



Full length article

Fentanyl and fentanyl-analog involvement in drug-related deaths

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ABSTRACT

Background: To describe and analyze the involvement of fentanyl and fentanyl analogs (FAs) in drug-related deaths in West Virginia (WV), United States.**Methods:** Retrospective analyses of all WV drug-related deaths from 2005 to 2017 were performed, including comparisons of demographic and toxicological characteristics among total deaths, deaths in which fentanyl/FAs were present, deaths in which they were absent, heroin-related deaths, and prescription opioid-related deaths. **Results:** Most of the 8813 drug-related deaths were overdoses, with about 11% resulting from transportation/other injuries in which drugs were contributors. Prescription opioid presence (without fentanyl) decreased by 75% from 2005–14 to 2015–17 (3545 deaths to 859 deaths, respectively), while fentanyl involvement in the deaths increased by 122% between these periods (487 to 1082 deaths). Ten FAs were identified (427 instances) after 2015. Alprazolam and ethanol were among the top five most frequently identified substances across years. Fentanyl, heroin and cocaine replaced oxycodone, diazepam and hydrocodone in the top five beginning in 2015. Few decedents had a prescription for fentanyl after 2015, with fewer prescriptions also present for other controlled substances identified.**Conclusions:** Fentanyl, rapidly emerging FAs, and other illicit drugs in recent years pose a serious health threat even though prescription opioid-related deaths decreased over the same time period.

1. Introduction

Opioid-related deaths continue to increase in the United States, resulting in a substantial public health burden of about five years of life lost per 1000 population (Gomes et al., 2018). Fentanyl and fentanyl analog (FA)-related deaths have increased dramatically with much of the fentanyl identified consisting of illicitly manufactured fentanyl (IMF) (Armenian et al., 2017; Suzuki and El-Haddad, 2017; Centers for Disease Control and Prevention CDC, 2018). Greater difficulty obtaining prescription opioids along with ready heroin availability may have contributed to increased IMF use (Hempstead and Yildirim, 2014). Potent FAs such as carfentanil (veterinary drug) and furanyl fentanyl maintain fentanyl's pharmacologic effects while being difficult to detect with standard toxicological testing (Armenian et al., 2017; Suzuki and El-Haddad, 2017). Since fentanyl is about 50–100 times and carfentanil approximately 10,000 times more potent than morphine, they and other illicit FAs pose serious health threats (Armenian et al., 2017; Suzuki and El-Haddad, 2017).

Fentanyl/FAs have been found in adulterated prescription drugs and in heroin, cocaine, and methamphetamine (Arens et al., 2016; Mars et al., 2017; McCall Jones et al., 2017; CDC, 2018), resulting in deaths of individuals misusing or abusing these substances (Frank and Pollack, 2017). Combining IMF/FAs with other opioids increases the overdose danger by potentiating respiratory and central nervous system depression, often resulting in rapidly occurring death (Fox et al., 2018; Slavova et al., 2017).

West Virginia (WV), which is predominantly rural, has the highest per capita drug overdose mortality in the United States (Hedegaard et al., 2017). Although heroin and synthetic opioids such as fentanyl contribute to an increasing number of drug-related deaths nationally (Rudd, 2016), studies have suggested that fentanyl overdoses might be more common in urban and suburban areas (Marshall et al., 2017). The objective of this study was to compare fentanyl and FA-related deaths to drug-related deaths not involving fentanyl/FAs in West Virginia.

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2. Methods

A forensic drug database (FDD) was created in 2005 in collaboration with the West Virginia Office of the Chief Medical Examiner (WVOCME) to compile data from all WV drug-related deaths. West Virginia uses a centralized medical examiner system and the WVOCME maintains files for WV deaths. Drug-related death data are available from 2005 through 2017 (a total of 78 [7%] of 2017 deaths were not available for entry at time of this manuscript). Each FDD case includes demographic information (e.g., age, sex, race, weight, height, date of death, zip code of residence), cause and manner of death, toxicology findings (e.g., drugs identified, concentrations, postmortem interval), whether a prescription was present within the past 30 days for controlled substances, autopsy findings, and medical history. Sources used by the OCME data entry personnel to compile the FDD data included the death certificate, autopsy report, external examination, investigator reports, medical records, police reports, toxicology reports, the West Virginia Controlled Substances Monitoring Program (WV CSMP), and any other relevant information in the decedent's file. Medical history information was obtained using a variety of sources, including county MEs, scene investigations, prescription records, autopsy reports, and medical records when available.

Deaths were defined as fentanyl or FA-related if one or more of these substances was found during postmortem toxicology testing and identified as a cause of or contributor to death in Parts I or II of the death certificate. Deaths included those in which overdose was the immediate cause of death, or a transportation-related or other injury (e.g., motor vehicle, ATV, drowning, etc.) was the immediate cause of death but drugs were believed to be significant contributors to death (e.g., fentanyl and heroin present during confirmatory toxicology in vehicle operator's death).

