



## Research paper

## Toxicosurveillance in the US opioid epidemic

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## Introduction

The opioid epidemic presents an ever-changing epidemiological, clinical, and forensic landscape that poses a significant challenge to regulators and legislators. Heroin is a long-standing contributor to opioid related death, but its use and consequences have markedly escalated over the past 20 years. US national surveillance mortality data suggests heroin deaths have more than quintupled since 2000, with 10,574 deaths reported in 2014 (Compton, Jones, & Baldwin, 2016). Changes in the heroin marketplace including increased purity, increased availability, and adulteration with synthetic opioids, specifically fentanyl and its congeners, contribute to its toxicity.

Although historically a drug used primarily in lower socioeconomic minority areas, heroin is increasingly abused across all demographic groups (Unick & Ciccarone, 2017). As a result, between 2002 and 2013, heroin overdose death rates in the US nearly quadrupled, from 0.7 deaths to 2.7 deaths per 100,000 population (Hedegaard, Chen, & Warner, 2015), totaling more than 8200 deaths in 2013 (Centers for Disease Control and Prevention, July 7, 2015). Between 2013 and 2014, age-adjusted rate of death increased by 26% (Rudd, Aleshire, Zibbell, & Gladden, 2016) and between 2014 and 2015, heroin overdose death rates increased by 20.6%, causing nearly 13,000 deaths in 2015 (Centers for Disease

Control and Prevention, January 26, 2017). In 2015, surveillance through the National Survey on Drug Use and Health (NSDUH) noted that 828,000 people aged 12 or older reported heroin use within the past year. Though slightly decreased from 2014 data, this represents an increase of 82% since 2013 (Center for Behavioral Health Statistics and Quality, 2015, 2016). NSDUH, which is administrated through the Substance Abuse and Mental Health Services Administration (SAMHSA), involves in-person interviews with approximately 70,000 households regarding personal drug use habits (National Survey on Drug Use and Health (NSDUH)). Despite the methodological limitation of reporting bias, this finding is concerning because, not surprisingly, rates of heroin use and dependence have a strong positive correlation with heroin-related deaths (Jones, Logan, Gladden, & Bohm, 2015).

Heroin overdose deaths have increased in many regions across the US, specifically the Northeast and areas of the Midwest. The National Drug Threat Assessment Survey of state, local, and tribal law enforcement agencies assessed the greatest reported drug threat by jurisdiction with respect to availability, demand, transportation, and distribution. In 2007, only 8% of respondents identified heroin as the largest drug threat in their jurisdiction. By 2016, heroin led all other drugs, with 45% of respondents identifying it as the largest drug threat (US Drug Enforcement Administration Intelligence Report, June 2016). Also, nine of the 21 domestic Drug Enforcement Administration (DEA) Field Divisions ranked heroin as the largest drug threat, with nine more divisions ranking it as the second largest threat (US Drug Enforcement Administration Intelligence Report, June 2016). The distribution of heroin throughout the US is also changing.

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Historically, the Mississippi River was the transition zone that divided heroin by type and origin. To its west, heroin was predominantly Mexican black tar and brown powder heroin, whereas eastern markets received Asian and South American derived white powder heroin (Ciccarone, Unick, & Kraus, 2009). Mexican traffickers have expanded their markets and are gaining a larger share of the Northeast and Midwest markets (US Drug Enforcement Administration Intelligence Report, June 2016).

There has been a significant change in the demographics of heroin use over the past two decades. Previously, in 2000, non-Hispanic black persons aged 45–64 had the highest rates of poisoning deaths involving heroin (2 per 100,000 population). However, the demographic balance has changed with the movement of heroin into non-urban communities along with use by younger people. Heroin use has more than doubled in the past 10 years among those aged 18–25 years (Centers for Disease Control and Prevention, July 7, 2015). In 2013, non-Hispanic white persons aged 18–44 had the highest rates of heroin-related death at 7.0 per 100,000 population (Hedegaard et al., 2015). This trend continued in 2015 when males aged 25–44 had the highest rates of death from heroin at 13.2 per 100,000 population, an increase of 22.2% from 2014 (Centers for Disease Control and Prevention, January 26, 2017). Increased use is also being seen among groups with historically low rates of heroin use, including women, the privately insured, and those with higher incomes (Centers for Disease Control and Prevention, January 26, 2017).

The heroin overdose epidemic is intertwined with the larger prescription opioid overdose epidemic (Unick, Rosenblum, Mars, & Ciccarone, 2013). Patients who abuse or who are dependent on prescription opioids are 40 times more likely to abuse or become dependent on heroin compared to those who do not use opioids for non-medical reasons (Jones et al., 2015). Among recent cohorts of heroin users entering treatment, nearly 75% report having abused prescription pain relievers within the past year (Centers for Disease Control and Prevention, January 26, 2017; Hughes et al., 2016, September). Another study reports that heroin users are 3.9 times as likely to report non-medical use of opioids in the previous year, and 2.9 times as likely to meet the criteria for abuse or dependence on opioids compared to persons who did not use heroin (Becker, Sullivan, Tetrault, Desai, & Fiellin, 2008).

