Published in final edited form as:

Addict Behav. 2022 February ; 125: 107158. doi:10.1016/j.addbeh.2021.107158.

Prevalences of and characteristics associated with single- and polydrug-involved U.S. Emergency Department Visits in 2018

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Abstract

Introduction: Nonfatal and fatal drug overdoses have recently increased. There are limited data describing the range of illicit, prescribed, and over-the-counter drugs involved in overdoses presenting to U.S. emergency departments (EDs).

Methods: Using 2018 Healthcare Cost and Utilization Project (HCUP) Nationwide ED Sample (NEDS) data, we calculated weighted counts and percentages by drug among overdose-related ED visits. Overdose-related ED visits were those having an International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) drug poisoning code falling under parent codes T36-T50 (codes involving alcohol were not explicitly queried). We identified the top 30 mutually exclusive polydrug combinations and compared characteristics of visits by polydrug status.

Results: In 2018, 908,234 ED visits had a T36-T50 drug poisoning code. The most frequently reported drugs involved were opioids (30.3% of visits; heroin: 15.2%), benzodiazepines (11.0%), stimulants (7.9%), other/unspecified antidepressants (7.1%), 4-aminophenol derivatives (6.6%), and other/unspecified drugs, medicaments, and biological substances (11.8%). Overdose was

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Contributors

Cassandra M. Pickens was responsible for study design, project administration, and leading the writing and editing of the manuscript. Brooke E. Hoots contributed to statistical analysis, study design, and writing and editing the manuscript. Shannon M. Casillas was responsible for study design, validation, data visualization, and writing the manuscript. Lawrence Scholl participated in study design, data visualization, and writing and editing the manuscript. All authors approved the final manuscript.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily reflect the official position of the Centers for Disease Control and Prevention.

CRediT authorship contribution statement

Cassandra M. Pickens: Conceptualization, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Brooke E. Hoots:** Conceptualization, Data curation, Formal analysis, Methodology, Software, Writing – original draft, Writing – review & editing. **Shannon M. Casillas:** Conceptualization, Methodology, Software, Validation, Visualization, Writing – original draft. **Lawrence Scholl:** Conceptualization, Methodology, Visualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

uncommon for most other drug classes (e.g., antibiotics). Polydrug visits were more likely to involve females (prevalence ratio [PR]: 1.14, 95% confidence interval [CI]: 1.12–1.16), be coded intentional self-harm (PR: 1.81, 95% CI: 1.77–1.85), and result in hospitalization (PR: 1.84, 95% CI: 1.79–1.89) or death (PR: 1.37, 95% CI: 1.22–1.53) compared to single-drug overdose-related visits. Benzodiazepines, opioids, and/or stimulants were most frequently involved in polydrug overdoses.

Conclusion: Opioids, benzodiazepines, and stimulants were most commonly reported in both single-drug and polydrug overdose-involved ED visits. Other drugs involved in overdoses included antidepressants and 4-aminophenol derivatives. Jurisdictions can use data on drugs involved in overdoses to better tailor prevention strategies to emerging needs.

Keywords

Drug overdose; Polydrug overdose; Surveillance; Emergency department; Discharge diagnosis

1. Introduction

Rates of nonfatal and fatal drug overdoses have increased in the United States in recent years (Ahmad et al., 2021; Centers for Disease Control and Prevention, 2021d).

Analysis of 2016–2017 emergency department (ED) discharge data documented increases in rates of nonfatal overdoses involving all drugs, all opioids, heroin, non-heroin opioids, and cocaine (Vivolo-Kantor et al., 2020). A study of 2018–2019 ED syndromic surveillance data identified increases in rates of suspected nonfatal overdoses involving opioids, cocaine, and amphetamines, as well as rates of polydrug overdoses involving both opioids and amphetamines (Liu et al., 2020). Similarly, ED syndromic data demonstrate increases in both counts and rates of nonfatal all-drug overdoses and opioid overdoses from December 29, 2019–March 14, 2020, and from March 15–October 10, 2020, as compared to the same time periods in 2019 (Holland et al., 2021). Complementing these findings, analysis of 2006–2016 ED discharge data found increases in rates of cocaine- and psychostimulant-involved overdoses, with and without opioid co-involvement (Hoots et al., 2020). In contrast, rates of nonfatal benzodiazepine-involved overdoses treated in EDs declined from 2016 to 2017 (Vivolo-Kantor et al., 2020) and 2018 to 2019 (Liu et al., 2020) but increased substantially from 2019 to 2020 (Liu et al., 2021). Rates of nonfatal overdoses involving both benzodiazepines and opioids increased at a faster pace than benzodiazepine overdoses not involving opioids from 2019–2020 (Liu et al., 2021).

Trends in fatal overdoses between 2003 and 2020 largely mirrored those of nonfatal overdoses (Ahmad et al., 2021; Kariisa et al., 2019; Mattson et al., 2021; Scholl et al., 2018). Deaths from overdoses overall, as well as overdoses involving heroin, synthetic opioids other than methadone (e.g., illicitly-manufactured fentanyl), cocaine, and psychostimulants with abuse potential (e.g., methamphetamine), increased from 2013 to 2019, while deaths involving prescription opioids declined (Mattson et al., 2021). Notably, from 2017 to 2018, rates of fatal overdoses involving all opioids, prescription opioids, and heroin declined, while those involving synthetic opioids increased (Wilson et al., 2020). In 2018 and 2019, opioids were involved in approximately 70% of drug overdose deaths, while

synthetic opioids were involved in approximately half of all overdose deaths (Mattson et al., 2021; Wilson et al., 2020). Polydrug overdose deaths involving both synthetic opioids and psychostimulants, cocaine, heroin, or prescription opioids also rose during 2013–2019 (Mattson et al., 2021). Between April–June 2019 and April–June 2020, overdose deaths involving benzodiazepines increased more than 40%, while those involving illicit benzodiazepines increased more than 500%; furthermore, from January–June 2020, over 92% of overdose deaths involving benzodiazepines also involved an opioid (Liu et al., 2021). Provisional mortality estimates from 2020 also demonstrate nearly a 30% increase in the number of predicted and reported overdose deaths compared to 2019 (Ahmad et al., 2021).

