, cocaine, and cocaine metabolites (benzoylecgonine (BE), ecgonine methyl ester (EME), norcocaine, p-hydroxycocaine, m-hydroxycocaine, p-hydroxybenzoylecgonine (pOHBE), and m-hydroxybenzoylecgonine (Kolbrich, 2006)).

We capture distributions across demographic characteristics (age, sex, race/ethnicity) and U.S. Census region. We restricted the analysis to jurisdictions meeting the data quality requirements established by prior SUDORS analyses: at least 75% death certificate coverage AND at least 90% of cases with a toxicology report for all included periods. Observations where sex, age, race/ethnicity, state where death occurred, and date of death were not available were excluded. January 2019 is the earliest available SUDORS data on all drug overdoses, determining the start date for this analysis, and June 2022 was the last available data for SUDORS data at time of analysis. We will study the dependence of counts of each outcome on covariates in the total study period and investigate the monthly trend of fatal overdose counts over time.

Analysis:

First, we calculated frequencies and percentages of overdose deaths involving fentanyl, a stimulant, and combinations of fentanyl and at least one stimulant among all drug overdose deaths across demographic characteristics and US Census region.

To examine the relationship between counts of overdose deaths of interest and covariates between January 2019-June 2022, we fit negative binomial regression models. Negative binomial regression was selected as the Chi-Squared values from Pearson Goodness-of-Fit tests for all three outcomes of interest were close to 1.00, suggesting that there is no lack of fit. Poisson regression model results did not pass Pearson Goodness-of-Fit as Chi-Square values were much larger than 1.00. Additionally, Akaike Information Criterion values for negative binomial regression models were lower than corresponding Poisson models, thus we continued with negative binomial regression results. Model coefficients will represent the change of log of mean count when predictor values change. We report unadjusted and adjusted estimated coefficients (CEs) and 95% Confidence Intervals. Confidence intervals that do not include 0.00 were considered statistically significant. Statistical analyses will be performed in R programming language (R 4.2.2 Project for Statistical Computing), specifically using the glm.nb() function of the “MASS” package Negative Binomial Poisson regression (Ripley, 2002).

To investigate overall trends in overdose deaths across the three outcomes of interest and to evaluate influential breakpoints during the study period, we modeled overdose death counts via continuous piecewise linear regression. In addition, to capture the periodic pattern observed in the data, we include the trigonometric functions, sine/cosine terms (also known as Fourier terms) with a 12-month seasonal period, in the model (Bhaskaran, 2013). Sine and cosine trigonometric functions have been used in many past public health studies assessing seasonal variation in time series analyses (Wojcik, 2023; Bhaskaran, 2013; Stolwijk, 1999; Barnett, 2010). Bhaskaran (2013) notes that pros of using this method include long-term patterns are modeled smoothly, using relatively few parameters. With this model, we simultaneously modeled the change in the trend and the seasonal pattern.

An example of simplified model with a breakpoint at t_0 and a 12-month period has the form

$$Y = \beta_0 + \beta_1 t + \beta_2 (t - t_0)_+ + \beta_3 \cos\left(\frac{2\pi t}{12}\right) + \epsilon$$

where t represents time in months, and $(t - t_0\ )_+$represents the time since the breakpoint t_0 , which is $t - t_0$ if $t > t_0$ and is 0 if $t \leq t_0$ .With this model, if t_0 represents a breakpoint observed in plotted overdose death counts, the parameter β1 represents the slope of time before that breakpoint (i.e., the changing rate of the mean of Y as t varies before the breakpoint), β2 represents change in the slope of time after the breakpoint (i.e., the difference of the changing rates of the mean of Y after and before the breakpoint), and β3 represents the seasonal effect across a 12-month period. We explored the best fitting models by assessing R-squared values for improvements in model fit, and reporting coefficients and 95% confidence intervals, where intervals that do not include 0.00 are considered statistically significant. Residual plots were reviewed to identify any severe linear regression assumption violations. Trend analyses were performed using lm() function of the "stats" package in R (R 4.2.2 Project for Statistical Computing).

Results

Descriptive statistics:

Forty-seven[d] jurisdictions reported 200,529 overdose deaths to SUDORS meeting this studies inclusion criteria between January 2019-June 2022. Among those, 62,461 (31.2%) were fentanyl

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[d] Jurisdictions included in this analysis: Alabama, Alaska, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, Florida, Georgia, Hawaii, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana, Nebraska, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, South Dakota, Tennessee, Texas, Utah, Vermont, Virginia, Washington, West Virginia, Wisconsin and the District of Columbia.

overdose deaths without stimulants, 34,366 (17.1%) were stimulant overdose deaths without fentanyl, and 77,797 (38.8%) were overdose deaths involving both fentanyl and stimulants. Counts and percentages of overdose death type by covariate are reported in Table 4.1. The following paragraphs will describe negative binomial regression results for each outcome.

Negative Binomial Regression Results:

Coefficient estimates represent the log mean count of outcome. Unadjusted and adjusted coefficient estimates (aCEs) and confidence intervals are provided in Table 4.2 and Table 4.3, respectively.

Fentanyl Overdose Deaths without Stimulants

Adjusted log of mean count of fentanyl overdose deaths among females was 1.03 less than that for males (adjusted CE (aCE): -1.03; 95% CI: -1.20,-0.86). This is equivalent to saying that mean count for females is 0.36 $[0.36 = exp(aCE)]$ times the mean count for males. Compared to 25–34-year-olds, log of mean counts of overdoses deaths were lower among all other age groups (aCE range: -2.25—-0.34). In other words, the mean counts of other age groups were between 11%–71% of the 25-34-year-olds. Compared to Whites, mean counts for fentanyl overdose death were 0.83%—32% (aCE range: -4.79—-1.14) of Whites. Mean count of fentanyl overdose deaths in the West was 0.64 times the odds in the Midwest (aCE: -0.45; CI: -0.71,-0.20). No statistically significant difference in log of mean counts was identified between deaths in the Northeast and South compared to Midwest.

Stimulant Overdose Deaths without Fentanyl

Adjusted mean counts of stimulant overdose deaths among females were 40% of males (aCE: -0.91; 95% CI: -1.06,-0.75). Mean counts of stimulant overdose death among 15-24 and 65+ age groups were 0.20% and 35% of that of 25–34-year-olds (aCE range: -1.59—-1.05), respectively. Additionally, adjusted mean count of stimulant overdose deaths among 35-44 and 45-54 year-olds were both approximately 22 % times of the 25-34 (aCE range: -1.51—-1.53). Compared to Whites, adjusted mean count of stimulant overdose deaths among other race/ethnicity categories were 2%-38% as high (aCE range: -4.19—-0.96). Compared to the Midwest, mean counts were 1.51 and 2.10 times as high in the South (aCE: 0.41; CI: 0.19,0.62) and West (aOR: 0.73; CI: 0.51,0.95) regions, respectively, but 0.62 times as high in the Northeast (aCE: -0.49; CI: -0.71,-0.26).

Overdose Deaths involving Both Fentanyl and a Stimulant

Adjusted mean count of overdose deaths involving both fentanyl and a stimulant were 39% as high in females compared to males (aCE: -0.94; 95% CI: -1.11,-0.77). Mean counts were between 7%-58% as high among 15-24, 45-54, 55-64, and 65+ year olds compared to 25-34 year-olds (aCE range: -2.65–-0.55). Compared to Whites, mean count of fentanyl and stimulant overdose deaths were between 2%-42% as high among all other race/ethnicity categories (aCE range: -4.84–-0.87). Mean count of overdose deaths in the West were 58% of the Midwest (aCE: -0.55; 95% CI: -0.80,-0.30). No statistically significant difference was identified between the South and Northeast compared to Midwest U.S. Census region.

Trend Results:

All trend analysis coefficient estimates (referred to as β) and 95% confidence intervals (CIs) are reported in Table 4.4. Plots of overall trends for counts of fentanyl-, stimulant- and combinations of fentanyl and stimulants-involved overdose deaths are available in Figures 4.1, 4.2 and 4.3, respectively, with fitted curves imposed. Alternative model and plot for fentanyl overdose death trends are provided in supplemental materials in the Appendix for comparison.

Fentanyl Overdose Death without Stimulants Trends

Fentanyl overdose death counts show an obvious increasing trend between the end of 2019 and beginning of 2021. Starting with little linear trend in 2019 (β: -0.30; 95% CI: -20.37,19.77), in February 2020, the slope of overdose deaths had a significant increase (β: 45.68; 95% CI: 13.26,78.10), leading to an increasing trend for overdose death counts from February 2020 to November 2020. In November 2020 the slope again increased by approximately 92 deaths per month (β: 91.61; 95% CI:

15.60,167.61), then decreased by 207 deaths per month in April 2021 (β: -206.99; 95% CI: -291.43,-122.55). Seasonal factors significantly impacted fentanyl overdose death trends as negative coefficients for the cosine terms described more fentanyl overdose deaths in warmer months [May-August] than cooler [November-February] (Cosine β: -76.34; 95% CI: -132.70,-19.98).