Drug screening is routinely performed on all deaths investigated by the WV OCME, with confirmatory toxicology tests conducted for most positive screens. Blood and/or tissue samples are screened for volatile compounds using gas chromatography with flame ionization detection and drugs of abuse using automated enzyme immunoassays. This latter test includes the following drugs/drug classes: amphetamines, barbiturates, benzodiazepines, buprenorphine, cocaine, fentanyl/fentanyl analogs, methadone, opiates (morphine, codeine, hydrocodone, hydromorphone, oxycodone, oxymorphone), and marijuana. In addition to the opiate immunoassay, a second immunoassay is specifically used to detect oxycodone and oxymorphone. Drugs or drug classes, including many therapeutic and nonprescription drugs, which screen positive undergo confirmation testing and quantitation. Fentanyl analogs were tested beginning in 2013 to coincide with national reports. Heroin was considered to have been used when the drug or its metabolite 6-monoacetylmorphine (6-MAM) was identified in any sample tested. Frequently 6-MAM is detectable in vitreous fluid or urine when no longer detectable in blood. The femoral or subclavian blood concentration ratio of morphine to codeine was also considered when heroin involvement in the death was suspected (Harruff et al., 2015). In a small number of cases, heroin was listed on the death certificate as a cause of or contributor to death on the basis of a compelling death scene investigation with toxicology reports identifying morphine (metabolite of 6-MAM) and small amounts to undetectable codeine.

Descriptive analyses were used to characterize the drug-related deaths. T-tests and Chi-square tests were used for continuous and categorical data comparisons, respectively. Co-intoxicants in fentanyl and FA-related deaths were compared between the 2005–2014 and the 2015–2017 time periods because the number of fentanyl and FA-related deaths did not increase substantially until 2015. The number of drugs with a valid prescription (defined as a prescription present within 30 days prior to death) was determined through use of the WV CSMP. Comorbidities identified through autopsy reports and other information in decedents files were defined as follows: cardiovascular (cardiomyopathy, cardiomegaly, hypertrophy, hypertensive cardiovascular

disease, ischemic heart disease, atherosclerotic coronary artery disease, cardiac disease, heart failure, myocardial infarction), psychiatric other than substance abuse disorder (Alzheimer's disease, anxiety disorder, attention deficit hyperactivity disorder, bipolar affective disorder, chronic fatigue, delusional disorder, dementia, depression, mania, mental/behavioral disorders, obsessive-compulsive disorder, panic attacks, posttraumatic stress disorder, psychosis, schizophrenia, suicide attempts/ideation, self-mutilation behavior), pulmonary (asthma, sleep apnea, chronic obstructive pulmonary disease, pneumoconiosis), hepatic (hepatitis, cirrhosis, alcoholic/other liver disease, hepatic necrosis, hepatic failure), pain (ankylosing spondylitis, migraine/headache syndromes, arthritis/polyarthritis/rheumatoid arthritis/osteoarthritis, systemic lupus, systemic sclerosis, neuropathy pain, acute pain, chronic pain, fibromyalgia, pancreatitis, systemic lupus, hip fracture), and history of substance abuse (drug, alcohol or other substance).

All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). A *P* value of less than 0.05 was considered statistically significant.

3. Results

A total of 8813 WV drug-related deaths from 2005 to 2017 were analyzed. Five data sources were reviewed on average per death, with toxicology, investigation and autopsy reports, and death certificates used most frequently. Of the 5924 drug-related deaths from 2005 to 2014, fentanyl was identified in 487 deaths (8.2%), most of which involved co-intoxicants with only one FA found (Table 1). Of the 2889 drug-related deaths from 2015 to 2017, 1082 (37.5%) involved fentanyl and/or FAs. The mean decedent age in fentanyl and/or FA-related deaths was significantly lower (~ seven years) compared to deaths involving prescription opioids. Overall, most decedents were male, with about 87% of deaths classified by the OCME as unintentional. Body mass index (BMI) did not differ between fentanyl/FA-related and prescription opioid deaths from 2005 to 2014, although BMI was slightly but statistically significantly lower compared to prescription opioid deaths during 2015–2017. Drug overdose was the primary cause of death across years and was significantly higher in the fentanyl/FA-related cases (99%) compared to prescription opioid or total drug deaths. A transportation-related accident or other injury (e.g., impaired/intoxicated individual hit by vehicle or falling) was the primary cause of death in approximately 11%, with one or more drugs considered contributors.

Multiple drug use was common (77.5%) among drug-related deaths (Table 1). A slight but statistically significantly greater number of co-intoxicants was identified in prescription opioid-related deaths during 2015–2017 (mean = 3.2) compared to fentanyl/FA-related deaths (mean = 2.9). Females tended to have only a slightly higher average number of co-intoxicants present than males. Involvement of fentanyl/FAs in the deaths increased dramatically during 2015–2017 (Fig. 1) while prescription opioid-related deaths, still a considerable problem, decreased (Table 1). From 2012 to 2017, the largest increases in the drugs identified were: fentanyl (1325%), methamphetamine (1375%), heroin (279%), and cocaine (171%), with most increases occurring from 2015 to 2017. Prescription opioids (not including fentanyl) were present in about 30% of 2015–2017 deaths compared to almost 60% of 2005–2014 deaths. Only age, manner of death, and cause of death were statistically significantly different between fentanyl/FA-related deaths and prescription opioid deaths from 2005 to 2014, with all characteristics compared significantly different during 2015–2017 (Table 1).