Recent surveillance of the U.S. overdose epidemic predominantly focused on overdoses involving opioids, stimulants, benzodiazepines, or other specific drug classes. Many analyses using U.S. syndromic, ED discharge, or vital statistics data either did not explicitly examine polydrug overdoses (Scholl et al., 2018; Vivolo-Kantor et al., 2020; Wilson et al., 2020) or evaluated overdoses from a limited number of polydrug combinations, mostly involving co-involvement of opioids with other drugs (Kariisa et al., 2019; Liu et al., 2020; Liu et al., 2021; Mattson et al., 2021). Existing studies have not focused more broadly on the *comprehensive set of drugs* involved in overdoses presenting to EDs, including illicit drugs, drugs that could be prescribed for medical conditions (e.g., cardiovascular or gastrointestinal agents, antiepileptics, autonomic nervous system drugs, muscular/respiratory agents), and over-the-counter (OTC) drugs such as non-steroidal anti-inflammatory drugs (NSAIDs). One recent nationally representative U.S. study examined which T36-T50 International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) drug overdose codes co-occurred with amphetamine-type stimulant overdoses presenting to EDs in 2017 (Vivolo-Kantor et al., 2020). The most common co-occurring drugs among amphetamine-type stimulant overdoses included benzodiazepines (9.3%), heroin (7.4%), cannabis (6.9%), cocaine (6.7%), and other opioids (4.3%) (Vivolo-Kantor et al., 2020). However, a similar analysis has not been performed among *all drug overdoses* with more recent data. In addition, many studies of drug overdoses are not nationally representative (Liu & Vivolo-Kantor, 2020; Liu et al., 2020; Liu et al., 2021; O'Donnell et al., 2020). For example, one study used latent class analysis to identify patterns of drug use/overdose among drug poisonings in EDs between 2017 and 2018. Although the analysis examined 13 classes of substances, including opioids, stimulants, benzodiazepines, alcohol, and anti-depressants, only 18 states were included in the analysis (Liu & Vivolo-Kantor, 2020). Several recent analyses used syndromic surveillance data (Liu & Vivolo-Kantor, 2020; Liu et al., 2020; Liu et al., 2021), which may include preliminary or missing (rather than final) discharge diagnosis codes.

Our objectives were to 1) examine the prevalence of specific T36-T50 drug poisoning codes *(note that codes for alcohol*, e.g.*, alcohol-related disorders or toxic effect of alcohol, were not explicitly queried)*, 2) compare demographic and clinical characteristics between single-drug and polydrug overdose-related visits, and 3) explore the most frequent drug combinations among polydrug overdoses in a nationally representative sample of U.S. ED visits in 2018.

2. Methods

Data were analyzed from the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project's (HCUP) 2018 Nationwide Emergency Department Sample (NEDS). The NEDS employs stratified random sampling from two files (the State Inpatient Databases and State Emergency Department Databases) to produce nationally representative estimates of U.S. ED visits. In 2018, 990 facilities from 36 states and Washington, D.C. were included, representing a 20% sample of U.S. hospital-based EDs (Healthcare Cost and Utilization Project, 2018) (N = 35,807,950 unweighted ED visits; N = 143,454,430 weighted national estimate of ED visits).

Drug overdose-related ED visits were identified using ICD-10-CM drug poisoning diagnosis codes T36-T50. ICD-10-CM codes included only initial encounters and only unintentional, intentional, assault, and undetermined intent codes; adverse effect and underdosing codes were excluded. All diagnoses (not solely the principal diagnosis) were searched. Weighted counts and percentages of all overdose-related ED visits, by drug, were calculated for each code falling under the parent codes T36-T50 (e.g., T40.1). These counts and percentages were not mutually exclusive; therefore, visits where a patient was exposed to multiple drugs were included in counts for each specific drug. Stimulant-involved overdoses were defined as those involving psychostimulants (ICD-10-CM code T43.6; e.g., methamphetamine, ecstasy, caffeine, or prescribed stimulants such as Ritalin or Adderall) or cocaine (T40.5). Alcohol and tobacco were not considered drugs in this analysis, which is consistent with major international and U.S. case definitions of drug poisoning, including those endorsed by the CDC National Center for Injury Prevention and Control (Centers for Disease Control and Prevention, 2013), the Injury Surveillance Workgroup 7 (Injury Surveillance Workgroup 7, 2012), and the World Health Organization (i.e., the ICD-9-CM (World Health Organization, 1980) and ICD-10-CM (World Health Organization, 2015).

Polydrug overdose-related ED visits were defined as those having more than one drug poisoning code; drug poisoning codes were summed over ED visits to create a count of drugs involved. Demographic and clinical characteristics of overdose-related ED visits were calculated by polydrug status (single-drug vs. polydrug), including sex, age group (≤14, 15–19, 20–24, 25–34, 35–44, 45–54, 55–64, and ≥ 65 years), hospital region (Northeast, Midwest, South, and West), hospital county urbanization (large central metro, large fringe metro, medium metro, small metro, micropolitan [nonmetro] and noncore [nonmetro]) (Ingram & Franco, 2013), percent hospitalized, percent deceased, and overdose intent (indicated by the 5th or 6th character in the ICD-10-CM drug poisoning code). Visits with multiple drug overdose codes indicating different intents were coded as missing for intent (<1% of total). To compare demographic and clinical characteristics by polydrug status, we generated prevalence ratios (PRs) and associated 95% confidence intervals (CIs) using predicted marginals from weighted bivariable logistic regression models in SAS-callable SUDAAN. Each PR compared the prevalence of a demographic/clinical characteristic in polydrug overdose-related visits to the prevalence among single-drug overdose-related visits. Multivariable models were not developed, as our goal was to describe how the prevalence of population characteristics differed between polydrug and single-drug overdose-related

ED visits, rather than to isolate an association between polydrug status and a particular characteristic.

We also identified the most frequent polydrug overdose combinations by first identifying the most common single drug poisoning codes among polydrug overdose-related visits (i.e., overdoses with more than one drug involved). Next, an array was created of all existing drug combinations with the top 30 most common poisoning codes (due to computing limitations) to determine the most frequent distinct polydrug overdose combinations. To describe the predominance of opioids and benzodiazepines in the top 30 most common polydrug overdose combinations, we grouped visits by whether they included both opioid and benzodiazepine poisoning codes, only opioid poisoning codes, only benzodiazepine poisoning codes, or neither opioid nor benzodiazepine poisoning codes. We also stratified the top 30 most common polydrug overdose combinations by sex and tested for statistical differences using chi-square tests. For the purpose of this analysis, illicit drugs were defined as heroin, cocaine, psychostimulants (ICD-10-CM code T43.6, primarily representing illicit methamphetamine), and other synthetic narcotics (ICD-10-CM code T40.4, likely primarily representing illicitly manufactured fentanyl). Survey procedures in SAS 9.4 (Cary, NC) were used to account for the complex survey design of HCUP NEDS. Data were de-identified. CDC considered this study to be public health surveillance; therefore, Institutional Review Board approval was not required.

