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Short Report

Epidemiology of fentanyl-involved drug overdose deaths: A geospatial retrospective study in Rhode Island, USA

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Introduction

Since late 2013, the North American opioid overdose epidemic has been exacerbated by deaths involving prescription and illicitly manufactured fentanyl, a synthetic opioid analgesic (Gladden, Martinez, & Seth, 2016; US Drug Enforcement Administration, 2015). More recently, Australia has also reported a sharp increase in fentanyl overdoses among people who inject drugs (Latimer, Ling, Flaherty, Jauncey, & Salmon, 2016). The high potency of fentanyl means that only a miniscule amount (less than 2 mg, the equivalent of two grains of salt) can lead to overdose and death (Hess, Stiebler, & Herz, 1972). Difficult to distinguish from other drugs, illicitly manufactured fentanyl is an increasingly common adulterant in heroin and other illicit substances (US Drug Enforcement Administration, 2016). Sharp increases in fentanyl contamination in counterfeit prescription pills have also been observed (Centers for Disease and Control Prevention, 2016), increasing the risk of fentanyl overdose among persons seeking medications on the illicit market—representing a large and geographically widespread population. Consequently, fentanyl overdose risk now extends well beyond those regions previously impacted by heroin.

States in the US, including Maryland, Massachusetts, Ohio, and Florida, have all reported dramatic increases in fentanyl-related deaths (Peterson et al., 2016). Among six states that publish data on fentanyl fatalities, the number of fentanyl-involved deaths increased by over 350% between 2013 and 2014, from 392 to over 1400 (Gladden et al., 2016). In British Columbia, Canada, the number of drug overdose deaths involving fentanyl has sharply increased from 13 in 2012 to over 330 in just the first nine months of 2016 (British Columbia Coroners Service, 2016). A recent study involving clients of the Sydney Medically Supervised Injecting Centre in Australia found injection of fentanyl increased more than any other drug between 2013–2015, and the overall risk for fentanyl-related overdose was nearly 4.5 times higher than risk for overdose with other opioids (Latimer et al., 2016).

Despite the recent surge in fentanyl-related overdose deaths, there is a paucity of data regarding the characteristics, circumstances, and toxicology of fentanyl overdose decedents. Moreover, few studies have examined whether the geospatial distribution of fentanyl-related overdose deaths differs from that of non-fentanyl deaths. To inform more targeted and improved overdose prevention efforts, we conducted a detailed epidemiological and geospatial investigation of fentanyl-associated overdose deaths in Rhode Island, a state with the fifth highest rate of overdose mortality in 2015 (Rudd, Seth, David, & Scholl, 2016).

Methods

We conducted a retrospective review of accidental drug overdose deaths occurring in Rhode Island between January 1, 2014 and September 30, 2016. In accordance with state policy (Rhode Island Department of Health, 2015), cases were considered confirmed accidental drug-related overdose fatalities if: (i) the death was pronounced in Rhode Island; (ii) the final manner of death was deemed an accident by the medical examiner, and (iii) a drug is listed on the death certificate as the primary cause of death or a significant contributing factor. Each case was reviewed independently by a minimum of two trained research assistants; discrepancies were resolved by consensus. The study was exempt from IRB review as the analysis was conducted on behalf of public health and did not involve living subjects.

Data regarding sociodemographic characteristics of the decedent, toxicological analyses, and circumstances of the overdose were abstracted from medical examiner files. For each case, a medical examiner had previously determined the drug type (i.e.,

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illicit drug, prescription drug, or combined) based on a number of factors, including the results of toxicological analyses, death scene investigation, autopsy, and prior history of illegal drug use. The Office of the Chief Medical Examiner also provided data on the type and number of drugs seemed contributory to the cause of death. Our research team then extracted additional data regarding the setting of each overdose and the suspected route of administration, based on a detailed review of medical examiner reports (e.g., recent track marks), police reports (e.g., drug paraphernalia), as well as death scene investigation photos. Toxicological reports confirmed drug presence and provided quantification of fentanyl and metabolites. Exact locations corresponding to the address at which each overdose occurred were mapped using ArcGIS software (version 10.4), and were categorized as urban, suburban, or rural based on standard US census definitions.

