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Naloxone For Heroin, Prescription Opioid, And Illicitly Made Fentanyl Overdoses: Challenges And Innovations Responding To A Dynamic Epidemic

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Abstract

Community-based overdose prevention programs first emerged in the 1990's and are now the leading public health intervention for overdose. Key elements of these programs are overdose education and naloxone distribution to people who use opioids and their social networks. We review the evolution of naloxone programming through the heroin overdose era of the 1990's, the prescription opioid era of the 2000's, and the current overdose crisis stemming from the synthetic opioid era of illicitly manufactured fentanyl and its analogues in the 2010's. We present current challenges arising in this new era of synthetic opioids, including variable potency of illicit drugs due to erratic adulteration of the drug supply with synthetic opioids, potentially changing efficacy of standard naloxone formulations for overdose rescue, potentially shorter overdose response time, and reports of fentanyl exposure among people who use drugs but are opioid naïve. Future directions for adapting naloxone programming to the dynamic opioid epidemic are proposed, including scale-up to new venues and social networks, new standards for post-overdose care, expansion of supervised drug consumption services, and integration of novel technologies to detect overdose and deliver naloxone.

Keywords

naloxone; overdose; fentanyl; synthetic opioids

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1. Introduction

The groundwork for the public health concept that opioid overdose death is preventable in the setting of illicit opioid use was first laid with research articles published in the 1970s describing the risk factors for opioid overdose (Brecher, 1972; Monforte, 1977). The first community-based overdose prevention programs for people who use opioids emerged in the 1990s (Darke, 2016). The key elements of these programs were the education of people who use opioids about how to reduce their overdose risk and equipping them with naloxone, the antidote to an opioid overdose, so that they could rescue each other. Since then, these programs have expanded substantially in the United States and Canada to become a leading public health intervention for the prevention of overdose mortality (Oluwajenyo Banjo et al., 2014; Wheeler et al., 2015).

These programs have emerged on a backdrop of a dynamic epidemic of opioid use and opioid overdose in the United States and Canada. In the 1990s and 2000s, expansion of the treatment of acute and chronic pain with prescription opioids was associated with concomitant rise in diversion of prescription opioids to the illicit market, opioid use disorders, and opioid overdose deaths (Centers for Disease & Prevention, 2011; Modarai et al., 2013; Piercefield, Archer, Kemp, & Mallonee, 2010; Shah, Lathrop, Reichard, & Landen, 2008). As the connection between increased opioid prescribing and rising overdose deaths was recognized and efforts were made to limit opioid prescriptions, heroin use increased, likely to meet the rising demand for illicit opioids (Rudd, Aleshire, Zibbell, & Gladden, 2016). Along with increased heroin use, the introduction of illicitly manufactured fentanyl and other synthetic opioids into many illicit opioid markets has resulted in an acute surge in overdose deaths in many communities (Peterson et al., 2016; Rudd, Aleshire, et al., 2016). These changes have brought challenges and raised new questions about what was previously known regarding overdose and our response to it.

1.1 The Heroin Era

In the late 1990s and early 2000s, when community overdose education and naloxone rescue kits initially emerged among programs serving people who inject drugs (PWID), heroin was the primary opioid involved in overdose events. In the United States and Canada, most naloxone programs were based in syringe needle access programs (SNAPs) that served people who injected heroin. In the 1990s, SNAPs were recognized as an important evidence-based public health strategy to reduce HIV transmission and the medical complications from injection drug use, yet U.S. federal funding ban was not lifted, in part, until January of 2016. While some local and state health departments supported these programs to reduce HIV and hepatitis rates among PWID, many programs relied on volunteers, foundation and individual funding and operate without any support from health departments.

