Editor's Choice

Polysubstance Overdose Deaths in the Fentanyl Era: A Latent Class Analysis

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Objectives: To elucidate the main latent classes of substances detected among overdose decedents, and latent class associations with age, sex, race, and jurisdiction of death in Maryland.

Methods: We used toxicology data from the Office of the Chief Medical Examiner of Maryland for all decedents. We analyzed all cases of drug overdose deaths that occurred from 2016 to 2018 (N = 6566) using latent class analysis and regression.

Results: Drug overdose deaths were concentrated in 2 of 24 counties in Maryland (Baltimore City and County). Fentanyl was involved in 71% of all drug overdose deaths, and the majority (76%) of these deaths included multiple substances. Three latent classes emerged: (1) fentanyl/heroin/cocaine (64%); (2) fentanyl/alcohol (18%); and (3) prescription drugs including opioids, benzodiazepines and antidepressants (18.0%). The fentanyl/heroin/cocaine class members were significantly younger (<30 years), female and White compared to the fentanyl/alcohol class, but more male and non-White than the prescription drugs class (all $P < 0.05$). Deaths in Baltimore City/County were more likely than in other locations to involve fentanyl/alcohol ($P < 0.05$).

Conclusions: The majority of fentanyl-involved overdose deaths in Maryland involved multiple substances, and several demographic and geographic differences in these patterns emerged. Geographically-targeted interventions that are tailored to reduce the harms associated with polysubstance use (including cocaine, alcohol, and prescription drugs) for different demographic groups are warranted.

Key Words: drug use, opioids, substance use

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Over the last 2 decades, more than 702,000 lives have been lost to drug overdose in the United States, and mortality rates remain at historically elevated levels.[1] The majority (69.5%) of overdoses in 2018 involved opioids.[2] The opioid epidemic is commonly framed as a triple epidemic, consisting of rises in prescription opioid deaths (late 1990s), heroin deaths (2010 to present), and deaths involving synthetic opioids including illicit fentanyl (2013 to present).[3] Less attention has focused on polysubstance-involved deaths—a hidden epidemic that substantially contributes to elevated synthetic opioid morbidity and mortality.[4,5] Eighty percent of synthetic opioid deaths in the United States involved another opioid (eg, prescription opioids, 21%; heroin, 30%), stimulants (eg, cocaine, 22%), nonopioid prescription drugs (eg, benzodiazepines, 17%), or alcohol (11%), painting a complex profile of polysubstance-related deaths.[5] National trends demonstrate large increases from 2012 to 2017 in overdoses involving a combination of illicit opioids and cocaine; these patterns have also emerged at the state level.[6]

Although the majority of studies to date have focused on the independent risks conferred by individual drugs, a growing body of literature has begun to disentangle patterns of polysubstance use (defined as the simultaneous use of 2 or more substances, or sequential use over a short period of time) and the relationship between polysubstance use and overdose risk. Certain combinations of substances carry more severe risk of overdose, such as the combined use of multiple respiratory depressants (eg, benzodiazepines or barbiturates with opioids), hepatoxic substances (eg, alcohol with benzodiazepines), or the combined use of cocaine and heroin (also known as "speedball use").[7–10] One review[11] found that polysubstance use is especially common among certain demographic groups of people who use drugs (PWUD), including high school students who report heroin use, young adult men, women who report nonmedical opioid use, and patients receiving medication for addiction treatment who report stimulant use.[12–14] Polysubstance use has also been linked

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to lower drug treatment initiation and worse health outcomes.[15,16,17] Recent community-based studies in the United States have demonstrated that PWUD with a polydrug/polyroute profile are significantly more likely to have a history of overdose, and less likely to access overdose trainings.[18] Shifting drug markets also add further complexity to understanding the drivers of overdose risk; illicitly-manufactured fentanyl and its analogs have been detected in samples of heroin, cocaine, and counterfeit prescription opioids.[19] Multiple calls have been made for research that improves our understanding of polysubstance use and deaths, particularly in the context of shifting drug markets.[5,11]

Overdoses involving illicit fentanyl and other synthetic opioids are on the rise, particularly in the Eastern and Midwest regions of the United States.[20] Maryland, a large Eastern state with a population of more than 6 million, has been hit hard by the drug overdose crisis. The state was ranked third in the nation in age-adjusted drug overdose mortality in 2018 with deaths driven primarily by illicit fentanyl exposure.[1] Toxicology data show that a range of substances, including cocaine, heroin, alcohol, and prescription drugs, are coinvolved in overdose deaths; however, the specific groupings of substances that drive overdose deaths have not been elucidated. In this study, we modeled the latent classes of substances involved in overdose deaths in the state of Maryland between 2016 and 2018 and examined the demographic and geographic correlates of class membership in order to broaden our knowledge on the patterns of polysubstance overdose deaths.