We compared fentanyl-associated with non-fentanyl-associated deaths using chi-square tests and Wilcoxon rank sum tests. We also examined changes in selected overdose characteristics over time using the Mantel–Haenszel test for trend. Log-binomial regression was used to estimate risk ratios and 95% confidence intervals. To determine factors independently associated with fentanyl overdose, variables significant at $P < 0.05$ were included in a multivariable model. Heroin as a contributing cause of death, overdose drug type, and oral route of administration was removed from the final model due to collinearity with other variables. Finally, we conducted a hot spot analysis and calculated Getis-Ord Gi* statistics to identify clusters of fentanyl and non-fentanyl attributable overdoses, respectively.

Results

A total of 778 accidental drug overdose deaths in Rhode Island were observed during the study period. In total, 358 (46.0%) were attributable to acute fentanyl intoxication, increasing from 84 (35.0%) in 2014 to 138 (55.6%) during the first nine months of 2016 ($P < 0.001$). The total number and proportion of deaths attributable to acute fentanyl intoxication by month is shown in Fig. 1. We did not observe significant changes over time in the proportion of deaths involving injection drug use or multiple drugs; however, the proportion of deaths that were illicit drug-related increased from 50.4% in 2014 to 62.9% in 2016 ($P = 0.011$).

Compared to non-fentanyl overdoses, fentanyl overdose decedents were significantly younger (median = 38 [IQR: 29–49] vs. 46 [IQR: 34–55], $P < 0.001$). More than one in four (28.2%) of fentanyl overdoses occurred among individuals aged 18–29. Fentanyl overdoses were also more likely to: be an illicit drug or a combined illicit drug & prescription drug death; have evidence of injection drug use; and have multiple drugs contribute to the cause of death (Table 1). Compared to non-fentanyl overdoses, fentanyl overdoses were significantly less likely to be attributed to an oral route of drug administration, and have heroin, oxycodone, methadone, or other prescriptions deemed contributory to the cause of death (see Table 1). In the final multivariable model, fentanyl overdoses were independently more likely to: occur in 2015 (adjusted risk ratio [ARR] = 1.41, 95%CI: 1.18–1.70) and 2016 (ARR = 1.47, 95%CI: 1.23–1.75) compared to 2014, respectively; occur among persons aged 18–29 (ARR = 1.41, 95%CI: 1.13–1.75); involve injection drug use (ARR = 1.36, 95%CI: 1.18–1.54); involve multiple drugs (ARR = 1.74, 95%CI: 1.44–2.09); and were less likely to have oxycodone (ARR = 0.67, 95%CI: 0.48–0.94) or methadone (ARR = 0.51, 95%CI: 0.33–0.80) deemed contributory to the cause of death.

Detailed fentanyl toxicological results were available from 345 (96.4%) cases. The majority (n = 301, 87.2%) was obtained from femoral blood samples. Of these, the median fentanyl concentration was 11.0 ng/ml (range: 0.3–110.0 ng/ml). Norfentanyl was