Programs distributing naloxone to PWID through SNAPs first emerged in the U.S. in Chicago in 1996, the Jersey Channel Islands in Europe in 1998, Berlin, Germany, in 1999, and New Mexico, in 2001 (Dettmer, Saunders, & Strang, 2001; Maxwell, Bigg, Stanczykiewicz, & Carlberg-Racich, 2006). Multiple ecological and other observational studies of community naloxone distribution programs demonstrated that PWID can learn overdose prevention and administer naloxone successfully (Doe-Simkins, Walley, Epstein, &

Moyer, 2009; Green, Heimer, & Grau, 2008; Seal et al., 2003; Seal et al., 2005; Tobin, Sherman, Beilenson, Welsh, & Latkin, 2009), and suggested potential ancillary benefits such as decreased substance use, social connection, and empowerment (Wagner et al., 2014; Wagner et al., 2010). San Francisco documented a dramatic reduction in heroin overdose mortality in the early 2000s, from approximately 180 heroin overdose deaths per year in the late 1990s to 10-11 per year from 2010-2012, although some of that decrease was a result of transitions to prescription opioids (Visconti, Santos, Lemos, Burke, & Coffin, 2015). Scotland's National Naloxone Programme, which started in 2011, was associated with a 36% reduction in the proportion of opioid-related deaths that occurred in the 4 weeks following release from prison (Bird, McAuley, Perry, & Hunter, 2016). Massachusetts demonstrated reduced opioid overdose mortality rates in communities where overdose education and naloxone distribution programs were implemented compared to communities where they were not implemented (Walley, Xuan, et al., 2013). Community overdose education and naloxone rescue programs have expanded substantially since the 1990s and are now present in 30 U.S. states (Wheeler et al., 2015).

Overdose education and naloxone rescue was not the only public health intervention associated with reductions in heroin overdoses. Baltimore documented a reduction in heroin overdose death that was attributed to expansion of methadone and buprenorphine treatment for opioid use disorder (Schwartz et al., 2013). Vancouver, Canada, responding to a dual epidemic of overdose and HIV infection that developed in the 1990s, opened North America's first supervised injection facility, Insite, in 2003. Research has demonstrated multiple benefits of Insite, including a substantial local reduction in opioid overdose mortality (Marshall, Milloy, Wood, Montaner, & Kerr, 2011). Since opening in 2003, no deaths have ever occurred at Insite.

1.2 The Opioid Analgesic Era

Increases in opioid prescribing drove rising opioid overdose death rates at the beginning of the 21st Century across the United States, resulting in the recognition of an opioid epidemic. Between 1999 and 2008, prescription opioid-related overdose deaths, sales of prescription opioids, and treatment admissions for prescription opioid use disorders, each increased by four-fold or more (Centers for Disease & Prevention, 2011). The rise in prescription opioid-related overdose deaths slowed in 2010, a year when the formulation of long-acting oxycodone was changed to make it harder to insufflate or inject (Cicero, Ellis, & Surratt, 2012), propoxyphene was taken off the market, and Florida restricted high volume opioid prescribing through pill mills (Dart et al., 2015; Kennedy-Hendricks et al., 2016; Larochelle, Zhang, Ross-Degnan, & Wharam, 2015; Rutkow et al., 2015). Prescription drug monitoring programs proliferated during this period as an effort to make opioid prescribing safer (Delcher, Wagenaar, Goldberger, Cook, & Maldonado-Molina, 2015; Green, Zaller, Rich, Bowman, & Friedmann, 2011; Paulozzi, Kilbourne, & Desai, 2011). In conjunction with these opioid stewardship initiatives, overdose education and naloxone rescue for people using prescription opioids was increasingly considered a necessary component of the response to the opioid epidemic. As a result, all but three U.S. states in 2016 have laws supporting naloxone provision to lay persons (Brodrick, Brodrick, & Adinoff, 2016). In recognizing opioid-related overdose as a major public health concern, the US Department of