3. Results

3.1. Prevalence of drug poisoning codes among 2018 overdose-related visits

In 2018, an estimated 908,234 U.S. ED visits had a discharge diagnosis code indicating a drug overdose, accounting for approximately 0.6% of all U.S. ED visits. Overall, 30.3% of drug overdose-related visits had at least one opioid poisoning code, with the most common of these indicating heroin (15.2%) and other opioids (e.g., prescription opioids such as oxycodone, hydrocodone, morphine, or codeine; 7.7%) (Table 1). Almost 5% of visits had a code for poisoning by other and unspecified narcotics (T40.6); this code is used when an opioid overdose is indicated without any further details on specific opioid type. Furthermore, 2.3% included a code for poisoning by other synthetic narcotics (also referred to as synthetic opioids, e.g., buprenorphine, tramadol, pethidine, or fentanyl). Overdose-related visits involving most types of non-opioid analgesics were rare, with the exceptions of 4-aminophenol derivatives (e.g., acetaminophen; 6.6%) and NSAIDs (4.3%). Almost 8% of drug overdose-related visits involved a stimulant, with 5.2% and 3.8% of overdose-related visits involving psychostimulants (e. g., amphetamines [including methamphetamine] and prescribed stimulants) and cocaine, respectively. Additionally, 3.2% of visits had a diagnosis code for cannabis poisoning.

Although the prevalence of most T42 subcodes for poisoning by antiepileptics and sedative-hypnotics was low, 11.0% of visits involved benzodiazepine poisoning (T42.4), while 4.8% involved poisoning by other antiepileptic and sedative-hypnotic drugs (T42.6). More than 7% of overdose-related visits involved poisoning by other and unspecified antidepressants (T43.2), and 1.2% involved poisoning by tricyclic/tetracyclic antidepressants (T43.0). Poisoning by most systemic/hematological agents was rare, but 3.7% of visits

involved poisoning by antiallergic and antiemetic drugs (T45.0). Around 4% of overdose-related visits involved a cardiovascular agent (e.g., “other antihypertensive drugs” [1.6% of visits], angiotensin-converting-enzyme inhibitors [0.8% of visits], or others). Almost 3% of overdose-related visits involved insulin and oral hypoglycemic drugs, but overdose-related visits involving other hormones were rare. Nearly 12% of drug overdose-related visits had a T50.9 code for poisoning by other and unspecified drugs, medicaments, and biological substances, and 10.6% of visits had solely a T50.9 code with no additional drug poisoning codes, making it impossible to identify a specific drug class. Prevalence of overdose-related visits involving other drug classes (e.g., autonomic system drugs, anesthetics, gastrointestinal agents) was low.

3.2. Comparison of single-drug and polydrug-related overdose ED visits

Among the estimated 908,234 drug overdose-related ED visits, 83.3% (n = 756,604) included one drug poisoning code, 11.8% (n = 107,239) included two drug poisoning codes, and 4.9% (n = 44,391) included three or more drug poisoning codes. Polydrug overdose-related ED visits were more likely than single-drug overdose-related visits to occur in females (PR 1.14, 95% CI: 1:12–1.16) (Table 2). While overdose-related ED visits most frequently occurred among those aged 25–34 years among both single-drug (21.0%) and polydrug visits (18.9%), the prevalence of adults aged ≥ 35 years was higher among polydrug (versus single-drug) visits. Polydrug overdose-related visits occurred more often in the West (PR: 1.10, 95% CI: 1.05–1.16), small metro areas (PR: 1.11, 95% CI: 1.05–1.18), and micropolitan (nonmetro) areas (PR: 1.12, 95% CI: 1.05–1.20) compared to single-drug overdose-related visits.

In addition, polydrug overdose-related visits, as compared to single-drug overdose-related visits, were more likely to be coded as intentional self-harm (PR: 1.81, 95% CI: 1.77–1.85) and less likely to be coded as unintentional (PR: 0.70, 95% CI: 0.68–0.71). Furthermore, notably more polydrug overdose-related visits resulted in hospital admission (PR: 1.84, 95% CI: 1.79–1.89) and death (PR: 1.37, 95% CI: 1.22–1.53).

3.3. Prevalence of polydrug-related overdose combinations

Fig. 1 displays the prevalence of the top 30 polydrug overdose combinations (prevalence was calculated *among polydrug overdose-related visits, i.e., visits with ≥ 2 drug poisoning codes*). The top 30 polydrug overdose combinations accounted for 32.5% of all polydrug overdose-related visits, and each of the top 30 combinations involved two drugs. Thirteen of the top 30 polydrug overdose combinations involved a benzodiazepine, ten involved an opioid, and eight involved a stimulant; five of the top 30 involved both an opioid and benzodiazepine. The most frequent polydrug overdose combinations were the following: 1) other opioids (e.g., prescription opioids such as oxycodone, hydrocodone, or morphine) and benzodiazepines (3.7%), 2) other and unspecified antidepressants and other and unspecified antipsychotics/neuroleptics (2.8%), 3) heroin and cocaine (2.3%), 4) benzodiazepines and other antiepileptic and sedative-hypnotic drugs (1.9%), and 5) 4-aminophenols and NSAIDs (1.6%) (Fig. 1). These top five polydrug overdose combinations accounted for approximately 12% of polydrug overdose-related visits. Polydrug overdose ED visits involving prescription and/or OTC medications were more likely to occur among females,

while polydrug overdose ED visits that involved an illicit drug were more likely to occur among males (data not shown). Among the top five polydrug overdose combinations overall, 56.4% of visits involving other opioids and benzodiazepines, 62.8% of visits involving other/unspecified antidepressants and other/unspecified antipsychotics/neuroleptics, 60.5% of visits involving benzodiazepines and other antiepileptic and sedative-hypnotic drugs, and 74.3% of visits involving 4-aminophenols and NSAIDs occurred among females ($p < .05$ for all differences by sex). Only 34.9% of polydrug overdose-related visits involving heroin and cocaine occurred among females ($p < .05$).

4. Discussion

This study highlights the complex nature of drug overdoses. More than 900,000 of 142.5 million U.S. ED visits in 2018 were drug overdose-related, of which the vast majority were nonfatal. Our analysis provides prevalence estimates of specific T36-T50 drug poisoning codes and polydrug overdose combinations and compares demographic and clinical characteristics between single-drug and polydrug overdose-related ED visits. It is important to consider these overdoses within the context of a multifaceted landscape of nonfatal and fatal overdoses that involve combinations of prescribed, illicit, and OTC drugs. Although overdoses most commonly involved opioids (30.3% of all drug overdose-related visits), a smaller proportion of these ED visits also involved benzodiazepines (11.0%), stimulants (7.9%), and unspecified antidepressants (7.1%). A notable proportion of ED visits also experienced overdoses involving medications typically provided OTC, including NSAIDs and 4-aminophenol derivatives such as acetaminophen. Additionally, more than one-tenth of overdoses involved unknown drugs. The prevalence of drug overdose was rare for most other drug classes. Notably, we did not explicitly examine alcohol diagnosis codes in this study, as alcohol is not considered a drug under ICD-9-CM (World Health Organization, 1980), ICD-10-CM (World Health Organization, 2015), or other major U.S. surveillance case definitions (Centers for Disease Control and Prevention, 2013; Injury Surveillance Workgroup 7, 2012). Consequently, it is possible some ‘single-drug’ overdoses in our study could have involved alcohol. However, a post-hoc analysis showed that only 0.05% and 0.35%, respectively, of the 908,234 drug overdose-related visits in our study had an ICD-10-CM T51.8 or T51.9 code for toxic effects of alcohol. Although 10.3% of the drug overdoses in our study had an F10 code for alcohol-related disorders, the intended purpose of F codes is to capture use disorders and not poisonings. Thus, it is not clear if those visits represented acute alcohol use or poisoning.

