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)

Cases: 3,631 patients died from stimulant-involved overdose, as identified through 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+ vs. 18 to 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 stimulants 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 healthcare use, point to distinct treatment needs based on stimulant use type.

Fatal drug overdose continues to be the leading cause of accidental death in the United States (1) and the leading cause of avoidable death among people who inject drugs worldwide (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 five years, fatal stimulant-involved overdoses, specifically including cocaine and methamphetamine overdoses, have increased in the US as well as other countries (4). National US data show a surge in fatal stimulant-involved overdoses: by 2017, 1 in 5 overdose deaths involved cocaine and 1 in 7 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; in the first half of 2019, data from 24 states and the District of Columbia showed that stimulants were involved in 5 out of 11 fatal overdoses, with nearly three-quarters (72.1%) also involving opioids (7). In 2020, the Centers

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for Disease Control issued a Health Alert Network Advisory about an acceleration in stimulantrelated 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 epidemiologic 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 healthcare 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 likely also by co-use of opioids. Cocaine use and overdose deaths are disproportionately in larger metropolitan areas and among non-Hispanic Blacks despite 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 non-Hispanic White people (3,11,12). Yet, 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 healthcare utilization among these individuals will inform the development and implementation of effective overdose prevention strategies. The current study links data from the largest integrated healthcare system in the US, 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 across stimulant-related overdose death profiles to inform where substance use treatment and overdose prevention efforts can be targeted to address this public health crisis.

### 2. Methods

This study was approved by the VA Ann Arbor Healthcare System IRB.

### Data sources and study population

National Death Index data (including date and cause of death) from the National Vital Statistics System mortality files (<u>https://www.cdc.gov/nchs/nvss/deaths.htm</u>) was linked with VHA patient data. As the only national healthcare system in the US, the VHA includes over 9 million enrolled veterans across a network of large medical centers and outpatient clinics throughout the US. The VHA provides the rare ability to link healthcare claims data capturing healthcare utilization, visit encounter types, and diagnoses with the cause of death. Type of overdose deaths were classified using the International Classification of Diseases, Tenth Revision (ICD-10). Individuals were included in the cohort if they had at least one inpatient 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 year 2012-2018. 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 Supplementary Tables 1-3. 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 Supplementary Table 4), and geographic locality (urban/rural) which were defined based on Rural-Urban Commuting Area codes (see Supplementary Table 5). 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 Supplementary Table 6). Burden of comorbid medical conditions were summarized as 0, 1, 2, or 3+ comorbid diagnoses in 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 (Supplementary Table 7). Finally, we report prescription fills from VHA pharmacies for central nervous system-active drugs (i.e., stimulants, opioids, benzodiazepines, antidepressants, antiepileptics, antipsychotics, Z-drugs) in the year prior to overdose death (Supplementary Table 8).

### 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 the 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 January 1 of the year 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 the goal of the current project 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; *Model 3* compared cocaine+opioid to cocaine alone (referent) overdoses. All models included patient demographics, geographic locality, and clinical characteristics as predictors. VHA site, defined as the site the Veteran had the most visits during the baseline period (1-year prior to death date) was included as random intercepts 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. Listwise 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

Descriptive outcomes

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Between 2012 and 2018, a total of 3.631 Veterans died from stimulant-involved overdoses. By comparison, 9,353 Veterans died from opioid-involved overdoses during the same timespan. 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, with the greatest increase in cocaine+opioid-related overdoses (4.22 times higher in 2018 than 2012; Figure 1). Of stimulant-involved overdoses, 66.5% (2,413) involved cocaine and 37.7% (1,369) involved methamphetamine. Of note, 54.1% (1,965) of all stimulant-related overdoses also involved an additional substance, including 48.0% (1,743) 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-square=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 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+nonopioid 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 (between 45 and 64 years old; 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 less often received treatment 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 healthcare 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.

Model-adjusted outcomes

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 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; Model 4: *aOR*=0.36, 95%CI:0.17-0.80 for those 65+ years old).

Stimulant-involved overdose deaths were overrepresented 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%Cl:0.05-0.10; Model 2: aOR=0.08, 95%Cl:0.04-0.15). This appears to be particularly notable in people overdosing from cocaine alone, with 62.4% of those fatalities among Black, non-Hispanics. People that 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%Cl:1.43-5.23; Model 2: aOR=1.79, 95%Cl: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%Cl:3.65-7.16; Model 4: aOR=6.29, 95%Cl: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).