Stimulant Overdose Death without Fentanyl Trends

Stimulant involved overdose death counts increased by about 10 per month from January 2019-November 2020 (β: 10.04; 95% CI: 6.03,14.05). In November 2020 there was a significant increase in slope (β: 37.02; 95% CI: 17.88,56.17), leading to a dramatically increasing trend (slope=$10.04 + 37.02 = 47.06$ between November 2020 and April 2021). Following April 2021, slope of trends in counts dropped by 58 units (CE: -58.12; 95% CI: -80.15,-36.10) per month, leading to a decreasing trend (slope= $10.04 + 37.02 - 58.12 = -11.06$ since April 2021). Seasonality significantly influenced the trend model of stimulant overdose counts as negative coefficients for the cosine term described more stimulant overdose deaths in warmer months than cooler (Cosine β: -44.82; 95% CI: -74.46,-15.17).

Both Fentanyl and a Stimulant Overdose Death Trends

Counts of overdose deaths involving fentanyl and a stimulant increased by about 50 deaths per month from January 2019 to November 2020 (β: 50.24; 95% CI: 40.40,60.07). Around November 2020, the slope significantly changed, increasing overall trend by an additional 69 deaths per month (β: 68.71; 95% CI: 22.31,115.10). Finally, slope of trend in counts significantly decreased in April 2021 (β: -116.73; 95% CI: -169.43,-64.03), leading to a slow increasing trend through the end of the study period (slope= $50.24 + 68.71 - 116.73 = 2.22$). Like the previous two outcomes, seasonality played a significant role in trends in overdose deaths involving fentanyl and a stimulant as positive coefficients for sine and negative coefficients for the cosine terms described more stimulant overdose deaths in spring months [March-May] than fall months [August-November] (Sine β: 102.14; 95% CI: 29.22,175.05; Cosine β: -122.85; 95% CI: -193.33,-52.36).

Discussion

Summary of findings

Between January 2019 and June 2022, approximately 31% of all captured overdose deaths involved only fentanyl, 17% only stimulants, and 39% involved combinations of fentanyl and stimulants. Mean counts of each overdose death type varied by demographic characteristic. Trends in overdose deaths varied over time.

Mean counts of overdose deaths for all three outcomes were greater among males. Mean count of overdose deaths with any fentanyl positivity (including fentanyl only and both fentanyl and a stimulant) were generally greater among 25–34-year-olds, however, 35-44 and 45-54-year-olds had greater mean counts of stimulant only overdose death. These findings align with studies of nonfatal and fatal overdoses involving opioids and stimulants in the US where overdose rates were greater among males and in the 25-44 age ranges (Rodda, 2020; Spencer, 2022).

Mean counts of overdose deaths among non-Hispanic Whites were greater for all three overdose death types compared to non-White races analyzed. Though our studies' outcomes differed, these findings align with Unick et al.'s (2017) observations where rates of POD and HOD hospitalization were highest among non-Hispanic Whites. Additionally, in a study of socio-economic factors and their relationship with drug overdose death between 2001-2014, Heyman et al. (2019) also observed highest drug overdose death rates among non-Hispanic Whites. Further investigation of polysubstance drug overdose deaths by race/ethnicity is necessary.

Mean counts of overdose death with fentanyl positivity contributing to cause of death, with and without stimulants, were greater in the Midwest compared to West. Meanwhile, stimulant only overdose deaths were greater than the Midwest in the South and West regions and less in the Northeast. Researchers note that supply and socioeconomic factors combined explain the wide variation in geographic and sociodemographic overdose risk (Heyman, 2019; Monnat, 2019). The present study adds to previously published research by providing statistical analysis of overdose deaths involving both opioids and stimulants. More regional and state-level analysis of polysubstance drug overdose death data is warranted.

Overdose deaths involving fentanyl without stimulants, stimulants without fentanyl, and combinations of fentanyl and stimulants increased over time. Trends in all three outcomes were influenced by seasonality with warmer, spring/summer months reflecting higher counts than cooler months. The slope of fentanyl only overdose deaths increased dramatically in February 2020, and again in November 2020, along with stimulant and combinations of fentanyl and stimulants overdose deaths before decreasing April 2021. Many states and the federal government pushed to facilitate telehealth services during 2020 (Drug Enforcement Administration & U.S. Department of Justice, 2020), however, the effects of the COVID-19 pandemic on drug overdoses are undeniable. A 2021 study describing trends in visits to substance use disorder treatment facilities noted that counties with higher COVID-19 rates had larger declines in weekly visits between March and August of 2020 (Cantor, 2021). Additionally, multiple sources reported decreases in use (Palamar, 2020; Stark, 2020) and availability of select drugs during early months of the pandemic (United Nations Office of Drugs and Crime, 2020) while several studies identified increases in nonfatal and fatal overdoses in the same timeframe (Ochalek, 2020; Glober, 2020; Rodda, 2020; Slavova, 2020). In a report on the opioid crisis and recent federal policy responses, the U.S. Congressional Budget Office [CBO] (2022) acknowledged that alongside socioeconomic factors and changes in the illegal opioid market, demand for opioids increased among people who experienced declining real wages and social circumstances like worsened mental health, more social isolation, and reduced access to treatment. To combat the evolving opioid overdose crisis, certain MOUD treatment barriers were reduced in March 2020, and the “American Rescue Plan Act” was signed in March 2021 to appropriate funds to address the crisis (CBO, 2022). The present findings align with recent publications on overdose deaths in Delaware, Kentucky, and Michigan where researchers observed yearly increases in opioid overdose deaths and similar seasonal trends leading up to and encompassing the same timeframe (Abraham, 2021; Slavova, 2023; Sadler, 2019). Additionally, in a study on trends in opioid overdose mortality rates in Kentucky, Slavova et al. (2023) observed increases in overdose deaths between 2019 and 2020 across all demographic groups studied. Several studies observed similar opioid-, stimulant-, and combined overdose death increases around this timeframe at the state and national level (Spencer, 2022; Trecki, 2022; Friedman, 2022; Han, 2021; Slavova, 2023; DiGennaro, 2021). Slavova (2023) also observed “significant increases in opioid involvement among cocaine-involved and other psychostimulant-involved deaths” in Kentucky between 2019 and 2020. Many researchers suggest that illicitly manufactured fentanyl (IMF) and synthetic opioids like parafluorofentanyl were key contributors to increases observed (Trecki, 2022; Friedman, 2022; DiGennaro, 2021). Additionally, researchers suggest that fentanyl analog and other novel synthetic opioid overdose deaths are underreported due to limitations in postmortem toxicology to identify substances consumed by decedents (Slavova, 2023).

This study observed significant seasonal effects on overdose deaths. Multiple studies of seasonal trends in nonfatal overdose observed similar findings prior to 2020 (Vivolo-Kantor, 2018; Vivolo-Kantor, 2019). The present study adds to current research by expanding the study period and by providing statistical backing to seasonal overdose death trends involving combinations of fentanyl and stimulants. Future analyses should consider examining national overdose death trends across all demographic groups.

Limitations:

This analysis had at least three limitations. First, it is not always possible to determine intent when analyzing polysubstance use and overdose, thus, we cannot speculate on behavioral reasons why polysubstance results may differ from fentanyl only or stimulant only overdoses. Additional consideration should be taken when developing prevention and intervention strategies geared toward self-harm versus unintentional overdose. Second, this analysis used “cause of death” to determine inclusion into the analytic dataset. While substances must be verified on a toxicology report, the status of “cause of death” is determined by individual coroners/medical examiners investigating each death based on myriad contextual factors. The selected outcomes could underestimate the true burden of overdose deaths involving fentanyl, stimulants, or combinations of both. Finally, this analysis did not capture trends by demographic characteristics, thus we cannot make any inferences to how trends varied by populations.

Next steps

Drug overdose experts recommend strategies that address characteristics overdoses involving illicitly manufactured fentanyl, preventing initiation of prescription opioid and stimulant misuse and illicit drug use (O’Donnell, 2020). Future analyses should consider incorporating descriptive and influential comparisons between fentanyl overdose deaths without stimulants and stimulant overdose deaths without fentanyl compared to overdose deaths involving both fentanyl and stimulants and to each other. Additionally, prevention and intervention strategists should consider changes in use patterns within the year to account for seasonal overdose burden fluctuations. Future analyses should consider analyzing trends in fentanyl, stimulant and polysubstance overdose deaths concurrently to better understand how the trends compare. Additionally, future analyses should compare polysubstance overdose death trends to polysubstance drug use and nonfatal overdose trends across similar timeframes to observe how the varying health outcomes influence each other. Finally, future analyses should investigate polysubstance overdose death trends by demographic characteristics and regions/states to identify groups with increasing risk.

