Drug and Alcohol Dependence Reports 4 (2022) 100069

Contents lists available at ScienceDirect

Drug and Alcohol Dependence Reports

journal homepage: www.elsevier.com/locate/dadr

Trends in opioid overdose fatalities in Cuyahoga County, Ohio: Multi-drug mixtures, the African-American community and carfentanil

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ARTICLE INFO

Keywords:
Opioid-related overdose
Overdose fatalities
Carfentanil
Polysubstance use
Cocaine
Harm reduction
Fentanyl

ABSTRACT

Background: Ohio's age-adjusted opioid overdose fatality rate is double the national average. In an ever-evolving epidemic, it is crucial to monitor trends to inform public health interventions.

Methods: A retrospective study was conducted using the Medical Examiner's decedent case files for all accidental opioid-related adult overdose deaths in Cuyahoga County (Cleveland), Ohio in 2017. Characterization of trends was based on autopsy/toxicology and first responder reports, medical records and death scene investigations.

Results: Of 543 accidental opioid-related adult overdose fatalities, 64.1% died from 3+ drugs. The most common cause of death (COD) drugs included fentanyl (63.4%), heroin (44.4%), cocaine (37.0%) and carfentanil (35.0%). There were four times as many African American decedents as two years prior. Three or more COD drugs was >50% more common in those with fentanyl (Prevalence Ratio (PR) = 1.56[1.34–1.70]; $p<.001$) or carfentanil (PR = 1.51[1.33–1.70]; $p<.001$) as a COD drug, more common with a history of prescription drug abuse (PR = 1.16[1.02–1.33]; $p=.025$), but less common in divorced/widowed decedents (PR = 0.83[0.71–0.97]; $p=.022$). Carfentanil was nearly 4 times as prevalent in those with previous illicit drug use (PR = 3.88[1.09–13.70]; $p=.025$), and less common in those with previous medical history (PR = 0.72[0.55–0.94]; $p=.016$) or age 50+ (PR = 0.72[0.53–0.97]; $p=.031$).

Conclusions: Accidental opioid-related overdose fatalities in Cuyahoga County adults were dominated by 3+ COD drugs, with cocaine/fentanyl mixtures driving sharp increases in African American fatalities. Carfentanil was more prevalent in people fitting the profile of recreational drug use. This data can inform harm reduction interventions.

1. Introduction

Opioid abuse and fatalities vary widely across the globe. Opioid over-prescribing that played such a large role in the opioid epidemic in the United States did not materialize in most other countries. Thus, while a 2019 report states that opioids accounted for more than four-fifths of overdose deaths in Europe, rates remain low (European Monitoring Centre for Drugs and Drug Addiction, 2019). India and China represent some of the largest heroin using populations in the world, yet Illicitly manufactured fentanyl (IMF) has yet to appear (Taylor et al., 2021). This is in sharp contrast to the experience in the United States.

In 2017, there were 70,327 unintentional drug overdose deaths in the United States (US), with a national age-adjusted rate of 21.7 per 100, 000 standard population (Hedegaard et al., 2018). Ohio has an age-adjusted overdose fatality rate of 46.3 per 100,000 standard population, significantly higher than the national average (Hedegaard et al., 2018). This is due, in part, to a sharp increase in IMF adulterated heroin overdose deaths since 2016 (Ohio Department of Health, 2021). There is a shift occurring to more dangerous drug mixtures as heroin and cocaine are now adulterated with IMF as a part of their illicit drug composition (Gilson et al., 2017; Park et al., 2021). In this paper, drug mixtures refer to all drugs contributing to the cause of death.

1.1. History of the epidemic

In an effort to address the apparent growing problem of the under treatment of pain, in 2001 pain was labelled the fifth vital sign by The Joint Commission. Physicians were instructed that opioids could be prescribed for chronic use with minimal risk of addiction (Baker, 2017). The aggressive marketing of opioid pain relievers (OPR) to physicians by pharmaceutical manufacturers led to an over-prescription of OPRs

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https://doi.org/10.1016/j.dadr.2022.100069
Received 22 November 2021; Received in revised form 9 June 2022; Accepted 13 June 2022

(Volkow and McLellan, 2016). As pharmaceutical manufacturers marketed OPRs as non-addictive pain relievers, physicians over-prescribed OPRs to patients, creating a dependence on the drug (Haffajee and Mello, 2017). OPRs contributed to the increased number of overdose deaths from 2002 to 2013 in Cuyahoga County and the United States (Gilson et al., 2017). Overprescribing led to the development of opioid use disorder (OUD), initiating a series of policies and laws that decreased the number of OPRs prescribed to patients. Prescribing education interventions were implemented to re-educate physicians in appropriate prescribing practices for OPR, an addictive substance. These changes gradually decreased access to prescription opioids and OPR overdose deaths began to level off in 2013 (Pitt et al., 2018). Concurrently, as prescribing practices limited access to OPRs, there was a surge in heroin deaths. This reflected the unintended consequences of decreasing access to OPRs and highlighted the lower cost of heroin (Pitt et al., 2018; Drug Enforcement Administration, 2016).