Nearly 17% of U.S. drug overdose-related visits in 2018 were coded as involving ≥ 2 drugs. Opioids, benzodiazepines, and/or stimulants were frequently involved in polydrug overdoses. Opioids and benzodiazepines were involved in one-third and nearly one-half of the 30 most common polydrug overdose combinations in our analysis, respectively. Combining opioids, which act as respiratory depressants (Boyer, 2012), with other central nervous system depressants such as sedatives or tranquilizers (e.g., benzodiazepines) increases the risk of overdose (Compton et al., 2021). It is particularly concerning that five of the top 30 polydrug overdose combinations in this study involved opioids and benzodiazepines. Mortality data from January–June 2020 show similar patterns, with the vast majority of benzodiazepine-involved deaths also involving opioids (primarily

illicitly manufactured fentanyl) (Liu et al., 2021). The burden of overdoses attributable to benzodiazepines and opioids highlights the risk associated with combining these drugs (Jones & McAninch, 2015; Sun et al., 2017) and the importance of accounting for prescribed and illicit benzodiazepine use in overdose prevention strategies (Nechuta et al., 2018; Votaw et al., 2019). Safe prescribing practices, including avoiding co-prescribing of benzodiazepines and opioids when possible, can help prevent drug overdoses (Dowell et al., 2016).

More than one-quarter of the 30 most common polydrug overdose combinations in this study involved stimulants such as cocaine or psychostimulants, a category that is likely driven by methamphetamine-involved visits (Substance Abuse and Mental Health Services Administration (SAMSHA), 2011). Overdose deaths involving psychostimulants have increased both with and without opioids in recent years (Hoots et al., 2020; Kariisa et al., 2019). In addition, mortality data demonstrate that recent increases in cocaine-involved overdose deaths have been largely driven by synthetic opioids such as illicitly-manufactured fentanyl (Kariisa et al., 2019; Mattson et al., 2021). Illicitly-manufactured fentanyl (including fentanyl analogs) may be mixed with stimulants, heroin, or other drugs either intentionally or unbeknownst to the user, which can increase the risk of overdose (Centers for Disease Control and Prevention, 2021a; Compton et al., 2021; National Institute for Drug Abuse, 2021). This can be particularly risky for opioid-naive individuals (National Institute for Drug Abuse, 2021; Jones et al., 2020).

Compared to single-drug overdose-related ED visits, polydrug overdose-related ED visits were more likely to be coded as intentional self-harm. This trend has been documented elsewhere (Gicquelais et al., 2020). Moreover, polydrug overdose-related ED visits overall, as well as polydrug overdose-related ED visits involving prescription or OTC medications, were more likely to occur in females than males in 2018. These findings align with those from other data sources. For instance, in the 2019 National Survey on Drug Use and Health (NSDUH), females ≥ 12 years were more likely than males to report any past-year use of pain relievers, benzodiazepines, tranquilizers, sedatives, or stimulants, while males were more likely to report past-year use of illicit drugs or misuse of pain relievers, opioids, or stimulants (Center for Behavioral Health Statistics and Quality, 2019). Another recent study found that opioid prescriptions, as well as concurrent opioid and benzodiazepine prescriptions, were more common among females (Guy et al., 2019).

Polydrug-related overdose visits in our study were also more likely to result in hospital admission and death. The increased morbidity and mortality among polydrug overdoses in our study may be related to the dangers of combining multiple respiratory or central nervous system depressants (e.g., an opioid and a tranquilizer) (Compton et al., 2021), as well as the frequency of highly potent illicitly manufactured fentanyl (National Institute for Drug Abuse, 2021) among polydrug overdose deaths (Kariisa et al., 2019; Mattson et al., 2021). Findings from our study converge with complementary analyses highlighting that both fatal (Hoots et al., 2020; Kariisa et al., 2019; Liu et al., 2021) and nonfatal (Hoots et al., 2020; Liu et al., 2020; Liu et al., 2021) polydrug overdoses co-involving opioids have risen during the last several years. Treatment data also show increases in methamphetamine use among individuals admitted for heroin treatment (Jones et al., 2020) or opioid use disorder

(Cicero et al., 2020). Confronting this changing landscape will require increasingly nimble and multifaceted, evidence-based prevention strategies led by a diverse set of partners (Centers for Disease Control and Prevention, 2021e). For instance, continued efforts to encourage safe prescribing practices can enhance overdose prevention efforts (Dowell et al., 2016). Healthcare providers should discuss the risks of substance use/misuse, substance use disorder, and overdose with their patients, examine information available in prescription drug monitoring program data, and continually monitor their patients for signs of illicit drug use, prescription drug misuse (Dowell et al., 2016), and suicidal thoughts or behavior. Providers can also educate their patients about the risks of using highly potent synthetic opioids such as illicitly manufactured fentanyl or fentanyl analogs (Centers for Disease Control and Prevention, 2021c).

Increasing awareness of the clinical presentation of stimulant overdoses is also important (Jones et al., 2020) given the increasing prevalence of cocaine and psychostimulant (e.g., methamphetamine) overdoses (Hoots et al., 2020; Kariisa et al., 2019; Liu et al., 2020; Mattson et al., 2021; Vivolo-Kantor et al., 2020). Improving health literacy among the U.S. population, particularly around appropriate medication dosage, could reduce the risk of unintentional overdose by OTC medications such as acetaminophen (Wolf et al., 2012). Additional drug overdose prevention strategies, such as linking and retaining persons in care, improving prescription drug monitoring programs, provision of naloxone as part of a post-overdose protocol in EDs, increasing access to overdose prevention education and medications for opioid use disorder, monitoring the illicit drug supply, communication campaigns (e.g., warnings about novel and emerging drugs and presence of counterfeit pills containing illicit fentanyl), and public safety partnerships are also important to curb the overdose epidemic (Centers for Disease Control and Prevention, 2021b,c,e; Green et al., 2020; Jones et al., 2020).