Alprazolam, oxycodone, ethanol, diazepam, and hydrocodone comprised the top five identified substances in unintentional deaths from 2005 to 2014, while fentanyl, heroin, ethanol, alprazolam, and cocaine were the most common substances in 2015–2017 (Table 2). During 2015–2017, the most frequent co-intoxicants found together with fentanyl/FAs were heroin (36.3%), cocaine (19.9%), alprazolam (15.5%), ethanol (15.1%), and methamphetamine (14.7%). Only

Table 1
Changes in fentanyl, fentanyl analog, heroin, and non-fentanyl prescription opioid-related deaths in West Virginia, 2005–2017 (n = 8813).

Characteristics	2005–2014					2015–2017				
	Total Drug-Related Deaths ^a n (%)	Fentanyl and/or Analogs ^b n (%)	Heroin ^c n (%)	Prescription Opioid(s) ^d n (%)	p - value ^e	Total Drug-Related Deaths ^a n (%)	Fentanyl and/or Analogs ^b n (%)	Heroin ^c n (%)	Prescription Opioid(s) ^d n (%)	p - value ^e
Total ^f	5924 (NA)	487 (8.2)	508 (8.6)	3545 (59.8)	NA	2889 (NA)	1082 (37.5)	290 (10.0)	857 (29.7)	NA
Age (mean, SD)	41.6 (11.8)	39.7 (11.3)	36.1 (10.7)	41.3 (11.4)	0.0039	42.1 (12.3)	39.2 (11.2)	38.2 (11.2)	46.4 (11.4)	< 0.0001
Male	3921 (66.2)	313 (64.3)	402 (79.1)	2240 (63.2)	0.6386	1952 (67.6)	766 (70.8)	202 (69.7)	515 (60.1)	< 0.0001
BMI (mean, SD)	28.9 (7.6)	29.2 (6.9)	28.4 (6.6)	29.6 (7.9)	0.2544	28.4 (7.8)	28.1 (7.0)	28.9 (7.7)	29.3 (8.4)	0.0010
Number of drugs present										
Single drug	1320 (22.3)	48 (9.9)	97 (19.1)	366 (10.3)	0.8711	664 (23.0)	140 (12.9)	59 (20.3)	74 (8.6)	0.0018
2 drugs	1539 (26.0)	126 (25.9)	164 (32.3)	967 (27.3)		833 (28.8)	309 (28.6)	123 (42.4)	235 (27.4)	
3 drugs	1354 (22.9)	138 (28.3)	129 (25.4)	941 (26.6)		659 (22.8)	302 (27.9)	63 (21.7)	237 (27.7)	
4 drugs	895 (15.1)	97 (19.9)	66 (13.0)	651 (18.4)		409 (14.2)	202 (18.7)	24 (8.3)	161 (18.8)	
5 or more drugs	816 (13.8)	78 (16.0)	52 (10.2)	620 (17.5)		324 (11.2)	129 (11.9)	21 (7.2)	150 (17.5)	
Number of drugs present by sex (mean, SD)										
Female	3.2 (1.7)	3.3 (1.6)	3.1 (1.7)	3.5 (1.7)	0.2543	3.0 (1.6)	3.1 (1.4)	2.6 (1.5)	3.5 (1.7)	0.0013
Male	2.6 (1.4)	3.1 (1.3)	2.6 (1.4)	3.0 (1.4)	0.3451	2.5 (1.4)	2.9 (1.3)	2.4 (1.1)	3.0 (1.5)	0.0246
Total	2.8 (1.6)	3.2 (1.5)	2.7 (1.4)	3.2 (1.5)	0.8893	2.7 (1.5)	2.9 (1.3)	2.4 (1.3)	3.2 (1.6)	< 0.0001
Manner of death										
Unintentional	4982 (84.1)	455 (93.4)	499 (98.2)	3141 (88.6)	0.0015	2670 (92.4)	1068 (98.7)	284 (97.9)	762 (88.9)	< 0.0001
Suicide	517 (8.7)	8 (1.6)	8 (1.6)	175 (4.9)		118 (4.1)	8 (0.7)	0 (0.0)	44 (5.1)	
Other (Could not be determined, homicide)	425 (7.2)	24 (4.9)	1 (0.2)	229 (6.5)		101 (3.5)	6 (0.6)	6 (2.1)	51 (6.0)	
Cause of death by category										
Overdose	5292 (89.3)	480 (98.6)	506 (99.6)	3401 (95.9)	0.0165	2568 (88.9)	1072 (99.1)	284 (97.9)	787 (91.8)	< 0.0001
Transportation (occupant, pedestrian, etc.)	197 (3.3)	2 (0.4)	1 (0.2)	40 (1.1)		223 (7.7)	5 (0.5)	4 (1.4)	50 (5.8)	
Other injuries (fall, firearm, drowning, etc.)	435 (7.3)	5 (1.0)	1 (0.2)	104 (2.9)		98 (3.4)	5 (0.5)	2 (0.7)	20 (2.3)	

NA: not applicable.

^a Includes deaths involving any drug or alcohol.

^b 2005–2014 included only 1 fentanyl analog identified in 1 death.

^c Any death involving heroin with no fentanyl and/or analogs.

^d Any death involving buprenorphine, codeine, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, propoxyphene, meperidine or tramadol; no fentanyl and/or analogs or heroin.