METHODS

Sample

We obtained records of all investigated deaths from 2016 through 2018 from the Maryland Office of the Chief Medical Examiner (OCME). Further details on the data are described elsewhere.[21] When overdose is suspected in a death, the medical examiner administers a comprehensive toxicology panel to identify which substances were involved. From these records, we included all drug overdose deaths that were identified. Between 2016 through 2018, there were 6840 drug overdose deaths recorded by the OCME. A small number (n = 166; 2.4%) of drug overdose deaths were missing toxicology reports and were therefore excluded from our analysis. We also excluded deaths containing drugs that were rare (ie, less than 4% prevalence among overdose deaths; n = 108), as our goal was to identify the most common patterns of substances involved among overdose deaths. This yielded a final analytic sample of 6566 drug overdose deaths.

Measures

Involved Substances

The OCME toxicology panel tests for a wide variety of substances, including many specific formulations within the same category of drugs. We combined some drugs into categories by drug type, as we would expect similar drugs to produce similar overdose risks. We created the following categories from a broad list of drugs and drug metabolites: *antidepressants* (eg, bupropion, fluoxetine, venlafaxine, amitriptyline, nortriptyline, doxepin, nordoxepin, mirtazapine, desmethylsertraline, sertraline, citalopram, paroxetine, trazodone), *nonbenzodiazepine anticonvulsants* (eg, primidone, tegretol, topiramate, lamictal, keppra), *neuroleptics* (eg, promethazine, chlorpromazine, thioridazine, clozapine, olanzapine, seroquel, haldol), and *prescription opioids* (eg, meperidine, tramadol, propoxyphene, oxycodone). Morphine was used to indicate heroin deaths instead of the 6-monacetylmorphine metabolite, which was not tested for by OCME systematically. Cases involving both quinine (a common street drug filler) and morphine were interpreted as indicating heroin use rather than medical morphine use. Stimulants were considered as observed in the dataset (eg, cocaine, methamphetamine, methylone, phencyclidine, etc). The analysis only included all substances/categories that had at least a 4% prevalence among overdose deaths. There were 11 substances/categories that met this criterion that were entered into the latent class analysis (LCA): alcohol, antidepressants, fentanyl, benzodiazepines, neuroleptics, cocaine, methadone, morphine/heroin, nonbenzodiazepine anticonvulsants, and prescription opioids.

Demographic Characteristics

The OCME records age, sex, and race for deceased individuals. We created a categorical variable for age: less than 30, 30 to 44, 45 to 59, and 60 and older. Sex was a binary variable (male/female). The OCME assigns race/ethnicity based on a physical autopsy as well as conversations with next of kin. In rare cases where there are no identifiable next of kin or other collateral informants, the estimates are made based on physical exam and other collected information (including full access to medical records through the State's electronic medical records database). Though imperfect, this method is identical to the methodology used by the Centers for Disease Control and Prevention (CDC) in the National Violent Death Reporting System and is an extension of standard practice. In order to analyze race/ethnicity, we created the categories of Non-Hispanic White and Other.

Location of Overdose

The county and city where each overdose occurred are also noted in the OCME records. Given the overall distribution of deaths, we divided these locations into 2 categories: Baltimore City/County, which is inclusive of a large metropolitan area in Maryland, and all other locations.

Quinine

The OCME tests for quinine in the postmortem toxicology panels, in addition to the drugs described above. Quinine is a common additive in street drugs, like heroin and cocaine. We included whether each decedent had quinine in their system as an indicator of whether they were likely using street drugs or prescription substances. This is particularly important in case of deaths involving morphine, as both heroin and some prescription opioids would register as positive for the morphine metabolites.