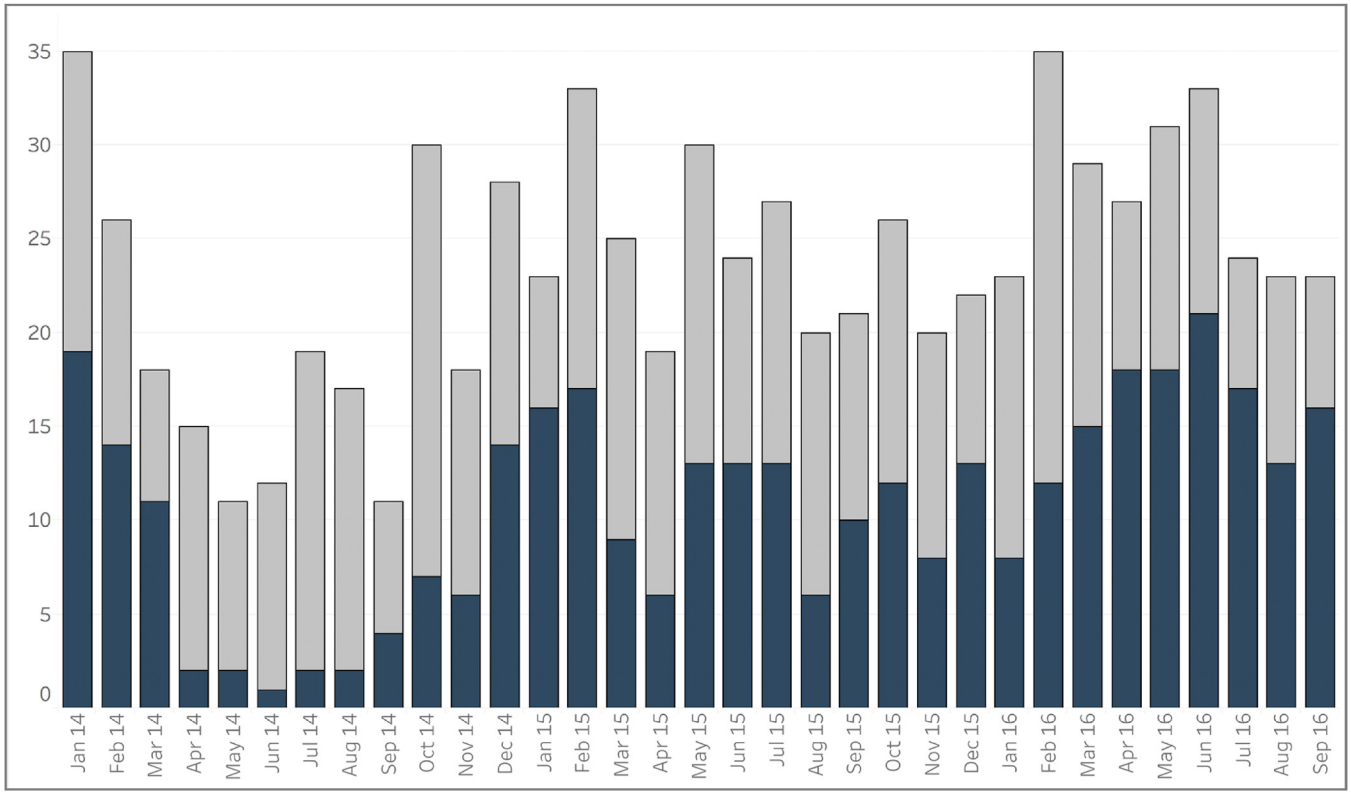

Fig. 1. Total number of overdose deaths by month (grey bars) and number attributable to acute fentanyl intoxication (blue bars) in Rhode Island, Jan 2014–Sep 2016 (for interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.).

Table 1
Characteristics of accidental drug overdose decedents, Rhode Island, 2014–2015.