4. 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 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 sociodemographic risk factors distinguish between overdose types. Fatal overdoses from methamphetamine compared to cocaine were more frequent among younger

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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 that died from stimulants and opioids in combination compared to opioids alone were more likely to be older, non-rural, experienced recent homelessness, and identify as non-Hispanic and Black (27). We found that people who identified as non-Hispanic, Black were overrepresented 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 socioeconomic 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 over 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 that 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. Across all patients that 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 on 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 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, the development of effective psychological or pharmacological treatments must identify alternative reinforcers to substitute for the role that substance use plays in people's lives to be widely effective. 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 on 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 postmortem toxicology reports are run and substances are indicated on death certificates, leading to underreporting 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). Furthermore, 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 portion of Veterans that died from stimulant-involved overdoses had received a prescription stimulant through the VHA system in 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). Nonetheless, 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 healthcare system that 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 healthcare 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.

Table 1. Sample characteristics by fatal stimulant-related overdose category.

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

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

Figure 1. Trends in stimulant-involved fatal overdose rates alone and in combination with opioids and other substances from annual years 2012 to 2018.



# References

- 1. Scholl L, Seth P, Kariisa M, Wilson N, Baldwin G. Drug and Opioid-Involved Overdose Deaths — United States, 2013–2017 [Internet]. Vol. 67, MMWR. Morbidity and Mortality Weekly Report. 2018. Available from: http://dx.doi.org/10.15585/mmwr.mm6751521e1
- 2. United Nations Office on Drugs and Crime. Analysis of the world situation [Internet]. United Nations Publications; 2017. Available from: https://www.un-ilibrary.org/drugs-crime-and-terrorism/report-of-the-international-narcotics-control-board-for-2016\_1817056c-en
- Kariisa M, Scholl L, Wilson N, Seth P, Hoots B. Drug Overdose Deaths Involving Cocaine and Psychostimulants with Abuse Potential - United States, 2003-2017. MMWR Morb Mortal Wkly Rep. 2019 May 3;68(17):388–95.
- 4. Australia's Annual Overdose Report [Internet]. Penington Institute; 2019. Available from: https://www.penington.org.au/wp-content/uploads/Australias-Annual-Overdose-Report-2019-1.pdf
- 5. Products Data Briefs Number 329 November 2018 [Internet]. 2019 [cited 2020 Nov 11]. Available from: https://www.cdc.gov/nchs/products/databriefs/db329.htm
- U.S. Drug Enforcement Agency. 2018 National Drug Threat Assessment [Internet]. U.S. Drug Enforcement Administration; 2018. Available from: https://www.dea.gov/sites/default/files/2018-11/DIR-032-18%202018%20NDTA%20final%20low%20resolution.pdf
- O'Donnell J, Gladden RM, Mattson CL, Hunter CT, Davis NL. Vital Signs: Characteristics of Drug Overdose Deaths Involving Opioids and Stimulants - 24 States and the District of Columbia, January-June 2019. MMWR Morb Mortal Wkly Rep. 2020 Sep 4;69(35):1189– 97.
- 8. Centers for Disease Control and Prevention. Increase in Fatal Drug Overdoses Across the United States Driven by Synthetic Opioids Before and During the COVID-19 Pandemic. Centers for Disease Control and Prevention; 2020 Dec. Report No.: HAN00438.
- Jones CM, Bekheet F, Park JN, Alexander GC. The Evolving Overdose Epidemic: Synthetic Opioids And Rising Stimulant-Related Harms. Epidemiol Rev [Internet]. 2020 Nov 6 [cited 2020 Nov 18]; Available from: https://academic.oup.com/epirev/advance-article-

