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The Evolving Overdose Epidemic: Synthetic Opioids and Rising Stimulant-Related Harms

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Abstract

The opioid overdose epidemic is typically described as having occurred in 3 waves, with morbidity and mortality accruing over time principally from prescription opioids (1999–2010), heroin (2011–2013), and illicit fentanyl and other synthetic opioids (2014–present). However, the increasing presence of synthetic opioids mixed into the illicit drug supply, including with stimulants such as cocaine and methamphetamine, as well as rising stimulant-related deaths, reflects the rapidly evolving nature of the overdose epidemic, posing urgent and novel public health challenges. We synthesize the evidence underlying these trends, consider key questions such as where and how concomitant exposure to fentanyl and stimulants is occurring, and identify actions for key stakeholders regarding how these emerging threats, and continued evolution of the overdose epidemic, can best be addressed.

Keywords

cocaine; fentanyl; heroin; methamphetamine; opioids; overdose; psychostimulants; stimulants

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INTRODUCTION

The overdose crisis in the United States has typically been described as an opioid overdose epidemic consisting of 3 waves (1), with morbidity and mortality accounted for predominantly by prescription opioids (1999–2010), heroin (2010–2013), and illicit fentanyl and other synthetic opioids (2014–present). Between 1999 and 2010, the volume of prescription opioids distributed in the United States increased 4-fold, corresponding with an approximate 4-fold increase in the rate of fatal overdoses involving prescription opioids (2). Deaths involving prescription opioids plateaued in 2010–2013, rose modestly until 2016–2017, and declined in 2018 (3), attributable to both reduced opioid prescribing and other prevention, treatment, and recovery efforts (4). Beginning in 2010, largely as a result of increased geographic availability of historically low-cost, high-purity heroin and increased demand for opioids, overdose deaths from heroin began to rapidly increase (5, 6). Then in 2013, coincident with the rapid increase of illicitly made fentanyl and fentanyl analogs, including the extremely potent analog carfentanil, in the US drug supply (7), there was a near exponential increase in overdose deaths involving fentanyl and other synthetic opioids, with the rate of overdose deaths involving these drugs increasing 890%, from 1.0 per 100,000 person in 2013 to 9.9 in 2018 (3).

Most recently, the United States has experienced increasing rates of overdose deaths from concomitant exposure to fentanyl and stimulants, primarily cocaine and methamphetamine, as well as rising stimulant overdoses without opioids. In 2018, 14,666 overdose deaths involved cocaine, up from 4,944 overdose deaths 5 years earlier in 2013; similarly, overdose deaths involving psychostimulants with abuse potential—primarily methamphetamine—increased from 4,298 in 2014 to 12,676 in 2018 (3). Evidence indicates that opioids, especially synthetic opioids, have been involved in many of these deaths, with 74.2% of cocaine-related overdose deaths involving opioids and 50.5% of psychostimulant-related overdose deaths involving opioids in 2018 (8, 9). These trends reflect the rapid evolution of the overdose epidemic, posing urgent and novel public health challenges.

An effective public health response is predicated on an understanding of these trends. Some lines of evidence indicate changing illicit drug supplies, potentially exposing an unsuspecting population of individuals to lethal doses of opioids. Other lines of evidence indicate that substance use patterns are changing, with both a rising concomitant use of opioids and stimulants and a rising use of stimulants alone, especially methamphetamine.

In this narrative review, we synthetize available evidence to address 5 key questions:

1. How have morbidity and mortality from opioids and stimulants, including their combined use, changed over time?
2. To what degree are changes in the illicit drug supply, such as the mixing of synthetic opioids with stimulants, responsible for these trends?
3. Are changes in substance use patterns also contributing to rising morbidity and mortality?
4. What challenges do these trends present for the public health response?

5. What evidence-based public health strategies can best overcome these challenges?

To address these key questions, we searched the peer-reviewed literature using PubMed, Google Scholar, and Web of Science, using search terms that combined 2 or more of the following: “opioids,” “synthetic opioids,” “fentanyl,” “stimulants,” “cocaine,” “methamphetamine,” “psychostimulants,” and “overdoses.” We focused on literature published since 2010. Team members manually screened search results to identify relevant concepts and studies, with iterative searches focused on quantitative or qualitative studies that reported on overdose mortality, nonfatal overdose or other morbidity from combined fentanyl or synthetic opioid and stimulant exposure, general stimulant use trends as well as polysubstance use trends, and analyses of postmortem toxicology or death certificate data. We manually screened articles by title and, for selected articles, full text. We also manually reviewed the references for each selected article, as well as citations to such articles, and we triangulated articles we identified with our own knowledge of the literature as well as, in some cases, consultation with local experts. Then, we used a template to organize information from articles that included author, year, study design, primary outcome, and key findings. Common themes were identified to facilitate the narrative review and evidence synthesis.

TRENDS IN MORBIDITY AND MORTALITY FROM OPIOIDS AND STIMULANTS

Rising morbidity from stimulants and combined stimulants/opioids: emergency department data

Emergency department (ED) visits are a commonly employed measure of substance-related morbidity. Using data from the 2006–2016 Nationwide Emergency Department Sample (NEDS), Hoots et al. (10) examined trends in ED visits involving cocaine with and without opioids, as well as ED visits involving psychostimulants with and without opioids. Between 2006 and 2016, ED visit rates involving cocaine with opioids increased (annual percentage change) 14.7% per year; ED visit rates involving cocaine without opioids increased 11.3% per year from 2006 to 2012 and then remained stable from 2012 to 2016. For psychostimulants, ED visit rates with opioids increased 49.9% per year from 2006 to 2011 and then increased 14.0% per year from 2011–2016; ED visit rates involving psychostimulants without opioids increased throughout the study period, rising 13.9% per year from 2006 to 2016.