1.2. Evolution of the epidemic

Since 2015, IMF-adulterated heroin and cocaine have contributed to a sharp increase in overdose deaths in Cuyahoga County (Gilson et al., 2017). People who use drugs may not be aware they are receiving IMF as it is usually sold to people who believe they are receiving heroin, oxycodone or cocaine. This is concerning because fentanyl is 50 times more potent than heroin (Delcher et al., 2020). Due to the increased potency of IMF, there has been a substantial increase in opioid overdoses, creating a public health emergency. IMF is likely being added to heroin and cocaine because it is synthetically manufactured, unlike heroin which is grown. (Kilmer et al., 2014). One fentanyl analog that made its way into the North American drug market in 2016 was a large animal tranquilizer, carfentanil (Delcher et al., 2020). It is 5000 times more potent than heroin, and substantially undermines harm reduction strategies employing naloxone (Fairbairn et al., 2017).

Another alarming trend is the increased prevalence of IMF and cocaine in cause of death (COD) drugs (). Cocaine is a stimulant, unlike heroin and IMF, which are opioids. This creates further public health concerns because people who use cocaine may be unaware that IMF is mixed in with their drugs. People who tend to use cocaine may lack opioid tolerance, increasing the likelihood of an overdose death from mixtures with IMF (Khatri et al., 2018; Tomassoni et al., 2017). Furthermore, if a cocaine-related overdose is suspected, naloxone may not be administered since it is an opioid overdose reversal tool. Connected to the trend in increased prevalence of cocaine in opioid-related overdose fatalities, was a doubling in African American opioid-related overdose fatalities from 2015 to 2016 in Cuyahoga County (Cuyahoga County Medical Examiner's Office, 2018). The emergence of both IMF and cocaine in the COD of decedents identifies a new at-risk population, which would benefit from tailored public health interventions. s of unintentional opioid related adult fatalities in Cuyahoga County (metropolitan Cleveland) in 2017. We analyzed opioid-related fatalities, including carfentanil and subgroups of decedents with different COD mixtures, and examined the socio-demographics associated with those drug mixtures and carfentanil. While the importance of adopting harm reduction interventions (take-home naloxone kits, syringe exchange programs, and supervised consumption sites)is self-evident in areas with rising rates of IMF-related fatalities around the US (Centers for Disease Control, 2020), epidemiologic analyses like the ones presented in this paper are needed to inform the design and targeting of these interventions.

2. Materials and methods

The Cuyahoga County Medical Examiner's Office (CCMEO) is responsible for investigating all unnatural and sudden, unexpected deaths that occur in Cuyahoga County (metropolitan Cleveland). This jurisdiction extends to all fatal drug overdoses. The CCMEO is fully accredited by the ANSI National Accreditation Board (ANAB), the National Medical Examiner's Association (NAME) and the American Board of Forensic Toxicology (ABFT). Death investigation at the CCMEO consists of an initial death scene investigation in all fatalities outside the health care setting by a certified medico-legal death investigator from the American Board of Medical Legal Death Investigators (ABMLDI). A complete autopsy in all cases of a suspected drug overdose is conducted by forensic pathologists where there is no interval of survival with documentation of injuries at a hospital. All autopsies are conducted by forensic pathologists certified by the American Board of Pathology (Davis et al., 2020). The toxicologic analysis is conducted at the toxicology section of the Cuyahoga County Regional Forensic Science Laboratory, which is accredited by the Society of Forensic Toxicologists. The CCMEO is well acclimated to the needs of the forensic science community and in its efforts to provide support and guidance for its citizens and public health.

This paper examines all unintentional, adult opioid-related overdose deaths that occurred in 2017. CCMEO decedent case files include medico-legal death investigation information from autopsy reports, toxicology and other laboratory reports, Emergency Medical Services incident reports, police reports, medical records, and death scene investigation reports. Death scene investigations include a recounting of the incident, collection of evidence on the scene, testimony from witnesses, and relevant decedent history determined by the decedent's family and friends. Pertinent information from decedent case files was then transferred to the Poison Death Review Form. Next, all information from the Poison Review Death Forms were abstracted into a Microsoft Excel file, deidentified and recoded to export data into SPSS Version 25 (Deo et al., 2021). Statistical analyses were run on the data abstracted to determine associations and patterns between variables in order to identify public health intervention points and inform policy decisions. There were 727 drug overdose deaths in 2017, 556 of which were due to opioids. However, only unintentional overdose cases and decedents 18 years of age or over were included in statistical analyses, resulting in 543 qualifying cases.