Analysis

We conducted LCA in order to identify common combinations of drugs and alcohol involved in overdose deaths in Maryland.[22,23] We used binary indicators for each of the 11

TABLE 1. Characteristics of Drug Overdose Deaths (N = 6556) in Maryland Using Data From the Office of the Chief Medical Examiner, 2016 to 2018

Variable	%
Year	
2016	31.51
2017	33.14
2018	35.35
Age	
Under 30	18.36
30–44	33.40
45–59	37.26
60 and older	10.97
Sex	
Female	28.35
Male	71.65
Race/Ethnicity	
Non-Hispanic White	65.20
Other	34.80
Location	
Baltimore City and Baltimore County	49.82
Other	50.18
Involved substances	
Fentanyl	71.40
Morphine/heroin	51.71
Alcohol	37.83
Cocaine	36.20
Antidepressants	22.19
Prescription opioids	16.57
Benzodiazepines	14.65
Methadone	10.66
Neuroleptics	7.25
Anticonvulsants	4.60
Number of involved substances, M (SD)	2.73 (1.19)

The vast majority of fentanyl cases are due to the use of illicit fentanyl for nonmedical purposes.

substances described above in the latent class model. We estimated a series of models with increasing numbers of classes and compared key LCA fit statistics including the Akaike Information Criteria and Bayesian Information Criteria. Specifically, we visualized these fit statistics to determine which number of classes best fit the data, with a preference for Bayesian Information Criteria over Akaike Information Criteria in making the final determination.[24] We also considered class sizes and substantive interpretations of classes to ensure that we were not overestimating the number of classes present in the sample or identifying small, unstable classes (ie, class prevalence lower than 10%). We then used the R3STEP procedure to assess the relationships between our latent classes and correlates of interest, while accounting for measurement error in the latent class enumeration.[25] Analyses were conducted using Mplus Version 8 (Muthén & Muthén; Los Angeles, CA).

RESULTS

The overall characteristics of the drug overdose deaths included in this study are summarized in Table 1. The distributions of drug overdoses were relatively even by year. Most deceased individuals were aged 30 to 44 (33.4%) or 45 to 59 (37.3%). The majority of decedents were male (71.7%) and White (65.2%). Approximately half of Maryland overdose deaths occurred in Baltimore City and County (49.8%). The most commonly involved substances in overdose deaths were fentanyl (71.4%), heroin (51.7%), alcohol (37.8%), and cocaine (36.2%).

Latent Classes of Substances Involved in Drug Overdose Deaths

The fit statistics for the latent class models are displayed in Table 2. We selected a 3-class model based on the fit statistics and a visual plot of these values (data not shown). The conditional probabilities of each substance indicator by latent class are displayed in Figure 1. The largest class (61.7%) had high levels of fentanyl and heroin and a moderate level of cocaine (class name: fentanyl-involved speedball, defined as deaths involving fentanyl, heroin, and cocaine). The next class (18.1%) was defined by alcohol and fentanyl involvement with moderate level of heroin and cocaine (class name: fentanyl/alcohol). The third class (18.0%) had moderate levels of a variety of prescription drugs, particularly nonheroin opioids and antidepressants (class name: prescription drugs).

Correlates of Latent Class Membership

Differences in correlates by latent class are displayed in Table 3. Overall, fentanyl-involved speedball deaths were more common in recent years than other classes of deaths (vs fentanyl/alcohol class; 2018 vs 2016: *b(log odds)* = 0.96, 95% CI: 0.68, 1.24). The fentanyl/ speedball class was also significantly younger than the fentanyl/alcohol class (ie, 30–44 vs 18–29: b = −0.56, 95% CI: −0.94, −0.18) and the prescription drugs class (ie, 30–44 vs 18–29: b = −0.55, 95% CI: −0.96, −0.14), while the other 2 classes did not differ from each other by age.

The fentanyl/speedball class was more likely to consist of females than the fentanyl/alcohol class (*b* = 0.76, 95% CI:

TABLE 2. Latent Class Analysis Fit Statistics

Classes	Smallest Class Size	Log Likelihood	AIC	BIC	Entropy	LMR
1	—	−31449.799	62919.598	62987.495	—	—
2	20.85%	−30967.799	61977.598	62120.181	0.589	**<0.001**
3	18.04%	−30786.211	61636.421	61853.691	0.619	**<0.001**
4	5.18%	−30706.66	61499.32	61791.276	0.703	**<0.001**
5	3.74%	−30635.721	61379.442	61746.083	0.578	**<0.001**
6	3.15%	−30600.139	61330.278	61771.606	0.602	0.1966

Bolded *P*-values denote statistical significance.
AIC indicates Akaike Information Criteria; BIC, Bayesian Information Criteria; LMR, Lo-Mendell-Rubin Likelihood Ratio Test.

