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RESEARCH REPORT

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Patient characteristics and treatment utilization in fatal stimulant-involved overdoses in the United States Veterans Health Administration

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Abstract

Background and Aims: This study aimed to (1) describe trends in stimulant-alone and stimulant and other substance use overdose deaths from 2012 to 2018 and (2) measure patient and service use characteristics across stimulant-related overdose death profiles.

Design: Retrospective cohort study of patients who died from stimulant-involved overdose between annual years 2012 and 2018.

Setting: United States Veterans Health Administration (VHA).

A total of 3631 patients died from stimulant-involved overdose, as identified through the National Death Index.

Measurements: Stimulant-involved overdose deaths were categorized by stimulant type (cocaine or methamphetamine/other) and other substance co-involvement. Cause of death data were linked to patient characteristics, including demographic and treatment use preceding overdose from VHA administrative data. We examined trends over time and compared treatment use factors between the following mutually exclusive overdose profiles: cocaine alone, methamphetamine alone, cocaine + opioid, methamphetamine + opioid, any stimulant + other substance and cocaine + methamphetamine.

Findings: The rate of overdose death was 3.06 times higher in 2018 than 2012, with increases across all toxicology profiles. Compared with cocaine-involved overdoses, methamphetamine-involved overdoses were less likely in people who were older [adjusted odds ratio (aOR) = 0.22, 95% confidence interval (CI) = 0.06–0.87 aged 65+ versus 18–29] and more likely among those who lived in rural areas (aOR = 2.73, 95% CI = 1.43–5.23). People who died from stimulant + opioid overdoses had lower odds of a stimulant use disorder diagnosis compared with stimulant alone deaths (cocaine: aOR = 0.55, 95% CI = 0.41–0.75, methamphetamine: aOR = 0.44, 95% CI = 0.29–0.68).

Conclusions: The rate of deaths among US Veterans from stimulant-related overdose was three times higher in 2018 than 2012. Key differences in characteristics of patients across overdose toxicology profiles, such as geographic location and health-care use, point to distinct treatment needs based on stimulant use type.

KEYWORDS
Methamphetamine, opioids, overdose, stimulants, substance use, veterans

INTRODUCTION

Fatal drug overdose continues to be the leading cause of accidental death in the United States (US) [1] and the leading cause of avoidable death among people who inject drugs world-wide [2]. Opioids have been a key focus of overdose prevention and treatment efforts, with the US Department of Health and Human Services declaring the opioid epidemic a public health emergency in 2017. However, recent trends show stark increases in stimulant-involved overdoses, with the majority of these overdoses deaths involving multiple classes of substances [3]. These more complex, polysubstance-involved overdose deaths necessitate an expansion from a singular opioid-centric focus to include other substances and consideration of the role of stimulant use on overdose risk to inform effective prevention and treatment efforts.

In the past 5 years, fatal stimulant-involved overdoses, specifically including cocaine and methamphetamine overdoses, have increased in the United States as well as in other countries [4]. National US data show a surge in fatal stimulant-involved overdoses: by 2017, one in five overdose deaths involved cocaine and one in seven involved other psychostimulants [3, 5]. Other psychostimulant-involved deaths will be referred to herein as methamphetamine-involved deaths, because 85–90% of these death certificates denote methamphetamine, which is thought to be an underestimate [6]. Of these overdoses in 2017, nearly three-quarters (72.7%) of cocaine-involved and half (50.4%) of methamphetamine-involved overdoses also included opioids [3]. Stimulant overdoses are continuing to escalate; during the first half of 2019, data from 24 states and the District of Columbia showed that stimulants were involved in five of 11 fatal overdoses, with nearly three-quarters (72.1%) also involving opioids [7]. In 2020, the Centers for Disease Control issued a Health Alert Network Advisory regarding an acceleration in stimulant-related overdoses with and without opioids in the wake of the COVID-19 pandemic [8].

The rising rates of stimulant-involved overdoses, often combined with opioids (largely synthetic opioids), highlights a dynamic and changing overdose landscape and poses urgent public health challenges to curb the evolving stimulant and opioid overdose syndemic [9]. Despite epidemiological evidence shining light on the rapid increase in stimulant-alone and co-involved stimulant and opioid overdoses, shockingly little is known about the people who overdose from stimulants and potential points of health-care contact to direct overdose prevention and substance use treatment efforts.

Stimulant-related overdoses differ by stimulant type, with substantial differences in patient characteristics by specific type of stimulant used (cocaine versus methamphetamine) and probably also by co-use of opioids. Cocaine use and overdose deaths are disproportionately in larger metropolitan areas and among non-Hispanic blacks, despite a higher prevalence of use among non-Hispanic whites [10]. Cocaine-involved fatalities are disproportionately attributed to combined cocaine and opioid use compared to methamphetamine overdose deaths [11]. In contrast, methamphetamine and other psychostimulant deaths, which are grouped together under a singular toxicology code preventing disentangling these causes of death from one another, tend to be among individuals who live in less densely populated areas, with the highest rates of use and fatalities among non-Hispanic whites [3, 11, 12]. However, little is known about clinical characteristics that differentiate different types of stimulant overdoses. Differences between cocaine and methamphetamine use and overdose, co-use with other substances such as opioids and different individual and contextual characteristics of use drive the need to understand patient characteristics and opportunities for intervention between cocaine and methamphetamine.

Identification of at-risk populations and patterns of health-care utilization among these individuals will inform the development and implementation of effective overdose prevention strategies. The current study links data from the largest integrated health-care system in the United States, the Veterans Health Administration (VHA), with National Death Index (NDI) cause of death data. The aims of the current study were to (1) describe trends in stimulant-alone and stimulant and other substance use overdose deaths from 2012 to 2018 and (2) compare patient and service utilization characteristics among stimulant-related overdose death profiles to inform where substance use treatment and overdose prevention efforts can be targeted to address this public health crisis.