Tables & Figures

Table 4.1 – Frequencies and Percentages of Fatal Overdoses Involving Fentanyl, Stimulants, and Combinations of Fentanyl and Stimulants among all Fatal Overdoses, January 2019-June 2022

All Drug Overdose Deaths N = 200,529 (%)	**Fentanyl Only** N = 62,461 (31.15)	**Stimulants Only** N = 34,366 (17.14)	**Fentanyl and a Stimulant** N = 77,797 (38.80)
Sex	N (% of category overdose deaths)		
Female N = 60,675 (30.26)	16,521 (27.23)	10,275 (16.93)	22,449 (37.00)
Male N = 139,854 (69.74)	45,940 (32.85)	24,091 (17.23)	55,348 (39.58)
Age Group	N (% of category overdose deaths)		
15-24 N = 13,144 (6.55)	6,426 (48.89)	1,028 (7.82)	4,479 (34.08)
25-34 N = 47,778 (23.83)	17,665 (36.97)	5,099 (10.67)	20,481 (42.87)
35-44 N = 52,834 (26.35)	15,577 (29.48)	8,040 (15.22)	23,062 (43.65)
45-54 N = 42,498 (21.19)	11,095 (26.11)	9,180 (21.6)	16,321 (38.4)
55-64 N = 34,817 (17.36)	9,165 (26.32)	8,619 (24.76)	11,444 (32.87)
65+ N = 9,458 (4.72)	2,533 (26.78)	2,400 (25.38)	2,010 (21.25)
Race/Ethnicity	N (% of category overdose deaths)		
White, Non-Hispanic N = 137,604 (68.62)	43,204 (31.4)	22,636 (16.45)	51,196 (37.21)
Black, Non-Hispanic N = 38,922 (19.41)	11,085 (28.48)	7,266 (18.67)	17,427 (44.77)
American Indian/Alaska Native, Non-Hispanic N = 2,518 (1.26)	653 (25.93)	729 (28.95)	847 (33.64)
Asian/Pacific Islander, Non-Hispanic N = 1,364 (0.68)	400 (29.33)	375 (27.49)	430 (31.52)
Multi-race, Non-Hispanic N = 1,628 (0.81)	526 (32.31)	374 (22.97)	575 (35.32)

Hispanic or Latino N = 18,493 (9.22)	6,593 (35.65)	2,986 (16.15)	7,322 (39.59)
U.S. Census Region	N (% of category overdose deaths)		
Midwest N = 55,332 (27.59)	17,196 (31.08)	8,286 (14.98)	22,981 (41.53)
Northeast N = 47,516 (23.70)	18,112 (38.12)	4,805 (10.11)	20,032 (42.16)
South N = 47,138 (36.97)	21,896 (29.53)	13,014 (17.55)	28,588 (38.56)
West N = 23,543 (11.74)	5,257 (22.33)	8,261 (35.09)	6,196 (26.32)

Table 4.2 – Unadjusted Coefficient Estimates (CEs) for Fatal Overdoses Involving Combinations of Fentanyl and Stimulants¶, Jan 2019-June 2022 [Negative Binomial Regression Results]

	Fentanyl Only CE (95% CI)	**Stimulant Only CE (95% CI)**	**Fentanyl & a Stimulant CE (95% CI)**
Sex			
Female	-1.01 (-1.40, -0.61)	-0.84 (-1.22, -0.46)	-0.89 (-1.30, -0.48)
Male (ref)	-	-	-
Age Groups (years)			
15-24	-0.99 (-1.67, -0.31)	-1.58 (-2.22, -0.94)	-1.50 (-2.18, -0.82)
25-34 (ref)	-	-	-
35-44	-0.13 (-0.80, 0.55)	0.46 (-0.18, 1.09)	0.12 (-0.56, 0.80)
45-54	-0.47 (-1.14, 0.21)	0.59 (-0.04, 1.22)	-0.23 (-0.90, 0.45)
55-64	-0.66 (-1.33, 0.02)	0.52 (-0.11, 1.16)	-0.58 (-1.26, 0.10)
65+	-1.92 (-2.60, -1.24)	-0.73 (-1.37, -0.10)	-2.30 (-2.98, -1.62)
Race/Ethnicity			
White, Non-Hispanic (ref)	-	-	-
Black, Non-Hispanic	-1.36 (-1.77, -0.95)	-1.14 (-1.56, -0.72)	-1.08 (-1.51, -0.64)
American Indian/Alaska Native, Non-Hispanic	-4.15 (-4.57, -3.73)	-3.39 (-3.82, -2.96)	-4.06 (-4.50, -3.61)
Asian/Pacific Islander, Non-Hispanic	-4.68 (-5.10, -4.26)	-4.10 (-4.53, -3.67)	-4.78 (-5.23, -4.33)
Multi-race, Non-Hispanic	-4.41 (-4.83, -3.99)	-4.10 (-4.53, -3.67)	-4.49 (-4.93, -4.05)
Hispanic or Latino	-1.88 (-2.29, -1.47)	-2.03 (-2.45, -1.60)	-1.94 (-2.38, -1.51)
U.S. Census Region			
Midwest (ref)	-	-	-
Northeast	0.08 (-0.48, 0.64)	-0.52 (-1.06, 0.03)	-0.11 (-0.68, 0.47)

South	0.24 (-0.31, 0.80)	0.45 (-0.09, 0.99)	0.22 (-0.35, 0.79)
West	-1.19 (-1.74, -0.63)	0.00 (-0.54, 0.54)	-1.31 (-1.88, -0.74)

¶ Stimulants include methamphetamine and cocaine.

Table 4.3 – Adjusted§ Coefficient Estimates (CE) for Fatal Overdoses Involving Combinations of Fentanyl and Stimulants¶, Jan 2019-June 2022 [Negative Binomial Regression Results]

	Fentanyl Only CE (95% CI)	**Stimulant Only CE (95% CI)**	**Fentanyl & a Stimulant CE (95% CI)**
Sex			
Female	-1.03 (-1.20, -0.86)	-0.91 (-1.06, -0.75)	-0.94 (-1.11, -0.77)
Male (ref)	-	-	-
Age Groups (years)			
15-24	-0.61 (-0.90, -0.32)	-1.59 (-1.87, -1.30)	-1.14 (-1.43, -0.84)
25-34 (ref)	-	-	-
35-44	-0.34 (-0.63, -0.06)	0.43 (0.17, 0.68)	-0.02 (-0.29, 0.26)
45-54	-0.74 (-1.03, -0.45)	0.41 (0.16, 0.67)	-0.55 (-0.83, -0.27)
55-64	-1.06 (-1.35, -0.76)	0.19 (-0.07, 0.45)	-1.02 (-1.31, -0.73)
65+	-2.25 (-2.56, -1.94)	-1.05 (-1.33, -0.78)	-2.65 (-2.96, -2.33)
Race/Ethnicity			
White, Non-Hispanic (ref)	-	-	-
Black, Non-Hispanic	-1.14 (-1.41, -0.86)	-0.96 (-1.21, -0.72)	-0.87 (-1.14, -0.59)
American Indian/Alaska Native, Non-Hispanic	-4.02 (-4.32, -3.71)	-3.60 (-3.86, -3.33)	-3.84 (-4.14, -3.55)
Asian/Pacific Islander, Non-Hispanic	-4.79 (-5.09, -4.48)	-4.19 (-4.47, -3.92)	-4.84 (-5.14, -4.53)
Multi-race, Non-Hispanic	-4.43 (-4.73, -4.13)	-4.16 (-4.44, -3.88)	-4.36 (-4.65, -4.06)
Hispanic or Latino	-1.93 (-2.21, -1.65)	-2.09 (-2.34, -1.84)	-1.93 (-2.21, -1.65)
U.S. Census Region			
Midwest (ref)	-	-	-
Northeast	-0.04 (-0.28, 0.20)	-0.49 (-0.71, -0.26)	-0.19 (-0.43, 0.05)
South	-0.04 (-0.27, 0.20)	0.41 (0.19, 0.62)	-0.04 (-0.27, 0.20)
West	-0.45 (-0.71, -0.20)	0.73 (0.51, 0.95)	-0.55 (-0.80, -0.30)

§ Adjusted models include the following covariates: sex, age group, race/ethnicity, and U.S. Census region.