Health and Human Services highlighted naloxone rescue kit access and emergency overdose response as one of three priority areas to address this crisis in 2015 (“HHS takes strong steps to address opioid-drug related overdose, death and dependence,” March 26, 2015). Though nation-wide systematic monitoring remains a challenge in Canada, similar increases in opioid prescribing and related harms were observed during the same time period (Fischer & Argento, 2012; Hospitalizations and Emergency Department Visits Due to Opioid Poisoning in Canada, 2016), with subsequent reductions in opioid prescribing following implementation of interventions, such as the adoption of prescription monitoring programs in the provinces of Ontario and British Columbia and delisting of long-acting formulations of oxycodone from public drug formularies in several provinces in 2012 (Murphy, Goldner, & Fischer, 2015).

Naloxone programming has demonstrated benefits in some localities in the context of escalating prescription opioid analgesic use and overdose. In San Francisco, for example, there was no increase in opioid overdose mortality during the period of expanding opioid access, notwithstanding data suggesting a large increase in the population of opioid injectors (San Francisco Sentinel Community Site (SCS) Drug Use Patterns and Trends, 2016, 2016). Nonetheless, a persistent number of opioid analgesic deaths – approximately 110 per year – led the local health department to offer naloxone prescriptions to patients on long-term opioids in selected primary care clinics. Some of the earliest efforts in naloxone co-prescription were made by Project Lazarus in Wilkes County, North Carolina, which saw a 70% decrease in prescription opioid-related overdose death rates during the implementation phase of the project from 2009 to 2010 (Albert et al., 2011). Naloxone co-prescribing was found to be acceptable to clinicians and it was associated with reductions in emergency department visits for opioid-related adverse events (Behar et al., 2016; Coffin et al., 2016).

These findings contributed to initiation of a national overdose education and naloxone distribution program through the Department of Veterans Affairs (Oliva et al., 2016) and informed the CDC chronic pain guidelines that encourage naloxone co-prescribing to patients on prescription opioids long-term for non-cancer pain (Dowell, Haegerich, & Chou, 2016).

1.3 The Synthetic Opioid Era

As opioid prescribing rates declined and novel opioid formulations that deter injection were developed, the United States and western Canada witnessed a dramatic increase in heroin overdose rates in the 2010s, during which time rates more than tripled (Illicit Drug Overdose Deaths in BC January 1, 2007– October 31, 2016 – October 31, 2016; Rudd, Seth, David, & Scholl, 2016). This brought attention back to illicit opioid users and the original target population of naloxone programming. Heroin use and heroin-related overdose have surged as people transition from prescription opioids (Mars, Bourgois, Karandinos, Montero, & Ciccarone, 2014; Rudd, Aleshire, et al., 2016; Unick, Rosenblum, Mars, & Ciccarone, 2013). However, the emergence of synthetic opioids in the illicit opioid markets (both traditional heroin and illicit prescription opioids) during this era have contributed to ongoing high overdose rates and presented new challenges to naloxone-based interventions.

Fentanyl, as an additive or substitute for heroin, offers several advantages or opportunities for individuals involved in the illicit drug trade. Because of the potency, it requires less bulk and weight to transport and distribute than heroin. It can be reliably manufactured from abundant chemical precursors in large quantities, whereas heroin requires an opium crop that must be produced in the open air. While fentanyl is currently the most popular illicitly manufactured opioid, there are many viable analogues that can be produced to evade distribution crimes (Suzuki & El-Haddad, 2017). People who use opioids may prefer to use fentanyl as it is highly lipid-soluble, thus rapid-acting, and 40 times more potent at the opioid receptor than heroin, which results in fast onset euphoria and pain relief. Many PWID describe the experience as like heroin, but more intense (Amlani et al., 2015; Ciccarone, Ondocsin, & Mars, 2017; Macmadu, Carroll, Hadland, Green, & Marshall, 2017). Like heroin, fentanyl has a half-life of approximately 3-7 hours (Trescot, Datta, Lee, & Hansen, 2008), however, the duration of action of fentanyl is briefer, only 30-60 minutes for an intravenous injection, compared to 4-5 hours for heroin. Heroin is lipophilic and therefore is transmitted rapidly to the central nervous system, however, once there it is converted to morphine, which is less lipophilic and therefore retained. However, fentanyl is highly and persistently lipophilic so it enters and exits the central nervous system rapidly. Therefore, fentanyl is both faster and shorter acting, and must be re-dosed frequently (meaning more injections per day).

