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## The Rise of Illicit Fentanyl, Stimulants and the Fourth Wave of the Opioid Overdose Crisis

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### Abstract

**Purpose of review:** This review provides an update on recent published literature on the rise of illicit fentanyl, risks for overdose, combinations with other substances, e.g. stimulants, consequences and treatment.

**Recent findings:** Overdose due to illicit synthetic opioids (e.g. fentanyl and fentanyl analogs) continues to rise in the US both preceding and during the COVID-19 pandemic. Fentanyl-related overdose is rising in new geographic areas e.g. the western US. Stimulant-related overdose is also increasing nationwide driven by methamphetamine and cocaine. Polysubstance use, e.g. the use of a stimulant along with an opioid is driving stimulant-related overdose. Other medical consequences of injection drug use are rising including HIV and hepatitis C infections. Medication approaches to treating opioid use disorder remain the standard of care and there are new promising pharmacological approaches to treating methamphetamine use disorder.

**Summary:** A ‘fourth wave’ of high mortality involving methamphetamine and cocaine use has been gathering force in the US. Availability and use of illicit fentanyl are still the major drivers of overdose deaths and the current rise in stimulant-related deaths appears entwined with the ongoing opioid epidemic.

### Keywords

Fentanyl; Stimulants; Overdose; HIV; Polysubstance use

### Introduction

The COVID-19 pandemic of 2020–21 has over-shadowed another escalating crisis, that of drug overdose. In the US from 1999 to 2018, more than 750,000 persons have died from a drug overdose; the majority of which involved an opioid [1]. The rising tide of these overdose deaths has been described as a triple wave phenomenon: deaths due to prescription

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Conflicts of interest:

Dr. Ciccarone has received compensation in the past 36 months for: being on the Scientific Advisory Board for Celero Systems; providing expert testimony for Motley Rice LLP; being a one-time consultant for Mallinckrodt Pharmaceuticals; and being a one-time consultant for Nektar Therapeutics; all outside the submitted work.

opioids (i.e. natural and semi-synthetics) rose from 1999 and peaked in 2017; heroin-related overdose started rising significantly after 2010 and also peaked in 2017; synthetic opioids-related (predominately illicit fentanyl and fentanyl analogs) overdose rose dramatically 2014 to present [2–4]. This review provides an update on recent published literature on the rise of illicit fentanyls, risks for overdose, combinations with other substances, e.g. stimulants, consequences and treatment.

## Current trends in drug overdose

The triple wave overdose phenomenon continues past 2018 with new and concerning permutations. As of this writing, the most recent formal US Centers for Disease Control and Prevention (CDC) report on overdose reveals a slight overall decline in opioid-related fatalities from 2017 to 2018 [1]. Deaths declined for all opioids (2%), prescription opioids (14%) and heroin (4%), yet increased for synthetic opioids (10%) in this time period. The overall downward signal was driven by declines in deaths related to prescription opioids. Seventeen states had noted declines in deaths due to prescriptions opioids and none had increases [5]. This decline has been attributed to reduced prescribing volume, esp. high dose (i.e. > 90 MME) prescribing [6]. A sudden decline, from 2017–2018, in availability of carfentanil, a highly potent synthetic opioid, has also been suggested as a downward driver of opioid deaths during this short time period [7].

This decline however, was just a temporary reprieve. Provisional data from the CDC show increasing overdose mortality in 2019 and early 2020 [8]. For the 12-month period ending December 31, 2019, there were 50,178 reported opioid-related overdoses, a 6.5 percent increase from the 12-month period ending December 2018 (47,096). Year-over-year increases were noted in synthetic opioid-related overdose (up 16.1% to 36,603) along with decreases in heroin-related (down 6.5%) and prescription opioid-related (down 5.2%) overdose. As of this writing, the CDC provisional overdose data is reporting up to the 12-month period ending September, 2020. Comparing that past 12-month period to the one ending September, 2019, we see a more dramatic picture. Overall opioid-related overdose deaths increased 33.9 percent (September, 2020: 64,472 deaths), driven by a dramatic increase in synthetic opioid-related overdose – a *53.1 percent increase* (September, 2020: 52,157 deaths). Prescription opioid-related overdose shows the first increase in years, 10.6 percent y-o-y. And heroin-related overdose continued a downward trend, declining 3.6 percent.