Given the rise in polysubstance use and overdose, overdose prevention and treatment efforts should increasingly target other substances beyond solely opioids (Compton et al., 2021). Prevention or treatment programs that improve decision-making skills or teach healthy coping mechanisms can help prevent not only harmful polysubstance use (Compton et al., 2021), but also suicidal thoughts and behaviors (Centers for Disease Control and Prevention, 2017). Evidence-based psychological treatments for stimulant use disorder, such as contingency management, should also be expanded (Centers for Disease Control and Prevention, 2021c; Jones et al., 2020). Furthermore, pharmaceutical treatments for cocaine use disorder and psychostimulant (e.g., methamphetamine) use disorder are urgently needed (Jones et al., 2020). Developing additional overdose reversal agents that target other drugs (similarly to how naloxone targets opioids) may also help mitigate polysubstance overdoses (Compton et al., 2021). In addition, communities can utilize primary prevention efforts that target general substance use initiation (Jones et al., 2020). Evidence-based primary prevention programs targeting youth substance use initiation exist (Spoth et al., 2017) and can be expanded (Compton et al., 2019), and evidence-based initiatives can be designed for adults, who may initiate substance use or abuse later in life (Compton et al., 2019). Finally, evidence-based suicide prevention strategies, such as expanding access to treatment for mental health conditions, strengthening delivery of suicide care, and enhancing economic supports (e.g., housing stabilization policies) may help reduce suicides overall (Centers for

Disease Control and Prevention, 2017), which may include those from intentional overdoses on single or multiple substances. Although prevalence was low for many drug classes, our analysis highlighted the broad range of drugs involved in overdoses and the importance of working to prevent these overdoses through targeted prevention strategies.

ICD-10-CM codes for opioids represent a combination of prescribed and illicit opioid drugs that were involved in one-third of the top 30 polydrug overdose combinations identified in our analysis. In 2019, more than half of overdose deaths involved a synthetic opioid, likely driven by increases in illicitly manufactured fentanyl (Mattson et al., 2021). Since 2013, the opioid overdose crisis has been amplified by the growing presence of illicitly-manufactured fentanyl (including fentanyl analogs) in the drug supply (Gladden et al., 2016; Mattson et al., 2021; Springer et al., 2019). Findings from studies of persons using drugs indicated a mix of perspectives regarding the presence of fentanyl in the drug supply, a combination of active avoidance of fentanyl and seeking of fentanyl (Carroll et al., 2017; Mars et al., 2018; Somerville et al., 2017). The increased supply of fentanyl (Centers for Disease Control and Prevention, 2020), coupled with potential demand for fentanyl, exacerbates overdose risk overall and further highlights the increased overdose risk from polydrug exposure.

There are a few limitations to our study. Although HCUP NEDS is a nationally representative sample of ED visits, more current data might identify different prevalence and polydrug combinations. Therefore, HCUP NEDS data should be used alongside complementary data sources such as ED syndromic surveillance data or emergency medical services (EMS) data, which may be available with minimal time lag. HCUP NEDS data include discharge diagnosis codes from hospital billing data, which are not generated primarily for surveillance but rather for insurance reimbursement. Additionally, many overdose-related ED visits do not receive toxicology testing, particularly if results would not result in a modified clinical treatment plan (Boyer, 2012; Wu et al., 2003). Limited toxicological testing in EDs might result in potential misclassification of drugs and an underestimation of polydrug overdoses. For example, fentanyl-involved overdoses in our analysis could have been captured by different ICD-10-CM codes. At the time of these 2018 ED visits, a specific ICD-10-CM code for nonfatal poisoning by fentanyl or fentanyl analogs was not available. Although some of these overdoses could have been captured using the T40.4 code for poisoning by other synthetic narcotics, it is possible that fentanyl-involved overdoses were captured using different codes for opioids (e.g., T40.2 for other opioids; T40.6 for unspecified/unknown narcotics). A specific ICD-10-CM code for fentanyl or fentanyl analogs (T40.41) was introduced on October 1, 2020, and future analyses can include this code to better understand the involvement of fentanyl in these nonfatal overdoses. The lack of toxicological testing is also evident in the high percentage of drug overdose-related ED visits coded as poisoning by other and unspecified drugs, medicaments, and biological substances (almost 12%). Continued comparisons between ED discharge data and data from confirmatory toxicological testing of ED specimens will increase our understanding of how to address potential misclassification. Finally, future studies might consider the occurrence of acute alcohol use in polysubstance overdoses.

5. Conclusion and future directions

Opioids, benzodiazepines, and stimulants were the most frequent drugs involved in both single-drug and polydrug overdose-related ED visits in 2018. Continued efforts to reduce missing data, including ICD-10-CM diagnosis codes for unknown drugs, as well as increased toxicological testing in EDs, will help advance drug overdose surveillance efforts and further elucidate which drugs are implicated in recent overdoses. Overdose prevention efforts should incorporate findings from diverse data sources, including nationally representative ED discharge data (e.g., HCUP NEDS) as well as complementary data from death certificates, medical examiner/coroner reports, syndromic surveillance, and EMS. Several of these complementary data sources are collected as part of CDC's Overdose Data to Action (OD2A) cooperative agreement (Centers for Disease Control and Prevention, 2021b), which funds jurisdictions to enhance timely data collection of overdose data, with an increased focus on polydrug and stimulant overdoses. Future work should continue to monitor the evolving landscape around polydrug overdoses and evaluate how other specific types of drug overdoses, beyond opioids, benzodiazepines, and stimulants, change over time.

Acknowledgment

The authors would like to thank Dr. Alana Vivolo-Kantor for her input on previous versions of the manuscript.

Role of funding sources

All authors are employed by the U.S. Department of Health and Human Services' Centers for Disease Control and Prevention. This manuscript was developed as part of ongoing work in the area of drug abuse and overdose prevention; there was no specific funding for this study. The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Abbreviations:

CI	confidence interval
ED	emergency department
HCUP	Healthcare Cost and Utilization Project
ICD-10-CM	International Classification of Diseases, 10th Edition, Clinical Modification
NEDS	Nationwide Emergency Department Sample
NSAID	nonsteroidal anti-inflammatory drug
OTC	over-the-counter
PR	prevalence ratio