Overdose deaths due to the use of illicitly manufactured fentanyl by people who use heroin have occurred sporadically for decades (Henderson, 1991; Martin et al., 1991). The first national outbreak of fentanyl-tainted heroin occurred across six jurisdictions in the eastern United States from 2005-2007, and accounted for an excess 1,013 deaths (Centers for Disease & Prevention, 2008). This outbreak seemed to be aborted by closure of a facility manufacturing illicit fentanyl in Mexico in 2006 (Centers for Disease & Prevention, 2008). The sharpest increase in synthetic opioid-involved deaths occurred in 2014, with a near doubling of rates from the previous year (Rudd, Aleshire, et al., 2016). Fentanyl-tainted heroin has primarily impacted areas where white powder heroin is prevalent, and includes the Northeast, Midwest and Southeast regions of the United States and Western Canada (CDC, 2016). In some Northeastern states, fentanyl accounts for more than half of all fatal overdoses (CDC, 2016). As of 2017, western United States and Eastern Canada have been relatively spared. In the case of the US western states, this may be because of the predominance of black tar heroin, which produces a high that is more distinct from fentanyl and is a thicker substance that may be more difficult to mix with fentanyl powder. Counterfeit pills (e.g. labeled as Oxycodone, Norco) produced with fentanyl and fentanyl analogues may have also contributed to the growing overdose epidemic (CDC, 2016). The emergence and proliferation of counterfeits create further confusion in the illicit marketplace, which contributes to inconsistency of source and greater safety concerns over drug products (Armenian et al., 2017; Green & Gilbert, 2016; Sutter et al., 2017).

Several communities with strong naloxone programming or supervised injection facilities have been deeply affected by fentanyl overdose mortality. Between 2005 and 2011, Massachusetts had an opioid-related overdose death rate that plateaued between 8.0 and 9.9 per 100,000 people. Since 2012, the rate has climbed substantially each year to an estimated 25.8 per 100,000 people in 2015 (Data Brief: Opioid-related Overdose Deaths among

Massachusetts Residents, 2016). Among opioid-related overdose deaths examined in 2016, 74% had toxicology positive for fentanyl. The province of British Columbia, Canada, has seen a steady increase in illicit drug overdose deaths from 5.9 per 100,000 in 2012 to 19.3 per 100,000 in 2016, with illicitly manufactured fentanyl-detected deaths accounting largely for the increase, despite rapid expansion of supervised injection facilities in the city of Vancouver and province-wide scale-up of overdose education and naloxone distribution (OEND) (Illicit Drug Overdose Deaths in BC, January 1, 2007– December 31, 2016 – December 31, 2016). Public health authorities are struggling to adapt previously effective strategies such as OEND and SIFs to a new landscape dominated by synthetic opioids, even in locales with long established and comprehensive programs. Naloxone provision alone will be insufficient to stop this epidemic.

2. Overdose response in the synthetic opioid era

The emergence of widespread fentanyl distribution and concomitant surges in overdose deaths compels us to revisit overdose prevention efforts to adapt to this changing epidemic. Research on overdose and naloxone needs to be reexamined through this new lens.