The trend in increasing overdose predates the beginning of the COVID-19 pandemic. Comparing the 12-month period ending February, 2020 with that of February, 2019, The CDC provisional data reveal a 10.1 percent y-o-y increase in all opioid overdose, driven by an increase in that due to synthetic opioids (up 21.4%); while declining in prescription opioid (down 2.2%) and heroin (down 7.3%) categories. Compared with the above data, the notion that overdose trends greatly accelerated during the early COVID era, March through September 2020, is supported [9–11].

## The continued rise of illicit fentanyls

The overdose epidemic is currently being driven by “synthetic opioids, not including methadone,” a CDC classification which currently includes predominately illicitly manufactured fentanyl and a rising number of chemical analogs of fentanyl [5, 12]; there are also small but rising proportions of non-fentanyl synthetic opioids e.g. isotonitazine and bupropion [13]. The rise in availability and use of fentanyls represents a heightened structural risk environment for persons who use drugs (PWUD) [3]. Understanding the supply forces is key to understanding this rising risk environment.

Historically, there have been a number of US overdose events where a fentanyl was implicated [14, 15]. However, the wave of overdose deaths attributed to illicit fentanyls since 2013 is unprecedented. The current rise of fentanyls is considered a positive supply shock, i.e., a supply-driven more than demand-driven event [16]. Evidence for this includes: fentanyls are generally sold as ‘heroin’ i.e., fentanyl-adulterated or substituted heroin (FASH) [17, 18]; wholesale distribution of FASH [19] and related overdose is regionally distributed with the Northeast and Midwest most affected followed by the South [20–22]; these are illicit products not diverted pharmaceuticals [19]; early on there was mixed desirability for FASH [17, 18, 23, 24]; and there is market incentive in that dose-for-dose fentanyl is cheaper to produce than heroin [3, 25]. The reasons why fentanyls were introduced during the current surge is complex; one argument, based on prior episodes, is that they replace heroin during periods of relative shortage [16, 26]. In *The Future of Fentanyl and other Synthetic Opioids*, Pardo et al highlight a confluence of supply-side factors to explain the rise of fentanyls, e.g., more-efficient synthesis methods, internet communication and commerce, and out-paced regulatory environments in source countries e.g. China [27].

The fentanyls problem is spreading. Globally, fentanyls have been detected or implicated in deaths in Europe, esp. Estonia, Latvia and Sweden [27]. Canada has been particularly hard hit by fentanyl-related overdose [28]. The spread of fentanyls is also happening in the US. From 2014–2017, the fentanyls problem was initially regionally isolated to the US Northeast and Midwest, followed to a lesser degree in the South [20, 22]. However, from 2017 to 2018 the region that had the highest relative change in overdose rates due to synthetic opioids was the West [5]. Examining CDC data, Shover and colleagues found the share of U.S. synthetic opioid overdose deaths attributable to seven western jurisdictions more than tripled from 2017 to 2019 [29]. Supply side data also support increasing fentanyls supply, esp. in the form of counterfeit pills, to the West [30]. And the supply is diversifying from China and Mexico to include India as a source country [31].

Demographic shifts in use and overdose patterns are notable. Overdose mortality rates were higher among non-Hispanic Whites and those aged 45–54 during the first wave of the overdose phenomenon [32]. This has been partly attributed to racial healthcare disparities and reduced access to opioid pain medications among Black and Latino populations [33]. Heroin use increased among non-Hispanic Whites, but declined in non-White groups during the first two waves [33, 34]. The overdose curve also shifted to younger age groups during the heroin-related overdose wave [35]. There is increasing concern that rates of overdose are

climbing among African-Americans; this notably first reported by the Chicago Urban League in their report: *Whitewashed: The African American Opioid Epidemic* [36]. From 2000–2013, drug poisoning rates involving heroin were highest among non-Hispanic Blacks 45–64 compared with other groups [37].

Moving into the fentanyl wave, while Whites have the highest population rates of synthetic opioid-related mortality, Blacks and Hispanics living in metro areas have greater rate increases in recent years [38]. Addressing racial disparities in healthcare esp. access to culturally sensitive and affordable substance treatment, is needed [39–41].