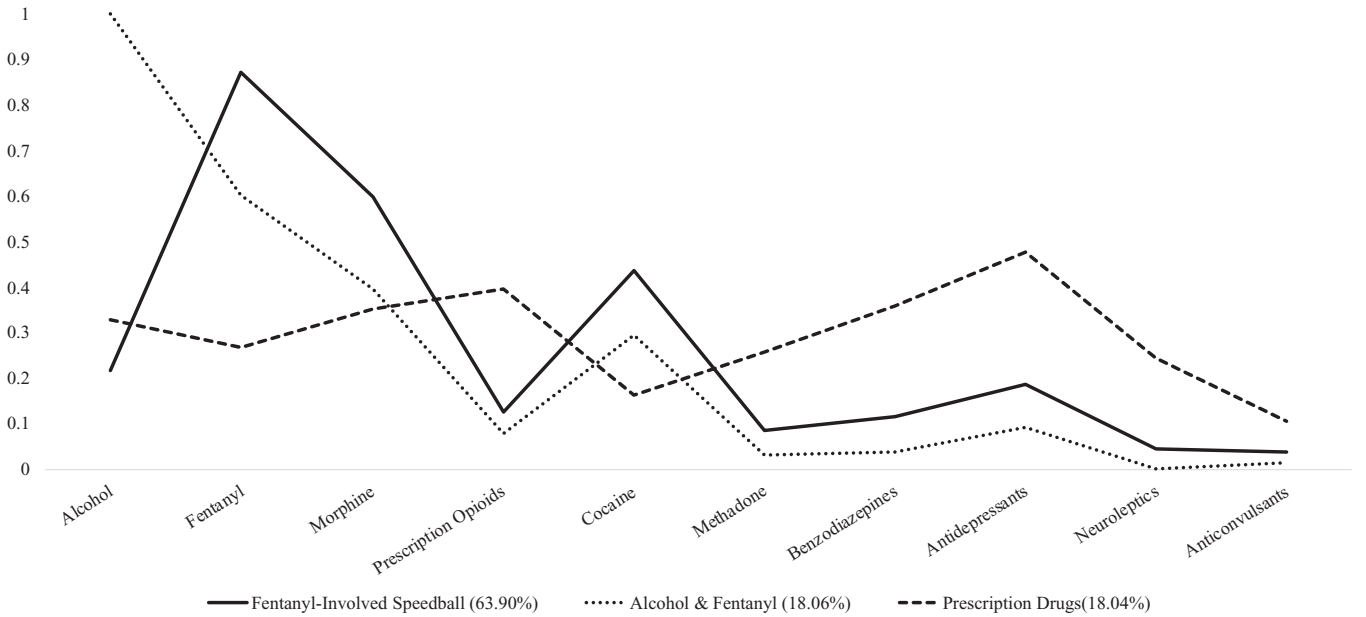

FIGURE 1. Latent classes of substances involved in drug overdose deaths in Maryland, 2016 to 2018. The vast majority of fentanyl cases are due to the use of illicit fentanyl for nonmedical purposes.

0.43, 1.08). However, the prescription drugs class was more likely to consist of females than the fentanyl/speedball class. In terms of race, the fentanyl/speedball class was more White than the fentanyl/alcohol class ($b = 0.51$, 95%CI: 0.26, 0.75) but less White than the other 2 classes. Lastly, overdoses in the fentanyl/speedball class were less likely in the Baltimore area compared to the fentanyl/alcohol class ($b = -0.25$, 95% CI: −0.49, −0.01). There were no other significant differences by location observed for the remaining 2 classes. The fentanyl/ speedball class had a higher probability of involving quinine than other classes (vs fentanyl/alcohol class: $b = 2.08$, 95% CI: 1.78, 2.38; vs prescription drug class: $b = 3.83$, 95% CI: 3.02, 4.63). The fentanyl/alcohol class involved more quinine than the prescription drugs class ($b = 1.75$, 95% CI: 0.91, 2.58).