2.1 Erratic drug supply

In addition to fentanyl, there are fifteen analogues identified by the Drug Enforcement Agency. Seizure data has detected rising prevalence of several fentanyl analogues (e.g. furanylfentanyl, acetylfentanyl, butyrylfentanyl) in certain jurisdictions across the United States (CDC, 2016). Carfentanil, an extremely potent synthetic opioid used exclusively for veterinary use with large animals and one hundred times more potent than fentanyl has been detected in at least one state in the U.S. (CDC, 2016). A recent study in British Columbia, Canada, detected the presence of carfentanil in 57 of 1766 urine drug tests conducted among drug users in early 2017, indicating the drug is present in the illicit drug supply in the region (“Lab test confirms carfentanil is being ingested,” 2017). It is not known whether the emergence of more potent synthetic opioids is being driven by increased demand from people using fentanyl regularly who have become tolerant or due to readily-available and inexpensive supply of these synthetic opioids.

Heroin fluctuation in purity is a known overdose risk (Darke, Hall, Weatherburn, & Lind, 1999) and the presence of illicit synthetic opioids contaminating the heroin supply has led to a particularly erratic “street dope” market that multiplies this risk (Ciccarone et al., 2017). People who use heroin are potentially exposed to large variations in drug potency depending on the extent of adulteration with synthetic opioids, thus increasing overdose risk. Seizure of fentanyl powder imported from foreign laboratories and confiscation of pill presses and counterfeit pills point to the same vulnerabilities to overdose among people who misuse prescription opioids (CDC, 2016). In addition to masquerading as heroin, fentanyl has been sold on the street as counterfeit prescription medications (Armenian et al., 2017; Green & Gilbert, 2016; Sutter et al., 2017).

Although it is challenging to study because of unmeasured forces influencing opioid overdose, existing data from settings where fentanyl and other synthetic opioids have already contaminated the illicit drug market continue to suggest real benefits of naloxone

(Somerville et al., 2017). Moreover, an important component of community overdose prevention programs is education that empowers people who use drugs to reduce overdose risk. Particularly relevant education in areas affected by fentanyl includes information about “tasting”, or using a small test dose to determine potency, using in the presence of others or in a supervised setting, and minimizing mixing with other sedative drugs. Overdose risk reduction education has been found to reduce self-reported overdose risk behavior among people who use prescription opioids (Bohnert et al., 2016). The changing potency and increased overdose risk also calls for emphasis on overdose prevention education not just at the site of naloxone provision, but in any healthcare interactions with people who use illicit opioids. Additionally, health authorities should provide funding and other resources to support drug user organizations to develop and distribute information and materials, and to conduct organizing activities as essential components of the overdose response.

2.2 Naloxone dose

The optimal dose range of naloxone and methods of administration for community lay reversal in general and whether it should be different in regions affected by fentanyl is not clear. The four currently available naloxone delivery systems have varying potency: (1) intramuscular naloxone drawn up from a vial with a needle, typically 0.4mg per 1ml injection; (2) an intramuscular autoinjector (Evzio™) with retractable needle, initially available in 0.4mg dose, but switched in 2017 to a 2mg dose per injection; (3) a multi-step off-label intranasal spray assembled with a naloxone-filled syringe attached to a nasal atomizer, typically delivered as 1mg per 1ml in each nostril for a total dose of 2mg; and (4) a single-step nasal spray (Narcan™), initially available in a 4mg per 0.1ml dose, but in 2017 also available in a 2mg per 0.1ml dose. Most community overdose prevention programs utilize vial intramuscular naloxone and multi-step nasal spray due to the early availability of these devices and the prohibitive costs of the newer FDA-approved devices. Community programs have reported nearly 100% post-administration survival rates prior to the synthetic opioid era (Clark, Wilder, & Winstanley, 2014). In the setting of fentanyl, there have been increasing reports of multiple doses of naloxone being required (Somerville et al., 2017; Sutter et al., 2017). This is likely due to the potency of fentanyl and the rapid onset of action. Because the length of time between substance use and death is shorter with fentanyl, there have been more reports of unsuccessful attempts to revive with naloxone despite administration of multiple or escalating doses. Some naloxone programs have begun providing more than the standard two doses of naloxone, and others have begun utilizing higher dose devices. It is not clear whether these approaches will prove efficacious. More potent, faster-acting synthetic opioids make it more difficult to balance the need for an effective opioid antidote with the risks of precipitated withdrawal (Neale & Strang, 2015). Further research is needed in real world circumstances to evaluate the efficacy of standard naloxone dosing and existing naloxone delivery devices in the synthetic opioid era and provide affordable access to efficacious devices to address the currently unmet public health needs to impact the overdose epidemic.