^e Comparison between fentanyl and/or analogs and prescription opioid(s).

^f Total drug-related deaths during time period.

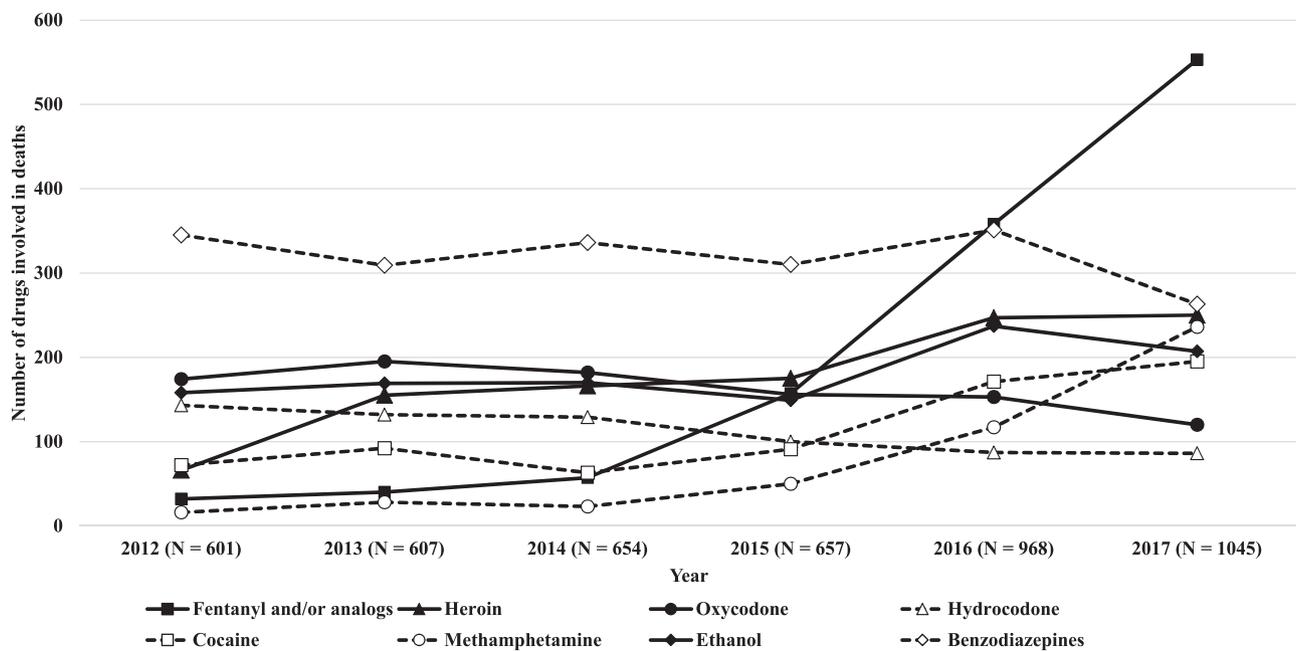


Fig. 1. Fentanyl ± FAs and other drug involvement in unintentional drug-related deaths in West Virginia, 2012–2017.

methamphetamine was found with similar frequency regardless of whether fentanyl/FAs were present or absent ($p = 0.6430$). Of the 1196 unintentional heroin-related deaths from 2005 to 2017, 6-MAM was identified in 1061 cases (88.7%) and morphine was present in all remaining cases ($n = 135$). A morphine/codeine concentration ratio in femoral or subclavian blood could be calculated in 29 (21.5%) of these latter deaths; the ratio was greater than 1 in all cases and greater than 3 in 28 of the 29 cases (96.6%). Scene investigations also helped determine the likelihood of heroin involvement in these deaths.

Since 2015, fentanyl/FA deaths outpaced those of other prescription opioids identified in unintentional deaths. The number of fentanyl/FA-related deaths exceeded those from other substances since 2016 and rose dramatically in 2017 (Fig. 1). Methamphetamine involvement has also rapidly increased from 2015 (7.6%) to 2017 (22.6%). Ethanol continues to maintain a significant presence in drug-related deaths each year (19.8% in 2017). Benzodiazepines were commonly found across years but decreased in 2017.

Ten different FAs were identified in any death from 2015 to 2017 (427 instances) (Table 3), with a single FA identified prior to 2015. The FAs identified include (in decreasing frequency): carfentanyl, furanyl fentanyl, para-fluoro(iso)butyryl fentanyl, acetyl fentanyl, acryl fentanyl, cyclopropyl fentanyl, butyryl fentanyl, 3-methyl fentanyl, methoxyacetyl fentanyl, and tetrahydrofuran fentanyl. They were often identified with co-intoxicant fentanyl, heroin, benzodiazepines, cocaine or other FAs. Fentanyl was a co-intoxicant in about 31–35% of deaths involving carfentanyl and furanyl fentanyl, 87.5% of deaths involving acetyl fentanyl, and 61.3% of deaths involving para-fluoro(iso)butyryl fentanyl. Among a total of 317 cases with at least one FA present, heroin and benzodiazepines were identified in 121 (38.2%) and 87 (27.4%), respectively, with other prescription opioids less commonly found (81 cases; 25.6%).