Characteristic	Fentanyl overdose n (%) n = 358	Non-fentanyl overdose n (%) n = 420	Risk ratio	95% CI	*P*-value
Year of death					
2016	138 (38.5)	110 (26.2)	1.59	1.30, 1.95	<0.001
2015	136 (38.0)	154 (36.7)	1.34	1.08, 1.66	0.007
2014	84 (23.5)	156 (37.1)	Ref.	Ref.	
Gender					
Male	267 (74.6)	290 (69.1)	1.16	0.97, 1.39	0.098
Female	91 (25.4)	130 (31.0)	Ref.	Ref.	
Race[a]					
Other	30 (8.4)	383 (91.2)	0.97	0.74–1.28	0.833
White	328 (91.6)	37 (8.8)	Ref.	Ref.	
Age at death					
18–29	101 (28.2)	70 (16.7)	1.83	1.45, 2.34	<0.001
30–39	87 (24.3)	89 (21.2)	1.54	1.19, 1.98	<0.001
40–49	96 (51.1)	92 (21.9)	1.59	1.24, 2.04	<0.001
50–59	62 (17.3)	131 (67.9)	Ref.	Ref.	Ref.
60+	12 (3.4)	38 (9.1)	0.75	0.44, 1.27	0.285
Overdose drug type					
Illicit drug	242 (67.6)	206 (49.1)	4.29	2.83, 6.53	<0.001
Illicit drug & Rx. medication	96 (26.8)	75 (17.9)	4.46	2.91, 6.87	<0.001
Rx. medication	20 (5.6)	139 (33.1)	Ref.	Ref.	
Route of administration					
Injection (yes vs. no)	180 (50.3)	97 (23.1)	1.83	1.56, 2.12	<0.001
Nasal (yes vs. no)	55 (15.4)	66 (15.7)	0.99	0.80, 1.22	0.893
Oral (yes vs. no)	67 (18.7)	195 (46.4)	0.45	0.36, 0.57	<0.001
Inhalation (yes vs. no)	29 (8.1)	34 (8.1)	1.00	0.76, 1.32	0.998
Route unclear (yes vs. no)	74 (20.7)	69 (16.4)	1.16	0.97, 1.39	0.113
Number of drugs in COD[b]					
More than one drug	262 (73.2)	191 (45.5)	1.96	1.63, 2.36	<0.001
Single drug	96 (26.8)	229 (54.5)	Ref.	Ref.	
Substances present[c]					
Alcohol (yes vs. no)	50 (22.7)	87 (28.1)	0.86	0.71, 1.04	0.114
Benzodiazepine (yes vs. no)	55 (25.0)	80 (25.8)	0.95	0.80, 1.14	0.611
Cocaine (yes vs. no)	71 (32.3)	106 (34.2)	0.89	0.76, 1.05	0.174
Methamphetamine (yes vs. no)	5 (2.3)	7 (2.3)	0.97	0.57, 1.63	0.894
Heroin (yes vs. no)	71 (32.3)	134 (43.2)	0.79	0.67, 0.95	0.010
Oxycodone (yes vs. no)	14 (6.4)	48 (15.5)	0.61	0.43, 0.85	0.003
Methadone (yes vs. no)	7 (3.2)	47 (15.2)	0.44	0.28, 0.68	<0.001
Buprenorphine (yes vs. no)	5 (2.3)	7 (2.3)	1.20	0.80, 1.80	0.373
Other opiates (yes vs. no)	21 (9.6)	37 (11.9)	0.80	0.61, 1.04	0.090
Other prescriptions (yes vs. no)[d]	60 (16.8)	121 (28.8)	0.72	0.57, 0.91	0.005
Incident location[e]					
Rural	47 (13.3)	82 (19.5)	0.77	0.60, 0.98	0.036
Suburban	66 (18.4)	66 (15.7)	1.06	0.87, 1.28	0.587
Urban	245 (68.4)	272 (64.8)	Ref.		
Incident place type[f]					
Public	34 (9.5)	37 (8.8)	1.03	0.84, 1.25	0.801
Other/missing	12 (3.4)	16 (3.8)	0.90	0.63, 1.28	0.562
Private residence	312 (87.1)	367 (87.4)	Ref.	Ref.	