Sociodemographic variables included: age, city of residence, education, occupation, sex, race/ethnicity, and marital status. Age was categorized into four groups: 18 – 34, 35 – 49, 50 – 64, and 65+. City of residence was categorized as: City of Cleveland, inner ring suburbs which include all cities bordering the city of Cleveland, outer ring suburbs which include cities that do not border the city of Cleveland but are within Cuyahoga County, and out of county. Education was categorized as no high school, high school (some or graduate) and college (some or graduate). Occupation was condensed into construction/manual labor, service industry, unemployed and other. Race/ethnicity was categorized as: White and African American.

Injury variables included: injury location (coded as "public" if death occurred outside of a private residence), using drugs with others, and others present but not using drugs. In addition to the individual drugs listed as the COD, some drugs were grouped into categories, such as "all opioids" and "all fentanyl". The number of drugs involved in the COD of a decedent was coded as 1, 2, 3 or more. To be considered a COD drug, there had to be a sufficient concentration to have contributed to the death.

In addition to frequencies of COD drugs and drug combinations, Fisher's exact tests were conducted to determine associations between the COD drug(s) and both sociodemographic and injury variables. Regression models were run for each of our two outcome variables: carfentanil as a COD drug, and 3+ COD drugs. Logistic regression was used to create odds ratios. Modified Poisson regressions were run to produce the more intuitive prevalence ratios, indicating how much more or less prevalent a characteristic was among those experiencing the outcome event. Odds ratios created by logistic regressions can greatly exaggerate risk when the outcome prevalence isn't close to 0 or 1, as in the outcome measures of this study. Due to this issue and the ease of interpretation of the more intuitive prevalence ratios (how much more/less

common something was), the prevalence ratios are used in the body of this manuscript but the tables include the odds ratios as well. Analyses were run using SAS 9.4 (SAS Institute Inc., Cary, NC). Modified Poisson regressions were calculated with generalized estimating equations with repeated measures, which forces use of robust error variance. Factors associated with carfentanil in the COD drugs regression used the following study variables: age, city of residence, education, occupation, race, marital status, sex, injury location, using drugs with others, others present but not using drugs, previous medical history, previous mental health history, previous prescription drug pill use, previous drug use, history of IV drug use. Regression models for factors associated with 3+ contributing drugs to the COD added two study variables: fentanyl and carfentanil as COD drugs. Since some variables, such as occupation, had many missing values, multiple imputation (SAS Proc MI) was used to generate 100 imputed data sets. Variables were imputed using the fully conditional specification method, with logistic regression for dichotomous variables and the discriminant function method for categorical variables with at least 3 levels. Results were combined using PROC MIANALYZE.

For each regression model, collinearity was tested in two ways. First, each variable was removed from the final model to determine its impact on the independent variables. Second, variance inflation factors were calculated.

3. Results

Of the qualifying 543 cases of unintentional adult opioid-related fatalities, fentanyl was present in the COD drugs in 63.4% of decedents, 44.4% had heroin, 37.0% had cocaine, 35.0% had carfentanil and 23.8% had fentanyl analogs. Table 1., lists the most common observed drug mixtures in the COD. Most of the common combinations involved fentanyl, with heroin (31.9%), cocaine (25.1%), ethanol (17.7%), fentanyl analogs (15.7%), carfentanil (15.1%). Heroin was commonly mixed with carfentanil (15.8%) and ethanol (11.1%). Cocaine was often combined with carfentanil (12.0%) and ethanol (11.2%).

Of the qualifying 543 cases, 78.5% were White, 19.9% African American, 0.4% Other Race and 1.3% Hispanic. Due to the very low numbers in the Other Race (n=2) and Hispanic (n=7) categories, and no Native Americans, subgroup and regression analyses only used White and African American (Tables 2–5). Table 2.has frequencies for sociodemographic, injury variables and decedent history: Overall and broken down by various COD drug categories. 70.5% were male, for 77.0% the highest level of education was high school (21.1% had a college level education) and 60.4% were never married (28.1% were divorced/widowed, 11.5% were married). 54.0% of decedents resided in Cleveland, 21.3% resided in the inner suburbs, 15.0% resided in the outer suburbs, and 9.7% of decedents resided out of county. It was found that 36.8% of decedents were 50–64 years old, 33.0% were 35 to 49 years old, 27.3% were 18 to 34 years old and 2.9% were age 65 or over. Construction/manual labor was the occupation of 39.8%, 17.1% service industry, 38.5% other and 4.6% unemployed. 90.0% overdosed in a residential location, 95.5% of decedents had evidence of a history of previous illicit drug use, and 32.2% had a history of previous prescription pill abuse. 74.7% had a significant medical history, 38.6% had a mental health history and 67.3% had previously used IV drugs. It was found that 14.0% of decedents were using drugs with others, and 66.7% of decedents had others present at the location that were not using drugs. Only 11.2% had a single COD drug, 24.7% had two and 64.1% had three or more.

