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Commentary

Tackling the overdose crisis: The role of safe supply

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ABSTRACT

North America is experiencing an unprecedented overdose crisis driven by the proliferation of fentanyl and its analogues in the illicit drug supply. In 2018 there were 67,367 drug overdose deaths in the United States, and since 2016, there have been more than 14,700 overdose deaths in Canada, with most related to fentanyl. Despite concerted efforts and some positive progress, current public health, substance use treatment, and harm reduction interventions (such as widespread naloxone distribution and implementation of supervised consumption sites) have not been able to rapidly decrease overdose fatalities. In view of the persistent gaps in services and the limitations of available options, immediate scale-up of low-barrier opioid distribution programs are urgently needed. This includes "off-label" prescription of pharmaceutical grade opioids (e.g., hydromorphone) to disrupt the toxic drug supply and make safer opioids widely available to people at high risk of fatal overdose.

North America is experiencing an unprecedented overdose crisis driven by the proliferation of illicitly-manufactured fentanyl, fentanyl analogues, and fentanyl-adulterated drugs (Public Health Agency of Canada, 2020; Jones, Einstein & Compton, 2018). Since the early 2000s, overdose deaths have more than tripled in the United States and Canada, with most related to opioids (Centres for Disease Control & Prevention, 2019; Government of Canada 2019b, June 17). In 2018 there were 67,367 overdose deaths in the United States, of which 47,600 involved opioids (Scholl, 2019). Since 2016, there have been more than 14,700 opioid-related overdose deaths in Canada, with 4614 occurring in 2018 alone (corresponding to a death rate of 12.4 per 100,000 population) (Public Health Agency of Canada, 2020). The overdose crisis has impacted all provinces and territories in Canada, with British Columbia (BC), Ontario, and Alberta reporting the highest number of opioid-related overdose deaths in 2018 (Public Health Agency of Canada, 2020). In the United States, Eastern States have seen a higher incidence of deaths involving illicitly-manufactured fentanyl, though there have been recent increases in Western States including Arizona, California, Colorado, Oregon, and Washington (Scholl, 2019). Overdose deaths are now one of the leading causes of accidental death and have contributed to a decline in life expectancy in North America (Government of Canada 2019b, June 17; King, Fraser, Boikos, Richardson & Harper, 2014). National and regional governments in both the United States and Canada have declared the overdose crisis a public health emergency (Department of Health & Human Services, 2017; Government of British Columbia, 2016).

The current toxic drug supply is responsible for the vast majority of North America's overdose fatalities. Seventy-six percent of all opioid-related overdose deaths in Canada in 2018 were related to fentanyl or fentanyl analogues including 74% in Ontario and 84% in Alberta, and 87% in BC (British Columbia Coroners Service, 2019; Public Health Agency of Canada, 2020). Synthetic opioids (including fentanyl) were involved in 60% of opioid-related overdose deaths in the United States in 2017 (a 45% increase from 2016), largely driven by illicitly-manufactured fentanyl (Scholl, 2019). In some jurisdictions, such as New York City and Boston, the presence of fentanyl in postmortem toxicology among overdose decedents is now almost universal (Freyer & Lukpat, 2019; New York State Department of Health, 2019). This has resulted from changes to illicit drug markets whereby the prevalence of fentanyl in local drug supplies varies considerably and is constantly changing, making drugs purchased on the street unreliable, and the strength of batches and individual doses unpredictable (Carroll, Marshall, Rich & Green, 2017a; Ciccarone, Ondocsin & Mars, 2017). This poses significant challenges for current overdose prevention

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interventions that respond to but do not prevent overdose events. What is urgently needed is a safer alternative (i.e., pharmaceutical grade) to the toxic drug supply to prevent overdose events resulting from illicitly-manufactured fentanyl and fentanyl-adulterated opioids. Providing access to pharmaceutical grade opioids to people at high fatal overdose risk will resolve the limitations of current overdose response measures by effectively reducing the occurrence of overdose events.

Harm reduction strategies (e.g., naloxone distribution, low-barrier supervised consumption service, drug checking technologies) have rapidly expanded in Canada in efforts to curb overdose fatalities (Fairbairn, Coffin & Walley, 2017; Karamouzian et al., 2018; Wallace, Pagan & Pauly, 2019). Efforts are currently being undertaken to implement supervised consumption sites in a number of U.S. cities (e.g., Seattle, New York, San Francisco) (Allyn, 2018), and a U.S. District Judge recently ruled that a bid to open a supervised injection site in Philadelphia does not violate the Controlled Substances Act, clearing the way for the operation of the first above-ground supervised consumption venue in the United Sates (Levenson & del Valle, 2020). And while many States have recently enacted laws to increase access to naloxone, significant barriers (e.g., stigma, low public awareness of prescribing laws) still restrict its dispensing and use (Bakhireva et al., 2018; Freeman, Hankosky, Lofwall & Talbert, 2018; Puzantian & Gasper, 2018). Where harm reduction strategies have been implemented, they have had considerable impact. For example, it is estimated that the recent scale-up of these treatment and harm reduction interventions in BC prevented more than 3000 potential overdose deaths between April 2016 and December 2017 (Irvine et al., 2019). However, the overdose mortality in BC (30.6/100,000 persons in BC), as elsewhere in North America, remains appallingly high (British Columbia Coroners Service, 2019), and these treatment and harm reduction interventions are limited in their ability to directly intervene to address the fentanyl-adulterated drug supply. In order to effectively reduce overdose events and mortality by limiting access to the toxic drug supply, immediate scale-up of pharmaceutical-grade opioid distribution is required to make safer opioids widely available to people at high fatal overdose risk (Tyndall, 2018).