METHODS

This study was approved by the VA Ann Arbor Healthcare System Institutional Review Board.

Data sources and study population

National Death Index data (including date and cause of death) from the National Vital Statistics System mortality files (https://www.cdc.gov/nchs/nvss/deaths.htm) were linked with VHA patient data. As the only national health-care system in the US, the VHA includes more than 9 million enrolled Veterans across a network of large medical centers and outpatient clinics throughout the country. The VHA provides the rare ability to link health-care claims data capturing health-care utilization, visit encounter types and diagnoses with the cause of death. Types of overdose deaths were classified using the International Classification of Diseases, 10th revision (ICD-10). Individuals were included in the cohort if they had at least one in- or outpatient VHA encounter, including emergency department visits, in the year prior to overdose death, aged 18 years or older and died from a stimulant-involved overdose during calendar years 2012–18. Underlying cause of death codes [13] used as the inclusion for the sample were poisonings/overdose that were unintentional (X40-X44), undetermined (Y10–Y14), intentional (X60-X69) or assault/homicide (X85-X90). In light of ambiguity and potential for misclassification around overdose intent [14] we also replicated this cohort including other intentional (not self-poisoning) causes of death (X70-X84, U03, Y87.0), which added 27 cases to the cohort, and are reported in Supporting information, Tables S1–S3. The sample was further

restricted to individuals whose death record included a diagnosis for cocaine overdose (T40.5) or other psychostimulant overdose (T43.6).

Measures

Fatal overdoses were categorized based on toxicology results using ICD-10 codes to categorize the population into six mutually exclusive groups: (1) cocaine only, (2) methamphetamine only, (3) cocaine + opioid, (4) methamphetamine + opioid, (5) stimulant + other non-opioid substance (here, cocaine and methamphetamine are considered together, due to a small number of overdose death fitting this criterion) and (6) both cocaine + methamphetamine, with or without opioids. Other non-opioid substances included barbiturates, benzodiazepines, alcohol and cannabis.

Demographic and patient characteristics were obtained from VHA records. Demographic characteristics included: age, sex, race, ethnicity, homelessness status (see Supporting information, Table S4) and geographic locality (urban/rural), which were defined based on rural–urban commuting area codes (see Supporting information, Table S5). Patient characteristics included primary location of care (medical center, community-based outpatient clinic, other sites), given prior work indicating differences in receipt of specialty care among patients receiving care at large medical centers compared to smaller community-based clinics that are affiliated with VHA medical centers [15–17]. We examined utilization of relevant common outpatient treatment settings including primary care, general mental health, primary care mental health integration (i.e. mental health services are co-located and provided in collaboration with primary care), substance use disorder (SUD) and post-traumatic stress disorder (PTSD) clinics prior to death (7 days, 3 months, 6 months and 12 months; see Supporting information, Table S6). The burden of comorbid medical conditions were summarized as 0, 1, 2 or 3+ comorbid diagnoses during the past year based on the Elixhauser Comorbidity Index [18–20]. We also included diagnoses of infectious diseases [HIV or hepatitis C (HCV)], depression, PTSD and stimulant use disorder, opioid use disorder or other SUD (Supporting information, Table S7). Finally, we report prescription fills from VHA pharmacies for central nervous system-active drugs (i.e. stimulants, opioids, benzodiazepines, antidepressants, anti-epileptics, anti-psychotics, Z-drugs) in the year prior to overdose death (Supporting information, Table S8).

Analyses

All analyses were conducted using SAS Enterprise Guide Software, version 7.1 [21]. Analyses were not pre-registered and should be considered exploratory. Fatal overdoses per year for each of the six stimulant-involved overdose profiles were computed and plotted to show trends from 2012 to 2018. Fatal overdoses are reported as overdoses per 100 000 per year based on the VHA population and weighted for total risk-time based on date of death for each overdose [22, 23]. Total risk-time was calculated starting on 1 January of the year that the patient died and continued until the date of death.

Sample characteristics across all demographic and patient characteristics are presented for each overdose profile. For opioid-involved overdose profiles, the most frequent types of opioids on the toxicology reports were documented and compared between cocaine + opioid and methamphetamine + opioid overdoses. Given that the goal of the current project was to determine what distinguishes cocaine- and methamphetamine-related overdoses, we fit four logistic regression models. Model 1 compared methamphetamine alone to cocaine alone (referent) overdoses; model 2 compared methamphetamine + opioid to cocaine + opioid (referent) overdoses; model 3 compared cocaine + opioid to cocaine alone (referent) overdoses; and model 4 compared methamphetamine + opioid to methamphetamine alone (referent) overdoses. All models included patient demographics, geographic locality and clinical characteristics as predictors. VHA site, defined as the site to which the Veteran had made the most visits during the baseline period (1-year prior to death date), was included as random intercept in all models to adjust for correlation among Veterans within the same site.

The only missing data were from cases without zip codes to determine locality. List-wise deletion of missing cases was used in the models resulting in 45 cases (2.79% of cases) being excluded from model 1, 28 cases (1.69% of cases) being excluded from model 2, 39 cases (1.86% of cases) being excluded from model 3 and 34 cases (2.90% of cases) being excluded from model 4.