The percentage of controlled substances for which decedents had a prescription decreased overall from 2005 to 2014 to 2015–2017, but the percentage steadily increased by age, from 9.8% of decedents aged

Table 2

Drugs most frequently present in total, 2005–2014, and in total and fentanyl ± fentanyl analog-related unintentional deaths in West Virginia, 2015–2017 ($n = 7652$).

2005–2014 (n = 4982)		2015–2017 (n = 2670)				
Substance	Total ^a n (%)	Substance	Total ^a n (%)	F ± FA Present (n = 1068) n (%)	F ± FA Absent (n = 1602) n (%)	p - value ^b
Alprazolam	1551 (31.1)	Fentanyl	899 (33.7)	NA	NA	NA
Oxycodone	1430 (28.7)	Heroin	672 (25.2)	388 (36.3)	284 (17.7)	< 0.0001
Ethanol	1262 (25.3)	Ethanol	593 (22.2)	161 (15.1)	432 (27.0)	< 0.0001
Diazepam	1244 (25.0)	Alprazolam	495 (18.5)	166 (15.5)	329 (20.5)	0.0011
Hydrocodone	1029 (20.7)	Cocaine	457 (17.1)	213 (19.9)	244 (15.2)	0.0015
Methadone	783 (15.7)	Oxycodone	429 (16.1)	95 (8.9)	334 (20.8)	< 0.0001
Cocaine	730 (14.7)	Methamphetamine	403 (15.1)	157 (14.7)	246 (15.4)	0.6430
Heroin	524 (10.5)	Diazepam	368 (13.8)	116 (10.9)	252 (15.7)	0.0003
Morphine	520 (10.4)	Hydrocodone	273 (10.2)	60 (5.6)	213 (13.3)	< 0.0001
Fentanyl	454 (9.1)	Gabapentin	248 (9.3)	30 (2.8)	218 (13.6)	< 0.0001
Oxymorphone	402 (8.1)	Clonazepam	217 (8.1)	63 (5.9)	154 (9.6)	0.0006
Clonazepam	358 (7.2)	Morphine	207 (7.8)	114 (10.7)	93 (5.8)	< 0.0001
Citalopram	301 (6.0)	Buprenorphine	189 (7.1)	46 (4.3)	143 (8.9)	< 0.0001
Diphenhydramine	299 (6.0)	Oxymorphone	145 (5.4)	20 (1.9)	125 (7.8)	< 0.0001
Tramadol	214 (4.3)	Methadone	95 (3.6)	22 (2.1)	73 (4.6)	0.0006

NA: not applicable; F: fentanyl; FA: fentanyl analogs.

^a Total drug-related unintentional deaths during time period (excludes cases with other manners of death).

^b Comparison between deaths in which F and/or FA were present or absent.

Table 3
Fentanyl analogs identified in drug-related deaths in West Virginia, 2015–2017 (n = 2889).