Demand for fentanyl has been described as “polarized”: while some PWUD seek out fentanyl others try hard to avoid it [16, 17]. FASH, sold as ‘heroin’, continues in the east [18], but fentanyls are increasingly sold as ‘fentanyl’ in the westward expansion of its supply (unpublished data). Two recent surveys of PWUD in four eastern US locations establish a range of preference for fentanyl between 27 and 44 percent in the two samples [42, 43]. It is unknown what the preference for fentanyl is among PWUD living in western US locations.

## Risks for overdose

There are a few individual-level risk factors for opioid, including heroin, overdose that are well known including: post-incarceration and post-detoxication return to use, polysubstance use, and injection drug use [44]. Little is known about additional individual risk factors for fentanyl-related OD. In a recent study of a sample of persons seeking treatment for opioid use disorder (OUD), those reporting overdose events both prior to and during the fentanyl era had post-traumatic stress disorder and fentanyl seeking as independent risks [45]. Frequent drug combining was the only independent risk factor for those reporting overdoses only in the third-wave fentanyl era [45].

Social and structural level risks are important to consider. A social determinants of health, aka “root causes,” argument has been proposed to examine and address the historic opioid overdose crisis [46]. Park et al [44] review the social risk factors for overdose, including incarceration, unstable housing [47] and public injecting [48], as well generational drivers e.g., deindustrialization, economic stagnation, and class-based despair [49–51]. The relationships between economic conditions and policies and the overdose crisis are getting increasing attention. Percent of the population living in poverty is associated with both prescription opioid- and heroin-related overdose hospitalizations [52]. Geographic and demographic variation in overdose rates can be partially explained by social-economic forces such as low social capital [53], economic and family distress [54], unemployment [55] and loss of jobs due to free trade policies [56]; this geographic heterogeneity, esp. as it relates to rural areas, is well explored by Rigg and colleagues [57]. These forces have synergistically put a whole generation at risk for ‘diseases of despair,’ including drug overdose [46], and continue the upward impetus on a 38-year exponential increase in drug mortality [58]. Recently, the COVID pandemic has magnified the risks that socially marginalized Americans, including PWUD, face including inequitable access to healthcare and disruptions in treatment and prevention services [9, 44, 59].

Structural forces leading to increased overdose risk include aspects of the drug supply [2]. Synthetic opioids enhance the risk environment by increased potency, vicissitudes in product and potency [3], and street marketing strategies [16–18]. Compared to heroin, fentanyl is 30–40 times more potent by weight [3]. Many fentanyl analogs of varying potency have emerged, ranging from approximately three times the strength of morphine (acetyl-alpha-methyl fentanyl) to 10 000 times stronger (carfentanil) [60]. The number of synthetic opioids continues to grow; a forensic chemical company currently sells reference standards to laboratories to test for 250 synthetic opioid compounds, including more than 210 fentanyl analogs [61]. Variations in fentanyl and fentanyl analogs by geography and over time have strong correlations with overdose [14]. The expansion of supply of illicit fentanyls to include western US states creates new geographic vulnerabilities.

Both supply and socioeconomic factors combined help explain the wide variation in geographic and sociodemographic overdose risk [62, 63]. These intertwined supply and demand forces likely conspire to creating the historic levels of overdose risk in the current triple wave crisis [2].

### The fourth wave: Stimulants in combination

While opioids have dominated the ‘triple wave epidemic’ of drug-related overdose deaths, a ‘fourth wave’ of high mortality involving cocaine and methamphetamine use has been gathering force. There has been a major rise in drug-related overdose deaths: a 3-fold increase for cocaine-related mortality (from 1.4 to 4.5/100,000 pop.) and a five-fold increase for psychostimulant-related (mostly methamphetamine) mortality (from 0.8 to 3.9/100,000), 2012–18 [1]. Rates for methamphetamine-involved deaths are higher among men and non-Hispanic American Indian or Alaska Native and non-Hispanic White individuals [64].

The drivers of rising stimulant mortality are poorly understood at present. Nationally the prevalence of past-year cocaine use in 2018 is estimated at 5.5 million, increasing since 2013 [65]. Methamphetamine use prevalence increased nationally 2016–18, but with considerable regional and demographic variation [66]. Methamphetamine use is rising in Massachusetts, a state in the US Northeast, a region with historically lower supply [67]. Methamphetamine supply, purity and potency have increased nationally to historically high levels following shifts in source and chemical production [68]. During the COVID-19 era, while methamphetamine supply dipped early on, by August, 2020 law enforcement seizures had peaked above pre-COVID-19 levels [69].