Postmortem toxicology testing from the National Vital Statistics System

Multiple studies have also used vital records to describe increasing concomitant exposure to opioids, in particular synthetic opioids, and stimulants among overdose decedents in the United States (Table 1). For example, in 2017, Jones et al. (11) used National Vital Statistics System (NVSS) data to quantify the rate and number of cocaine-involved overdose deaths involving opioids between 2000 and 2015. Over the time period examined, cocaine-related overdose deaths involving opioids increased significantly from 0.37 to 1.36 per 100,000

individuals, whereas cocaine deaths not involving opioids declined from 0.89 to 0.78 per 100,000 individuals (Table 1).

In a subsequent study, Jones et al. (9) used NVSS data to specifically quantify the involvement of synthetic opioids in drug overdose deaths involving cocaine, psychostimulants, and other drugs. Among all overdose deaths, synthetic opioid involvement increased from 7.8% of deaths in 2010 to 30.5% of deaths in 2016. These increases were reflected among deaths involving cocaine, in which 4.0% of cocaine-involved deaths involved synthetic opioids in 2010, increasing to 40.3% in 2016 (Table 1). More modest increases were observed among deaths involving psychostimulants and synthetic opioids, rising from 3.9% in 2010 to 13.8% in 2016.

Kariisa et al. (12) used NVSS data to update these analyses, focusing on overdose deaths involving cocaine and psychostimulants between 2016 and 2017. They documented continued increases in rates of overdose deaths involving cocaine and psychostimulants, both with and without opioids, from 3.2 (2016) to 4.3 (2017) per 100,000 individuals for cocaine and 2.4 (2016) to 3.2 (2017) per 100,000 individuals for psychostimulants (Table 1). Among these deaths, in 2017, 72.2% of cocaine-related and 50.4% of psychostimulant-related overdose deaths involved an opioid (Table 1). Kariisa et al. (12) also found that the likelihood of stimulant use and the type of stimulant used (e.g., cocaine, methamphetamine) vary across both different regions and subpopulations in the United States. For example, from 2016 to 2017, overdose deaths involving cocaine were highest in the Northeast, while overdose deaths involving psychostimulants with abuse potential, such as methamphetamine, were highest in the West. Similarly, from 2016 to 2017, overdose deaths involving cocaine were most common among non-Hispanic Blacks, and while Whites had the most overdose deaths involving psychostimulants, American Indians had the highest rate per 100,000 persons.

Most recently Hoots et al. (10) reported that rates of overdose deaths involving cocaine with opioids decreased 12.0% per year from 2006 to 2010, remained stable from 2010 to 2014, and increased 46.0% per year from 2014 to 2017 (Table 1); rates without opioids decreased 21.2% per year from 2006 to 2009, remained stable from 2009 to 2014, and increased 23.6% per year from 2014 to 2017. For psychostimulants, overdose death rates with opioids remained stable from 2006 to 2010, increased 28.6% per year from 2010 to 2015, and increased 50.5% per year from 2015 to 2017 (Table 1); rates without opioids remained stable from 2006 to 2008 and increased 22.6% per year from 2008 to 2017. The 2018 NVSS mortality data indicate that any opioids and synthetic opioids were involved in 50.5% and 28.5% of psychostimulant-related overdose deaths, respectively, in 2018; for cocaine-related overdose deaths, 74.2% and 59.0% of these deaths involved any opioid and synthetic opioids (7).

Postmortem toxicology testing from other vital records systems

Other studies have used regional or statewide vital records to describe fentanyl in stimulant-involved deaths. For example, from 2015 to 2016, the rate of cocaine-related overdose deaths in New York, New York, increased from 5.2 to 10.4 per 100,000 residents, with 90% of this increase explained by deaths involving cocaine and fentanyl (13). An analysis

using Florida's Medical Examiner toxicology reports from 2016 through 2018 yields similar findings; the number of overall cocaine deaths almost doubled from 1,739 in 2016 to 3,027 in 2017, and the proportion of these deaths involving fentanyl increased from 32.6% in 2016 to 52.4% in 2017 (14) (Table 1).

In summary, data derived from emergency departments and corroborated by both national and regional vital records systems indicate significant increases in morbidity and mortality from both stimulants and combined stimulants and opioids between approximately 2006 and approximately 2018.

CHANGES IN THE ILLICIT DRUG SUPPLY

Changes in the illicit drug supply, including the proliferation of synthetic opioids, mixing of synthetic opioids with stimulants and increased availability of methamphetamine and cocaine, raise important questions regarding what is contributing to these changes and, in the case of fentanyl being combined with stimulants, whether people who use drugs are aware of them. Mortality and drug testing data cannot answer these questions. In some cases, fentanyl exposure appears to be unintentional, with individuals mistaking fentanyl for cocaine (15) or methamphetamine (16). On a more macro level, unintentional cross-contamination of cocaine or psychostimulants with fentanyl or other synthetic opioids by drug suppliers and distributors has been suggested as a possible mechanism for exposure (17). Drug-trafficking organizations and distributors typically deal with multiple illicit drug types, and the same equipment and surfaces could be used for the preparation of different drug products. Given fentanyl's potency, even minute quantities could potentially cause such cross-contamination, particularly if dealers are unaware of or indifferent to its dangers. This is particularly true for the extremely potent fentanyl analog carfentanil, which has been associated with large overdose death outbreaks in multiple states (18-20).