Characteristic	Carfentanil n (%)	Fentanyl n (%)	Para-fentanyl n (%)	Para-fluoro(iso) butyryl fentanyl n (%)	Acetyl fentanyl n (%)	Cyclopropyl fentanyl n (%)	Butyryl fentanyl n (%)	3-Methyl fentanyl n (%)	Methoxyacetyl fentanyl n (%)	Tetrahydrofuran fentanyl n (%)
Total No. of cases	117	104	75	56	29	20	10	8	7	1
First identified date	2016/Aug	2015/Jan	2015/Jan	2013/Jan	2015/Jan	2017/Jun	2016/Dec	2016/Sept	2017/Sept	2017/April
Age (mean, SD)	38.8 (11.7)	40.1 (11.2)	40.9 (11.3)	37.4 (9.7)	35.0 (9.2)	39.6 (11.6)	44.1 (8.6)	33.6 (10.2)	43.4 (14.2)	26.0 (.)
Male	75 (64.1)	69 (66.3)	60 (80.0)	35 (62.5)	20 (69.0)	17 (85.0)	10 (100.0)	6 (75.0)	5 (71.4)	0 (.)
Number of drugs present (mean, SD)	3.2 (1.6)	3.9 (1.4)	4.1 (1.3)	3.8 (1.4)	3.5 (1.3)	3.2 (1.6)	4.7 (1.8)	2.4 (0.5)	4.4 (1.9)	4 (.)
Single drug	16 (13.7)	2 (1.9)	1 (1.3)	1 (1.8)	2 (6.9)	4 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2 drugs	27 (23.1)	14 (13.5)	9 (12.0)	8 (14.3)	5 (17.2)	3 (15.0)	1 (10.0)	5 (62.5)	1 (14.3)	0 (0.0)
3 drugs	28 (23.9)	26 (25.0)	12 (16.0)	17 (30.4)	9 (31.0)	5 (25.0)	2 (20.0)	3 (37.5)	1 (14.3)	0 (0.0)
4 drugs	24 (20.5)	32 (30.8)	29 (38.7)	17 (30.4)	7 (24.1)	4 (20.0)	2 (20.0)	0 (0.0)	2 (28.6)	1 (100.0)
5 or more drugs	22 (18.8)	30 (28.8)	24 (32.0)	13 (23.2)	6 (20.7)	4 (20.0)	5 (50.0)	0 (0.0)	3 (42.9)	0 (0.0)
Cases with concurrent										
Fentanyl	41 (35.0)	32 (30.8)	46 (61.3)	49 (87.5)	14 (48.3)	9 (45.0)	6 (60.0)	1 (12.5)	6 (85.7)	0 (0.0)
Other fentanyl analog(s)	28 (23.9)	31 (29.8)	41 (54.7)	1 (1.8)	15 (51.7)	5 (25.0)	5 (50.0)	2 (25.0)	3 (42.9)	1 (100.0)
Other prescription opioid (s) ^a	28 (23.9)	25 (24.0)	14 (18.7)	20 (35.7)	3 (10.3)	2 (10.0)	3 (30.0)	2 (25.0)	2 (28.6)	1 (100.0)
Heroin	26 (22.2)	48 (46.2)	42 (56.0)	29 (51.8)	17 (58.6)	6 (30.0)	5 (50.0)	1 (12.5)	2 (28.6)	1 (100.0)
Benzodiazepine(s) ^b	34 (29.1)	39 (37.5)	19 (25.3)	15 (26.8)	3 (10.3)	4 (20.0)	3 (30.0)	0 (0.0)	1 (14.3)	0 (0.0)
Ethanol	13 (11.1)	18 (17.3)	9 (12.0)	10 (17.9)	2 (6.9)	0 (0.0)	2 (20.0)	0 (0.0)	1 (14.3)	0 (0.0)
Methamphetamine	28 (23.9)	13 (12.5)	5 (6.7)	4 (7.1)	6 (20.7)	6 (30.0)	2 (20.0)	1 (12.5)	4 (57.1)	0 (0.0)
Cocaine	19 (16.2)	20 (19.2)	22 (29.3)	12 (21.4)	3 (10.3)	6 (30.0)	3 (30.0)	4 (50.0)	2 (28.6)	0 (0.0)
Most frequently occurring analog co-intoxicant	Fentanyl, 17 (14.5)	Para-fluoro(iso) butyryl/butyryl fentanyl, 32 (30.8)	Fentanyl, 32 (42.7)	Fentanyl, 13 (23.2)	Fentanyl, 13 (44.8)	Para-fluoro(iso) butyryl fentanyl, 2 (10.0)	Para-fluoro(iso) butyryl fentanyl, 5 (50.0)	Carfentanil, 1 (12.5)	Carfentanil, 2 (28.6)	Carfentanil, 1 (100.0)

^a Any death involving buprenorphine, codeine, hydrocodone, hydromorphone, methadone, morphine, oxycodone, propoxyphene, meperidine or tramadol; no fentanyl or heroin.
^b Benzodiazepines include alprazolam, clonazepam, chlordiazepoxide, diazepam, lorazepam, oxazepam, temazepam.

Table 4
Comorbid medical conditions in unintentional drug-related deaths (n = 7652) - fentanyl + FAs vs. non-fentanyl + FAs in West Virginia, 2005–2017.

Medical Conditions	Total Deaths n (%)	Fentanyl and/or Analogs Present n (%)	Fentanyl and/or Analogs Absent n (%)	p - value ^b
Total ^a	6837	1420	5417	–
Cardiovascular	3306 (48.4)	584 (41.1)	2722 (50.3)	< 0.0001
Psychiatric	1342 (19.6)	299 (21.1)	1043 (19.3)	0.128
Pulmonary	1622 (23.7)	241 (17.0)	1381 (25.5)	< 0.0001
Hepatic	660 (9.7)	142 (10.0)	518 (9.6)	0.6192
Pain	738 (10.8)	154 (10.9)	584 (10.8)	0.9447
History of Abuse	4915 (71.9)	1244 (87.6)	3671 (67.8)	< 0.0001

^a Total cases with available medical history data; percentages calculated using total number as denominator.

^b Comparison between fentanyl and/or analogs present vs. fentanyl and/or analogs absent.

18–24 years to 42% of those 65 years and older. Fewer decedents had a prescription for hydrocodone (51.4% vs. 38.8%), oxycodone (39.3% vs. 37.3%), morphine (19.9% vs. 9.7%), alprazolam (44.5% vs. 34.5%), and diazepam (28.9% vs. 22.6%) during 2015–2017 compared to the earlier period. Very few decedents had a prescription for methamphetamine. For deaths involving methadone, commonly used in medication-assisted treatment for opioid abuse, a prescription was found with slightly higher frequency during 2015–2017 compared to earlier years (31.2% to 24.2%, respectively), although the number of methadone-related deaths was much lower recently. Most notable was the recent decline in the percentage of decedents who had a prescription for identified fentanyl (23.9% to 1.7%).

Medical records were accessed for 25.6% (2259/8813) of all deaths (Table 4). Of these, a history of substance abuse (drugs and/or alcohol) was significantly higher in unintentional deaths involving fentanyl/FAs compared to deaths in which they were absent (87.6% vs. 67.8%), while co-morbid cardiovascular (41.1% vs. 50.3%) and pulmonary diseases (17.0% vs. 25.5%) were significantly less common in fentanyl/FA-related deaths. There were no significant differences in co-morbid psychiatric, pain, or hepatic conditions between deaths with or without fentanyl/FAs, with percentages in all groups relatively low (less than 20%).