DISCUSSION

This study examined the latent patterns underlying polysubstance deaths using data collected between 2016 and 2018 from Maryland. Our analysis, which was conducted within the era of illicit fentanyl, uncovered 3 distinct classes of substances involved in overdose deaths. The most common class was fentanyl-involved speedball, followed by fentanyl/ alcohol and prescription drugs. Individuals in the fentanyl-involved speedball class were more likely to be younger and to use street drugs (as indicated by the presence of quinine)

TABLE 3. Demographic and Geographic Correlates of Latent Classes of Drug Overdose Deaths in Maryland, 2016 to 2018

	Fentanyl-Involved Speedball vs Fentanyl/Alcohol		Fentanyl-Involved Speedball vs Prescription Drugs		Fentanyl/Alcohol vs Prescription Drugs	
	b (95% CI)	*P*	*b* (95% CI)	*P*	*b* (95% CI)	*P*
Year						
2016	–	–	–	–	–	–
2017	0.61 (0.32, 0.89)	**<0.001**	0.66 (0.35, 0.98)	**<0.001**	0.06 (−0.26, 0.38)	0.723
2018	0.96 (0.68, 1.24)	**<0.001**	1.30 (0.98, 1.61)	**<0.001**	0.34 (−0.00, 0.67)	0.052
Age						
18–29	–	–	–	–	–	–
30–44	−0.56 (−0.94, −0.18)	**0.004**	−0.55 (−0.96, −0.14)	**0.009**	0.01 (-0.50, 0.52)	0.959
45–59	−1.08 (−1.45, −0.71)	**<0.001**	−0.95 (−1.36, −0.53)	**<0.001**	0.13 (−0.37, 0.63)	0.604
≥60	−1.47 (−1.94, −1.00)	**<0.001**	−1.90 (−2.41, −1.39)	**<0.001**	−0.43 (−1.02, 0.16)	0.149
Female Sex	0.76 (0.43, 1.08)	**<0.001**	−1.06 (−1.33, −0.80)	**<0.001**	−1.82 (−2.18, −1.47)	**<0.001**
White race	0.51 (0.26, 0.75)	**<0.001**	−1.10 (−1.44, −0.77)	**<0.001**	−1.61 (−1.95, −1.27)	**<0.001**
Baltimore City/County	−0.25 (−0.49, −0.01)	**0.042**	−0.06 (−0.33, 0.22)	0.678	0.19 (-0.10, 0.48)	0.190
Quinine	2.08 (1.78, 2.38)	**<0.001**	3.83 (3.02, 4.63)	**<0.001**	1.75 (0.91, 2.58)	**<0.001**

Cases with missing data were removed listwise (n = 44). The vast majority of fentanyl cases are due to the use of illicit fentanyl for nonmedical purposes. Estimates represent betas and associated *P*-values. Bolded *P*-values denote statistical significance.

compared to the other 2 classes; this class was also more likely to be female and White compared to the fentanyl/alcohol class, but more male and non-White compared to the prescription drugs class. The correlates also differed by location, with fentanyl/alcohol deaths being more likely in Baltimore City and Baltimore County. In fact, these 2 geographically proximate urban and suburban jurisdictions accounted for almost half of all drug overdose deaths in Maryland between 2016 and 2018. This disproportionate burden highlights the need for place-based overdose prevention planning and programming. These findings could be used by health agencies, clinicians, and policymakers to shape and target interventions to improve prevention and treatment outcomes in Maryland and beyond.

Polysubstance-involved deaths accounted for the majority of overdose deaths in Maryland, which is consistent with existing national reports.[5,26] Unlike national trends, however, the majority of deaths in Maryland involved fentanyl whereas less than half of drug overdoses in the United States did in the same period, which is likely due to regional shifts in the illicit drug supply.[19] The patterns that we identified in this study and the implications of the findings demonstrate the complexity of the overdose epidemic, which involves illicit opioids, stimulants, prescription medications, and alcohol. Key gaps remain in current biomedical interventions that are available for addressing polysubstance use and death. For example, despite the substantial involvement of cocaine in overdose deaths (with and without opioids), medications to reverse the effects of cocaine overdoses that are analogous to naloxone for opioid overdose do not currently exist, and FDA-approved medications that treat stimulant dependence are currently unavailable, though many are under active investigation.