Increasing availability of cocaine and methamphetamine: Drug Enforcement Administration data

According to the Drug Enforcement Administration's (DEA's) 2019 National Drug Threat Assessment, cocaine is increasingly available in the United States. Methamphetamine is also readily available throughout the United States, both in the Midwest and West, where it has historically been accessible, as well as in areas of the United States that have historically not been major methamphetamine markets, particularly the Northeast (17).

Increasing synthetic opioids in cocaine and methamphetamine supplies: drug seizure data

In addition to increased availability of cocaine and methamphetamine, drug seizure data also indicate the increasing prevalence of fentanyl in illicit supplies of cocaine and methamphetamine (21-23) (Table 2). For example, according to the DEA's 2019 National Drug Threat Assessment, the mixture of cocaine with fentanyl and other synthetic opioids remains a significant threat throughout the United States (17). High availability of both cocaine and fentanyl is contributing to this trend expanding into new illicit markets, including in the Midwest. Since 2013, law enforcement laboratories have submitted reports of "speedball" (cocaine and heroin) and "super speedball" (cocaine, heroin, and fentanyl)

mixtures to the DEA's National Forensic Laboratory Information System (NFLIS), with an increase from 18 reports from 5 states in 2013 to 2,695 reports from 34 states, Puerto Rico, and Washington, DC, in 2017. Throughout 2018, multiple nontraditional cocaine markets, those outside the traditional markets on the East Coast and in the Midwest, began reporting noteworthy levels of cocaine and fentanyl mixtures. Increasing reports of these mixtures in Wisconsin and Maine correlated with a sharp rise in cocaine-involved overdose deaths, both with and without fentanyl. However, according to the DEA, the overwhelming majority of cocaine, heroin, and fentanyl reports submitted to the NFLIS are not cross-contaminated and contain only 1 drug; therefore, most "speedball" and "super speedball" mixtures are thought to remain mostly unintentional at the retail-level after the product enters the United States, rather than large-scale mixing by drug-trafficking organizations.

Similar to data on cocaine, the DEA also reports rising seizures of methamphetamine mixed with fentanyl and other synthetic opioids since 2015 (17). Many of these mixtures have methamphetamine as the primary substance, with fentanyl or other synthetic opioids as a secondary or tertiary substance in the sample. Although the number of these mixtures has increased over 1,342% percent since 2015, as with mixtures of cocaine and fentanyl, reports of methamphetamine and fentanyl mixtures represent a small fraction of the total methamphetamine reports in the DEA's NFLIS. For example, in 2017, such combinations accounted for approximately 2% of the nearly 300,000 methamphetamine reports in NFLIS, which might indicate that these mixtures are the result of unintentional contamination during methamphetamine processing and/or packaging for resale by polydrug traffickers rather than an intentional combination.

Community-based samples and case series: combined stimulant and fentanyl exposure occurrence and awareness

Community-based research and case series provide additional context and insight regarding whether combined fentanyl and stimulant exposures are due to intentional mixing, unintentional cross-contamination, or intentional concomitant use. It has also been well-established that many people knowingly engage in opioid-stimulant polysubstance use, including using speedballs (heroin and cocaine) and goofballs (heroin and methamphetamine) (24-27). More recent research also indicates that people who use drugs often use fentanyl in combination with, or immediately after, the use of stimulants (23, 28-30).

However, several studies have documented a high degree of uncertainty among people who use drugs about the presence of fentanyl in the drug supply (31-35). Among people who used drugs and engaged with harm reduction programs in British Columbia, Canada, in 2015, 73% of individuals testing positive for fentanyl reported that they had not knowingly used fentanyl in the past 3 days (16). Among this sample, most reported recent methamphetamine (59% of sample, with 38% of these testing positive for fentanyl), crack (32% of the sample, of which 27% tested positive for fentanyl), or powder cocaine (27% of the sample, with 25% testing positive for fentanyl) use. Such trends might be changing, with increasing awareness of fentanyl exposure among individuals using cocaine or psychostimulants (36, 31). For example, a 2018 study of individuals engaging with harm

reduction programs in British Columbia found that 60.3% of participants tested positive for fentanyl, and among those testing positive, nearly two-thirds (64%) reported knowingly having used fentanyl within the past 3 days (37).

Despite these trends, other studies suggest unintentional exposures to fentanyl among unsuspecting individuals. In 2016, during a less than 8-hour period, 12 individuals in New Haven, Connecticut, presented to the emergency department with symptoms consistent with opioid overdose after exposure to white powder that had been marketed to them as cocaine (16) (Table 3). While the route of intoxication was unclear, the drug, which was acquired from illicit sources, was presumed to have been snorted in most cases. Several other case reports describe fentanyl exposure among individuals using powdered or crack cocaine, most featuring a cluster of patients presenting urgently with opioid overdose symptoms after consuming what was believed to be a stimulant (38-41). At least some of these exposures were inadvertent, many were associated with fatalities, and many required repeated or continuous naloxone administration to maintain respiratory function, suggesting opioid naivety, substantial fentanyl exposure, or both.