Some form of fentanyl was present in 89.7% of decedents. Carfentanil was present in 35.0% of overdoses fatalities, particularly clustered in the summer months. Deaths attributed to a combination of cocaine and any opioid comprised 37.0% of deaths. Most of these were cocaine and some form of fentanyl (34.1%). Deaths attributed only to heroin made up 3.1% of deaths. Deaths attributed to prescription drugs only comprised 5.9% of deaths.

Decedents without fentanyl as a COD were older, more likely to have attended college, less likely to work in construction, much less likely to have a history of illicit drug use and had fewer COD drugs. Those who died from a combination of cocaine and an opioid were more likely to be African American and more likely to have 3 or more COD drugs. Those who died from a mixture of cocaine and any form of fentanyl were older, more likely to live in the city of Cleveland or an inner ring suburb, more likely to be African American and die from 3 or more COD drugs.

African American decedents were older, less likely to have a reported mental health history or have abused prescription drugs than white decedents (Table 3). African American decedents were also more likely to have had cocaine as a COD drug with any opioid or specifically with fentanyl.

Table 4 presents the regression results for three or more drugs related to the COD. Having three or more COD drugs was 17% less prevalent in divorced decedents compared to those who never married (PR=0.83 [0.71–0.97]; p=.022), 16% more prevalent in decedents with a previous history of prescription drug abuse (PR=1.16 [1.02–1.33]; p=.025), 56% more prevalent in those with fentanyl as a COD (PR=1.56 [1.34–1.70]; p<.001), and 51% more prevalent in those with carfentanil as a COD drug (PR=1.51 [1.33–1.70];p<.001). The c- statistic for this regression was 0.614.

Table 5 presents results of the regressions for carfentanil-related fatalities. Carfentanil was almost 4 times as common in those with previous illicit drug use (PR=3.88 [1.09–13.70]; p=.025), while 28% less common in decedents age 50 or over compared to age 35–49 (PR=0.72 [0.53–0.97]; p=.031) and those with previous medical history (PR=0.72 [0.55–0.94]; p=.016). Marital status was not quite statistically significant, with carfentanil 39% more common in married decedents (PR=1.39 [0.97–2.01]; p=.075) and 29% more common in those who were divorced or widowed (PR=1.29 [0.97–1.72]; p=.078) compared to decedents who were never married. The c-statistic of this regression was 0.611.

Tests showed no signs of collinearity in the regression models. Removing each variable from the final models had negligible impact on the independent variables and all variance inflation factors were small (<2).

Table 1
Most observed drug mixtures in opioid related overdose deaths.

	Cocaine (%)	Heroin (%)	Fentanyl (%)	Fentanyl Analogs (%)
Cocaine		17.3	25.1	8.8
Heroin	17.3		31.9	9.6
Fentanyl	25.1	31.9		15.7
Fentanyl Analogs	8.9	9.6	15.7	
Carfentanil	12.0	15.9	15.1	5.2
Benzos	4.6	7.8	11.3	2.6
Ethanol	11.2	11.1	17.7	5.9
Other Opioids	4.8	5.3	8.1	2.0
Other	5.9	6.6	10.9	3.9

* fentanyl analogs, including carfentanil are usually found in the presence of fentanyl.

Table 2
Description of all unintentional adult opioid overdoses by different drug mixtures.