2.3 Time to respond

Research on heroin overdose has pointed to a window for opportunity for intervention with naloxone as death typically does not occur until at least 20-30 minutes after use (Darke &

Duflou, 2016). By comparison, when used intravenously, fentanyl can cause life-threatening respiratory depression within two minutes (Green & Gilbert, 2016). The rapid onset of action and remarkable potency of fentanyl and its analogues can lead to dramatic central nervous system depression (Amlani et al., 2015) as well as potential chest wall rigidity (Burns, DeRienz, Baker, Casavant, & Spiller, 2016), that may further complicate overdose response.

Additionally, ingestion of counterfeit pills containing fentanyl may result in late overdose presentation requiring repeat dosing or naloxone infusions due to delayed toxicity (Sutter et al., 2017). OEND programs should emphasize the importance of calling 911 and transfer to hospital for post-overdose care in case naloxone in the field runs out or there is need for prolonged naloxone administration. The American Heart Association has incorporated naloxone into its emergency response algorithms (Lavonas et al., 2015). More advanced resuscitation skills, such as chest compressions and use of automatic defibrillators, may need to be more widely incorporated into community emergency response training in the synthetic opioid era if responsiveness to naloxone administration is inadequate or delayed. Supervised consumption facilities, where naloxone can be provided promptly in the event of an overdose, should also be urgently expanded in affected regions across North America.

2.4 Unintentional exposure in the opioid naïve

Overdose prevention programs currently target people who use opioids and people who are likely to witness an opioid overdose. However, surveillance data has detected another phenomenon in the fentanyl era: contamination of non-opioid drugs with illicit synthetic opioids. An overdose outbreak in British Columbia, Canada, where high doses up to 3.0 mg of naloxone were required for resuscitation and one fatality occurred was determined to be due to furanylfentanyl-laced crack cocaine (Klar et al., 2016). A similar episode was reported in New Haven, CT, with fentanyl distributed as white powder cocaine resulting in 9 non-fatal and 3 fatal overdoses in a 6-hour period (Tomassoni et al., 2017). An outbreak of poisoning due to counterfeit alprazolam (labeled as Xanax) tablets containing fentanyl occurred in 2015 in San Francisco (Arens et al., 2016), resulting in 8 deaths and no related reports of lay naloxone use.

Individuals purchasing pills illicitly may not be expecting an opioid, familiar with the effects of opioids, aware of naloxone programming, or knowledgeable about how to respond to an opioid overdose. When presenting for emergency care, a low suspicion for opioid overdose may lead to delays in diagnosis and targeted therapy. The expansion of illicit opioids into this market raises multiple concerns and suggests that OEND programs should broaden their target audience. OEND programs may, for example, collaborate with programs that promote safety in dance party settings. Emergency medical staff should have a low threshold to consider opioid toxicity, even in patients who may not have elected to use opioids. Naltrexone, an opioid antagonist medication that is also effective for treatment of alcohol use disorder, may be considered as a novel overdose prevention intervention for polysubstance users who are at high risk for inadvertent exposure to contaminated drugs. For example, offering naltrexone as part of a comprehensive treatment plan for a patient with

cocaine use disorder could be considered in regions where overdose outbreaks linked to fentanyl contamination of cocaine have been documented.