abstract/doi/10.1093/epirev/mxaa011/5957255

- 10. Cano M, Oh S, Salas-Wright CP, Vaughn MG. Cocaine use and overdose mortality in the United States: Evidence from two national data sources, 2002–2018. Drug Alcohol Depend. 2020 Sep 1;214:108148.
- 11. Hoots B, Vivolo-Kantor A, Seth P. The rise in non-fatal and fatal overdoses involving stimulants with and without opioids in the United States. Addiction. 2020;115(5):946–58.
- Jones CM, Compton WM, Mustaquim D. Patterns and Characteristics of Methamphetamine Use Among Adults - United States, 2015-2018. MMWR Morb Mortal Wkly Rep. 2020 Mar 27;69(12):317–23.
- 13. National Death Index user's guide. Hyattsville, MD: National Center for Health Statistics; 2013.
- 14. Bohnert ASB, Ilgen MA. Understanding Links among Opioid Use, Overdose, and Suicide. N Engl J Med. 2019 Jan 3;380(1):71–9.
- 15. Lin LA, Bohnert ASB, Blow FC, Gordon AJ, Ignacio RV, Kim HM, et al. Polysubstance use and association with opioid use disorder treatment in the US Veterans Health Administration. Addiction. 2021 Jan;116(1):96–104.
- 16. Gawron LM, Pettey WBP, Redd AM, Suo Y, Gundlapalli AV. Distance to Veterans administration medical centers as a barrier to specialty care for homeless women Veterans. Stud Health Technol Inform. 2017;238:112–5.
- 17. Malhotra A, Vaughan-Sarrazin M, Charlton ME, Rosenthal GE. Comparison of colorectal cancer screening in veterans based on the location of primary care clinic. J Prim Care Community Health. 2014 Jan 1;5(1):24–9.
- Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi J-C, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005 Nov;43(11):1130–9.
- 19. van Walraven C, Austin PC, Jennings A, Quan H, Forster AJ. A modification of the Elixhauser comorbidity measures into a point system for hospital death using administrative data. Med Care. 2009 Jun;47(6):626–33.
- 20. Menendez ME, Neuhaus V, van Dijk CN, Ring D. The Elixhauser comorbidity method outperforms the Charlson index in predicting inpatient death after orthopaedic surgery. Clin Orthop Relat Res. 2014 Sep;472(9):2878–86.
- 21. SAS Institute Inc. SAS/ACCESS® 9.4 Interface to ADABAS: Reference. Cary, NC: SAS Institute Inc. 2013;

- 22. McCarthy JF, Valenstein M, Kim HM, Ilgen M, Zivin K, Blow FC. Suicide mortality among patients receiving care in the veterans health administration health system. Am J Epidemiol. 2009 Apr 15;169(8):1033–8.
- Bohnert ASB, Ilgen MA, Galea S, McCarthy JF, Blow FC. Accidental poisoning mortality among patients in the Department of Veterans Affairs Health System. Med Care. 2011 Apr;49(4):393–6.
- 24. Ellis MS, Kasper ZA, Cicero TJ. Twin epidemics: The surging rise of methamphetamine use in chronic opioid users. Drug Alcohol Depend. 2018 Dec 1;193:14–20.
- 25. Strickland JC, Havens JR, Stoops WW. A nationally representative analysis of "twin epidemics": Rising rates of methamphetamine use among persons who use opioids. Drug Alcohol Depend. 2019 Nov 1;204:107592.
- Jones CM, Olsen EO, O'Donnell J, Mustaquim D. Resurgent Methamphetamine Use at Treatment Admission in the United States, 2008–2017. Am J Public Health. 2020 Apr 1;110(4):509–16.
- 27. Barocas JA, Wang J, Marshall BDL, LaRochelle MR, Bettano A, Bernson D, et al. Sociodemographic factors and social determinants associated with toxicology confirmed polysubstance opioid-related deaths. Drug Alcohol Depend. 2019 Jul 1;200:59–63.
- 28. Office of Health Equity: Racial and Ethnic Minority Veterans [Internet]. U.S. Department of Veteran Affairs. [cited 2021 Feb 24]. Available from: https://www.va.gov/HEALTHEQUITY/Race\_Ethnicity.asp
- 29. Substance Abuse and Mental Health Services Administration (SAMHSA). 2019 National Survey of Drug Use and Health (NSDUH) detailed tables [Internet]. 2020. Available from: https://www.samhsa.gov/data/report/2019-nsduh-detailed-tables
- 30. Palamar JJ, Davies S, Ompad DC, Cleland CM, Weitzman M. Powder cocaine and crack use in the United States: an examination of risk for arrest and socioeconomic disparities in use. Drug Alcohol Depend. 2015 Apr 1;149:108–16.
- 31. Fothergill K, Ensminger ME, Doherty EE, Juon H-S, Green KM. Pathways from Early Childhood Adversity to Later Adult Drug Use and Psychological Distress: A Prospective Study of a Cohort of African Americans. J Health Soc Behav. 2016 Jun;57(2):223–39.
- Huang B, Grant BF, Dawson DA, Stinson FS, Patricia Chou S, Saha TD, et al. Raceethnicity and the prevalence and co-occurrence of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, alcohol and drug use disorders and Axis I and II disorders: United States, 2001 to 2002 [Internet]. Vol. 47, Comprehensive Psychiatry. 2006. p. 252–7. Available from: http://dx.doi.org/10.1016/j.comppsych.2005.11.001
- 33. Baker R, Leichtling G, Hildebran C, Pinela C, Waddell EN, Sidlow C, et al. "like yin and