RESULTS

Model-adjusted outcomes

Between 2012 and 2018, a total of 3631 Veterans died from stimulant-involved overdoses. By comparison, 9353 Veterans died from opioid-involved overdoses during the same time-span. Of stimulant-involved overdose deaths, 857 Veterans in the National Death Index database died of cocaine alone, 755 of methamphetamine alone, 1235 of cocaine + opioids, 418 from methamphetamine + opioids, 222 from stimulant + another non-opioid substance and 144 from cocaine + methamphetamine. The rate of stimulant-involved overdoses tripled from 2012 to 2018 (3.06 times higher in 2018 than 2012), with the greatest increase in cocaine + opioid-related overdoses (4.22 times higher in 2018 than 2012; Fig. 1). Of stimulant-involved overdoses, 66.5% (2413) involved cocaine and 37.7% (1369) involved methamphetamine. Of note, 54.1% (1965) of all stimulant-related overdoses also involved an additional substance, including 48.0% (1743) of stimulant-related overdoses co-involving opioids. Of stimulant + opioid-involved overdoses, 45.0% involved heroin, 46.1% involved synthetic opioids (e.g. fentanyl) and 25.9% involved prescription opioids. Type of opioid significantly differed by stimulant type ($\chi^2 = 47.42$, $p < 0.01$), with synthetic opioids more frequently involved in cocaine-related overdoses and prescription opioids more frequently involved in methamphetamine-related overdoses. Other

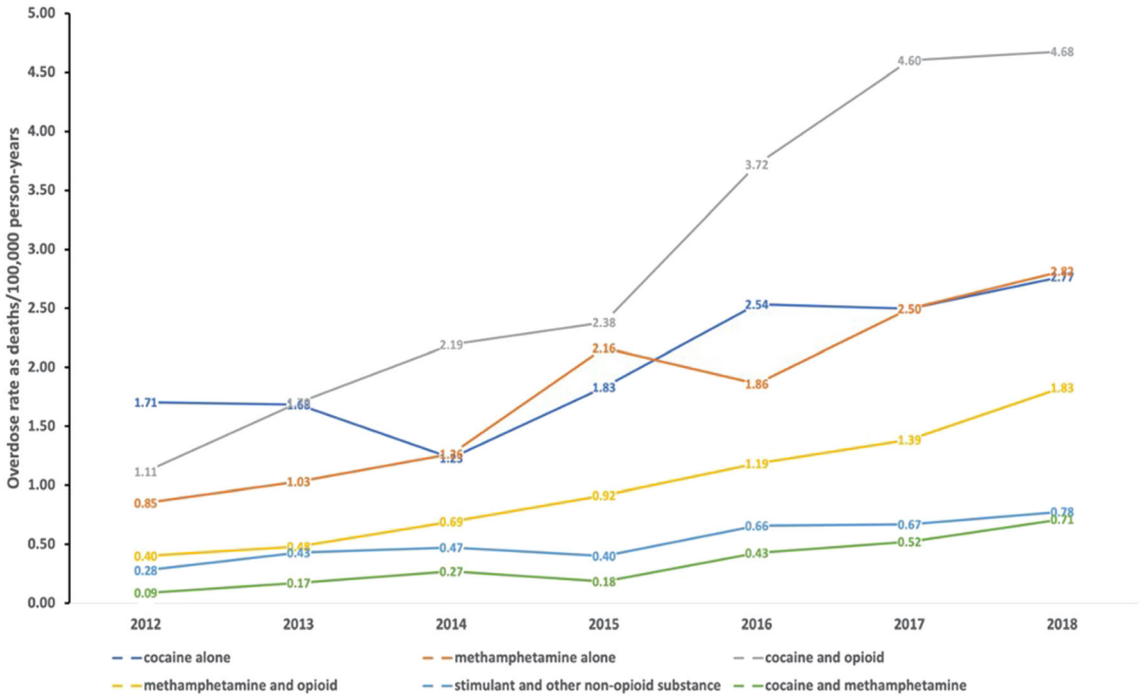

FIGURE 1 Trends in stimulant-involved fatal overdose rates alone and in combination with opioids and other substances from annual years 2012–18

substances were documented in 31.2% of stimulant + opioid overdoses. Alcohol was the most common additional substance, documented in 18.4% of stimulant + opioid deaths. Of all stimulant-involved deaths, the most common substance other than opioids was also alcohol, which was involved in 13.9% of stimulant-related overdoses. Of deaths where stimulants + non-opioid substances were involved, 76.3% involved alcohol, 19.1% involved barbiturates or benzodiazepines and 4.6% involved cannabis.

The majority of stimulant-related overdose deaths in this Veteran population were among middle-aged (aged between 45 and 64 years; 62.1%), white non-Hispanic (54.9%) men (95.8%). More than half of all stimulant-related overdoses occurred in people with a mental health diagnosis (41.7% had a depressive disorder and 27.8% had a diagnosis of PTSD), but only one-third (37.8%) had a stimulant use disorder diagnosis.

Compared to fatal overdoses involving cocaine, those involving methamphetamine were more common in rural localities (11.8% of methamphetamine alone and 12.4% of methamphetamine + opioid compared to 3.0% of cocaine alone and 4.9% of cocaine + opioid), and occurred less often among people with a diagnosis of a stimulant use disorder (28.1% of methamphetamine alone and 27.3% of methamphetamine + opioid compared to 42.1% of cocaine alone and 44.6% of cocaine + opioid). People who died from methamphetamine-related overdoses had received treatment less often in a SUD specialty clinic (17.7% of methamphetamine alone and 29.7% of methamphetamine + opioid compared to 23.5% of cocaine alone and 42.1% of cocaine + opioid). A higher percentage of people who died from an overdose involving stimulants + opioids had a mental health diagnosis. For example, 50.8 and 41.9% of those who died from cocaine + opioid and methamphetamine + opioid, respectively, had a depression diagnosis, compared to those who died from cocaine (34.9%) or methamphetamine (32.7%) alone. Similarly, those who died from stimulant + opioid overdoses had higher health-care utilization across clinical settings (PTSD, SUD, mental health, primary care and primary care mental health integration). See Table 1 for characteristics of patients whose cause of death contained stimulants.