In summary, information from federal sources and field surveys of people who use drugs suggest increasing accessibility of cocaine and methamphetamine, varied mechanisms whereby fentanyl is being combined with them, and varied levels of awareness of individuals who use drugs regarding such exposure. While increasing, the direct mixing of fentanyl within cocaine or psychostimulant supplies remains uncommon.

CHANGES IN SUBSTANCE USE PATTERNS

Changing substance use patterns, rather than changing drug supplies, might also contribute to evolving morbidity and mortality. Between 2015 and 2017, among adults in the United States with a heroin use disorder, 22.2% met diagnostic criteria for a cocaine use disorder and 19.8% met diagnostic criteria for a methamphetamine use disorder (42). Similarly, among adults reporting use of methamphetamine in the past year in 2015–2018, 40.4% reported past-year misuse of prescription opioids and 16.9% reported past-year use of heroin. In multivariable analysis, controlling for demographic, mental health, and other substance use variables, the adjusted odds of reporting past-year methamphetamine use were significantly elevated for adults reporting past-year prescription opioid misuse (adjusted odds ratio = 2.17, 95% CI: 1.66, 2.84) and past-year heroin use (adjusted odds ratio = 5.10, 95% CI: 3.63, 7.17) (43).

The prevalence of co-occurring use, in particular use of methamphetamine and opioids, also appears to be increasing. For example, among people who inject drugs engaging with syringe services programs (SSPs) in King County, Washington, combined heroin and methamphetamine injection in the past 3 months increased from 18% in 2009 to 31% in 2017 among men who have sex with men and from 10% to 53% among those who are not men that have sex with men (44) (Table 4). Other studies in sentinel sites have found similar trends (45, 21).

Among people seeking treatment for opioid use disorder from approximately 170 treatment facilities in the United States, Ellis et al. (27) found that past-month use of methamphetamine increased from 18.8% in the second quarter of 2011 to 34.2% in the first quarter of 2017 (Table 4). Among the subset using both opioids and methamphetamine, 79.9% reported using both substances on the same day, with 38.9% reporting at the same time, 9.4% reporting using immediately before or immediately after one another, and 31.5% reporting on the same day but at different times. The mean number of days of co-occurring use was 14.6 days per month in an average month. Primary thematic motivations for co-occurring use included high-seeking and synergistic effects (51% of respondents), balance of effect between the 2 drugs (38.6%), and methamphetamine as a substitute when opioids were not available (15.2%). In a subsequent study, the same authors reported that among people coming in to treatment for opioid use disorder, past-month use of methamphetamine increased from 19.6% in the second half of 2011 to 36.4% in the first half of 2018, whereas past-month cocaine use remained stable during the study period: 35.0% in the second half of 2011 and 33.2% in the first half of 2018 (46).

At the national level, using data from the 2008–2017 Treatment Episode Data Set (TEDS), there was a 23.4% annual increase in reported methamphetamine use among individuals admitted for heroin use disorder, from 2.1% of treatment admissions in 2008 to 12.4% in 2017 (Table 4); methamphetamine use among those admitted for heroin use increased among both male and female persons, all age and race/ethnicity groups, and in all US census regions (47). A separate study found that reporting any methamphetamine use at treatment admission and reporting methamphetamine as the primary substance of use at treatment admission increased significantly overall, among most demographic groups, and all US census regions between 2008 and 2017 (48). Any methamphetamine use at treatment admission increased from 15.1% of drug-related treatment admissions in 2008 to 23.6% in 2017, and treatment admissions for methamphetamine as the primary substance of use followed a similar pattern. Consistent with the above studies indicating rising co-occurring use of opioids and methamphetamine, heroin use increased from 5.3% of methamphetamine-related treatment admissions in 2008 to 23.6% in 2017 (Table 4), representing a 346% increase.

Analyses of urine drug tests also suggest increasing fentanyl exposure among cocaine and methamphetamine-positive results. For example, Larue et al. (49) performed a cross-sectional analysis of urinary drug tests assessed as part of routine clinical care and submitted to a laboratory vendor between 2013 and 2018. The laboratories reflected various US health-care settings and were a convenience sample of 1 million unique patient specimens. Among this sample, between 2013 and 2018, nonprescribed fentanyl increased from 0.9% to 17.6% among cocaine-positive results and from 0.9% to 7.9% among methamphetamine-positive results (Table 5). A follow-up analysis with data through October 2019 on 1,050,000 unique patients found that the positivity rate for methamphetamine in urine drug tests increased from 1.4% of all urine drug test samples in 2013 to 8.4% in 2019; cocaine positivity increased from 4.1% to 4.9%; and the nonprescribed fentanyl positivity rate increased from 1.1% to 4.7% (50). Cocaine positivity rates peaked in 2016 and declined thereafter; however, positivity rates for methamphetamine and fentanyl continued to increase through 2019. Among the nonprescribed fentanyl positive tests, positivity rates for co-occurring

methamphetamine increased from 2.2% in 2013 to 30.4% in 2019; positivity rates for cocaine increased from 5.3% in 2013 to 33.5% in 2019 (Table 5).

In summary, changing substance use patterns are also likely contributing to increasing rates of overdose deaths from concomitant exposure to fentanyl and stimulants, as well as rising stimulant overdoses without opioids.