Indeed, providing alternatives to illicit opioids is not new. Currently, such approaches are primarily implemented as oral medications, such as methadone and buprenorphine, for the treatment of opioid use disorder (OUD). These medication-based treatments (most commonly referred to as opioid agonist therapies or opioid substitution therapies, OAT or OST, respectively), have been demonstrated to improve social functioning and reduce opioid-related morbidity and mortality (Ahamad et al., 2015; Degenhardt et al., 2011; Perlman et al., 2015). However, they are not without limitations, including poor retention rates and negative side effects (Blanco & Volkow, 2019; Farré, Mas, Torrens, Moreno & Camí, 2002; Fischer, Rehm, Kim & Kirst, 2005; Hunt, Lipton, Goldsmith, Strug & Spunt, 1985; Schwartz et al., 2008; Socías et al., 2018). Recent efforts to improve uptake of medication-based treatments in the United States include increasing prescribing limits of buprenorphine for physicians (from 100-patient limit to 275-patient limit) in order to increase medication access, however they remain largely underutilized (Cooper et al., 2020; Donroe, Socias & Marshall, 2018; Huhn & Dunn, 2017; Jones, Campopiano, Baldwin & McCance-Katz, 2015) and cannot remedy the loss of access to pharmaceutical opioids as prescribing practices have been increasingly restricted resulting in people transitioning to more potent and cheaper alternatives (i.e., via the illicit drug market supply) (Beletsky & Davis, 2017; Dasgupta, Beletsky & Ciccarone, 2017). A number of jurisdictions in Canada have expanded injectable hydromorphone, an opioid traditionally used to treat pain, as a medication-based treatment for OUD (Oviedo-Joekes et al., 2016), providing prescribed hydromorphone (in either liquid or tablet form) to people with OUD to reduce harms and provide safer alternatives to the fentanyl-adulterated drug supply. These programs build on a previous trial (the Study to Assess Long-term Opioid Maintenance Effectiveness) demonstrating the effectiveness of injectable diacetylmorphine and hydromorphone in treating OUD (Oviedo-Joekes et al., 2009, 2016). However, these programs are not suitable for all people with OUD (e.g., individuals who do not inject, people difficult to keep engaged with the healthcare system), and are difficult to scale up and implement in rural and remote settings due to the significant resource capacity required (e.g., dedicated clinic/office infrastructure, extensive staffing including medically trained staff).

While there remains a critical need to expand treatment options and overdose response interventions for people with OUD at high risk of fatal overdose, reducing exposure to fentanyl will be a key step to mitigating the overdose crisis. This is especially imperative given that concurrent drug use is common among some people receiving traditional OAT, exposing them to significant overdose risk even while in treatment (Dobler-Mikola et al., 2005; McNeil et al., 2020; Roux et al., 2016; Tran et al., 2018). Further, emerging evidence indicates low uptake and engagement of people exposed to illicitly-manufactured fentanyl in traditional OAT programs (Arfken, Suchanek & Greenwald, 2017; Carroll, Marshall, Rich & Green, 2017b; Stone, Carroll, Rich & Green, 2018). It is also important to recognize a wide range of drug use patterns, including people who use illicit drugs who are not interested in drug treatment, and those for whom traditional forms of drug treatment are not suitable or desirable. For these reasons, the non-treatment-based distribution of safer opioids is essential to fully address the overdose crisis. Providing easy access to a consistent supply of unadulterated opioids will not only prevent overdose events, but also potentially reduce drug-related harms (e.g., violence related to the illicit drug market) and improve overall health and well-being, as evidenced by studies demonstrating the effectiveness (e.g., high retention rates, improved social functioning) of prescribed heroin (i.e., diacetylmorphine) and hydromorphone (Van den Brink et al., 2003; Haasen et al., 2007; March, Oviedo-Joekes, Perea-Milla & Carrasco, 2006; Oviedo-Joekes et al., 2016, 2019). Safe supply programs are built on the premise that prescribing pharmaceutical-grade opioids such as hydromorphone and diacetylmorphine to people at high risk of fatal overdose will reduce their use of fentanyl-adulterated opioids obtained from the illicit drug market, and subsequently prevent overdose events and reduce overdose mortality (Canadian Association of People Who Use Drugs, 2019).