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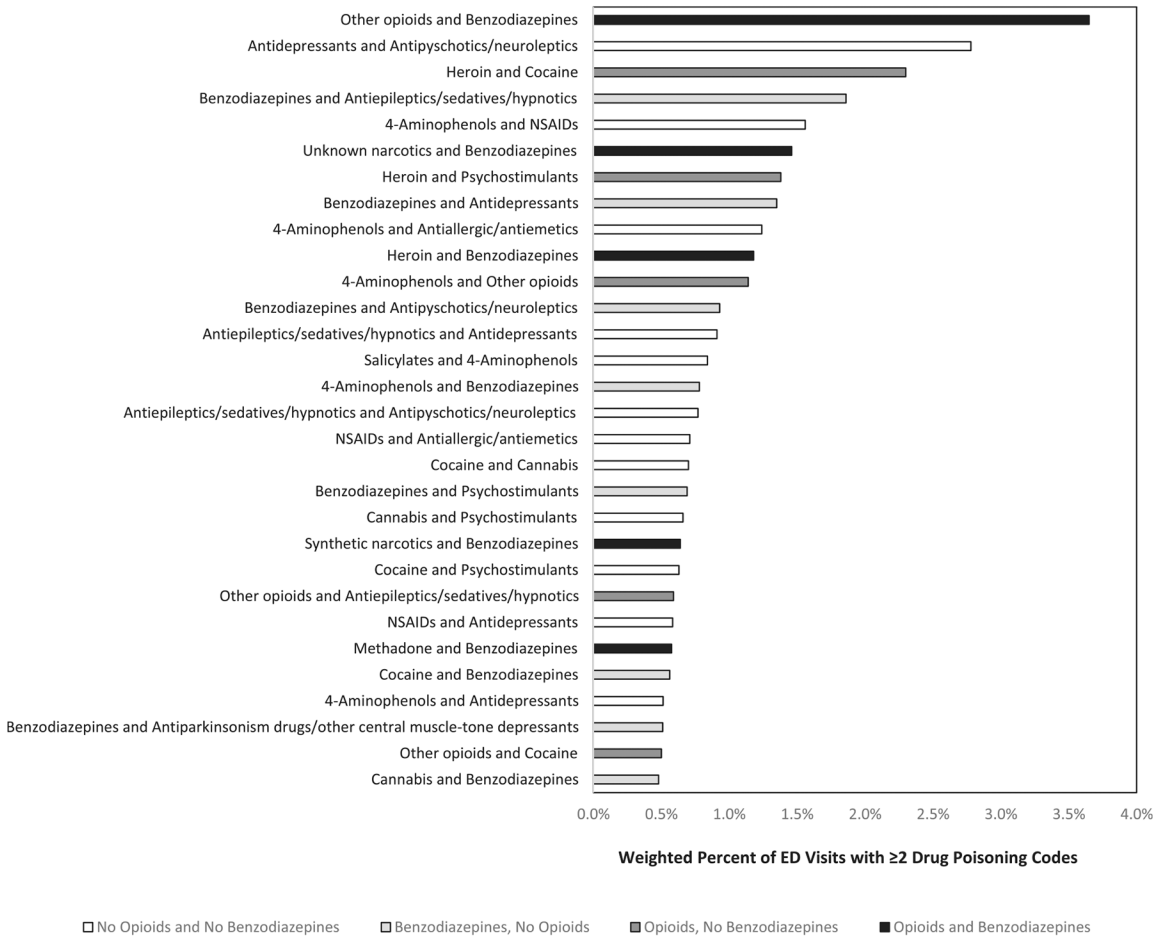

Fig. 1. Thirty Most Frequent Polydrug Overdose Combinations among U.S. Polydrug Overdose-Related Emergency Department Visits in 2018.

Abbreviations: ED, Emergency Department; NSAID, nonsteroidal anti-inflammatory drug. This figure shows the weighted prevalences of the top 30 most frequent polydrug overdose combinations among all U.S. polydrug overdose-related emergency department visits in 2018. All top 30 combinations involved two drugs. Prevalences were calculated among polydrug overdose-related emergency department visits (i.e., visits with ≥2 drug poisoning codes). Drug poisoning codes included ICD-10-CM codes T36 through T50; ICD-10-CM codes involving alcohol, e.g., alcohol-related disorders or toxic effects of alcohol, were not explicitly queried. The bars are shaded according to whether the polydrug overdose included opioids only, benzodiazepines only, both, or neither. Drug poisoning codes occurring in the top 30 polydrug overdose combinations are as follows: T39.0, salicylates; T39.1, 4-Aminophenol derivatives (e.g., acetaminophen); T39.3, other NSAIDS; T40.1, heroin; T40.2, other opioids (e.g., oxycodone, hydrocodone, morphine, hydromorphone, oxymorphone, and codeine); T40.3, methadone; T40.4, synthetic narcotics (e.g., fentanyl, tramadol, buprenorphine, or pethidine); T40.5, cocaine; T40.6, other and unspecified narcotics; T40.7, cannabis; T42.4, benzodiazepines; T42.6, other antiepileptic and sedative-hypnotic drugs; T42.8, antiparkinsonism drugs and other central muscle-tone depressants;

T43.2, other and unspecified antidepressants; T43.5, other and unspecified antipsychotics and neuroleptics; T43.6, psychostimulants; and T45.0, antiallergic and antiemetic drugs.

Table 1

Prevalence of Specific Drug Poisoning Codes among U.S. Emergency Department Drug Overdose-Related Visits, 2018.[1]