Table 2 shows the adjusted models for methamphetamine compared to cocaine alone fatal overdoses and a separate model for methamphetamine + opioid compared to cocaine + opioid fatal overdoses. Table 3 shows the adjusted models for cocaine + opioid compared to cocaine alone and a separate model of methamphetamine + opioid compared to methamphetamine alone. Compared to people who died from either cocaine or methamphetamine alone, fatal overdoses that also involved opioids had lower odds of occurring during middle or later life compared to people under age 30 [model 3: adjusted odds ratio (aOR) = 0.15, 95% confidence interval (95% CI) = 0.06–0.42); and model 4: aOR = 0.36, 95% CI = 0.17–0.80 for those aged 65+ years].

Stimulant-involved overdose deaths were over-represented among people identifying as black non-Hispanic (31.3% of all overdoses; Table 1). Across models, a pattern emerged where overdoses involving methamphetamine, with or without opioids, were significantly less common among people identifying as black compared to overdoses involving cocaine (model 1: aOR = 0.07, 95% CI = 0.05–0.10; model 2: aOR = 0.08, 95% CI = 0.04–0.15). This appears to be particularly notable in people overdosing from cocaine

TABLE 1 Sample characteristics by fatal stimulant-related overdose category

Total number (%)	Contains stimulants	Cocaine only	Methamphetamine only	Cocaine + opioids	Methamphetamine + opioids	Stimulants + others	Cocaine + methamphetamine
Total	***n* = 3631**	***n* = 857**	***n* = 755**	***n* = 1235**	***n* = 418**	***n* = 222**	***n* = 144**
Age group (years)							
18–29	157 (4.32)	6 (0.70)	21 (2.78)	79 (6.40)	35 (8.37)	9 (4.05)	7 (4.86)
30–44	615 (16.94)	61 (7.12)	90 (11.92)	299 (24.21)	105 (25.12)	24 (10.81)	36 (25.00)
45–64	2254 (62.08)	572 (66.74)	491 (65.03)	726 (58.79)	232 (55.50)	151 (68.02)	82 (56.94)
65+	605 (16.66)	218 (25.44)	153 (20.26)	131 (10.61)	46 (11.00)	38 (17.12)	19 (13.19)
Sex (male)	3480 (95.84)	828 (96.62)	737 (97.62)	1169 (94.66)	398 (95.22)	213 (95.95)	135 (93.75)
Race/ethnicity							
White non-Hispanic	1994 (54.92)	231 (26.95)	526 (69.67)	706 (57.17)	335 (80.14)	102 (45.95)	94 (65.28)
Black non-Hispanic	1138 (31.34)	535 (62.43)	79 (10.46)	389 (31.50)	17 (4.07)	91 (40.99)	27 (18.75)
Hispanic	188 (5.18)	30 (3.50)	48 (6.36)	63 (5.10)	23 (5.50)	13 (5.86)	11 (7.64)
Other[a]	311 (8.57)	61 (7.12)	102 (13.51)	77 (6.23)	43 (10.29)	16 (7.21)	12 (8.33)
Homelessness	1207 (33.24)	259 (30.22)	243 (32.19)	449 (36.36)	135 (32.30)	74 (33.33)	47 (32.64)
Rurality							
Urban	3299 (90.86)	812 (94.75)	640 (84.77)	1155 (93.52)	358 (85.65)	199 (89.64)	135 (93.75)
Rural	251 (6.91)	26 (3.03)	89 (11.79)	60 (4.86)	52 (12.44)	17 (7.66)	7 (4.86)
Missing[b]	81 (2.23)	19 (2.22)	26 (3.44)	20 (1.62)	8 (1.91)	6 (2.70)	2 (1.39)
Primary care location							
VAMC	2034 (56.02)	486 (56.71)	398 (52.72)	752 (60.89)	199 (47.61)	119 (53.60)	80 (55.56)
CBOC	1003 (27.62)	239 (27.89)	236 (31.26)	282 (22.83)	144 (34.45)	71 (31.98)	31 (21.53)
Other	594 (16.36)	132 (15.40)	121 (16.03)	201 (16.28)	75 (17.94)	32 (14.41)	33 (22.92)
Key clinical diagnoses							
PTSD	1008 (27.76)	192 (22.40)	144 (19.07)	435 (35.22)	132 (31.58)	58 (26.13)	47 (32.64)
Depressive disorder	1514 (41.70)	299 (34.89)	247 (32.72)	627 (50.77)	175 (41.87)	104 (46.85)	62 (43.06)
Opioid use disorder	834 (22.97)	75 (8.75)	59 (7.81)	493 (39.92)	135 (32.30)	33 (14.86)	39 (27.08)
Stimulant use disorder	1373 (37.81)	361 (42.12)	212 (28.08)	551 (44.62)	114 (27.27)	87 (39.19)	48 (33.33)
Other SUD	1607 (44.26)	340 (39.67)	262 (34.70)	651 (52.71)	173 (41.39)	120 (54.05)	61 (42.36)
HIV/HCV	482 (13.18)	127 (14.75)	82 (10.65)	170 (13.77)	48 (11.43)	32 (14.10)	23 (15.86)
Comorbidities							
0	475 (13.08)	73 (8.52)	136 (18.01)	142 (11.50)	74 (17.70)	23 (10.36)	27 (18.75)
1	433 (11.93)	96 (11.20)	101 (13.38)	130 (10.53)	62 (14.83)	26 (11.71)	18 (12.50)
2	529 (14.57)	129 (15.05)	109 (14.44)	187 (15.14)	55 (13.16)	26 (11.71)	23 (15.97)
3+	2194 (60.42)	559 (65.23)	409 (54.17)	776 (62.83)	227 (54.31)	147 (66.22)	76 (52.78)
CNS-active prescriptions[b]							
Stimulants	101 (2.78)	9 (1.05)	18 (2.38)	40 (3.24)	25 (5.98)	6 (2.70)	3 (2.08)
Opioids	1293 (35.61)	309 (36.06)	251 (33.25)	448 (36.28)	164 (39.23)	69 (31.08)	52 (36.11)
Benzodiazepines	513 (14.13)	76 (8.87)	83 (10.99)	212 (17.17)	89 (21.29)	29 (13.06)	24 (16.67)
Antidepressants	1891 (52.08)	395 (46.09)	316 (41.85)	769 (62.27)	221 (52.87)	118 (53.15)	72 (50.00)
Anti-epileptics	1374 (37.84)	273 (31.86)	208 (27.55)	578 (46.80)	179 (42.82)	77 (34.68)	59 (40.97)
Anti-psychotics	913 (25.14)	204 (23.80)	153 (20.26)	379 (30.69)	96 (22.97)	47 (21.17)	34 (23.61)
Z-drugs	225 (6.20)	32 (3.73)	26 (3.44)	94 (7.61)	47 (11.24)	14 (6.31)	12 (8.33)