PUBLIC HEALTH CHALLENGES

The available data suggests that multiple factors are contributing to the rise in opioid- and stimulant-related harms, including expanded availability of stimulants in the illicit drug supply, contamination of the stimulant illicit drug supply with fentanyl and other synthetic opioids, and changing substance use patterns suggesting that co-occurring use of opioids and stimulants is prevalent and increasing, especially for methamphetamine. Encouragingly, there appears to be some increasing awareness about fentanyl and other synthetic opioid contamination in the illicit drug supply among people who use drugs. Undoubtedly, the increasing presence of synthetic opioids in the stimulant drug supply, as well as rising stimulant-related harms even in the absence of opioid exposure, pose several urgent and novel public health challenges:

- Epidemiology remains poorly defined.
- There are no FDA-approved treatments for stimulant use disorders.
- Combined opioid/stimulant use is associated with higher risk.
- Fentanyl and other synthetic opioids are unusually potent and lethal.
- Some exposures to fentanyl and other synthetic opioids are unintentional.
- People who use stimulants might not be captured through opioid prevention and response strategies.

First, significant aspects of the epidemiology remain poorly defined. There is no single source of data that can address many of the most pressing questions regarding how and why the trends we describe are occurring. Information derived from surveys of treatment-seeking individuals, urine toxicology testing, drug seizures, or postmortem toxicology is necessarily incomplete. Quantitative and qualitative data gathered from people who use drugs might be especially valuable in order to identify knowledge, motivations, and behaviors accounting for trends apparent in secondary data sources such as national vital statistics systems or drug seizure data.

Second, at least some exposures are occurring unintentionally, and the presence of fentanyl or other synthetic opioids in the illicit stimulant supply chains increases the potential for the exposure of individuals who are opioid-naive. Such exposures are complicated further by the potency, lethality, and quick onset of action of fentanyl and other synthetic opioids, and the fact that people who use stimulants are less likely to engage with SSPs and other community-based programs offering naloxone and overdose prevention education (25, 51).

Third, the combined use of stimulants and opioids is associated with increased risk for overdose, riskier injection practices, more frequent use, and worse treatment outcomes (21, 52, 53). Thus, individuals using both opioids and stimulants represent a particularly vulnerable population at high-risk for overdose and infectious disease transmission, among other health and social consequences, who would benefit from access to a spectrum of integrated health, substance use, mental health, and social services that are lacking in many communities (43, 54, 55).

Finally, while there are pharmacologic products under development (56), as well as evidence-based behavioral approaches to treat stimulant use disorders (57,58), there are no FDA-approved pharmacologic treatments for these disorders. Although evidence-based behavioral approaches do exist, such as cognitive behavioral therapy, the community reinforcement approach, and contingency management, they have modest effect sizes and are most effective when implemented in combination, presenting logistical challenges for patients, providers and payers alike (59).

PUBLIC HEALTH REPONSE

The evolving overdose crisis requires an expanded public health response to build upon work already underway to address the opioid epidemic. Given important regional differences in substance use epidemiology, such a response must be driven by and customized to the needs of local communities. While there is longstanding recognition that polysubstance use is the norm, rather than the exception, for most individuals with substance use disorders (6), the patterns that we describe, in the context of investments to address the opioid overdose epidemic, add new relevance and timeliness to these efforts.

Coordinated multiagency response

In settings where fentanyl and other synthetic opioid exposures are occurring among unsuspecting individuals, especially those who might be opioid-naive and highly susceptible to the respiratory depressive effects of opioids (17, 39), the ability to implement a rapid, coordinated-response system among emergency departments, poison control centers, public health departments, public safety, and first responders is critical. Such efforts could include the rapid notification of law enforcement agencies who might be especially well-equipped to identify and eliminate further sources of exposure, equipping first responders with naloxone and training them on overdose response involving co-use of stimulants and opioids, and rapidly communicating to the drug use community about changes in the illicit drug supply so that people who use drugs can take measures to protect themselves.

Workforce preparation

It is also vital that clinicians, first responders, and lay persons likely to respond to an overdose are trained on the risks of synthetic opioids and the potential need for multiple naloxone doses to reverse opioid exposure (15, 35, 37, 38). Such preparation might be especially important to manage unintentional exposures among individuals who are opioid-naive. Further, overdoses involving stimulants present their own unique challenges due to central nervous system stimulation, potentially resulting in dangerous elevations in heart rate

and blood pressure, cardiac arrythmias, violent or aggressive behavior, and psychosis (60); clinicians and both medical and nonmedical responders should be trained to recognize and address stimulant overdose.

Treatment

Despite the absence of FDA-approved pharmacologic treatments for stimulant use disorder, as mentioned above, evidence-based treatments for cocaine and methamphetamine addiction exist, including cognitive behavioral therapy, the community reinforcement approach, and contingency management (61, 62). While each of these represents a psychological therapy, their approaches differ, with cognitive behavioral therapy based on an effort to modify individuals' "cognitive distortions" and behaviors to improve the way they feel, the community reinforcement approach intended to make abstinence more rewarding than continued substance use, and contingency management designed to use tangible incentives and rewards to motivate changes in behavior. For individuals with opioid use disorder as well, such psychological interventions can be combined with provision of medications for opioid use disorder. Assessing the adequacy of insurance coverage and payment policies for these behavioral therapies, as well as the availability of well-trained clinicians to provide them, is an essential first step in expanding their availability to people with stimulant use disorders.