	All Opioids N = 543	All Fentanyl N = 487 (89.7%)	Carfentanil N = 190 (35.0%)	Cocaine and All Opioids N = 201 (37.0%)	Cocaine and All Fentanyl N = 185 (34.1%)
Age					
18 - 34	27.3	28.5*	26.3	25.4	26.0*
35 - 49	33.0	33.1*	39.0	31.3	31.4*
50 - 64	36.8	35.5*	32.1	41.3	40.5*
65 and over	2.9	2.9*	2.6	2.0	2.2*
Residence					
Cleveland	54.0	54.7	57.4	58.6	60.3*
Inner Ring Suburb	21.3	21.7	21.0	19.0	19.6*
Outer Ring Suburb	15.0	13.9	12.6	14.0	12.0*
Out of County	9.7	9.7	9.0	8.5	8.2*
Education					
No High School	1.9	1.5*	0.6	2.1	2.3
High School	77.0	78.4*	78.1	79.2	78.5
College	21.1	20.1*	21.3	18.8	19.2
Occupation					
Construction/Manual Labor	39.8	41.0*	40.9	39.2	39.9
Service	17.1	17.7*	17.4	17.6	18.1
Unemployed	4.6	3.7*	3.8	4.1	2.5
Other	38.5	37.6*	37.9	39.2	39.9
Race					
White	79.8	79.4	79.9	75.0**	73.9**
African American	20.2	20.6	20.1	25.0**	26.1**
Marital Status					
Single	60.4	61.6	57.4	63.0	64.1
Married	11.5	11.2	13.2	10.6	10.3
Divorced	28.1	27.3	29.5	26.5	25.5
Gender					
Male	70.5	71.9	69.5	69.7	90.1
Female	29.5	28.1	30.5	30.4	9.9
Injury Location					
Home	90.0	89.6	86.6	89.4	90.1
Public	10.0	10.5	13.4	10.6	9.9
Previous Illicit Drug Use	95.5	97.7***	98.9**	97.3	97.7
Previous Prescription Pill Use	32.2	31.7	28.9	29.4	29.8
Previous Medical Treatment	74.7	73.4	66.9**	71.3	71.1
Mental Health History	38.6	38.0	35.2	38.6	37.9
Previous IV drug use	67.3	70.7	70.0	66.9	67.0
Using Drugs with Others	14.0	14.0	17.4	16.6	16.4
Others Present, But Not Using Drugs	66.7	67.1	63.3	62.8	62.9
Number of Drugs					
1	11.2	10.3***	10.0***	N.A.	N.A.
2	24.7	23.6***	14.2***	19.9***	17.3***
3 or more	64.1	66.1**	75.8***	80.1***	82.7***

*=$p<.05$; **=$p<.01$; ***=$p<.001$. N.A. = Not Applicable.

4. Discussion

4.1. Carfentanil

The transition of the opioid drug market from heroin to fentanyl was particularly devastating due to change in potency of the drugs beings used. Fentanyl is 50 times as potent as heroin, leading to an increase in overdose fatalities. Carfentanil presents a similar scenario as it is 100 times as potent as fentanyl (Delcher et al., 2020). The change in potency in the drug market increases the numbers of fatalities because people who use drugs are unaware of what is in their drugs, and cannot dose accordingly. While carfentanil accounted for 35.0% of all opioid-related overdose fatalities in 2017, it was particularly devastating from June to August 2017 when it became the driver of fatalities for Cuyahoga County. As September approached, there was a decrease in the presence of carfentanil in drug overdoses deaths, and seizures in Cuyahoga County (Cuyahoga County Medical Examiner's Office, 2017). The presence of carfentanil was more common in people likely to be using drugs recreationally: it was four times as common in decedents with a history of previous illicit drug use, and less common in people who were older or without a relevant medical history.

4.2. IMF and cocaine

Another detrimental aspect of IMF was the emergence of IMF in the cocaine market, with 37.0% of all opioid-related overdose deaths also involving cocaine. This is more than twice the national rate in 2014–2015 (Kandel et al., 2017). Other studies have reported that nearly 2/3 of cocaine overdose deaths involve opioids (Jones et al., 2017; Mattson et al., 2021). Fentanyl was the most common drug to be found in combination with cocaine in the study sample, at 25.0%. The increase presence of cocaine as a COD drug has led to a change from the initial demographics of the opioid epidemic. We found that Asians and Hispanics were only about one-fifth as prevalent in the opioid decedents than they are in the general population of Cuyahoga county (U.S. Census Bureau, 2021). African Americans were also underrepresented, but that is changing due to the combination of cocaine and opioids as COD drugs. In this study, African Americans made up 24.9% of those adult, accidental opioid-related deaths involving cocaine compared to 30.5% of the county population. However, this was only 17.0% of adult, accidental opioid-related deaths when cocaine was not involved. In 2015, in Cuyahoga county, there were just 25 African-American opioid overdose deaths involving cocaine, but this increased to 48 in 2016 and 100 in

Table 3
Characteristics of overdose fatalities by race.

	White	African American
Age* **		
18 - 34	29.4	18.5
35 - 49	34.9	25.0
50 - 64	33.6	50.0
65 and over	2.1	6.5
Residence		
Cleveland	51.0	65.7
Inner Ring Suburb	21.6	20.4
Outer Ring Suburb	17.6	4.6
Out of County	9.7	9.3
Education		
No High School	2.1	1.0
High School	76.2	80.4
College	21.7	18.6
Occupation		
Construction/Manual Labor	41.7	32.9
Service	14.7	25.9
Unemployed	4.9	3.5
Other	38.6	37.7
Marital Status		
Single	59.7	63.0
Married	11.3	12.0
Divorced	28.9	25.0
Gender		
Male	69.7	74.1
Female	30.3	25.9
Injury Location		
Home	89.3	92.9
Public	10.7	7.1
Previous Illicit Drug Use	95.4	95.7
Previous Prescription Pill Use**	35.1	20.4
Previous Medical Treatment	75.4	71.6
Mental Health History*	40.8	29.5
Previous IV Drug use		
Using Drugs with Others	14.5	12.2
Others Present, But Not Using Drugs	65.5	72.0
Number of Drugs		
1	12.0	8.3
2	23.0	31.5
3 or more	65.1	60.2
All Fentanyl	89.2	91.7
Carfentanil	34.9	35.2
Cocaine and Any Opioid*	34.7	46.3
Cocaine and Any Fentanyl*	31.5	44.5

*=$p<.05$; **=$p<.01$; ***=$p<.001$.