¶ Stimulants include methamphetamine and cocaine.

Table 4.4a Overall Trends of Fatal Overdoses Involving Combinations of Fentanyl and Stimulants¶, Jan 2019-June 2022 [Continuous Piecewise Linear Regression Results]

Parameters	
Fentanyl Only	**Estimates (95% Confidence Intervals)** $R^2 = 0.90$
Time	-0.30 (-20.37, 19.77)
Time since February 2020 Breakpoint	45.68 (13.26, 78.10)
Time since November 2020 Breakpoint	91.61 (15.60, 167.61)
Time since April 2021 Breakpoint	-206.99 (-291.43, -122.55)
Seasonality Variable (Sine 24-month period©)	-296.26 (-418.76, -173.75)
Seasonality Variable (Cosine 12-month period)	-76.34 (-132.70, -19.98)
Stimulants Only	**Estimates (95% Confidence Intervals)** $R^2 = 0.85$
Time	10.04 (6.03, 14.05)
Time since November 2020 Breakpoint	37.02 (17.88, 56.17)
Time since April 2021 Breakpoint	-58.12 (-80.15, -36.10)
Seasonality Variable (Cosine 12-month period)	-44.82 (-74.46, -15.17)
Fentanyl and a Stimulant	**Estimates (95% Confidence Intervals)** $R^2 = 0.95$
Time	50.24 (40.40, 60.07)
Time since November 2020 Breakpoint	68.71 (22.31, 115.10)
Time since April 2021 Breakpoint	-116.73 (-169.43, -64.03)
Seasonality Variable (Sine 12-month period)	102.14 (29.22, 175.05)
Seasonality Variable (Cosine 12-month period)	-122.85 (-193.33, -52.36)

¶ Stimulants include methamphetamine and cocaine.

©The best fitting model included a sine factor with a 24-month period. This parameter, though statistically significant, was not interpreted as available data did not include four complete years (or two 24-month periods). The second-best fitting model that does not include the 24-month period sine factor is included in Chapter 4 Supplemental Materials in the Appendix.

Figure 4.1a

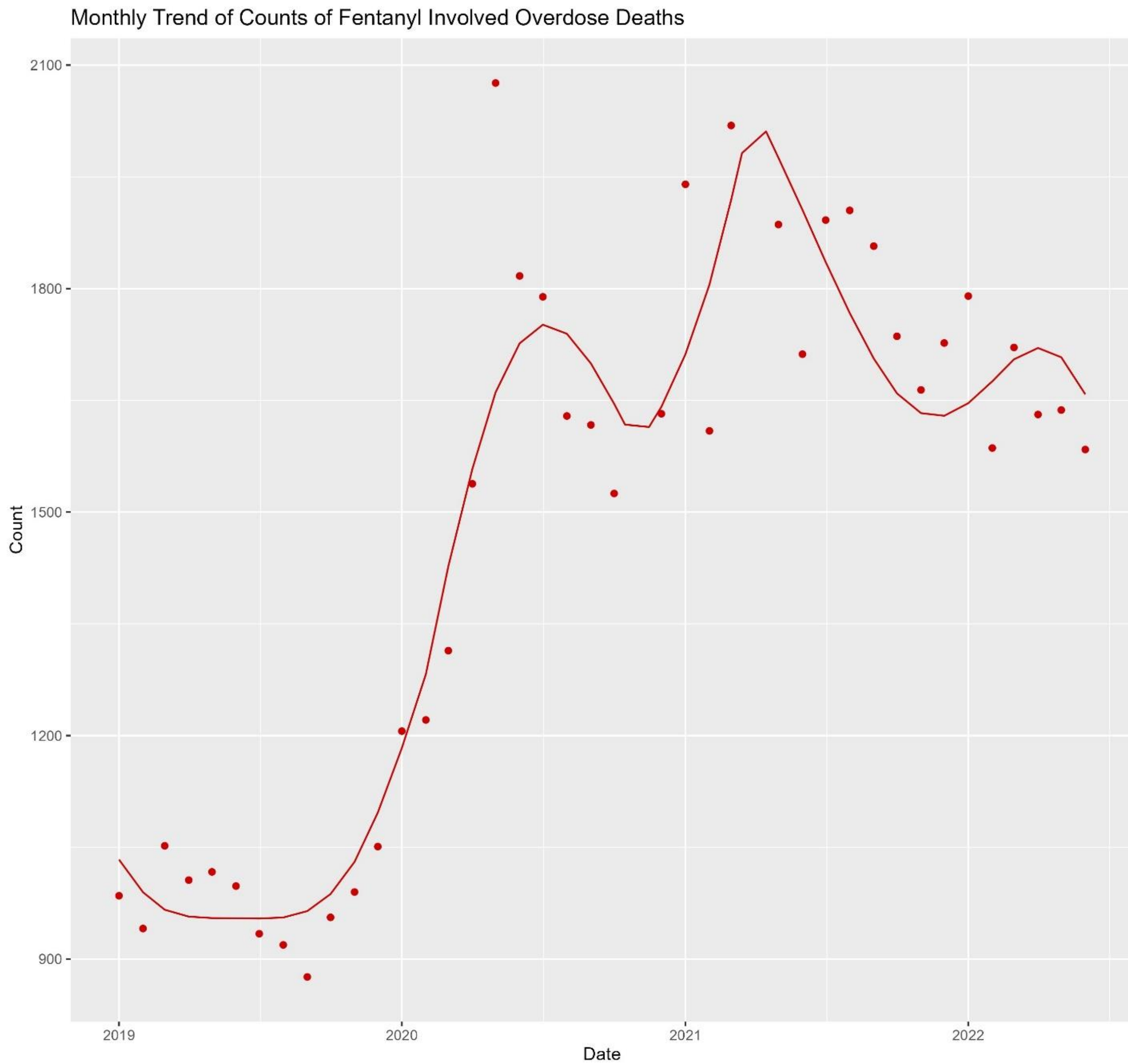
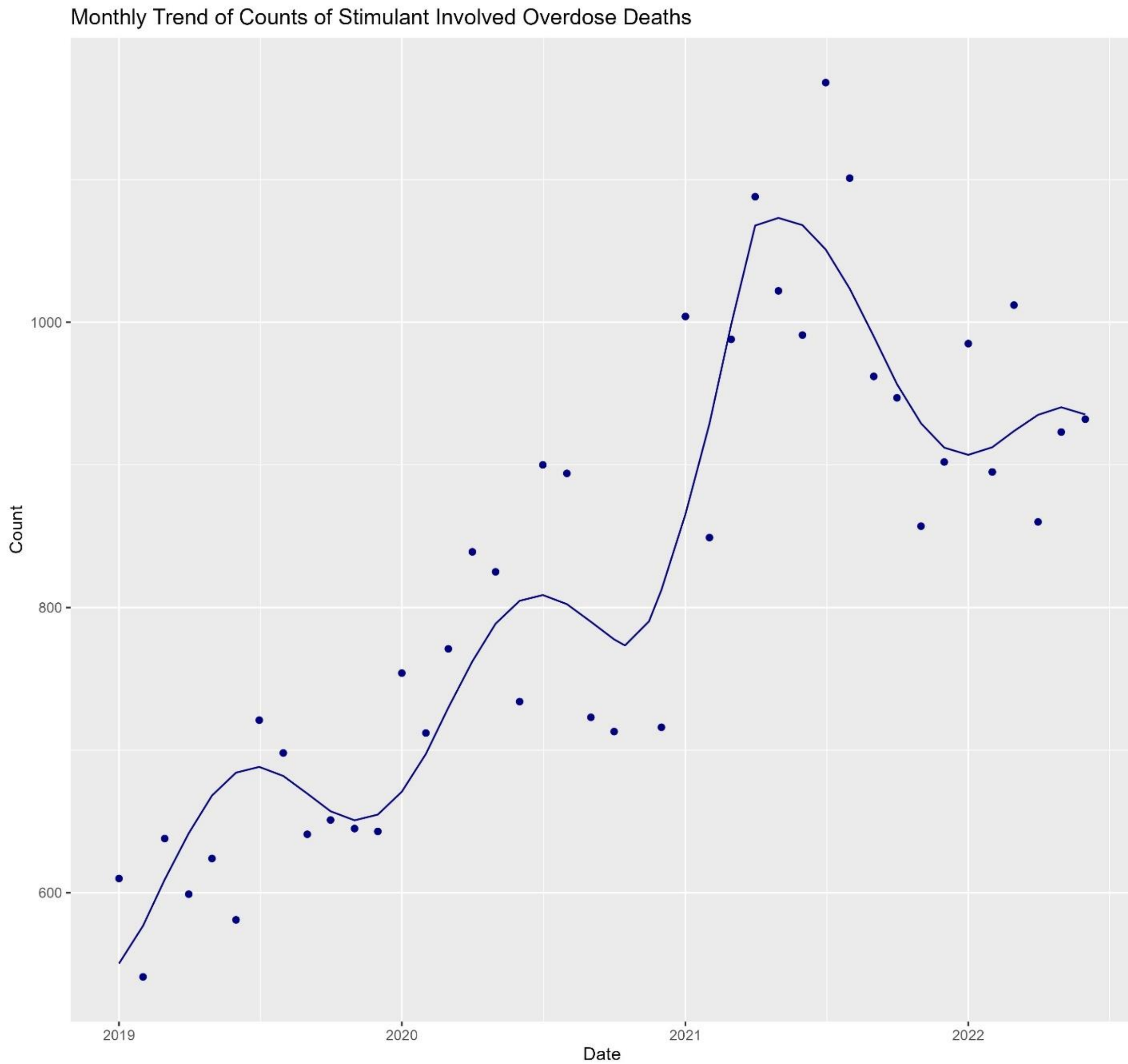
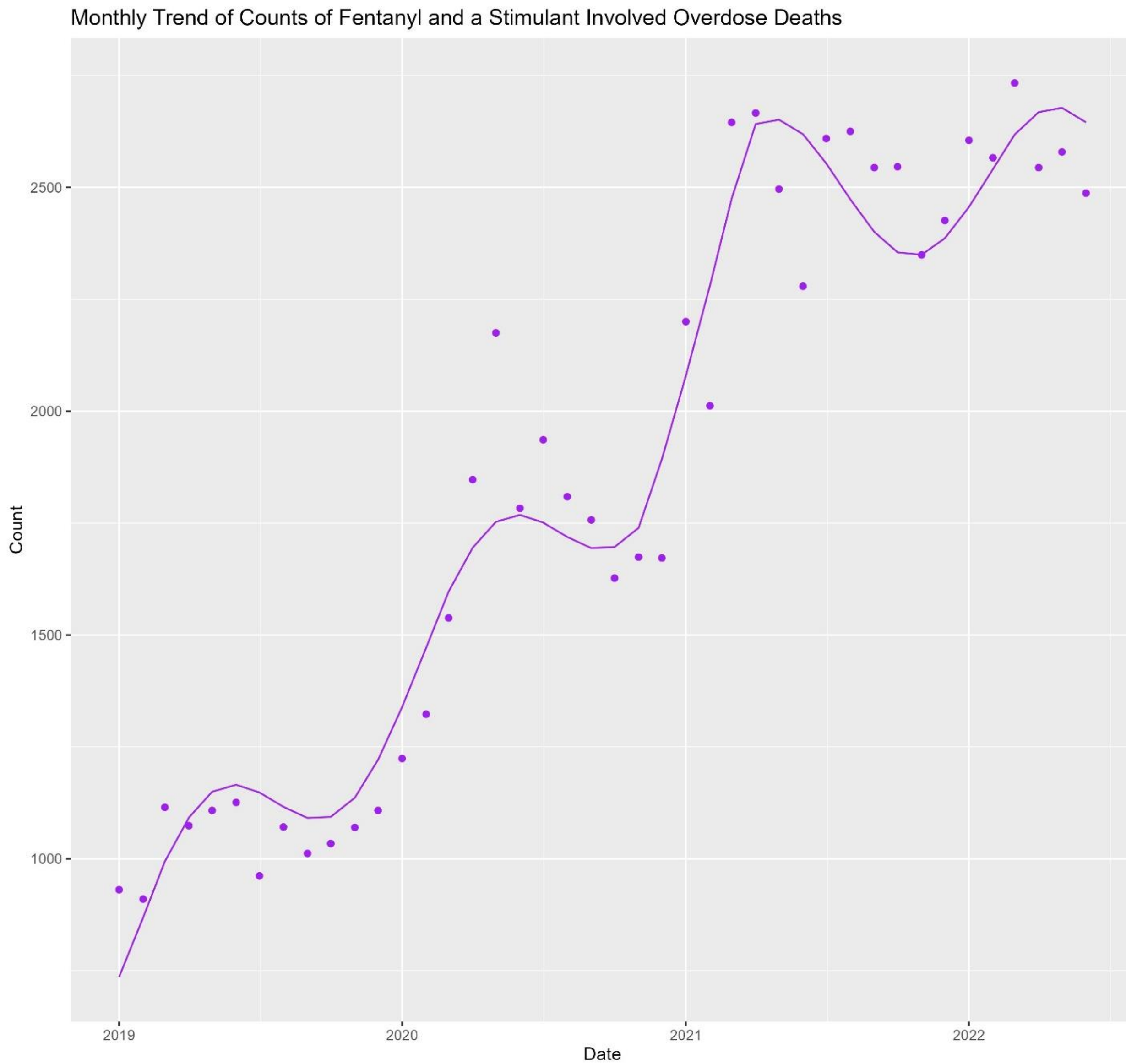