Public safety

Public safety plays an important role in addressing the increasing presence of synthetic opioids mixed in the illicit drug supply, as well as rising availability of stimulants. Some public safety interventions are natural extensions of best practices that have evolved in response to surging opioid-related deaths, such as educating law enforcement officials regarding addiction and stigma (63) and equipping and training officers to recognize and help individuals in need of effective response and care (e.g., through naloxone "leave behind" programs) (64). Implementing and strengthening Good Samaritan laws can empower bystanders to seek help without the risk of arrest (65). Moreover, the potential for increased highly potent opioid contamination of nonopioid illicit drug supplies underscores the importance of public safety investigations into sources of these drug combinations along the distribution chain. Disrupting access to highly potent synthetic opioids, such as carfentanil and precursor chemicals, among local communities also requires collaboration between local, state, and federal public safety officials and a focus on upstream interventions by federal agencies in the United States (66).

Harm reduction

The substantial risks for morbidity and mortality among people using opioids and stimulants also underscores the importance of advancing harm reduction strategies to mitigate this risk. SSPs provide a critical venue to reach individuals who use drugs (67). However, SSPs might not engage some individuals at risk of fentanyl or other synthetic opioid exposure, who might rarely or never inject drugs. Thus, efforts to expand comprehensive SSPs that reach the broadest possible cohort of people who use drugs are needed. Immediate naloxone resupply and augmentation for first responders is also critical, as are efforts to accelerate the distribution of naloxone to people who use drugs and their friends or family. Fentanyl testing

has also been adopted by some jurisdictions as a means to potentially help reduce risk in the context of an unpredictable illicit drug supply (68). Overdose prevention sites are another harm reduction approach, where people may use previously purchased substances under supervision. While established in Canada, Europe, and Australia, personal possession of illicit narcotics remains illegal in the United States under the Federal Controlled Substances Act, and overdose prevention sites remain unsanctioned (69).

Public health communication

Public education is critical to raise awareness of emerging threats from synthetic opioids and stimulants, as well as to serve as one component of multifaceted strategies to positively change health behaviors (68). The potential for unintentional exposures to fentanyl and other synthetic opioids among unsuspecting individuals who believe they are using stimulants such as cocaine or methamphetamine might require rapid public health alerts as part of a rapid, coordinated-response system.

Primary prevention

Primary prevention interventions are an essential part of the long-run strategy to address rising substance use generally and use of opioids and stimulants specifically; however, they are currently underutilized (70). Universal prevention programs that focus on strengthening youth social-emotional learning skills and other protective factors and reducing risk factors have demonstrated lasting protective effects in reducing substance use, including methamphetamine and opioid use (71). Communities could consider implementation of these programs as a central component of substance use prevention efforts.

CONCLUSION

The overdose epidemic in the United States is a complex, multifaceted, and dynamic phenomenon (72). Although much focus has been given to a 3-wave opioid epidemic, characterized by mortality attributable to prescription opioids, heroin, and illicit synthetic opioids, the epidemic continues to evolve, most recently with rising stimulant-related morbidity and mortality and continued increases in morbidity and mortality related to synthetic opioids. These changes pose urgent and novel public health challenges. While the causes and consequences of these emerging trends are important to understand, it is equally important to consider the context of the broader polysubstance use that is common among individuals with substance use disorders (73, 74). There is an urgent need to mobilize public health prevention, treatment, and response strategies to address these rising harms, and to do so in tandem with efforts already underway to reduce opioid-related morbidity and mortality.

Abbreviations:

DEA	Drug Enforcement Administration
ED	emergency department
NFLIS	National Forensic Laboratory Information System

NVSS	National Vital Statistics System
SSP	syringe services program

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Table 1.

Combined Fentanyl and Stimulant Exposures Derived From Postmortem Toxicology Testing in the United States

First Author, Year (Reference No.)	Data Source	Time Period	Outcome	Key Findings
Jones, 2017 (11)	National Vital Statistics System	2000–2015	Rate and number of cocaine-involved overdose deaths involving natural or synthetic opioids	Cocaine-related deaths increased significantly from 0.37 (2000) to 1.363 (2015) per 100,000; those not involving opioids declined from 0.89 to 0.78 per 100,000.
Jones, 2018 (9)	National Vital Statistics System	2010–2016	Rate and number of synthetic opioid-involved overdose deaths	Synthetic opioid involvement in overdose deaths involving illicit drugs or alcohol increased from 7.8% (2010) to 30.5% (2016); synthetic opioid involvement in overdose deaths involving cocaine rose from 4.0% (2010) to 40.3% (2016).
Kariisa, 2019 (12)	National Vital Statistics System	2003–2017	Rate and number of combined cocaine- and psychostimulant-involved overdose death rates	Death rates increased 34.4% from 3.2 (2016) to 4.3 (2017) per 100,000. In 2017, 72.2% of cocaine and 50.4% of stimulant deaths involved an opioid.
Nolan, 2019 (13)	New York City death certificates	2015–2016	Contribution of opioids and fentanyl to the increase in cocaine-involved overdose in New York City	Increase in deaths involving fentanyl and cocaine accounted for 90% of the increase in cocaine-related mortality.
Hoots, 2020 (10)	Healthcare Cost and Utilization Project's Nationwide Emergency Department Sample; National Vital Statistics System	2006–2016 2006–2017	Trends in nonfatal and fatal overdoses involving stimulants with and without opioids	Emergency department visits involving cocaine with opioids experienced a 14.7% APC increase from 2006–2016; visits involving psychostimulants with opioids experienced a 49.9% APC increase from 2006 to 2011 and then 14.0% APC increase from 2011 to 2016. Among overdose deaths, overdose deaths involving cocaine and opioids decreased 12.0% per year from 2006 to 2010, remained stable from 2010 to 2014, and increased 46.0% per year from 2014 to 2017. For psychostimulants, overdose death rates with opioids remained stable from 2006 to 2010, increased 28.6% per year from 2010 to 2015, and increased 50.5% per year from 2015 to 2017.
Wang, 2020 (14)	Florida Drug-Related Outcomes Surveillance and Tracking System	2016–2018	Polysubstance-involved deaths with distinction between "co-involved" and "present" drugs	Cocaine-related deaths increased from 1,739 (2016) to 3,027 (2017), and the proportion of these deaths involving fentanyl rose from 32.6% (2016) to 52.4% (2017).