(Continues)

TABLE 1 (Continued)

Total number (%)	Contains stimulants	Cocaine only	Methamphetamine only	Cocaine + opioids	Methamphetamine + opioids	Stimulants + others	Cocaine + methamphetamine
Total	***n* = 3631**	***n* = 857**	***n* = 755**	***n* = 1235**	***n* = 418**	***n* = 222**	***n* = 144**
Treatment utilization							
PTSD clinics							
12 months	316 (8.70)	49 (5.72)	28 (3.71)	173 (14.01)	34 (8.13)	20 (9.01)	12 (8.33)
6 months[b]	212 (5.84)	34 (3.97)	19 (2.52)	124 (10.04)	15 (3.59)	10 (4.50)	10 (6.94)
3 months[b]	146 (4.02)	20 (2.33)	15 (1.99)	86 (6.96)	8 (1.91)	8 (3.60)	9 (6.25)
7 days[b]	38 (1.05)	3 (0.35)	3 (0.40)	22 (1.78)	3 (0.72)	3 (1.35)	4 (2.78)
SUD clinics							
12 months	1086 (29.91)	201 (23.45)	133 (17.62)	520 (42.11)	124 (29.67)	71 (31.98)	37 (25.69)
6 months[b]	794 (21.87)	137 (15.99)	84 (11.13)	404 (32.71)	94 (22.49)	51 (22.97)	24 (16.67)
3 months[b]	602 (16.58)	99 (11.55)	56 (7.42)	323 (26.15)	68 (16.27)	38 (17.12)	18 (12.50)
7 days[b]	184 (5.07)	30 (3.50)	13 (1.72)	100 (8.10)	21 (5.02)	13 (5.86)	7 (4.86)
General mental health clinics							
12 months	2269 (62.49)	475 (55.43)	414 (54.83)	879 (71.17)	264 (63.16)	145 (65.32)	92 (63.89)
6 months[b]	1846 (50.84)	384 (44.81)	322 (42.65)	737 (59.68)	211 (50.48)	115 (51.80)	77 (53.47)
3 months[b]	1456 (40.10)	301 (35.12)	249 (32.98)	598 (48.42)	156 (37.32)	87 (39.19)	65 (45.14)
7 days[b]	347 (9.56)	70 (8.17)	55 (7.28)	165 (13.36)	22 (5.26)	20 (9.01)	15 (10.42)
Primary care							
12 months	3104 (85.49)	760 (88.68)	640 (84.77)	1063 (86.07)	336 (80.38)	191 (86.04)	114 (79.17)
6 months[b]	2566 (70.67)	649 (75.73)	504 (66.75)	881 (71.34)	275 (65.79)	164 (73.87)	93 (64.58)
3 months[b]	1844 (50.78)	469 (54.73)	342 (45.30)	657 (53.20)	197 (47.13)	112 (50.45)	67 (46.53)
7 days[b]	281 (7.74)	75 (8.75)	52 (6.89)	96 (7.77)	33 (7.89)	13 (5.86)	12 (8.33)
Primary care mental health integration							
12 months	441 (12.15)	79 (9.22)	89 (11.79)	174 (14.09)	55 (13.16)	30 (13.51)	14 (9.72)
6 months[b]	245 (6.75)	43 (5.02)	47 (6.23)	100 (8.10)	30 (7.18)	14 (6.31)	11 (7.64)
3 months[b]	148 (4.08)	28 (3.27)	28 (3.71)	64 (5.18)	15 (3.59)	7 (3.15)	6 (4.17)
7 days[b]	20 (0.55)	3 (0.35)	3 (0.40)	9 (0.73)	2 (0.48)	2 (0.90)	1 (0.69)

VAMC = Veterans Administration Medical Center; CBOC = community-based outpatient clinic; HIV/HCV = human immunodeficiency virus/hepatitis C; PTSD = post-traumatic stress disorder; SUD = substance use disorder; CNS-active = central nervous system active.

[a]This race category includes American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, and unknown by patient or declined to answer.