4. Discussion

Drug-related deaths continue to rise in the United States (Armenian et al., 2017; Frank and Pollack, 2017; O'Donnell et al., 2017; Suzuki and El-Haddad, 2017; CDC, 2018). Fentanyl-related WV deaths have continued unabated since 2015, with a steep recent increase. Drug involvement in the deaths has also changed, from predominantly prescription opioids to illicit drugs, generally with co-intoxicants. This recent shift from predominantly prescription opioids to illicit drugs suggests that programs to reduce prescription opioid deaths, e.g., prescription drug monitoring programs (PDMPs), are decreasing fatal intoxications from such opioids. However, when prescription opioids are less readily available, drug users often switch to cheaper, illicit substitutes (Alexander et al., 2016; Fink et al., 2018; Nam et al., 2017; Pergolizzi et al., 2018; Seth et al., 2018; Slavova et al., 2017). Our finding of fewer decedents with prescriptions for identified controlled substances is consistent with these reports. Although a recent review found that PDMPs appeared to reduce overdose deaths, albeit based on low-strength evidence (Compton and Wargo, 2018), they have continued to increase in WV. This increase might also be explained in part by geographical isolation, poverty, limited medical resources, heavy economic burdens, and social obstacles that could exacerbate the fentanyl problem in rural areas (Jozaghi and Marsh, 2017).

Similar to other reports (Hayashi et al., 2018), the mean decedent age was significantly younger in fentanyl/FA-related deaths compared to other drugs or those involving prescription opioids. Compared to non-fentanyl prescription opioids, fentanyl/FA-related deaths in 2015–2017 had a significantly greater proportion of males, lower BMI, and were more likely to be unintentional in nature. Thus, it is important

that efforts to reduce fentanyl abuse encompass the younger male population.

Characterizing the co-intoxicants involved in fentanyl-related deaths is important. Fentanyl or a FA was present as a single drug in a minority of deaths (12.9%), although to a significantly greater extent than single drug prescription opioids (9% of deaths). Co-intoxicants identified prior to 2015 were predominantly benzodiazepines and prescription opioids; more recently, they were likely to be illicit although benzodiazepine involvement continues to be high. Heroin, cocaine, and methamphetamine were present in 36.3%, 19.9%, and 14.7% of all unintentional fentanyl/FA-related deaths during 2015–2017, respectively, consistent with reports describing regular heroin and cocaine use as risks for fentanyl overdose (Baldwin et al., 2018; Hayashi et al., 2018; Mars et al., 2017; McCall Jones et al., 2017; Rubin, 2017). Crystal methamphetamine use has been significantly associated with fentanyl identification (Amlani et al., 2015; Baldwin et al., 2018; Hayashi et al., 2018), with fentanyl/FAs found to an increasing extent in confiscated methamphetamine (CDC, 2018). Methamphetamine was present to a similar extent in WV fentanyl/FAs present or absent deaths.

Fentanyl-related deaths with multiple co-intoxicants might partly result from the use of fentanyl-laced or counterfeit heroin, cocaine, opioids and benzodiazepines (CDC, 2016a; Marinetti and Ehlers, 2014; Unick and Ciccarone, 2017; CDC, 2018). This could help explain the rapid rise in fentanyl-related deaths in WV, a state with traditionally high prescription opioid deaths. A prescription was present in a very small percentage of our recent fentanyl deaths, indicating predominantly IMF use or diversion.

Heroin was identified in over a third of fentanyl/FA-related deaths during 2015–2017 but can be difficult to detect due to its very rapid metabolism to 6-monoacetylmorphine, which has a slightly longer but still relatively short half-life (Harruff et al., 2015). Thus, the morphine/codeine concentration ratio can assist in identifying heroin involvement in deaths. Codeine in small concentrations is often present in illicit heroin batches. A morphine/codeine ratio greater than three likely indicates that heroin use was the source of codeine present, while a ratio smaller than one typically indicates codeine ingestion (Harruff et al., 2015). In cases where 6-MAM was present in our study, all had a ratio greater than one, with most having a morphine/codeine ratio above three. Similar results were found in suspected heroin deaths in which 6-MAM was absent and a morphine/codeine ratio could be determined. Thus, only a relatively small number of 6-MAM-negative deaths might be falsely attributed to heroin, although some cases with heroin involvement could be missed.

The rapid increase in FA deaths represents an unprecedented public health threat (CDC, 2018), with prescription opioids and benzodiazepines still contributing to a significant number of deaths. Although relatively new to WV, FAs were identified for several years in other areas of the country (Hibbs et al., 1991). A total of ten different FAs were identified in WV deaths during 2015–2017, usually with co-intoxicant fentanyl, heroin, benzodiazepines, cocaine or other FAs. Carfentanil and furanyl fentanyl were present most often, but new FAs continue to

be identified.

Additional trends from the more recent drug-related deaths deserve special mention. Recent increases in methamphetamine involvement is of particular concern, particularly with the prevalence of cardiovascular disease in WV (CDC, 2016b). Heroin and cocaine were infrequently involved in WV deaths in past years but now constitute serious health threats. Alcohol should not be overlooked since it has consistently been among the top substances identified in WV drug-related deaths, present in almost a quarter of such deaths.