yang": Perceptions of methamphetamine benefits and consequences among people who use opioids in rural communities. J Addict Med [Internet]. 2020 Jun 9; Available from: https://journals.lww.com/10.1097/ADM.00000000000669

- 34. Lin LA, Fernandez AC, Bonar EE. Telehealth for Substance-Using Populations in the Age of Coronavirus Disease 2019: Recommendations to Enhance Adoption. JAMA Psychiatry [Internet]. 2020 Jul 1; Available from: http://dx.doi.org/10.1001/jamapsychiatry.2020.1698
- 35. Park JN, Rashidi E, Foti K, Zoorob M, Sherman S, Alexander GC. Fentanyl and fentanyl analogs in the illicit stimulant supply: Results from U.S. drug seizure data, 2011–2016. Drug Alcohol Depend. 2021 Jan 1;218:108416.
- 36. Trivedi MH, Walker R, Ling W, Cruz AD, Sharma G, Carmody T, et al. Bupropion and Naltrexone in Methamphetamine Use Disorder [Internet]. Vol. 384, New England Journal of Medicine. 2021. p. 140–53. Available from: http://dx.doi.org/10.1056/nejmoa2020214
- De Crescenzo F, Ciabattini M, D'Alò GL, De Giorgi R, Del Giovane C, Cassar C, et al. Comparative efficacy and acceptability of psychosocial interventions for individuals with cocaine and amphetamine addiction: A systematic review and network meta-analysis. PLoS Med. 2018 Dec;15(12):e1002715.
- 38. Ronsley C, Nolan S, Knight R, Hayashi K, Klimas J, Walley A, et al. Treatment of stimulant use disorder: A systematic review of reviews. PLoS One. 2020 Jun 18;15(6):e0234809.
- 39. Ainscough TS, McNeill A, Strang J, Calder R, Brose LS. Contingency Management interventions for non-prescribed drug use during treatment for opiate addiction: A systematic review and meta-analysis. Drug Alcohol Depend. 2017 Sep 1;178:318–39.
- Peirce JM, Petry NM, Stitzer ML, Blaine J, Kellogg S, Satterfield F, et al. Effects of Lower-Cost Incentives on Stimulant Abstinence in Methadone Maintenance Treatment [Internet]. Vol. 63, Archives of General Psychiatry. 2006. p. 201. Available from: http://dx.doi.org/10.1001/archpsyc.63.2.201
- 41. Lappan SN, Brown AW, Hendricks PS. Dropout rates of in-person psychosocial substance use disorder treatments: a systematic review and meta-analysis. Addiction. 2020 Feb;115(2):201–17.
- 42. McKay JR. Making recovery more rewarding: difficult with possible unintended consequences, but successful examples are out there. Addiction. 2017 May;112(5):763–4.
- 43. Bohnert ASB, Sen S. Deaths Attributed to Psychiatric Disorders in the United States, 2010–2018. Am J Public Health. 2020 Dec 1;110(12):1825–7.
- 44. Nashold RD, Naor EM. Alcohol-related deaths in Wisconsin: the impact of alcohol on mortality. Am J Public Health. 1981 Nov;71(11):1237–41.

- 45. Han B, Cotto J, Etz K, Einstein EB, Compton WM, Volkow ND. Methamphetamine Overdose Deaths in the US by Sex and Race and Ethnicity. JAMA Psychiatry [Internet]. 2021 Jan 20; Available from: http://dx.doi.org/10.1001/jamapsychiatry.2020.4321
- 46. Rowe CL, Santos G-M, Kornbluh W, Bhardwaj S, Faul M, Coffin PO. Using ICD-10-CM codes to detect illicit substance use: A comparison with retrospective self-report. Drug Alcohol Depend. 2021 Apr 1;221:108537.