Abbreviations: CI, confidence interval.
Note: not all columns add to 100% due to missing data.
[a] Other includes Asian, American Indian or Alaska Native, Black, Native Hawaiian/Other Pacific Islander, and Unknown; No ethnicity information was ascertained.
[b] Refers to the number of drugs deemed contributing to the cause of death (COD). Note: alcohol was excluded from measure.
[c] Drugs found by the medical examiner to contribute to the cause of death.
[d] Includes prescription drugs such as antidepressants, muscle relaxants, stimulants, etc. (excludes over-the-counter medications such as antihistamines and antiemetics.
[e] Urbanicity categorized based on Rhode Island Land Use 2000: State Land Use Policies (http://www.planning.ri.gov/documents/tp/TP 149.pdf).
[f] Public locations included city parks, parking lots, malls, construction sites, wooded areas, etc.; Other locations included shelters, treatment facilities, prisons, hospitals, etc. Note: incident place type could be ascertained for 16 (3.2%) of cases; the proportion with missing data not vary between the fentanyl and non-fentanyl overdose ($P = 0.613$).

present in 222 (74.5%) of femoral samples, with a median concentration of 2.3 ng/ml (range: 0.2–39.0 ng/ml). Acetylfentanyl was present in 23 (6.7%) cases, with a median concentration of 3.7 ng/ml and a range of 0.1–350.0 ng/ml.

Although the spatial distributions for fentanyl and non-fentanyl overdoses were similar (Fig. 2), fentanyl overdoses were less common in rural areas of the state (Table 1). For both types of overdoses, we observed statistically significant "hot spots" in the major urban center of Providence and immediately surrounding communities, as well as a smaller, post-industrial urban centre in northern Rhode Island.

Discussion

This study shows that the number and proportion of overdose deaths involving fentanyl has increased rapidly and significantly in Rhode Island. Fentanyl is now the primary or contributing cause of death in over half of all overdose fatalities. Diverse population groups appear to be affected, with those who engage in injection drug use at particularly high risk of fentanyl overdose. Although fentanyl overdoses were somewhat more common in urban and suburban areas, geospatial analysis demonstrated similar clustering patterns of fentanyl and non-fentanyl overdoses. Overall, these results suggest a widespread distribution of fentanyl-involved overdose deaths, and indicate broad penetration of fentanyl in the illicit drug supply.

Given the rapid growth of fentanyl-involved overdoses, communities are urged to scale-up overdose intervention efforts that demonstrate the greatest potential for reducing fentanyl's harm. Fentanyl causes rapid and more profound respiratory depression than other opioid analgesics, which significantly narrows the window of opportunity for reversal with naloxone (Green & Gilbert, 2016). Because fentanyl overdoses happen much faster than those from other opioids, overdose prevention efforts must address specific factors—such as the rapid onset of overdose symptoms and the increased dosage of naloxone required for overdose reversal (Centers for disease and Control Prevention, 2016). Programs and policies to address the urgency of fentanyl-involved overdoses are critical. For example, having a bystander able to administer naloxone and call emergency medical services if they witness a suspected overdose is vital to prevent fentanyl overdose death. As such, programs to increase distribution of naloxone to people who use drugs, their acquaintances, and their loved ones are urgently required (Walley et al., 2013). We have shown that geospatial analyses can be used to identify emerging "hot spots" of fentanyl overdoses; future research is needed to determine whether such methods can be used to target interventions (e.g., naloxone distribution) more effectively.