[b]Indicates variables/categories that were not included in adjusted analyses presented in Tables 2 and 3.

alone, with 62.4% of those fatalities among black non-Hispanics. People who died from methamphetamine alone or in combination with opioids had higher odds of living in a rural locality than people who died from cocaine alone or in combination with opioids (model 1: aOR = 2.73, 95% CI = 1.43–5.23; model 2: aOR = 1.79, 95% CI = 1.04–3.11). Unsurprisingly, people who died from a stimulant + opioid overdose (regardless of stimulant type) had higher odds of receiving an opioid use disorder diagnosis (model 3: aOR = 5.11, 95% CI = 3.65–7.16; model 4: aOR = 6.29, 95% CI = 4.00–9.89). However, more strikingly, people with stimulant + opioid overdoses had significantly lower odds of receiving a stimulant use disorder diagnosis compared to those with fatal overdoses from stimulants alone (model 3: aOR = 0.55, 95% CI = 0.41–0.75; model 4: aOR = 0.44, 95% CI = 0.29–0.68).

DISCUSSION

In this large national US sample of Veterans the rate of deaths from stimulant-related overdose, including cocaine and methamphetamine, alone and in combination with other substances, was three times higher in 2018 than 2012. We observed similar trends in overdoses that co-involved stimulants and opioids with recent and stark increases, especially in those dying from opioid and cocaine-involved overdoses. Among polysubstance-involved stimulant overdoses, 88% include opioids, most frequently heroin or synthetic opioids such as fentanyl. However, co-involved types of opioids differed by type of stimulant, with synthetic opioids commonly involved in cocaine-related overdoses and prescription opioids more frequently involved in methamphetamine-related overdoses. Importantly, nearly half of

TABLE 2 Model-adjusted associations between methamphetamine compared to cocaine-related fatal overdoses

Characteristics	Model 1 Methamphetamine alone compared to cocaine alone (referent) aOR (95% CIs)	Model 2 Methamphetamine + opioid compared to cocaine + opioid (referent) aOR (95% CIs)
Age group (years)		
18–29	ref.	ref.
30–44	0.47 (0.12, 1.92)	1.27 (0.65, 2.48)
45–64	0.35 (0.09, 1.32)	1.14 (0.59, 2.21)
65+	0.22 (0.06, 0.87)[a]	1.32 (0.58, 2.99)
Sex (ref = female)	1.21 (0.47, 3.10)	0.90 (0.42, 1.94)
Race/ethnicity		
White non-Hispanic,	ref.	ref.
Black non-Hispanic	0.07 (0.05, 0.10)[a]	0.08 (0.04, 0.15)[a]
Hispanic	0.72 (0.36, 1.48)	0.32 (0.14, 0.71)[a]
Other	0.54 (0.32, 0.90)[a]	0.57 (0.31, 1.05)
Homelessness	1.19 (0.81, 1.75)	0.92 (0.63, 1.33)
Rurality		
Urban	ref.	ref.
Rural	2.73 (1.43, 5.23)[a]	1.79 (1.04, 3.11)[a]
Primary location of care		
VAMC	ref.	ref.
CBOC	1.09 (0.75, 1.57)	1.52 (1.04, 2.21)[a]
Other	1.20 (0.62, 2.31)	0.87 (0.47, 1.61)
Key clinical diagnoses		
PTSD	0.93 (0.61, 1.42)	1.05 (0.72, 1.55)
Depressive disorder	1.25 (0.86, 1.83)	0.81 (0.56, 1.19)
Opioids use disorder	1.35 (0.76, 2.40)	1.42 (0.93, 2.18)
Stimulants use disorder	0.64 (0.42, 0.97)[a]	0.59 (0.39, 0.89)[a]
Other substance disorder	1.12 (0.74, 1.68)	0.98 (0.64, 1.49)
HIV/HCV	0.76 (0.47, 1.22)	0.72 (0.44, 1.18)
Comorbidities		
0	ref.	ref.
1	0.91 (0.46, 1.80)	1.26 (0.64, 2.49)
2	0.72 (0.37, 1.39)	0.78 (0.39, 1.53)
3+	0.77 (0.40, 1.46)	1.22 (0.62, 2.40)
Treatment utilization (1 year)		
PTSD clinics	0.70 (0.33, 1.47)	0.85 (0.49, 1.48)
SUD clinics	0.82 (0.51, 1.32)	0.91 (0.58, 1.43)
General mental health clinics	1.12 (0.76, 1.67)	0.90 (0.58, 1.38)
Primary care	1.00 (0.50, 2.00)	0.87 (0.47, 1.61)
Primary care mental health integration	1.57 (0.95, 2.58)	1.24 (0.80, 1.92)

aOR = adjusted odds ratio; 95% CIs = confidence intervals; ref. = referent; VAMC = Veterans Affairs Medical Center; CBOC = community-based outpatient clinic; HIV/HCV = human immunodeficiency virus/hepatitis C; PTSD = post-traumatic stress disorder; SUD = substance use disorder.
[a]Indicates significance at $p < 0.05$ level.

stimulant-involved overdose deaths did not include other substances and although fatal cocaine-involved overdoses remain more prevalent, overdoses involving methamphetamine are increasing. The escalating fatalities related to methamphetamine use are also driven less by combined substances, but rather are attributed, at least in part, to increased potency, availability and affordability of methamphetamine since the 1990s [6], a pattern that is consistent with increased illicit drug supply of methamphetamine, epidemiological observations of increasing methamphetamine use and increases in methamphetamine-related treatment admissions [12, 24–26].