Code	Drug class	Wt n	(Wt %)	Code	Drug class	Wt n	(Wt %)
T36	**Antibiotics**	**6367**	**0.70**	**T44**	**Autonomic nervous system drugs**	**25,704**	**2.83**
T36.0	Penicillins	2336	0.26	T44.0	Anticholinesterase agents	164	0.02
T36.1	Cephalosporins	1056	0.12	T44.1	Other parasympathomimetics (cholinergics)	653	0.07
T36.2	Chloramphenicol group	9	0.001	T44.2	Ganglionic blocking drugs	0	
T36.3	Macrolides	226	0.02	T44.3	Other parasympatholytics (anticholinergics and antimuscarinics) and spasmolytics	4794	0.53
T36.4	Tetracyclines	793	0.09	T44.4	Predominantly alpha-adrenoreceptor agonists	470	0.05
T36.5	Aminoglycosides	35	0.004	T44.5	Predominantly beta-adrenoreceptor agonists	2272	0.25
T36.6	Rifampicins	52	0.01	T44.6	Alpha-adrenoreceptor antagonists	2731	0.30
T36.7	Antifungal antibiotics	73	0.01	T44.7	Beta-adrenoreceptor antagonists	13,043	1.44
T36.8	Other systemic antibiotics	1353	0.15	T44.8	Centrally-acting and adrenergic-neuron-blocking agents	558	0.06
T36.9	Unspecified systemic antibiotic	700	0.08	T44.9	Other and unspecified drugs primarily affecting the autonomic nervous system	1676	0.18
T37	**Anti-infective and antiparasitics**	**2991**	**0.33**	**T45**	**Systemic/hematological agents**	**51,131**	**5.63**
T37.0	Sulfonamides	752	0.08	T45.0	Antiallergic and antiemetic drugs	33,341	3.67
T37.1	Antimycobacterial drugs	72	0.01	T45.1	Antineoplastic and immunosuppressive drugs	1934	0.21
T37.2	Antimalarials and drugs acting on other blood protozoa	50	0.01	T45.2	Vitamins	3267	0.36
T37.3	Other antiprotozoal drugs	327	0.04	T45.3	Enzymes	20	0.002
T37.4	Anthelminthics	123	0.01	T45.4	Iron and its compounds	1611	0.18
T37.5	Antiviral drugs	910	0.10	T45.5	Anticoagulants and antithrombotic drugs	10,887	1.20
T37.8	Other specified systemic anti-infectives and antiparasitics	812	0.09	T45.6	Fibrinolysis-affecting drugs	23	0.003
T37.9	Unspecified systemic anti-infective and antiparasitics	12	0.001	T45.7	Anticoagulant antagonists, vitamin K and other coagulants	273	0.03
T38	**Hormones**	**31,747**	**3.50**	T45.8	Other primarily systemic and hematological agents	373	0.04
T38.0	Glucocorticoids and synthetic analogues	2988	0.33	T45.9	Unspecified primarily systemic and hematological agent	17	0.002
T38.1	Thyroid hormones and substitutes	3056	0.34	**T46**	**Cardiovascular agents**	**33,625**	**3.70**
T38.2	Antithyroid drugs	135	0.01	T46.0	Cardiac-stimulant glycosides and drugs of similar action	1649	0.18
T38.3	Insulin and oral hypoglycemic drugs	24,251	2.67	T46.1	Calcium-channel blockers	7292	0.80
T38.4	Oral contraceptives	214	0.02	T46.2	Other antidysrhythmic drugs, not elsewhere classified	1216	0.13
T38.5	Other estrogens and progestogens	197	0.02	T46.3	Coronary vasodilators	916	0.10

Code	Drug class	Wt n	(Wt %)	Code	Drug class	Wt n	(Wt %)
T38.6	Antigonadotrophins, antiestrogens, antiandrogens, NEC	51	0.01	T46.4	Angiotensin-converting-enzyme inhibitors	7342	0.81
T38.7	Androgens and anabolic congeners	177	0.02	T46.5	Other antihypertensive drugs	14,483	1.59
T38.8	Other and unspecified hormones and synthetic substitutes	944	0.10	T46.6	Antihyperlipidemic and antiarteriosclerotic drugs	2743	0.30
T38.9	Other and unspecified hormone antagonists	34	0.004	T46.7	Peripheral vasodilators	782	0.09
T39	**Nonopioid analgesics**	**106,006**	**11.67**	T46.8	Antivaricose drugs, including sclerosing agents	21	0.002
T39.0	Salicylates	12,823	1.41	T46.9	Other and unspecified agents primarily affecting the cardiovascular system	242	0.03
T39.1	4-Aminophenol derivatives	60,358	6.65	**T47**	**Gastrointestinal agents**	**6524**	**0.72**
T39.2	Pyrazolone derivatives	81	0.01	T47.0	Histamine H2-receptor blockers	1106	0.12
T39.3	Other nonsteroidal anti-inflammatory drugs	39,024	4.30	T47.1	Other antacids and anti-gastric-secretion drugs	2809	0.31
T39.4	Antirheumatics, NEC	52	0.01	T47.2	Stimulant laxatives	505	0.06
T39.8	Other nonopioid analgesics and antipyretics, not elsewhere classified	1118	0.12	T47.3	Saline and osmotic laxatives	204	0.02
T39.9	Unspecified nonopioid analgesic, antipyretic and antirheumatic	537	0.06	T47.4	Other laxatives	982	0.11
T40	**Narcotics and hallucinogens**	**329,382**	**36.27**	T47.5	Digestants	206	0.02
T40.0	Opium	1416	0.16	T47.6	Antidiarrheal drugs	846	0.09
T40.1	Heroin	137,953	15.19	T47.7	Emetics	38	0.004
T40.2	Other opioids[2]	70,185	7.73	T47.8	Other agents primarily affecting gastrointestinal system	71	0.01
T40.3	Methadone	7406	0.82	T47.9	Unspecified agents primarily affecting the gastrointestinal system	18	0.002
T40.4	Other synthetic narcotics[3]	20,617	2.27	**T48**	**Muscular/respiratory agents**	**20,985**	**2.31**
T40.5	Cocaine	34,749	3.83	T48.0	Oxytocic drugs	80	0.01
T40.6	Other and unspecified narcotics[4]	44,634	4.91	T48.1	Skeletal muscle relaxants (neuromuscular blocking agents)	7784	0.86
T40.7	Cannabis	28,963	3.19	T48.2	Other and unspecified drugs acting on muscles	1215	0.13
T40.8	Lysergide (LSD)	2589	0.29	T48.3	Antitussives	5493	0.60
T40.9	Other and unspecified psychodysleptics (hallucinogens)	2559	0.28	T48.4	Expectorants	3554	0.39
T41	**Anesthetics**	**2335**	**0.26**	T48.5	Other anti-common-cold drugs	1463	0.16
T41.0	Inhaled anesthetics	276	0.03	T48.6	Antiasthmatics, not elsewhere classified	1738	0.19
T41.1	Intravenous anesthetics	24	0.003	T48.9	Other and unspecified agents primarily acting on the respiratory system	43	0.005
T41.2	Other and unspecified general anesthetics	1307	0.14	**T49**	**Topical agents**	**10,030**	**1.10**
T41.3	Local anesthetics	610	0.07	T49.0	Local antifungal, anti-infective and anti-inflammatory drugs	3063	0.34
T41.4	Unspecified anesthetic	36	0.004	T49.1	Antipruritics	63	0.01