2.5 Scaling up OEND via new venues and social networks

In addition to stepping up overdose prevention through harm reduction programs, it is important for other high-risk venues and social networks to be targeted. There is accumulating evidence for engaging primary care providers who prescribe pain medication and addiction treatment programs in delivering overdose prevention, including naloxone rescue kits (Coffin et al., 2016; Walley, Doe-Simkins, et al., 2013). High risk venues and populations include people leaving settings where tolerance is reduced (incarceration, hospital, detoxification programs, residential treatment). Pharmacies are ripe for scale up because they are the most common and community-based health facilities with longer hours of operation than many other health care facilities (Bounthavong et al., 2017; Jones, Lurie, & Compton, 2016; Shafer, Bergeron, Smith-Ray, Robson, & O'Koren, 2017; Stopka, Donahue, Hutcheson, & Green, 2017). Many states have instituted policies to encourage wider provision of naloxone through pharmacies. Other venues that warrant special consideration and innovation include public bathrooms, which are commonly used as drug consumption spaces (Wolfson-Stofko, Bennett, Elliott, & Curtis, 2017). With the rapidity of fentanyl overdoses, these are the places where people increasingly overdose. Funeral homes are another venue where overdose prevention may be deployed, because as deaths mount, the fentanyl-using social networks are spending more time in these locales. Some communities not only equip their EMS and firefighter first responders with naloxone to respond to an overdose (Davis, Southwell, Niehaus, Walley, & Dailey, 2014), but encourage them to distribute naloxone to people likely to witness a future overdose.

2.6 Innovations in post-overdose care

Although there is some variation, most emergency medical services transport overdose patients to the emergency department for a period of observation. Emergency department post-overdose care can be an overwhelming and potentially traumatic experience for users (Damon et al., 2016), as well as a potentially inefficient use of limited resources. An innovative example of post-overdose care is Vancouver's Mobile Medical Unit (MMU) (Woo, 2017). The MMU arose because the hospital emergency department serving most PWID in the city was overwhelmed by overdose presentations (>6000 in 2016) and first responders had become unable to attend every overdose on time when making frequent trips to the hospital. Staffed by emergency nurses and addiction medicine physicians, the MMU was developed as a specialized facility in Vancouver's Downtown Eastside, the epicenter of the overdose crisis. Patients rarely require repeat resuscitation with naloxone after initial resuscitation by first responders in the field and are discharged from the MMU after 1-2 hours of supervision. Another innovative example of post-overdose care is the Supportive Place for Observation and Treatment (SPOT) opened in 2016 by the Boston Healthcare for the Homeless program in response to safety concerns over public intoxication and overdoses (Gaeta, Bock, & Takach, August 31, 2016). The SPOT is for people who typically use substances in unsafe spaces such as street corners, alleyways, or public bathrooms. It offers medical monitoring by medically trained healthcare providers during the period of acute intoxication from drugs. Staff support over-sedated participants with vital sign monitoring,

oxygen and intravenous fluids and are equipped with naloxone. Both the MMU and the SPOT provide low-threshold care and can serve as a voluntary and consensual entry point to longitudinal primary care and addiction treatment.

The strongest risk factor for a fatal overdose is a previous non-fatal overdose (Coffin et al., 2007). While non-fatal overdoses may never come to medical attention, those resuscitated overdoses that involve medical personnel offer an opportunity to engage and do post-overdose outreach to high-risk individuals and their social networks. The Anchor Recovery Coach outreach program deployed in partnership with Rhode Island hospitals is one such effort that has emerged to enhance post-overdose care (Samuels, 2014; Wilkins et al., 2016). In several communities in Massachusetts, post-overdose outreach teams of public health workers and police, fire, or emergency medicine personnel provide overdose prevention and addiction treatment referrals to overdose survivors and their social networks (Wilkins, 2016).