Abbreviation: APC, annual percent change.

Table 2.

Selected Drug Enforcement Administration Reports, United States

First Author, Year (Reference No.)	Design	Primary Outcome	Key Findings
Harm Reduction Ohio, 2019 (23)	Serial cross-sectional analysis of crime laboratory data from Ohio Bureau of Criminal Investigation in 2018	Association between risk of fentanyl contamination and size of cocaine package	Cocaine confiscations of 100 g or more were free of fentanyl. Three midsize packages of 99, 85, and 35 g were positive for fentanyl. The presence of fentanyl continued to increase as the size of package decreased, and 14.1% of cocaine packets less than one-tenth of a gram contained fentanyl.
DEA, National Drug Threat Assessment, 2019 (17)	Integration of reporting from law enforcement, intelligence, and public health agencies	Assessment of threat posed by domestic and international drug trafficking	Cocaine: Availability is increasing, along with export quality. Price has seen an overall decrease from 2012–2018. Treatment Episode Data Set shows that admissions for treatment have declined over 78%. Methamphetamine: Price has decreased, while potency has increased, indicating increased availability.
DEA Bulletin, 2018 (21)	Analysis of seized cocaine in Florida from 2016–2017	Contamination of cocaine in Florida	Cocaine and fentanyl combination found in 180 exhibits of cocaine in Florida, although the number of cocaine exhibits without fentanyl was unclear. Report also cites Florida's Medical Examiners Commission as reporting that 2,499 of the 2,882 state cocaine deaths involved cocaine in combination with another drug.
DEA Bulletin, 2018 (22)	Analysis of seized cocaine in Pennsylvania from 2015–2017	Contamination of cocaine in Pennsylvania	Analysis of 30,914 cocaine exhibits. Noted a 112% increase from 2016 to 2017 of 63 to 134 exhibits.

Abbreviation: DEA, Drug Enforcement Administration.

Table 3.

Selected Case Reports of Combined Fentanyl and Stimulant Exposures, United States

Location	Month/Year	Type of Stimulant	No. of Overdoses	Time Period, hours	Fatalities	Context
New Haven, Connecticut	June 2016	Cocaine	12	8	3	Route of intoxication unknown; most likely insufflation. Product found to be fentanyl with trace cocaine.
British Columbia, Canada	July 2016	Crack cocaine	43	96	1	Patients had smoked crack cocaine. Select samples tested by the Health Canada Drug Analysis Service positive for fentanyl.
San Diego, California	September 2018	Cocaine	5	48	3	Patients insufflated what was believed to be cocaine laced with fentanyl.
Philadelphia, Pennsylvania	2018	Cocaine	18	96	3	Patients had smoked crack cocaine. Fifteen individuals had confirmed fentanyl exposure and absence of other opioids.
Fresno, California	January 2019	Cocaine	4	48	1	Route of intoxication reported as insufflation. Three blood and urine samples positive for fentanyl.
Chico, California	January 2019	Cocaine	15	24	1	Postmortem testing confirmed fentanyl. Toxicology reports for 14 other cases unavailable, though in close proximity to Fresno and with similar presentations.

Table 4.

Clinical Studies on Increasing Methamphetamine Use Among Individuals Using Opioids and Opioid Use Among Individuals Using Methamphetamine, United States