Although only 4% of prescription opioid users are expected to become heroin users, the substantial number of prescription drug misusers (3.8 million with past month misuse of prescription pain relievers (Center for Behavioral Health Statistics and Quality, 2016)), highlight the significance (Compton et al., 2016; Jones et al., 2015). Between 2010 and 2012, the death rate from heroin overdose in 28 states more than doubled from 1.0 to 2.1 per 100,000 population (increase from 1779 to 3635 deaths) whereas deaths from prescription opioid pain relievers slightly decreased from 6.0 to 5.6 per 100,000 population. For prescription drug abusers who are used to using prescription opioids with known constituents and concentrations, the use of heroin with its unpredictable purity and potential for adulteration creates significant problems. Not surprisingly, the risks of death related to prescription opioid misuse compared to heroin use are not the same. In 2014, 10.3 million people used prescription pain relievers non-medically as opposed to 914,000 people who used heroin (Center for Behavioral Health Statistics and Quality, 2015). Despite a greater than 10-fold difference in number of users, the risk of death from heroin is much greater. In fact, of the 18,893 overdose deaths related to opioid analgesics in 2014, 10,574 were attributable to heroin (Compton et al., 2016).

Factors likely associated with the increased use of heroin include decreased price compared to prescription opioids and higher purity (Mars, Bourgois, Karandinos, Montero, & Ciccarone, 2014). The US DEA reports that the amount of heroin confiscated at

the southwest border of the US as  $\leq 500$  kg annually during the years 2000–2008. This amount more than quadrupled to 2196 kg in 2013 (Centers for Disease Control and Prevention, January 26, 2017). Across the US, the National Seizure System reports that heroin seizures have increased by 80% over 5 years to 6722 kg in 2015 (US Drug Enforcement Administration Intelligence Report, June 2016). Heroin traffickers are also transporting heroin in much larger amounts than previously.

The most substantive factor contributing to the rising recent death rates related to heroin is its adulteration with synthetic opioids, specifically fentanyl and its analogs. Fentanyl is about 100 times more potent than morphine and 30–50 times more potent than heroin. Historically, fentanyl and fentanyl analogs were often combined with or sold as heroin, with or without the users' knowledge, resulting in microepidemics. For example, during a 3-month period from September to November 1988, Allegheny County, PA reported a 13-fold increase in opioid overdoses due to "China White" (adulterated with 3-methyl fentanyl) (Martin et al., 1991). In 2006, increased reports of overdoses in multiple different US states prompted the CDC to form an ad-hoc case finding and surveillance system to identify overdoses related to non-pharmaceutical fentanyl (NPF) in six states and local jurisdictions (Centers for Disease Control and Prevention, 2008). Between April 4, 2005 and March 28, 2007, they identified 1013 deaths related to NPF, leading to a DEA raid and closure of a main NPF production facility in Toluca, Mexico in May 2006 and regulation of *N*-phenethyl-4-piperidone, a chemical precursor used in the production of NPF in April 2007 (Centers for Disease Control and Prevention, 2008).

Though these steps taken were effective at curbing NPF in the mid-2000s, it was accurately predicted that given the ease of production and availability of obtaining precursors for production, NPF was likely to be a recurring problem. In late 2013 and 2014, the DEA National Heroin Threat Assessment Summary noted spikes in overdose deaths related to fentanyl and its analog, acetyl-fentanyl, most predominantly in the eastern US, where white powder heroin is used (Jones et al., 2015; US Drug Enforcement Administration Intelligence Report, June 2016). NPF was often mixed with white powder heroin or sold disguised as heroin. In March 2015, the US DEA issued a nationwide alert regarding the dangers of fentanyl and fentanyl analogs and identified them as significant threats to public health and safety (US Drug Enforcement Administration, March 2015). Between 2012 and 2014, the National Forensic Laboratory Information System (NFLIS) reported a more than 8-fold increase in the total number of fentanyl drug seizures (CDC Health Alert Network, October 2015). The NFLIS, part of the US DEA, systematically collects and analyzes the results from law enforcement chemistry laboratories across the country (Drug Enforcement Administration & Diversion Control Division). The observation that increased numbers of drug seizures positively correlates with opioid overdose deaths has been reemphasized in 27 states in the US. An increase in drug products obtained by law enforcement that tested positive for fentanyl increased by 426% (from 1015 in 2013 to 5343 in 2014) and deaths from synthetic opioids increased 79% (from 3105 in 2013 to 5544 in 2014) over the same time period (including fentanyl and other synthetic opioids such as tramadol—although these numbers are largely driven by NPF as identified by supplementary data in eight high burden states) (Gladden, Martinez, & Seth, 2016). Law enforcement encounters where the drug is submitted for analysis that have tested positive for NPF have sharply increased between 2014 and 2015, from 5343 to 13,882 (Centers for Disease Control and Prevention, August 24, 2016). In addition, since 2014 US law enforcement agencies have been seizing more 'counterfeit medications' containing fentanyls (US Drug Enforcement

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