2.7 New Technologies

Technology, such as utilizing apps or local monitoring of vital signs, may also have an impact on the synthetic opioid overdose epidemic. Recent examples include Trek Medics and OD Help mobile phone-based apps that are designed to connect potential opioid overdose victims with a crowd-sourced network of naloxone carriers (“Beacon Dispatch: Community-based overdose response,” 2017; Lurie, 2016). Personal safety apps for women (e.g. Kitestring, bSafe, and Women Safety) could potentially be repurposed with similar features. The OD Help app is also working to operationalize an additional feature to monitor a person's respiratory rate and trigger an alert when diminished breathing is detected. A pilot study to investigate the feasibility of a novel mobile device to monitor vital signs in opioid-injecting individuals is currently underway in Vancouver, Canada (“The Mobile Monitoring of Vital Signs in Opioid Users (MOVE),” 2015). A device that automatically administers naloxone in response to a reduction in respiratory rate or oxygen saturation has been considered for development (“SBIR Phase I - Automated Naloxone Delivery System,” 2012).

2.8 Beyond Overdose Response

The depth of the current crisis points to a need to consider upstream strategies to plan for safer use to enhance overdose prevention efforts. One such strategy includes drug checking facilities, common in Europe, particularly among people who use ecstasy and stimulants, that allow people who use drugs to check for presence of illicit opioids prior to use and bridges to low barrier access to harm reduction and other services (Brunt et al., 2017; Caudevilla et al., 2016). Drug checking has existed since at least the beginning of the 21st century (“EcstasyData,” 2017), but there is an increased interest in the context of overdose prevention, including the recent announcement of the first International Drug Checking Day on May 31st, 2017 (“Drug Checking Day,” 2017). In Vancouver, drug checking services are available at Insite (Mcelroy, 2016). Current drug checking services test for the presence of various substances, including fentanyl, and some drug checking services also identify the amount of each drug detected (“EcstasyData,” 2017). Detection of a potent opioid may encourage people to adapt their drug use practice (e.g. not use at all, use a smaller amount) and use in a supervised setting with access to naloxone and health care providers in the event

of overdose. It additionally allows for surveillance to monitor trends in the ever-changing landscape of street opioids and facilitates rapid response when new batches of contaminated drugs are detected. Additionally, fentanyl use by injection route conveys the greatest overdose risk due to rapid introduction to the bloodstream of an unknown dose. Research is needed to determine whether alternate consumption routes such as smoking or inhaling fentanyl, could be useful as harm reduction strategies with fentanyl.

Another important consideration to address overdose risk attributable to the erratic drug supply is increased access to oral OAT (e.g. methadone and buprenorphine/naloxone), as well as alternative therapies such as injectable OAT. Supervised consumption services can be expanded to include injectable OAT programs that provide prescribed opioids such as heroin or hydromorphone from an addiction physician that are self-administered by the patient in a supervised injection setting where naloxone is available in the event of an overdose. These medications are typically self-administered up to three times daily at a stable and predictable dose and provide a controlled source that removes the potential for fentanyl exposure. Low dose methadone is available in the evenings to cover patients through the night. The North American Opiate Medication Initiative (NAOMI) out of Vancouver found that injectable diacetylmorphine (i.e. prescription heroin) administered under medical supervision was more efficacious than oral methadone for engagement in treatment (Oviedo-Joekes et al., 2009). A follow-up study found that injectable hydromorphone was as effective as injectable diacetylmorphine (Oviedo-Joekes et al., 2016), making this therapy an option in jurisdictions where diacetylmorphine faces legal hurdles to prescribing.

3. Conclusion

The changing overdose eras underscore naloxone's crucial role in the overdose response and a pressing need to identify areas for further study and innovation to adapt to a changing illicit drug market. A coordinated overdose response must remain nimble and able to adapt to an ever-changing landscape in order to have a meaningful impact on overdose rates. Innovative strategies should continuously be explored and expanded rapidly to optimize the potential benefits of these life-saving interventions.

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