First Author, Year (Reference No.)	Design and Data	Population	Primary Outcome	Key Findings
Al-Tayyib, 2017 (24)	Serial cross-sectional analysis of individuals recruited from National HIV Behavioral Surveillance System	Aged 18 years or older, had injected drugs during the preceding 12 months, resided in Denver, Colorado, metropolitan area	Differences among heroin injection, methamphetamine injection, and combined injection	Reports of methamphetamine as the most frequently injected drug increased from 2.1% (2005) to 29.6% in (2015); 296 of the 592 participants reported injecting both heroin and methamphetamine in the past 12 months.
Cicero, 2020 (46)	Serial cross-sectional analysis of individuals entering treatment centers for opioid use disorder, 2011–2018	Individuals admitted to one of 270 substance use treatment centers in the Key Informant network belonging to the Survey of Key Informants' Program (n = 15,741)	Temporal trends in opioid drug use, nonopioid drug use, and polysubstance use	Prevalence of methamphetamine use significantly increased by 85%. The average number of unique, nonopioid drugs used in the past month significantly increased for people who use heroin/nonprescription fentanyl, from 2.3 to 2.5.
Ellis, 2018 (30)	Serial cross-sectional analysis of individuals entering a substance use treatment program, 2011–2017	Individuals ≥18 years of age admitted to substance use treatment centers in the Key Informant network belonging to the Survey of Key Informants' Program (n = 13,521)	Prevalence and motivation for opioid and methamphetamine use	Percentage of people who use opioids reporting methamphetamine use doubled from 18.8% (second quarter 2011) to 34.2% (first quarter 2017), with increases attributed to increased community accessibility as well as appeal of high from dual use.
Glick, 2018 (44)	Serial cross-sectional analysis of PWID in King County, Washington, 2009–2017	Clients of Seattle and King County NSEP and Seattle-Area NHBS Injection Drug Use (NSEP, n = 2,135, 2009–2017) (NHBS, n = 1,709, 2009–2015)	Trends in methamphetamine use and injection equipment sharing in King County among MSM and non-MSM PWID	Percentage of people who inject methamphetamine reporting combined use with opioids increased from 18% in 2009 to 31% in 2017 among MSM and from 10% to 53% among non-MSM.
Jones, 2019 (42)	Serial cross-sectional analysis of individuals responding to the National Surveys on Drug Use and Health, 2015–2018	Individuals ≥12 years of age that were interviewed in person about the use of drugs, alcohol, and tobacco (n = 171,766)	Prevalence and characteristics of methamphetamine use	Odds of reporting past-year prescription opioid misuse were significantly elevated for adults reporting methamphetamine use (aOR = 2.17, 95% CI: 1.66, 2.84) and past-year heroin use (aOR = 5.10, 95% CI: 3.63, 7.17).
Jones, 2020 (47)	Serial cross-sectional analysis of TEDS, 2008–2017	Individuals ≥12 years of age admitted to substance use treatment centers receiving federal funding (n = 15,747,334)	Trends and characteristics associated with methamphetamine use at treatment admission	Reports of smoking as the route of use of methamphetamine decreased to 58.8% of admissions from 67.3%. Injection was reported in 28.4% of admissions, up from 17.5%. Reports of heroin use increased from 5.3% of admissions to 23.6%, and prescription opioids increased from 3.8% to 8.3%.
Jones, 2020 (48)	Serial cross-sectional analysis of TEDS, 2008–2017	Individuals ≥12 years of age admitted to substance use treatment centers receiving federal funding (n = 3,547,977)	Heroin treatment admissions involving methamphetamine	Percentage of heroin treatment admissions reporting methamphetamine use increased from 2.1% (2008) to 12.4% (2017), with highest prevalence among individuals 12–24 years of age.

Abbreviations: aOR, adjusted odds ratio; CI: confidence interval; HIV, human immunodeficiency virus; MSM, men who have sex with men; NHBS, National HIV Behavioral Surveillance; NSEP, needle and syringe exchange program; PWID, people who inject drugs; TEDS, Treatment Episode Data Set.

Table 5.

Clinical Studies on Fentanyl/Stimulant Exposure, United States

First Author, Year (Reference No.)	Design	Population	Primary Outcome	Key Findings
Amlani, 2015 (16)	Cross-sectional analysis of surveys of demographics and substance usage and UDTs	Clients at harm reduction sites in British Columbia, Canada (n = 242)	Correlation of demographics and substance use with positive fentanyl UDTs	Crystal methamphetamine was most significantly correlated with positive fentanyl UDTs. Odds ratio = 3.50, 95% confidence interval = (1.77, 6.86). No other variables were significantly correlated.
Karamouzian, 2020 (37)	Cross sectional analysis of UDTs	Clients of harm reduction sites in British Columbia, Canada (n = 303)	Compare reports of known or unknown fentanyl use with UDT results	Of 303 clients, 117 (38.7%) reported known fentanyl use, 66 (21.7%) had unknown fentanyl use, and 120 (39.6%) had no recent fentanyl use.
LaRue, 2019 (49)	Serial cross-sectional analysis of UDTs, 2013–2018	Convenience sample of tests from US health-care practices (20% substance use treatment, 33.5% pain management, 23.7% primary care, 10% behavioral health, 6% ob/gyn, 6% other) (n = 1,000,000)	Nonprescribed fentanyl among cocaine- or methamphetamine-positive urinalysis results	Nonprescribed fentanyl increased from 0.9% to 17.6% among cocaine-positive results and from 0.9% to 7.9% among methamphetamine-positive results.
Twillman, 2020 (50)	Serial cross-sectional analysis of UDTs, 2013–2019	Convenience sample of tests from US health-care practices (22.67% substance use treatment, 33.25% pain management, 22.8% primary care, 13.25% behavioral health, 1.76% ob/gyn, 6.27% other) (n = 1,050,000).	Nonprescribed fentanyl among cocaine- or methamphetamine-positive urinalysis results	Nonprescribed fentanyl increased from 5.3% to 33.5% among cocaine-positive results and from 2.2% to 30.4% among methamphetamine-positive results. Fentanyl among methamphetamine-positive results and among cocaine-positive increased significantly from 2016–2019 (P < 0.001).

Abbreviations: ob/gyn, obstetrics/gynecology; UDT, urinary drug test.