2017 (Cuyahoga County Medical Examiner's Office, 2018). Similarly, Barocas et al. (2019), reported that non-Hispanic African Americans are twice as likely to die from a combination of an opioid and stimulant. A study in Indianapolis also shows the combination of cocaine and fentanyl to be more prevalent in African Americans (Ray et al., 2020). Aside from the issue of opioids adulterating cocaine, this increase in deaths may also be caused by the combined use leading to an increase in the strength or frequency of use of opioids (Khatri et al., 2018; Tomassoni et al., 2017; Glick et al., 2018). Public health interventions will need to reflect the increasing incidence of African-American decedents with cocaine and fentanyl contributing to their cause of death, which had hitherto been less affected by the opioid epidemic. This is further supported by a recent paper of 67 communities in Ohio that showed opioid fatalities increasing at a 40% greater rate in African-Americans (Larochelle et al., 2021).

4.3. Three or more drugs

In 2017, only 17 (3.1%) decedents died of a heroin-only overdose (Cuyahoga County Medical Examiner's Office, 2018). Illicit drug markets continue to be adulterated with IMF, sometimes resulting in more fentanyl and fentanyl analogs in illicit drugs than heroin. Nationally, IMF was involved in 75% of all opioid related deaths in 2019 (O'Donnell et al., 2020) Nearly two-thirds of decedents overdosed on a mixture of at least 3 different COD drugs. Heroin and fentanyl were found to be mixed in 31.9% of cases, heroin and cocaine 17.3% of cases, ethanol and fentanyl in 17.7% of cases. Having three or more drugs was 56% more prevalent in decedents with fentanyl, and 51% more prevalent in decedents with carfentanil as a COD. These findings speak to the growing variability and toxicity of the illicit drug supply in Cuyahoga County, and around the U.S in 2021. This highlights the importance of surveillance of emerging trends through a coroner/medical examiner's office, and the dire need for innovative harm reduction implementation in the U.S.

4.4. Public health implications

Public health educational interventions need to increase focus on the African American community because the rise in deaths from mixtures of cocaine and opioids disproportionately affects this subgroup. These interventions need to be implemented to inform people who use cocaine that their cocaine may contain fentanyl, a drug for which they may lack tolerance. This reinforces the importance of harm reduction programs that provide naloxone kits to the public to reverse overdoses in a timely manner. This trend also highlights the need for widespread availability of fentanyl testing strips regardless of the type of drugs someone is using.

Table 4
Factors associated with three or more cause of death drugs.

	Logistic Regression			Modified Poisson Regression		
	OR	CI	P-value	PR	CI	P-value
Age						
18 - 34	0.68	0.38 - 1.21	0.195	0.92	0.78 - 1.10	0.355
35 – 49 (reference)	–	–	–	–	–	–
50 and over	1.15	0.66 - 2.01	0.624	1.03	0.89 - 1.20	0.666
Residence						
City of Cleveland (reference)	–	–	–	–	–	–
Inner ring suburb	1.28	0.73 - 2.26	0.388	1.06	0.92 - 1.22	0.413
Outer ring suburb	0.85	0.46 - 1.58	0.616	0.97	0.79 - 1.20	0.786
Outside of County	0.72	0.33 - 1.58	0.411	0.88	0.68 - 1.14	0.319
Education						
High School or GED (reference)		–	–	–	–	–
College	1.19	0.69 - 2.07	0.519	1.04	0.90 - 1.20	0.586
Occupation						
Construction	1.01	0.56 - 1.84	0.962	1.00	0.85 - 1.19	0.944
Food (service industry)	0.72	0.35 - 1.50	0.383	0.90	0.73 - 1.10	0.313
Other occupation (reference)	–	–	–	–	–	–
Unemployed	0.59	0.18 - 1.87	0.372	0.78	0.47 - 1.27	0.310
Race						
White						
Minority	0.87	0.49 - 1.56	0.646	0.99	0.84 - 1.16	0.872
Marital Status						
Single (reference)	–	–	–	–	–	–
Married	1.03	0.48 - 2.20	0.943	0.99	0.84 - 1.18	0.914
Divorced and Widowed	0.53	0.30 - 0.92	0.025	0.83	0.71 – 0.97	**0.022**
Gender						
Male (reference)	–	–	–	–	–	–
Female	1.34	0.77 - 2.33	0.300	1.08	0.93 - 1.26	0.298
Injury Location						
Home (reference)	–	–	–	–	–	–
Public	0.79	0.34 - 1.82	0.5726	0.93	0.72 - 1.20	0.592
Using Drugs With Others	0.82	0.45 - 1.53	0.545	0.94	0.78 - 1.13	0.520
Others Present	0.69	0.42 - 1.11	0.127	0.89	0.78 - 1.01	0.062
Previous Medical History	1.00	0.58 - 1.71	0.992	1.00	0.87 - 1.16	0.970
Previous Mental Health History	0.75	0.47 - 1.21	0.245	0.941	0.82 - 1.08	0.385
Previous Prescription Pill Use	1.73	1.05 - 2.85	0.031	1.16	1.02 - 1.33	**0.025**
Previous Illicit Drug Use	0.89	0.30 - 2.61	0.826	1.01	0.70 - 1.47	0.949
History of IV Drug Use	0.61	0.34 - 1.09	0.096	0.88	0.76 - 1.03	0.103
Fentanyl	4.82	2.86 - 8.14	<0.001	1.56	1.34 - 1.70	**<0.001**
Carfentanil	5.30	3.01 - 9.35	<0.001	1.51	1.33 - 1.70	**<0.001**