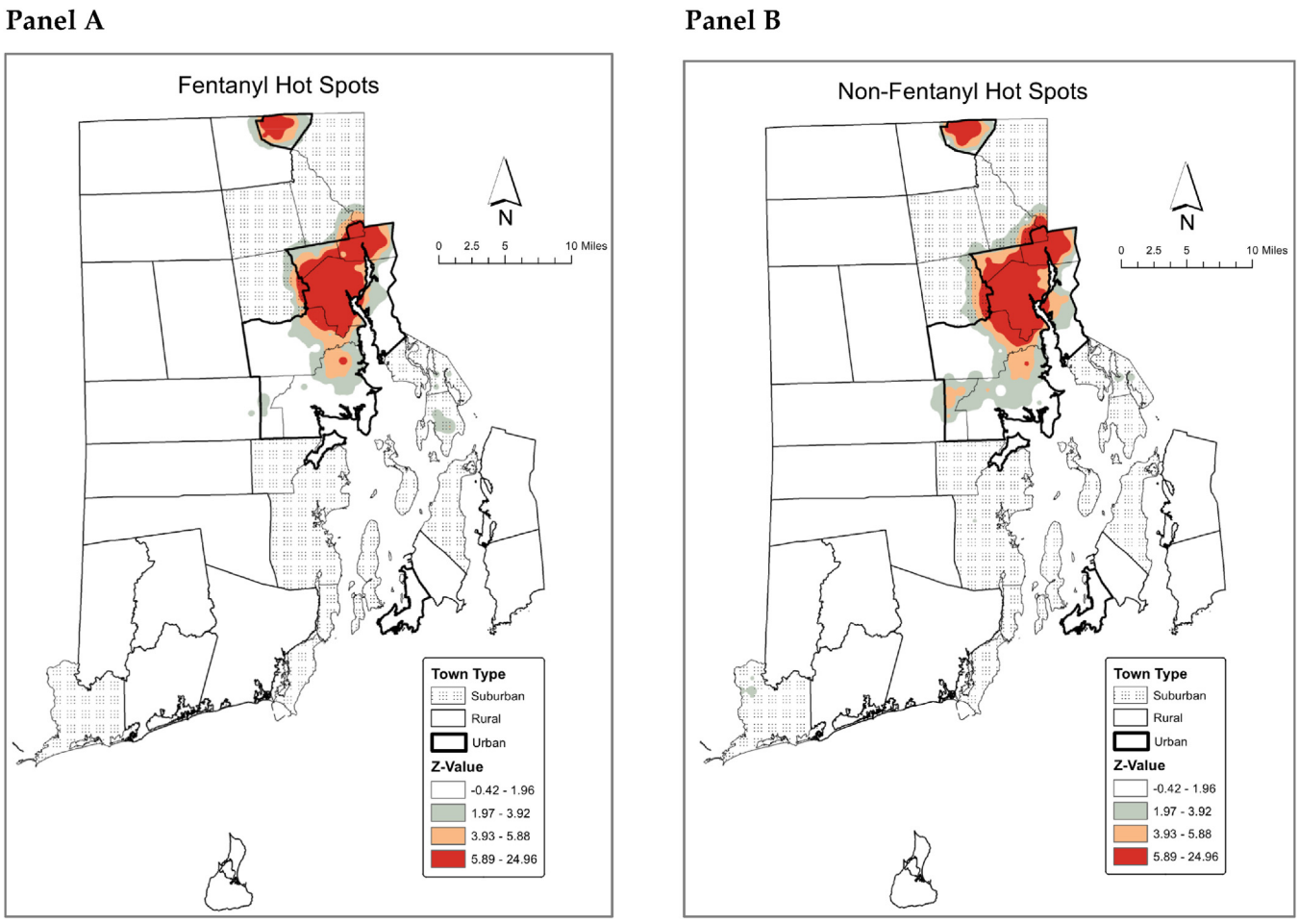

Fig. 2. Geographic distribution of fentanyl (Panel A) and non-fentanyl (Panel B) fatal overdoses, Rhode Island.
Note: 14 (2.8%) overdoses that occurred outside of Rhode Island were not analysed and are not shown on the maps.
Urbanicity categorized based on Rhode Island Land Use 2010: State Land Use Policies (derived from standard US census definitions and available at: http://www.planning.ri.gov/documents/tp/TP149.pdf).
Note: Z-scores represent Getis-Ord Gi* statistics, in which a value of >1.96 (or <−1.96) indicates a cluster of overdoses that are more (or less) likely to be fentanyl-related than would be expected by chance alone (at $P < 05$).