Several socio-demographic risk factors distinguish between overdose types. Fatal overdoses from methamphetamine compared to

TABLE 3 Model-adjusted associations between stimulant and opioid overdoses compared to stimulant alone fatal overdoses

	Model 3 Cocaine + opioid compared to cocaine alone (referent)	Model 4 Methamphetamine + opioid compared to methamphetamine alone (referent)
Characteristics	**aOR (95% CIs)**	**aOR (95% CIs)**
Age group (years)		
18–29	ref.	ref.
30–44	0.47 (0.17, 1.30)	0.82 (0.38, 1.75)
45–64	0.23 (0.09, 0.61)[a]	0.45 (0.22, 0.93)[a]
65+	0.15 (0.06, 0.42)[a]	0.36 (0.17, 0.80)[a]
Sex (ref = female)	0.83 (0.47, 1.48)	0.83 (0.37, 1.83)
Race/ethnicity		
White non-Hispanic,	ref.	ref.
Black non-Hispanic	0.43 (0.33, 0.55)[a]	0.44 (0.24, 0.82)[a]
Hispanic	0.93 (0.51, 1.68)	0.54 (0.27, 1.05)
Other	0.53 (0.33, 0.84)[a]	0.65 (0.40, 1.06)
Homelessness	1.03 (0.79, 1.34)	0.91 (0.63, 1.29)
Rurality		
Urban	ref.	ref.
Rural	1.41 (0.81, 2.48)	1.02 (0.65, 1.60)
Primary location of care		
VAMC	ref.	ref.
CBOC	0.80 (0.61, 1.05)	1.27 (0.92, 1.76)
Other	1.16 (0.75, 1.79)	1.38 (0.78, 2.45)
Key clinical diagnoses		
PTSD	1.06 (0.79, 1.42)	1.47 (1.01, 2.14)[a]
Depressive disorder	1.42 (1.08, 1.87)[a]	1.09 (0.77, 1.55)
Opioids use disorder	5.11 (3.65, 7.16)[a]	6.29 (4.00, 9.89)[a]
Stimulants use disorder	0.55 (0.41, 0.75)[a]	0.44 (0.29, 0.68)[a]
Other substance disorder	1.22 (0.91, 1.65)	1.01 (0.69, 1.48)
HIV/HCV	1.03 (0.75, 1.41)	1.46 (0.93, 2.30)
Comorbidities		
0	ref.	ref.
1	0.83 (0.50, 1.38)	1.04 (0.60, 1.82)
2	0.72 (0.44, 1.19)	0.86 (0.48, 1.51)
3+	0.55 (0.34, 0.90[a]	0.85 (0.49, 1.46)
Treatment utilization (1 year)		
PTSD clinics	1.32 (0.84, 2.05)	1.09 (0.56, 2.11)
SUD clinics	0.96 (0.69, 1.32)	1.24 (0.80, 1.91)
General mental health clinics	1.18 (0.88, 1.58)	1.07 (0.75, 1.53)
Primary care	0.88 (0.55, 1.41)	0.70 (0.40, 1.21)
Primary care mental health integration	1.33 (0.94, 1.90)	0.96 (0.62, 1.48)

aOR = adjusted odds ratio; 95% CIs = confidence intervals; ref = referent; VAMC = Veterans Affairs Medical Center; CBOC = community-based outpatient clinic; HIV/HCV = human immunodeficiency virus/hepatitis C, PTSD = post-traumatic stress disorder; SUD = substance use disorder.
[a]Indicates significance at $p < 0.05$ level.

cocaine were more frequent among younger Veterans. Overdoses that involved both stimulants and opioids were also more common in younger Veterans compared to overdoses involving only stimulants (regardless of stimulant type). These findings may be related to an increased potency and/or higher risk patterns of use associated with methamphetamine alone and polysubstance use more broadly, increasing the chances for fatal overdose at an early age [6]. A recent report comparing co-involved stimulant + opioid overdose deaths to opioid deaths in Massachusetts using insurance claims data found that people who died from stimulants and opioids in combination

compared to opioids alone were more likely to be older, non-rural, experienced recent homelessness and identified as non-Hispanic and black [27]. We found that people who identified as non-Hispanic black were over-represented relative to VHA racial and ethnic composition [28], specifically among those who died of cocaine-involved fatal overdose, both related to cocaine alone and cocaine + opioid co-involvement. This may reflect the intersection of differences in cocaine use by race with racial disparities in social determinants of health. Despite higher prevalence of past-year cocaine use among whites than blacks, past-year use of crack cocaine remains higher in blacks [29, 30]. This, within the context of disproportionate socio-economic disadvantage, adversity, racial distribution by geography and comorbidities, may contribute to this disparity and fatal overdose deaths among non-Hispanic blacks [31, 32].

People in rural areas had a greater risk of fatal overdose from methamphetamine compared to cocaine with or without co-involved opioids. This finding fits within the context of methamphetamine being more prevalent, easily accessible, available at a low cost and perceived as less harmful and stigmatized compared to other illicit drugs such as heroin in rural areas [12, 33]. There is an enduring need to increase access and reach of effective prevention and treatment interventions to address this urban–rural disparity in methamphetamine use. To reduce fatal overdoses in rural areas, a focus on enhanced screening, diagnosis and referral to treatment is needed. In addition to improving treatment access for rural individuals with stimulant use disorders there is a need to reduce barriers (e.g. long distances to treatment providers) to increase the reach of effective treatments. One option to improve treatment access and reach is to leverage the recent wide-scale implementation of telehealth models in the wake of COVID-19 [34] to provide specialized substance use treatment to people with stimulant use disorders even when they live some distance from specialized care facilities.