People who use drugs can test their drugs before using and alter their behavior, such as using a smaller dose than their regular (Pieper et al., 2019).

Although there was a significant decrease in overdose fatalities in 2018 following the record-setting numbers of 2017, 2019 to 2021 continue the trend of an adulterated drug supply with IMF (Hedegaard et al., 2020; CDC HAN Alert, 2020). These trends signal the growing need for expanding resources to coroners and medical examiners to conduct comprehensive toxicology testing and increase harm reduction services that have previously been unpopular in the U.S such as a safe supply or supervised consumption sites. These services would allow people who use drugs to do so in a safe environment, with a reduced risk of a fatal overdose, and be easily connected to services when they are ready (Kral et al., 2020).

4.5. Strengths

A strength of this research study is that it is a complete data set covering all accidental opioid-related overdose fatalities in adults within Cuyahoga County, and not a sample. The large sample size of 543 decedents allowed for statistically significant sub-group analyses such as the drug mixture comparisons. Also, the drug mixture categories were based on comprehensive toxicology reports rather than anecdotal evidence, which was important for capturing the differences between heroin, cocaine, fentanyl, and fentanyl analogs. Many coroner/medical examiner's offices do not have access to comprehensive toxicology testing, resulting in limited information in the COD drugs. COD may be reported with more generalized nomenclature such as acute opioid toxicity (Repp et al., 2019). The Cuyahoga County Regional Forensic Science Laboratory (CCRFSL) conducted comprehensive toxicology on all decedents, and all COD drugs can be identified and listed in the COD. The CCRFSL is the primary DNA and forensic science analysis laboratory for Cuyahoga County and the region, accredited by the American Board of Forensic Toxicology. This robust practice allows for the early detection of emerging trends in drug overdoses and the ability to delineate combinations of drugs. Furthermore, this study benefitted from thorough medico-legal death investigations that resulted in many variables of interest spanning sociodemographic, scene of injury and history of drug use. It is applicable to the growing number of IMF related drug overdoses in recent years in the western US in 2019 and 2020 (CDC HAN Alert, 2020), areas which have previously not seen large amounts of IMF.

4.6. Limitations

A limitation of this study is that the results are from fatal overdoses only, and cannot be generalized to nonfatal overdoses or the population of all opioid users. Studies of non-fatal overdoses, and users in general, are needed to better understand trends in the community at large. Another limitation on the generalization of this research is that the overdose epidemic is constantly evolving and there are important changes that need to be identified and information that needs to be dis-

Table 5
Factors associated with carfentanil-related overdose deaths.