Nonetheless, bystanders often have limited access to the additional doses of naloxone necessary for reversing a fentanyl-involved overdose (Centers for disease and Control Prevention, 2016). Thus, calling emergency medical services is necessary to ensure access to higher dosages of naloxone. To reduce fear of arrest after witnessing or reporting an overdose, the continued adoption and promotion of Good Samaritan Laws (which protect bystanders from prosecution in the event of reporting an overdose) are needed (Evans, Hadland, Clark, Green, & Marshall, 2016).

Our data demonstrate a relatively high prevalence of other illicit drugs (e.g., cocaine) and prescription medications (e.g., benzodiazepines) among fentanyl-involved overdose decedents. Further work is needed to determine whether these cases are due to intentional fentanyl use or unintentional polysubstance exposure (due to the adulteration of illicit drugs and counterfeit pills with non-pharmaceutical fentanyl). Nonetheless, the identification of fentanyl and fentanyl analogues in non-opioid drugs in other settings (Green & Gilbert, 2016; Klar et al., 2016; Marinetti & Ehlers, 2014), emphasizes the importance of broadening overdose prevention programs beyond those targeting opioid users. For example, supervised injection facilities (SIFs), in which persons can inject pre-obtained illegal drugs under the supervision of medical personnel, have been shown to reduce population-level fatal overdose rates in communities with a high burden of injection drug use (Marshall, Milloy, Wood, Montaner, & Kerr, 2011). Additionally, peer-based programs, including peer recovery referral services to persons who experience a non-fatal overdose (Samuels, 2014), should be implemented and warrant further evaluation. Such programs have the capacity to increase overdose education and naloxone distribution to populations at highest risk for overdose.

Alarmingly, one quarter of fentanyl-associated overdose fatalities were among people less than 29 years of age. Several factors may explain the dramatic increase in fentanyl overdose rates among young adults. For example, although opioid agonist therapy (OAT) is an effective treatment for opioid use disorder, including among youth (Woody et al., 2008), nearly nine in ten young people suffering from addiction do not receive any treatment (Han, Hedden, Lipari, Copello, & Kroutil, 2015). Thus, interventions to improve access to evidence-based treatment for young adults are paramount. Increased access to OAT has been associated with reductions in overdose deaths in the US (Schwartz et al., 2013). Thus, the continued expansion of OAT programs, including an increase in the number of physician waivered to prescribe buprenorphine, should be a public health priority, particularly in areas affected by fentanyl overdose.

There are several limitations of this study that should be noted. First, we were unable to definitively differentiate deaths involving prescription vs. illicitly manufactured fentanyl. However, the high prevalence of evidence of injection drug use and polysubstance use among the fentanyl-involved overdoses suggest that the vast majority were due to non-pharmaceutical fentanyl adulteration of the illicit drug supply. Second, although trained research assistants were used to extract detailed information from each medical examiner case file, some variables (e.g., route of administration) may be subject to misclassification.

Fentanyl-associated deaths represent an emerging and troubling public health problem. The lethality of fentanyl portends major challenges for state and national efforts to reduce overdose deaths. To address this problem, regional efforts must target overdose prevention among people who use and inject drugs, including among young people who use drugs. Immediate and continued scale-up of evidence-based interventions are necessary to prevent fentanyl-involved deaths, particularly overdose education and naloxone distribution, Good Samaritan Laws, supervised injection facilities, peer-based recovery programs, and access to opioid agonist therapy.

Author contributions

BDLM had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses. BDLM and TCG designed the study. BDLM conducted the literature review and drafted the manuscript. BDLM and MSK conducted the statistical analyses. JLY, PO, PB, NEAS, JDR, and TCG helped interpret the data and critically revised successive drafts of the manuscript for important intellectual content.

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Role of the funding source

The funders had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; nor in the decision to submit the article for publication.

Disclaimer

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Competing interests

The authors declare no conflicts of interest.

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