People who died of stimulant + opioid overdoses compared to stimulants alone were significantly more likely to have an opioid use disorder but were less likely to have a stimulant use disorder diagnosis. This pattern may be a result of the national emphasis on the opioid epidemic during the past two decades at the expense of necessary policy and institutional level emphasis on increasing stimulant use and overdose. Additionally, providers are less likely to provide medication for opioid use disorder to patients with other SUDs, including stimulant use disorders [15] and concerns about losing access to buprenorphine or other medications for opioid use disorder may reduce the willingness of patients to disclose stimulant use [33]. Increasingly, the illicit stimulant drug supply is adulterated with opioids [8, 35]. Extending naloxone distribution initiatives to people who use stimulants will provide the opportunity to reverse stimulant + opioid overdoses and mitigate fatalities. Finally, increased national coverage of the growing stimulant and polysubstance use overdose crisis in addition to clinician training to ensure proper screening, diagnosis and treatment for stimulant and other substance misuse is needed to curtail these rising overdose death rates.

This study includes important policy and intervention implications, including highlighting vulnerable patient characteristics to prioritize prevention and treatment efforts in addition to highlighting gaps in healthcare utilization among these particularly high-risk patients. Among all patients who died of stimulant-involved overdoses in this sample, we found that only 29.9% were seen in specialty substance use settings in the past year, underscoring the need to enhance appropriate screening, referral and retention efforts, with a keen focus upon minimizing barriers to access in order to capture these patients in the clinics where they are most likely to receive the level of care and expertise needed. Although there are highly effective Food and Drug Administration (FDA)-approved medications for the treatment of opioid use disorder, no such medications exist for stimulant use disorder; however, off-label uses of some medication combinations show initial promise for reducing methamphetamine use [36]. The most empirically supported treatment for stimulant use disorder is a behavioral treatment called contingency management [37, 38]. Contingency management provides reinforcement for abstinence and/or treatment engagement. Initial evidence on the combined efficacy of medication for opioid use disorder and contingency management for stimulant use disorder shows a potential for additive effects by addressing both SUDs concurrently using these empirically supported interventions [39, 40]. However, treatment retention, especially over longer periods, remains a major limiting factor, especially for stimulant use disorder treatments [41], with a critical need for strategies to increase treatment retention to mitigate risks related to relapse and subsequent overdose.

More broadly, to be widely effective psychological or pharmacological treatments must target alternative reinforcers to substitute for the role that substance use plays in people's lives. Medication for opioid use disorder and contingency management are both treatments that patients perceive as helpful and reinforcing [42]. This is in contrast to the vast majority of psychosocial or other pharmacological treatments for SUDs. Medication for opioid use disorders and contingency management provide positive reinforcing effects, a property that is largely missing from other substance use treatments which focus upon reducing substance use, often at the exclusion of building up healthier, prosocial alternatives. Treatments that address the critical reward deprivation of abstinence are expected to be perceived as more tolerable by patients, may bolster treatment-seeking and, critically, may improve treatment retention, which all serve the end goal to improve substance use treatment outcomes.

Our study has several limitations. Stimulant-related deaths, as well as the role of other substances that may heighten overdose risk, can only be identified to the degree that post-mortem toxicology reports are run and substances are indicated on death certificates, leading to under-reporting of substance involvement and significantly limiting the ability to detect, study and prospectively prevent these deaths in the future [43, 44]. Moreover, stimulant-related mortality may extend beyond stimulant-related overdose deaths. Indeed, stimulant use may cause behavior change, hallucinations and other causes of heightened risk for death not captured in the current analyses. Furthermore, the cause of death coding for stimulant-involved overdoses only discriminates between cocaine and other psychostimulants with abuse potential, which is primarily methamphetamine. Unfortunately, this does not differentiate between illicit or prescribed stimulants. However, death certificates indicate that the vast majority of deaths involving other psychostimulants with abuse potential (T43.6) specifically mention

methamphetamine. Nationally, there are clear increases in rates of methamphetamine-related consequences, including treatment admissions, and involvement in overdose deaths nationally as well as sharp increases in methamphetamine in the illicit drug supply [6, 26, 45]. Nonetheless, it is not possible to definitively parse out the degree to which these trends are driven by licit or illicit psychostimulants. Although only a small proportion of Veterans who died from stimulant-involved overdoses had received a prescription stimulant through the VHA system during the year prior to fatal overdose (2.8%), those with stimulant prescriptions, and similarly those with documented stimulant use disorders, may be under-identified in claims data [46]. Given low prevalence of stimulant prescriptions, targeting stimulant overdose prevention only to those receiving stimulant prescriptions does not appear to be a logical approach to overdose risk reduction in this population. In addition, the sample is limited to Veterans who received care within the VHA, which may limit the generalizability of our findings. Lastly, this analysis does not include services that Veterans may have received outside of the VHA, and therefore may underestimate treatment utilization.

In summary, our study of patients in a national health-care system who died from stimulant-related overdose indicates an escalating public health crisis with an urgent need to increase awareness and access to effective treatments. Future research is needed to help health-care systems identify those at risk for stimulant overdose death and increase reach of effective SUD treatments. A particular focus on improving polysubstance use treatment, such as for stimulant and opioid use disorder, in addition to enhancing treatment retention by increasing the reinforcing aspects of treatments and reducing barriers to sustaining treatment, will improve treatment and reduce deaths by overdose. Together, these public health and research initiatives will heighten awareness of the role of stimulants and polysubstance use in overdose deaths in addition to promoting equitable and highly effective provision of substance use treatment for those with SUDs.

TRIAL REGISTRATION

None.

DECLARATION OF INTERESTS

None.

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AUTHOR CONTRIBUTIONS

Lara Coughlin: Formal analysis; methodology. **Lan Zhang:** Data curation; formal analysis. **Amy Bohnert:** Conceptualization; funding acquisition. **Donovan Maust:** Conceptualization. **Jason Goldstick:** Conceptualization; formal analysis. **Lewei Lin:** Conceptualization; formal analysis; funding acquisition; methodology; supervision.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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