	Logistic Regression			Modified Poisson Regression		
	OR	CI	p-value	PR	CI	P-value
Age						
18 - 34	0.73	0.43 - 1.25	0.246	0.84	0.62 - 1.14	0.255
35 – 49 (reference)	–	–	–	–	–	–
50 and over	0.56	0.34 - 0.94	0.027	0.72	0.53 - 0.97	**0.031**
Residence						
City of Cleveland (reference)	–	–	–	–	–	–
Inner ring suburb	0.84	0.52 - 1.39	0.497	0.91	0.67 - 1.22	0.510
Outer ring suburb	0.59	0.32 - 1.09	0.091	0.72	0.49 - 1.08	0.114
Outside of County	0.53	0.25 - 1.14	0.102	0.69	0.44 - 1.07	0.090
Education						
High School or GED (reference)	–	–	–	–	–	–
College	1.18	0.71 - 1.94	0.521	1.12	0.83 - 1.48	0.487
Occupation						
Construction	0.95	0.52 - 1.71	0.852	0.96	0.67 - 1.37	0.823
Food (service industry)	1.08	0.55 - 2.12	0.835	1.04	0.71 - 1.53	0.840
Other occupation (reference)	–	–	–	–	–	–
Unemployed	0.44	0.12 - 1.58	0.209	0.59	0.23 - 1.53	0.281
Race						
White (reference)	–	–	–	–	–	–
African American	0.94	0.55 - 1.62	0.825	0.97	0.70 - 1.35	0.862
Marital Status						
Single (reference)	–	–	–	–	–	–
Married	1.81	0.94 - 3.52	0.078	1.39	0.97 - 2.01	0.075
Divorced and widowed	1.57	0.94 - 2.62	0.083	1.29	0.97 - 1.72	0.078
Gender						
Male (reference)	–	–	–	–	–	–
Female	1.15	0.69 - 1.93	0.585	1.09	0.81 - 1.47	0.587
Injury Location						
Home (reference)	–	–	–	–	–	–
Public	1.85	0.87 - 3.96	0.112	1.37	0.93 - 2.04	0.116
Using Drugs with Others	1.25	0.70 - 2.22	0.448	1.13	0.83 - 1.54	0.440
Others Present	0.85	0.55 - 1.33	0.477	0.92	0.71 - 1.19	0.511
Previous Medical History	0.56	0.35 - 0.89	0.015	0.72	0.55 - 0.94	**0.016**
Previous Mental Health History	1.03	0.67 - 1.61	0.881	1.02	0.79 - 1.32	0.880
Previous Prescription Pill Use	0.80	0.50 - 1.27	0.346	0.88	0.66 - 1.17	0.346
Previous Illicit Drug Use	5.93	1.26 - 27.97	0.025	3.88	1.09 - 13.70	**0.025**
History of IV Drug Use	1.09	0.64 - 1.85	0.750	1.05	0.77 - 1.43	0.758

seminated in a timelier manner. Key stakeholders need access to more timely and interconnected data from different avenues such as law enforcement, hospitals, rehabilitation facilities and the medical examiner's offices. Medical claims tend to lag a few years behind, and researchers do not have access to state data on emergency room nonfatal overdoses. Data from a medical examiner's office can be delayed due to lack of resources for electronic data entry, and not all medical examiners have the resources to investigate as thoroughly as in Cuyahoga County. Lastly, some witness testimonies may have recall bias that could affect the accuracy of information on decedents, though information is double-checked through medical records by the forensic pathologists and death investigators.

Another limitation of this study is the large amount of missing data for certain variables. There were four variables with more than 10% of the observations missing, with the highest being for occupation (28%) and history of IV drug use (34%). However, recent research and guidance suggests that multiple imputation is appropriate even for large proportions of missing values, with some suggesting that when more than 40% is missing, the results should only be considered hypothesis generating (Lee, 2021; Madley-Dowd, 2019; Dong, 2013; Jakobsen et al., 2017). In this study, none of the variables with higher proportions of missing data proved to be important in the regression models.

5. Conclusions

In summary, in Cuyahoga County, most fatal drug overdoses are the result of mixtures of three or more drugs. Many drug overdoses include both cocaine and opioids in the COD, bringing possibly unintended exposure of opioids in greater numbers to the African-American population. Carfentanil use was more common in those fitting the profile of people who use drugs recreationally.

These trends highlight the importance of increasing access to take home naloxone kits to reverse overdoses, and fentanyl testing strips so all drugs can be tested prior to use. Further, with the increased number of drugs in the cause of death (3 or more), and potential adulteration with the extremely potent carfentanil, it may be time to reconsider safe supply and supervised consumption sites, which historically have been unpopular in the United States.

Studies are needed in other locations to see if these results are generalizable to other urban counties.

Role of funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Contributors

All authors made substantial contributions to this manuscript. All authors shared in the conceptualization of this study. Ms. Bhullar did the data curation under Dr. Gilson's supervision. Investigation was done by Dr. Gilson. Methodology was designed by Ms. Bhullar and Dr. Singer. Ms. Bhullar and Dr. Singer conducted the formal analysis under Dr. Singer's supervision. Ms. Bhullar wrote the original draft under Dr. Singer's supervision. Review and editing of the manuscript were done by

all authors. All authors reviewed and edited the manuscript. All authors approved the final manuscript.

Conflict of Interest

There are no conflicts of interest or personal or financial interests to declare.

Acknowledgments

This project was determined by the Case Western Reserve University Institutional Review Board to be non-human subjects researchand exempt from IRB review.

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