Code	Drug class	Wt n	(Wt %)	Code	Drug class	Wt n	(Wt %)
T41.5	Therapeutic gases	95	0.01	T49.2	Local astringents and local detergents	1257	0.14
T42	**Antiepileptics, sedative-hypnotics**	**159,196**	**17.53**	T49.3	Emollients, demulcents and protectants	754	0.08
T42.0	Hydantoin derivatives	3145	0.35	T49.4	Keratolytics, keratoplastics, and other hair treatment drugs and preparations	1682	0.19
T42.1	Iminostilbenes	5064	0.56	T49.5	Ophthalmological drugs and preparations	437	0.05
T42.2	Succinimides and oxazolidinediones	38	0.004	T49.6	Otorhinolaryngological drugs and preparations	885	0.10
T42.3	Barbiturates	2334	0.26	T49.7	Dental drugs, topically applied	184	0.02
T42.4	Benzodiazepines	99,855	10.99	T49.8	Other topical agents	1662	0.18
T42.5	Mixed antiepileptics	16	0.002	T49.9	Unspecified topical agent	117	0.01
T42.6	Other antiepilileptic and sedative-hypnotic drugs	43,586	4.80	**T50**	**Diuretics and other unspecified drugs**	**118,756**	**13.08**
T42.7	Unspecified antiepileptic and sedative-hypnotic drugs	3244	0.36	T50.0	Mineralcorticoids and their antagonists	543	0.06
T42.8	Antiparkinsonism drugs and other central muscle-tone depressants	14,057	1.55	T50.1	Loop (high-ceiling) diuretics	2374	0.26
T43	**Psychotropics**	**157,886**	**17.38**	T50.2	Carbonic-anhydrase inhibitors, benzothiadiazides and other diuretics	3070	0.34
T43.0	Tricyclic and tetracyclic antidepressants	10,621	1.17	T50.3	Electrolytic, caloric and water-balance agents	1347	0.15
T43.1	Monoamine-oxidase-inhibitor antidepressants	130	0.01	T50.4	Drugs affecting uric acid metabolism	285	0.03
T43.2	Other and unspecified antidepressants	64,346	7.08	T50.5	Appetite depressants	724	0.08
T43.3	Phenothiazine antipsychotics and neuroleptics	2129	0.23	T50.6	Antidotes and chelating agents	316	0.03
T43.4	Butyrophenone and thiothixene neuroleptics	1442	0.16	T50.7	Analeptics and opioid receptor antagonists	3201	0.35
T43.5	Other and unspecified antipsychotics and neuroleptics	45,261	4.98	T50.8	Diagnostic agents	575	0.06
T43.6	Psychostimulants	46,899	5.16	T50.A	Bacterial vaccines	27	0.003
T43.8	Other psychotropic drugs	1051	0.12	T50.B	Viral vaccines	25	0.003
T43.9	Unspecified psychotropic drugs	492	0.05	T50.Z	Other vaccines and biological substances	87	0.01
				T50.9	Other and unspecified drugs, medicaments and biological substances	107,036	11.79

[1] We examined T36-T50 drug poisoning codes (“poisoning by drugs, medicaments and biological substances”) found in the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) Chapter 19 (“Injury, poisoning, and certain other consequences of external causes”). ICD-10-CM codes involving alcohol (e.g., alcohol-related disorders or toxic effects of alcohol) were not explicitly queried. Because visits could have ≥ 1 drug poisoning code, weighted sample sizes and prevalences in this table are not mutually exclusive, and the prevalences will sum to> 100%. The weighted n and prevalence of each parent drug category (e.g., T36 or T37) represents the number/prevalence of visits with at least one code in that parent category.

[2] Prescription opioids such as oxycodone, hydrocodone, morphine, hydromorphone, oxymorphone, or codeine.

[3] Buprenorphine, tramadol, pethidine, or fentanyl.

[4] This code is used when an opioid overdose is indicated without any further details on specific opioid type.

Table 2

Demographic and Clinical Characteristics of U.S. Emergency Department Overdose-Related Visits by Polydrug Status, 2018.

	Single-drug overdose-related visits Wt n (col %)		Polydrug overdose-related visits Wt n (col %)		PR (95% CI)[1]
All	**756,604**		**151,630**		
Sex					
Female	378,756	(50.1)	86,501	(57.1)	1.14 (1.12–1.16)
Male	377,772	(49.9)	65,110	(42.9)	-
Age group, years					
≤14	86,367	(11.4)	9584	(6.3)	0.55 (0.52–0.59)
15 to 19	78,583	(10.4)	17,368	(11.5)	1.10 (1.06–1.15)
20 to 24	69,794	(9.2)	14,165	(9.3)	1.01 (0.97–1.05)
25 to 34	159,100	(21.0)	28,595	(18.9)	0.90 (0.87–0.92)
35 to 44	111,529	(14.7)	23,747	(15.7)	1.06 (1.03–1.10)
45 to 54	92,275	(12.2)	22,194	(14.6)	1.20 (1.17–1.24)
55 to 64	81,850	(10.8)	19,663	(13.0)	1.20 (1.16–1.24)
≥65	77,059	(10.2)	16,305	(10.8)	1.06 (1.01–1.10)
Census region					
Northeast	137,932	(18.2)	25,432	(16.8)	0.92 (0.86–0.98)
Midwest	193,425	(25.6)	40,387	(26.6)	1.04 (0.99–1.10)
South	281,431	(37.2)	54,004	(35.6)	0.96 (0.92–1.00)
West	143,817	(19.0)	31,807	(21.0)	1.10 (1.05–1.16)
County urbanization level					
Large central metro	214,365	(28.7)	40,736	(27.3)	0.95 (0.91–0.99)
Large fringe metro	170,694	(22.9)	32,166	(21.5)	0.94 (0.90–0.99)
Medium metro	169,645	(22.7)	34,360	(23.0)	1.01 (0.96–1.06)
Small metro	76,287	(10.2)	16,991	(11.4)	1.11 (1.05–1.18)
Micropolitan (nonmetro)	72,110	(9.7)	16,205	(10.8)	1.12 (1.05–1.20)
Noncore (nonmetro)	42,903	(5.8)	8995	(6.0)	1.05 (0.97–1.12)
Overdose intent[2]					
Unintentional	514,982	(68.2)	70,053	(47.5)	0.70 (0.68–0.71)
Intentional self-harm	208,155	(27.6)	73,602	(49.9)	1.81 (1.77–1.85)

	Single-drug overdose-related visits Wt n (col %)		Polydrug overdose-related visits Wt n (col %)		PR (95% CI)[1]
All	**756,604**		**151,630**		
Assault	1542	(0.2)	163	(0.1)	0.54 (0.37–0.78)
Undetermined	30,867	(4.1)	3793	(2.6)	0.63 (0.58–0.68)
Admission to hospital					
Yes	240,139	(31.7)	88,425	(58.3)	1.84 (1.79–1.89)
No	516,465	(68.3)	63,205	(41.7)	-
Died					
Yes	6320	(0.8)	1732	(1.1)	1.37 (1.22–1.53)
No	747,929	(99.2)	149,594	(98.9)	-

Abbbreviations: CI, confidence interval; col, column; PR, prevalence ratio; Wt, weighted. Numbers may not add to totals due to missing values.

[1]Referent for prevalence ratios is single-drug overdose-related visits. Prevalence ratios and associated 95% confidence intervals were calculated from predicted marginals from weighted bivariable logistic regression in SAS-callable SUDAAN. The PR for females can be interpreted as follows: The prevalence of females was 1.14 (95% 1.12–1.16) times higher in polydrug overdose-related visits than in single-drug overdose-related visits. Other prevalence ratios can be interpreted similarly.

[2]Visits with multiple drug overdose codes indicating different intents were coded as missing for the intent variable only.