Unlike previous stimulant epidemics which tended to alternate with those of other drugs, the current rise in stimulant-related deaths appears entwined with the ongoing opioid epidemic [66, 70–72]. Polydrug use has long been implicated in drug overdose deaths, particularly when opioids are involved [73]. Co-use of stimulants and opioids is increasingly common [66], e.g., the 3-fold increase in methamphetamine use among those reporting past-month heroin use in a national survey, 2015–17 [74]; and this may partially explain the rise in stimulant-related deaths. Co-use with fentanyls is particularly concerning. Nationally, synthetic opioids are involved in deaths attributable to cocaine (40%) and psychostimulants (14%) [71]. In Massachusetts, 34% of opioid-related deaths had co-occurring

methamphetamine [75]. The reasons for co-use of potent opioids and stimulants in this historic era remain unelucidated.

## Consequences other than overdose

Reversing long-term declines in national HIV trends [76], HIV diagnoses have begun to rise among persons who inject drugs (PWID) [77]. This following a number of documented injection-drug-related HIV clusters around the country [78]. A two-fold increase in acute hepatitis C (HCV) rates nationally was seen as corresponding to the rise in treatment admissions for opioid use disorder during the first two waves of the opioid overdose epidemic [79]. In line with the third and fourth waves, rises in local availability and use of fentanyl [80] and methamphetamine [66] use appear related to local HIV outbreaks [78]. In a recent national study, use of both opioids and methamphetamine was associated with higher prevalence of injection of drugs and viral hepatitis compared with opioid use alone [81]. Another study confirmed this: combination stimulant and heroin use and injection drug use were independent predictors of blood-borne virus infection [82].

Other injection-drug-related problems appear to be on the rise. Rates of hospitalizations for skin and soft tissue infections [83] and infectious endocarditis [84] have gone up during the past two decades. Methamphetamine use is associated with a number of chronic morbidities [85].

## Treatment issues

A comprehensive public health approach to address the opioid overdose crisis has been advocated for. Aspects of this approach include increased spending on treatment and harm reduction, stigma-reduction campaigns, and criminal justice policy reform among other prevention, treatment and policy ideas [86]. Medications to treat opioid use disorder, including methadone and buprenorphine, have strong evidence for efficacy, yet disparities in access and biases against medication treatment remain barriers to full coverage [87]. New approaches in pharmacotherapy for methamphetamine use disorder hold some promise [88, 89].

Supply side approaches have mixed evidence of effectiveness [90]. In the current situation, interdiction efforts are more challenged by the high potency-to-volume of fentanyls [2]. Vicissitudes in fentanyls' supply are correlated with mortality and real-time surveillance may be exploited as part of an early warning system [14]. Given the vicissitudes and increasing unknowns of the street drug supply, calls for improved surveillance [14, 91], advanced harm reduction [92] including remote access [93], drug checking [94–97] and supervised consumption spaces are growing in chorus [15]. Integration of SUD treatment and HIV prevention, and co-location of services, is needed to curb rising HIV and hepatitis rates [98]. Workforce development, including building diversity, equity and inclusion, in addiction medicine is the call of a generation [99, 100].

## Conclusion

The opioid overdose crisis continues to worsen and evolve: fentanyl is spreading westward in the US and a new wave of stimulant and polydrug use is upon us. The COVID-19 pandemic is accelerating the overdose crisis as well as its racial and economic inequities. Addressing disparities in access to treatment and prevention services as well as criminal justice reforms are necessary [41] to address this persistent syndemic [101]. Reducing morbidity and mortality will require significant expansion of resources for treatment and prevention [102].

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**Key points:**

- The historic US overdose epidemic continues
- The COVID-19 pandemic is accelerating the overdose crisis as well as its racial and economic inequities
- Illicit synthetic opioids, e.g., fentanyl and fentanyl analogs have expanded westward
- A ‘fourth wave’ of overdose mortality is growing due to stimulant- and poly-substance-related deaths