Monthly Trend of Counts of Fentanyl Involved Overdose Deaths
2100
1800
1500
1200
900
Count
2019
2020
2021
2022
Date

Figure 4.2



Monthly Trend of Counts of Stimulant Involved Overdose Deaths
Count
1000
800
600
2019
2020
2021
2022
Date

Figure 4.3



Monthly Trend of Counts of Fentanyl and a Stimulant Involved Overdose Deaths
Count
2500
2000
1500
1000
2019
2020
2021
2022
Date

Chapter 5: Dissertation Summary and Future Directions in Research

Summary

This collection of studies observed polysubstance use characteristics among substance use treatment populations, characteristics and trends in nonfatal overdoses involving opioids and stimulants, and characteristics and trends in fatal overdoses involving fentanyl and stimulants.

Manuscript #1 Summary

The first study described fentanyl-only, stimulant-only and co-positivity from urine drug test (UDT) results among populations receiving substance use disorder (SUD) treatment compared to other types of care between January 2022-June 2023. Using UDT specimens provided by Millennium Health positivity rates were calculated and multinomial logistic regression models were built to calculate unadjusted and adjusted odds ratios by sex, age group, provider type, primary payer, rural-urban classification, opioid prescription status, and medications for opioid use disorder (MOUD) prescription status. Of specimens meeting our inclusion criteria, this analysis found that patients receiving SUD treatment had more than twice the adjusted odds of fentanyl-only, stimulant-only and co-positivity compared to patients receiving primary care. These findings reiterate the need for healthcare providers developing SUD treatment programs to incorporate interventions that address polysubstance use.

Manuscript #2 Summary

The second study examined relationships between demographic characteristic and nonfatal overdoses presenting in emergency departments (ED) involving opioids, stimulants, and combinations of opioids and stimulants between January 2017-December 2022. Additionally, this study examined overall trends in nonfatal overdoses across the three outcomes. Using data from ED facilities sharing overdose records to the National Syndromic Surveillance Program (NSSP) ESSENCE platform, we calculated relative rates by fitting negative binomial regression models across covariates age, sex, race/ethnicity, and US Census region. Relative rates of overdose were greater among males, patients 25-44 years old, and patients in the West for all three outcomes. Rates varied by race/ethnicity.

To examine trends over the study period, we executed continuous piecewise linear regression models on nonfatal overdose rates and counts. Increasing overall trends in overdose ED visit rates and counts involving opioids, stimulants, and combinations of both were observed leading into April 2020. The 2020 COVID-19 pandemic had a significant impact on trends for all outcomes, aligning with numerous other studies observing increases in overdose rates and counts during that timeframe (Ochalek, 2020; Glober, 2020; Rodda, 2020; Slavova, 2020). Seasonality played a key role in overdose trends as well, as overdose rates and counts tended to increase in warmer months and decrease in cooler months. These findings, again, amplify the need to better understand the nonfatal overdose burden and how it is changing in time.

Manuscript #3 Summary

The third study explores demographic characteristics and overall trends of fatal overdose deaths involving fentanyl, stimulants, and combinations of fentanyl and stimulants between January 2019-June 2022. Using data provided by CDC's State Unintentional Drug Overdose Reporting System (SUDORS) between January 2019-June 2022, we calculated demographic distributions by outcome among all overdose deaths and mean counts across demographics using negative binomial regression. To examine trends over the study period, we executed continuous piecewise linear regression models on fatal overdose counts over time.