About 89% of WV drug deaths represented overdoses. Deaths were also included in which a transportation-related accident or other injury was the immediate cause of death, but drugs and/or alcohol were contributors. While not classified as overdoses, these deaths might have been avoided if the person was unimpaired. A total of 953 deaths between 2005 and 2017 fell into transportation or other injury categories (e.g., falling, drowning, choking/suffocating, being hit by trains or cars, ATV or other vehicular accidents) influenced by the presence of one or more substances. Of 321 such deaths from 2015 to 2017, fentanyl was found in 10 (3%) and prescription opioids were contributors in 70 (22%) (Table 1). By preventing overdose deaths, substance-related injury deaths might also be reduced. Further studies should explore trauma-related deaths directly or indirectly attributed to impairment.

Most study decedents had a history of drug and/or alcohol abuse, a known risk factor for opioid-related mortality (Webster, 2017). This history was significantly more common in fentanyl/FA associated deaths, consistent with the illicit nature of FAs and the very low percentage of prescriptions present for fentanyl in the recent deaths. However, significantly lower rates of co-morbid cardiovascular and pulmonary conditions, also reported as risk factors for opioid-related death (Webster, 2017), were found in WV decedents with fentanyl/FAs present. Existing diagnoses of psychiatric conditions and pain, reported to be risk factors for opioid mortality (Webster, 2017), were found in about 20% and 11%, respectively, of our decedents' files. Since comprehensive medical histories were not available in most cases, these figures are likely incomplete. Further studies involving direct linkages with medical records are needed to examine the association of underlying medical conditions with drug mortality risk.

Most drug-related death reports have focused on overdoses based on ICD-10 codes (O'Donnell et al., 2017; Unick and Ciccarone, 2017). A particular strength of this study is the use of multiple data sources, including death certificates, autopsy reports, CSMP information, and toxicology analyses that allow individual opioids and drug combinations involved to be identified. A centralized medical examiner system in WV enables fairly complete decedent data to be compiled.

This study also has potential limitations. Accurately determining intent for manner of death (i.e., unintentional vs. suicide) is difficult postmortem. The WV OCME certifies deaths with the understanding that the potential for under-reporting suicides is substantial, and the number of suicides related to drug overdose deaths are likely underestimated (Rockett et al., 2018). Relevant data might be missing or incorrectly entered in the case file or FDD. However, data were checked for inconsistencies or missing values, with follow-up to the extent possible. Heroin can be difficult to identify in decedents due to rapid metabolism, so heroin in some cases might be missed. When fentanyl was found as a co-intoxicant, it cannot be determined whether the decedent used fentanyl in addition to heroin/other drugs or if heroin/other drugs were taken that unknowingly contained fentanyl. Due to the frequency in which new FAs are appearing in the deaths, it is possible that as yet unknown analogs were not detected. A small number of drug-related deaths from 2017 were not yet entered into the FDD at the time of this study. However, preliminary review of these cases found that 31 (39.7%) had fentanyl present. Finally, West Virginia is a rural state with a high per capita drug overdose death rate. Although these findings might not be representative of other geographic areas, they are consistent with reports of increasing FA deaths in several states (CDC, 2018).

The substances involved in drug-related deaths must be closely monitored to ensure that appropriate harm reduction strategies are used. The frequency at which new FAs and IMF are appearing is particularly concerning since controlled substances monitoring programs cannot track these substances. Routine toxicological detection of FAs is difficult, and clandestine laboratories can easily modify fentanyl and its derivatives. Expanded access to addiction treatment and ready availability of naloxone to treat acute opioid overdoses are needed (Frank and Pollack, 2017; Klebacher et al., 2017; Samet and Kertesz, 2018; Thomson et al., 2017; CDC, 2018). Multifaceted fentanyl outbreak identification, prevention, harm reduction, and expanded treatment strategies that consider social, economic, and other contributing factors are needed to address the opioid and illicit drug crisis (Dasgupta et al., 2018; CDC, 2018). Education and training of health providers, public health professionals, and health professions students are necessary to implement such strategies (Frank and Pollack, 2017; Samet and Kertesz, 2018; Thomson et al., 2017). Public health, law enforcement, and other government agencies must work in collaboration to halt the production and supply of IMF, FAs and other illicit drugs.

5. Conclusions

Fentanyl involvement increased substantially over time in WV drug-related deaths from 2005 to 2017, with ten different FAs identified since 2015. Prescription opioid presence decreased by about half with fentanyl, heroin, ethanol, alprazolam and cocaine constituting the top five identified drugs in these deaths since 2015. Alprazolam and ethanol were consistently among the top five drugs identified since 2005, with methamphetamine involvement increasing. In contrast, the presence of a prescription for most controlled substances identified in the deaths has been decreasing. Deaths involving fentanyl and newly identified FAs could represent the “tip of the iceberg” since fentanyl derivatives are often not readily detected.

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Contributors

ZD, MA and GS formulated the research question and designed the study. ZD conducted statistical analyses and drafted the initial manuscript. MA and GS designed the tables and MA incorporated suggestions from all co-authors. MA, GS, JK and AK contributed to the conception of the analyses, interpretation of the results and manuscript writing. All authors had full access to all of the data and approved the final manuscript.

Conflict of interest

No conflict declared.

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