The role of alcohol on the fentanyl epidemic has received less attention, even though alcohol-opioid intoxication is correlated with higher risk of overdose.[27] Alcohol use disorder has been found to interfere with treatments for opioid dependence; previous studies have found alcohol present in 24% of fentanyl-related deaths, with a higher proportion among male decedents, consistent with our predominantly male fentanyl/alcohol class.[28] The identification of this fentanyl/alcohol class highlights the importance of addressing comorbid alcohol use in those at risk of fentanyl overdose. Emerging research shows that combining psychotherapy with medications to treat addiction may be effective in treating comorbid alcohol and opioid use disorder.[29]

These data demonstrate that it is imperative that there be widespread access to evidence-based treatment for opioid dependence (including methadone, buprenorphine/naloxone, naltrexone) and comorbidities, as well as psychosocial and behavioral interventions, in both urban and suburban jurisdictions. Efforts to maintain adequate coverage of treatment, prevention, and harm reduction services are more important than ever in the face of the COVID-19 pandemic, which continues to burden healthcare systems all around the country. In the case of an overdose, we need to ensure that community members and those who actively use drugs are not afraid to call EMS or administer naloxone should they witness an overdose. Improving the implementation of Good Samaritan laws that provide legal protections for individuals who call 911 or attempt to assist someone during an overdose could help improve access to emergency care.[30,31] Educational public health campaigns that are developed to tackle opioid use should be attuned to the role of polysubstance use, including alcohol and stimulant use in deaths. Such campaigns should also be tailored to reach high-risk populations (eg, the demographics most likely to experience each class of overdose).

In addition to treatment and prevention, harm reduction is a critical component of a comprehensive overdose strategy, particularly for PWUD who are unwilling to enter treatment.[32] Although much attention has focused on the dangers associated with fentanyl and other potent synthetic opioids, there is an underlying concern about the ''black box'' nature of the global illicit drug supply, which remains unregulated and unpredictable, posing serious risks to PWUD. There have been multiple reports of unintentional fentanyl exposures that have led to overdoses among individuals in California, Pennsylvania, and Connecticut who thought they were using cocaine.[33] Community-based studies conducted in urban settings suggest that PWUD rely on subjective assessments (eg, color, taste) and word-of-mouth to seek or avoid fentanyl, and can be unsure whether their drugs contain fentanyl.[34–36] Drug checking programs, including take-home fentanyl test strips and on-site drug checking (eg, spectrometry), provide concrete information about the drug supply and encourage the adoption of risk reduction behaviors.[36,37] Overdose prevention sites (OPS), also known as safe consumption spaces or supervised injection facilities, are another powerful intervention that could be rapidly deployed to mitigate the risks associated with intentional and unintentional polysubstance use. OPS are places where people can use drugs in the presence of trained personnel who can provide education, linkage to care, and respond to emergencies (eg, administer naloxone). Like drug checking programs, OPS are evidence-based and have been successfully adopted in Europe and Canada. Unsanctioned OPS are already operating in the United States and researchers have documented broad support for OPS among PWUD and the public.[38,39]

Our analysis was limited due to several factors. First, studies that rely on postmortem death data cannot distinguish between intentional and unintentional use; the latter can happen in the case of contaminated drugs or false marketing. Second, we did not have access to the route of drug administration, which would add depth to the findings. However, this study was the first to employ LCA to examine polysubstance-involved deaths in Maryland and could provide the foundation for future work.

Future studies should examine the perceived benefits and drawbacks of polysubstance use among PWUD, the influence of peer norms, and the macro-level factors such as unemployment, poverty, racism, and disruptions to drug supplies, including those due to COVID-19, which may impact polysubstance morbidity and mortality.[32] Developing strategies to improve treatment outcomes for comorbid substance use disorders and biomedical interventions for cocaine dependence and overdose also remain a priority.

Our analysis sheds light on the latent patterns of polysubstance-involved overdose deaths in a U.S. state burdened by the fentanyl epidemic. These data demonstrate that large differences exist by demographics and geography, with disproportionate levels of drug overdose rates occurring in the Baltimore metropolitan area. Major shifts to policy and practice are warranted, including improved coordination between strategies that address opioids, stimulants, and alcohol, as well as the integration of harm reduction interventions like drug checking and OPS into federal, state and local planning. Without decisive action, the overdose crisis will continue to place heavy health, social and economic burdens on society for the foreseeable future.

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