Mean counts varied by demographic characteristics. For all three outcomes mean counts were greater among males. Decedents 25-34 [reference group] years old had greater mean counts for fentanyl only and combined fentanyl and stimulant overdose deaths than other age groups, but stimulant only death mean counts were greater among 35–54-year-olds. Regarding race/ethnicity, mean counts were greatest among non-Hispanic Whites for all three outcomes. Mean counts varied by US Census region. Overdose deaths involving fentanyl, stimulants, and combinations of fentanyl and stimulants increased over time. This study saw dramatic increases in November 2020 followed by decreases in April 2021. Like nonfatal overdose, seasonality played a significant role in fatal overdose deaths. Some researchers suggest that key contributors to these increases were illegally made fentanyl (IMF) and other synthetic opioids (Trecki, 2022; Friedman, 2022). This study's findings bolster other recent statewide analyses documenting alarming increases in overdose deaths involving fentanyl, stimulants and combinations of the two (Spencer, 2022; Trecki, 2022; Friedman, 2022; Han, 2021; Slavova, 2023).

Policy Implications

The present research has important policy implications as multiple studies have identified strong correlations between opioid use disorder, nonfatal overdoses and subsequent overdose deaths (Goldman-Mellor, 2020; Florence, 2020; Slavova, 2023). As noted in earlier chapters, multiple past studies observed evidence of demographic disparities in health that were amplified during the COVID-19 pandemic, including within the overdose epidemic (Yancy, 2020; Dowling 2020; Galea, 2020; Khatri, 2021; Slavova, 2023). These studies reiterate the need for post-overdose programs to reduce harm, especially in the context of societal events, like a pandemic or an economic crisis, that magnify health disparities.

To really drive the message home for policymakers, one study estimated the economic burden of opioid use disorder (OUD) and fatal opioid overdose in the US in 2017 to be $1.02 TRILLION (Florence, 2020). A new study of economic burden is not currently available, but with increases in overdose morbidity and mortality, one can infer that the burden has only continued to grow. Along with these, the emotional burden of losing hundreds of thousands of fathers, sons, mothers, daughters, friends, and colleagues each year is incalculable.

It is important to acknowledge recent policy changes made thus far while recognizing there is more work to be done. As mentioned in Chapter 4, some MOUD treatment barriers were eliminated in March 2020, however this study's observation of trends in overdose morbidity and mortality indicate that more prevention strategies were needed. In March 2021, Congress signed the "American Rescue Plan Act" which included $30 million in grants for harm reduction services (CBO, 2022; SAMSHA, 2022). The 2022 National Drug Control Strategy promoted 7 priorities: 1) expanding access to evidence-based treatment, 2) advancing racial equity in drug policy, 3) enhancing evidence-based harm reduction efforts, 4) supporting evidence-based prevention efforts to reduce youth substance use, 5) reducing the supply of illicit substances, 6) advancing recovery-ready workplaces and expanding the addiction workforce, and 7) expanding access to recovery support services (The White House, 2022). The 2024 National Drug Control Strategy, released earlier this year in May 2024, expands upon these goals (The White House, 2022).

Future Direction in Research

Future research should consider multiple factors while investigating the overdose epidemic. First, a better understanding of trends in drug use among persons who use drugs is needed, especially as emerging drugs tend to be more potent and/or have varying effects on users (Trecki, 2022; Friedman, 2022). For example, in recent years the non-opioid sedative, xylazine, has been identified in toxicology reports of drug overdoses involving fentanyl (D'Orazio, 2023; Hays, 2024). Greater investigation of polysubstance trends by demographic characteristics is warranted to understand how quickly the overdose landscape is changing and anticipate future burden.

Alongside the present findings, researchers emphasize that individual, social and structural level risks must be considered when working to reduce risks of overdose (Ciccarone, 2021). Individual risk factors include elements like post-incarceration and post-detoxication return to use, and post-traumatic stress disorder (Park, 2020; Kline, 2021). Social risk factors include unstable housing, deindustrialization, economic stagnation, and class-based despair (Park, 2020). Ciccarone et al. (2019) note in past research that structural forces associated with increased overdose risk include aspects of drug supply. More recently, Ciccarone (2021) and colleagues note that the COVID-19 pandemic magnified risks that socially marginalized Americans face including inequitable access to healthcare and disruptions in treatment and prevention services (Wakeman, 2020; Park, 2020; Volkow, 2020). In conclusion, the future of drug overdose surveillance and epidemiology must be multifaceted, agile, and exhaustive to continue to inform evidence-based strategies. We must incorporate all stakeholders to find meaningful, lasting solutions.

Appendix

Chapter 3 Supplemental Material

CDC Opioid Overdose Syndrome Definition v4:
https://knowledgerepository.syndromicsurveillance.org/sites/default/files/2024-02/CDC%20All%20Opioid%20Overdose%20v4%20Parsed%20Technical%20Brief%20and%20Factsheet.pdf

CDC Stimulant Overdose Syndrome Definition v4:
https://knowledgerepository.syndromicsurveillance.org/sites/default/files/2024-02/CDC%20All%20Stimulant%20Overdose%20v4%20Parsed%20Technical%20Brief%20and%20Fact%20Sheet%20.pdf

Table 3.4b – Trend Analysis♦ of Counts and Rates♦♦ of Nonfatal Overdoses involving Opioids [Continuous Piecewise Linear Regression Results]

	Overall Trend	
Parameters	**Estimates♦♦♦ (95% Confidence Intervals)**	
Opioids	**Rates** $R^2 = 0.70$	**Counts** $R^2 = 0.92$
Time	0.32 (0.25, 0.38)	85.87 (75.46, 96.29)
Time Passed since April 2020 Breakpoint	-0.37 (-0.5, -0.24)	-34.43 (-55.55, -13.31)
Seasonality Variable (Cosine)	-1.75 (-2.68, -0.83)	-423.68 (-576.78, -270.58)
Stimulants	**Rates** $R^2 = 0.84$	**Counts** $R^2 = 0.79$
Time	0.05 (0.04, 0.05)	13.39 (11.62, 15.17)
Time Passed since April 2020 Breakpoint	-0.14 (-0.15, -0.12)	-21.02 (-24.62, -17.41)
Seasonality Variable (Cosine)	-0.36 (-0.47, -0.24)	-75.15 (-101.27, -49.02)
Both Opioids and Stimulants	**Rates** $R^2 = 0.66$	**Counts** $R^2 = 0.85$
Time	0.01 (0.01, 0.01)	3.05 (2.63, 3.47)
Time Passed since April 2020 Breakpoint	-0.02 (-0.03, -0.02)	-2.89 (-3.75, -2.03)
Seasonality Variable (Cosine)	-0.09 (-0.12, -0.05)	-18.28 (-24.5, -12.07)

♦ Linear models of outcome including parameters for time in months, before vs after April 2020, and seasonality.
♦♦ Outlier rates in April and May of 2020 were omitted from calculation to simplify the model.
♦♦♦ Parameter estimates represent how the slope of overdose rates over time change.

Figure 3.1b Opioid ED Visit Rates Trend:

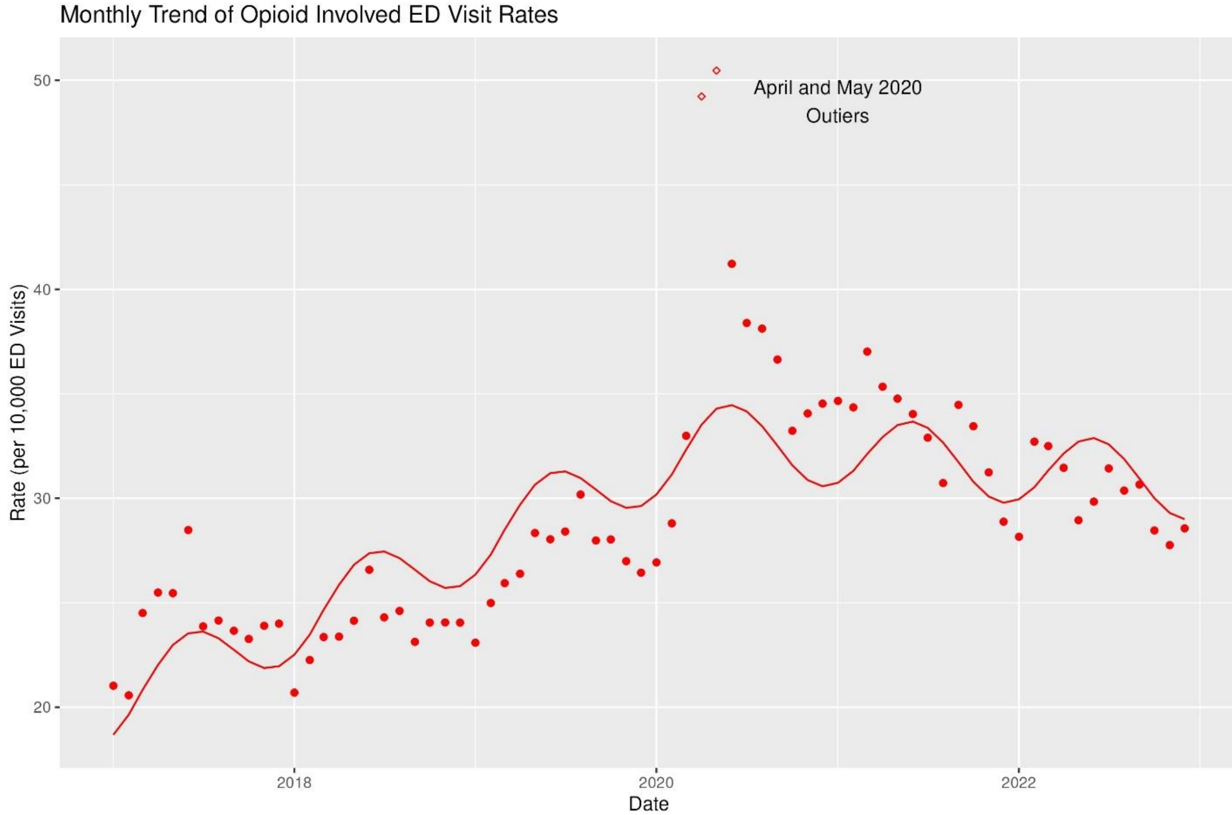


Figure 3.2b Stimulant ED Visit Rates Trend:

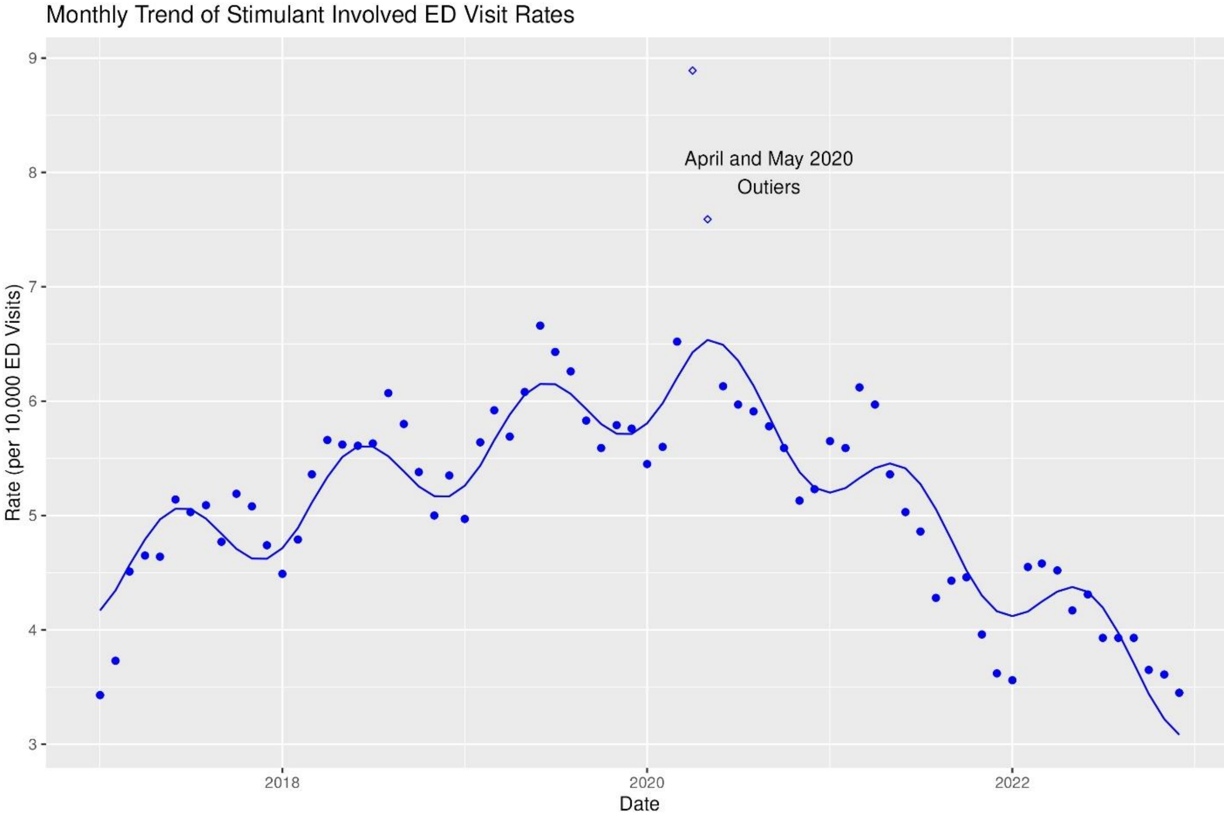
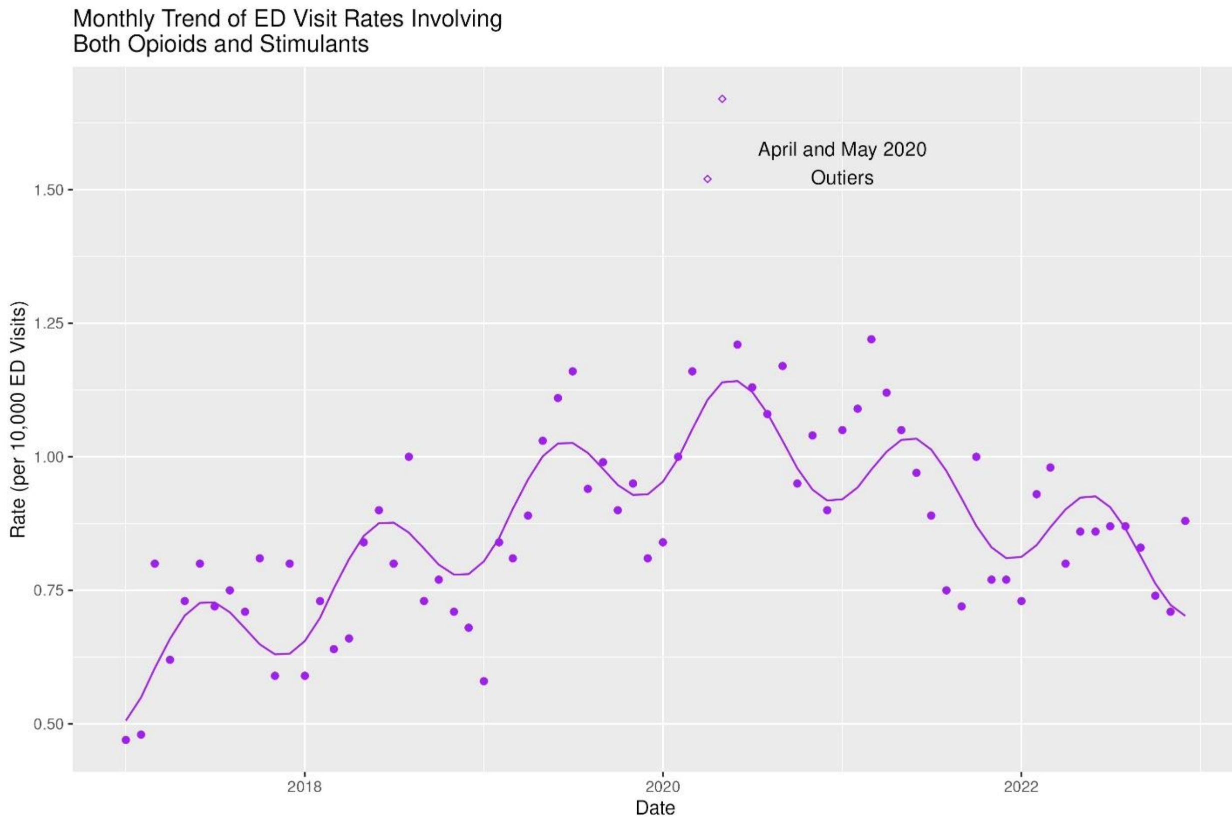


Figure 3.3b Both Opioid and Stimulants ED Visit Rates Trend:



Chapter 4 Supplemental Material

Table 4.4b ***Second Best*** *Overall Trend of Fatal Overdoses Involving Fentanyl Only Jan 2019-June 2022 [Continuous Piecewise Linear Regression Results]*

Parameters	
Fentanyl Only	**Estimates (95% Confidence Intervals)** R^2 = **0.88**
Time	1.22 (-21.46, 23.91)
Time since December 2020 Breakpoint	246.75 (120.2, 373.29)
Time since February 2020 Breakpoint	-220.75 (-351.37, -90.13)
Time since November 2020 Breakpoint	6.22 (-55.2, 67.64)
Time since April 2021 Breakpoint	-54.71 (-105.32, -4.1)
Seasonality Variable (Cosine 12-month period)	-60.23 (-122.62, 2.17)

Figure 4.1b

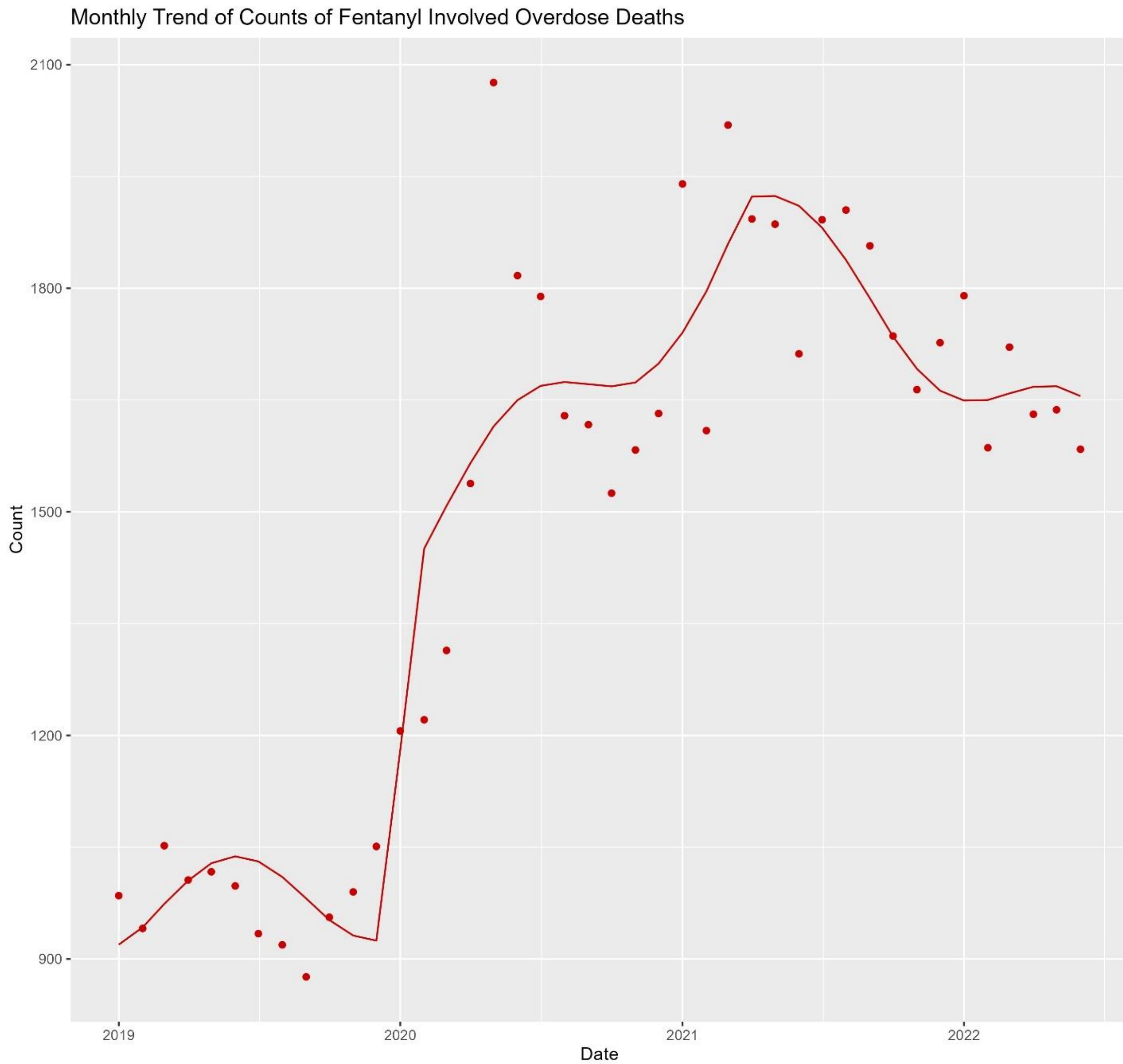
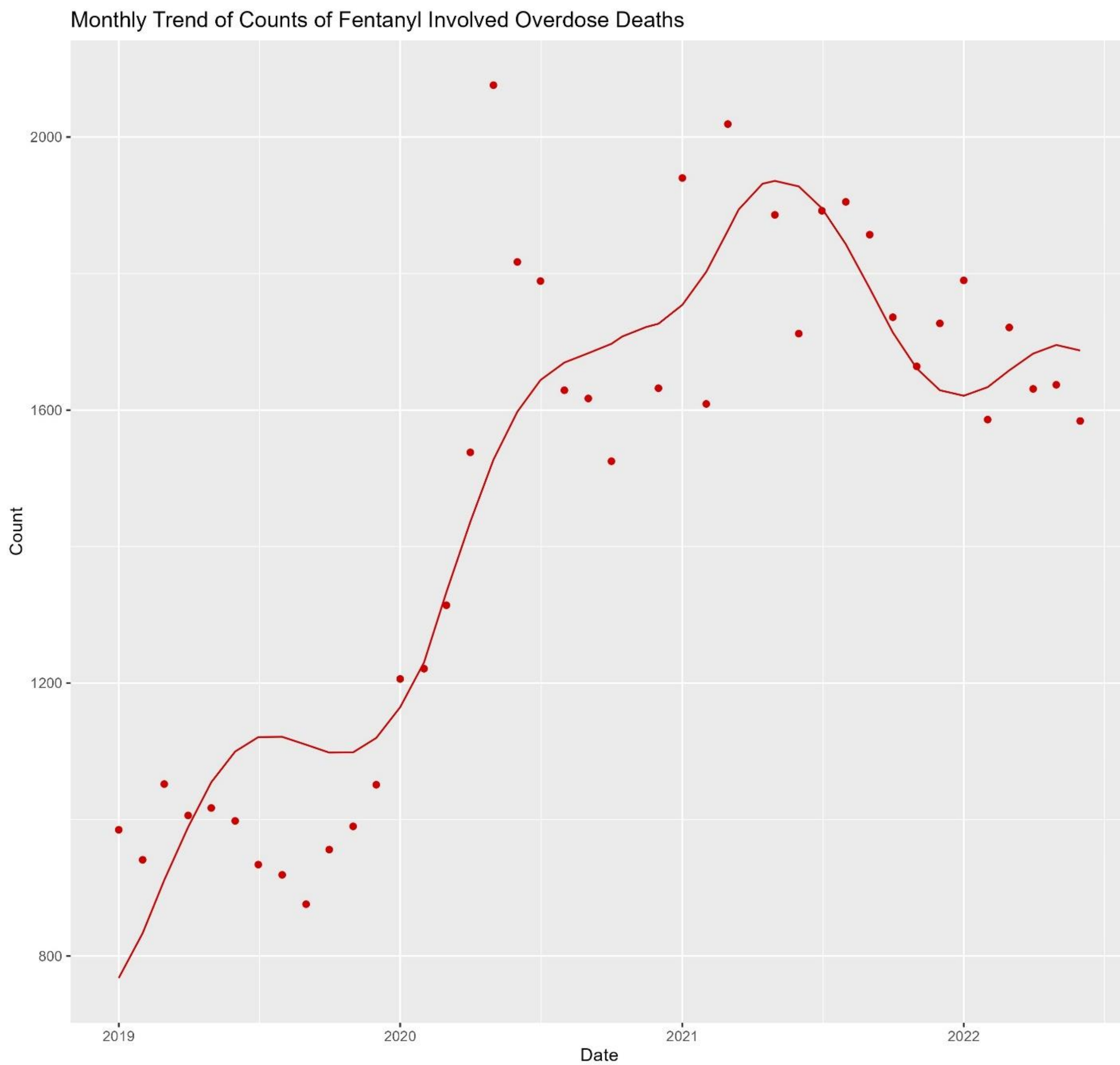


Table 4.4c ***Third Best*** *Overall Trend of Fatal Overdoses Involving Fentanyl Only Jan 2019-June 2022 [Continuous Piecewise Linear Regression Results]*

Parameters	
Fentanyl Only	**Estimates (95% Confidence Intervals)** R^2 = **0.84**
Time	33.32 (14.81, 51.83)
Time since February 2020 Breakpoint	23.75 (-16.67, 64.18)
Time since November 2020 Breakpoint	-37.79 (-104.2, 28.63)
Time since April 2021 Breakpoint	-40.23 (-98.83, 18.36)

Seasonality Variable (Cosine 12-month period)	-91.71 (-164.49, -18.93)

Figure 4.1c



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