Injectable hydromorphone, which was recently approved by Health Canada to treat OUD (Government of Canada, 2019c, May 15), has been shown to be a suitable alternative to diacetylmorphine in treating individuals with OUD (Oviedo-Joekes et al., 2016), and can be pursued immediately in many jurisdictions with minimal need for additional resource capacity if implemented within existing public health/harm reduction services (Olding et al., 2020). Recent expansion of injectable hydromorphone programs in Vancouver, BC suggest that large-scale expansion is possible. Optimally, a range of pharmaceutical-grade opioids should be made available to people at high risk of fatal overdose through various avenues, including, for example, proposed “heroin compassion clubs” (British Columbia Centre on Substance Use, 2019) in which eligible individuals could purchase (without criminal/legal sanctions) pharmaceutical grade opioids, the expansion of injectable hydromorphone and similar opioid distribution models, and the “off-label” prescription of opioids. Off-label hydromorphone prescription represents the most feasible and easily implementable method of safe supply distribution, with the capacity to reach the greatest number of people to significantly reduce illicit opioid use and overdose events. Despite this, a number of concerns have been raised over off-label hydromorphone prescription including the potential for diversion, increased risk of infection/endocarditis, and a concern that patients will choose safe supply options over traditional OAT (Bromley, 2020; Willows, Brasch, Sobey, Tanguay & Martell, 2020). While these concerns are, respectively, anecdotal and perhaps discriminatory, not fully supported by evidence (endocarditis is only associated with use of controlled-release hydromorphone, see: Kasper et al., 2019; Silverman

et al., 2020), and hypothetical, they also rest on calls for reducing barriers, and increasing access, to traditional OUD treatments. However, as noted above, not all people who use opioids are interested in treatment, nor is conventional treatment suitable for all people who use opioids. Continuing to rely on conventional treatment models amidst evidence that these do not work for everyone represents a fundamental failure of our attempt to adequately address the overdose crisis. In light of this, a number of physicians in Ontario and British Columbia have been prescribing hydromorphone tablets off-label to successfully reduce the illicit opioid use of patients considered at high overdose risk (Browne, 2019).

Two limited-capacity off-label hydromorphone tablet distribution programs currently operate in Vancouver, Canada. One is embedded within an overdose prevention site (the Molson Overdose Prevention Site and Learning Lab) in which a daily amount of hydromorphone is administered to program participants (approximately 70) by a trained nurse (Olding et al., 2020). Participants can receive two 8 mg tablets at a time, must wait a minimum of one hour between doses, with a maximum of five doses daily. The hydromorphone can be consumed orally, intranasally, or by injection, and must be consumed within the OPS room. To prevent diversion the tablets are crushed by the nurse and oral and intranasal use are witnessed, while those injecting must return used injection equipment to the nursing station. The other hydromorphone tablet program, situated within a harm reduction organization beside an overdose prevention site, distributes hydromorphone tablets via an automated dispensing machine which program participants (approximately 15 as of April 2020) use offsite (Thibault, 2020, January 17). Individual doses vary in this program, the highest being 16 8 mg tablets daily, which are split into smaller dose accessed over the course of a day (e.g., four tablets accessible four times a day, with a minimum two-hour period between doses).

These programs are examples of the feasibility of low-barrier safe supply distribution, and are a first step in tackling the overdose crisis by providing individuals an alternative to the toxic drug supply that is currently killing thousands of people in North America each year. However, while low-barrier programs nested within existing services likely facilitate engagement among vulnerable people who use drugs, off-label prescription does not necessarily require significant resource capacity (e.g., nursing stations within overdose prevention sites or specifically designed dispensing machines), but wider support from the medical community and governments. British Columbia recently released new provincial guidelines on safe supply prescribing and access amid the COVID-19 pandemic, opening up access to safer opioids, stimulants, and benzodiazepines to individuals at high overdose risk, including options for daily or weekly deliveries, take-home doses, and extended (suggested 23 day minimum) prescriptions (British Columbia Centre on Substance Use, 2020; Uguen-Csenge, 2020). We urge all Canadian provincial governments to follow suit, and extend safe supply access beyond the COVID-19 pandemic. Current U.S. Federal regulations (Title 42 of the Code of Federal Regulations Part 8) serve as a barrier to off-label use of opioids and other scheduled substances. State-level regulations that induce fear among, or outright penalize, physicians for opioid-prescribing (Davis, Lieberman, Hernandez-Delgado & Suba, 2019; Schatman & Shapiro, 2019) are likely to further impede safe supply program implementation and require supporting regulatory changes. Further, the lack of evidence supporting these regulations (Davis, Piper, Gertner & Rotter, 2020) only further points to the public health imperative to instead shift emphasis to harm reduction. Given the dire consequences of accessing opioids from fentanyl-adulterated illicit drug markets, particularly in the context of COVID-19, serious consideration should be given in the U.S. context to revising prescribing regulations to facilitate safe supply interventions. Further, clinical trials examining the efficacy of hydromorphone in treating OUD should be supported by the Food and Drug Administration and the National Institutes of Health.

Lower-barrier programs nested within existing social and health services (e.g., drop-in centres, supervised consumption sites) would provide a viable and necessary alternative to existing medication-based treatment programs. However, given that the majority of overdose fatalities occur indoors (British Columbia Coroners Service, 2019; Siegler, Tuazon, Bradley O'Brien & Paone, 2014), and that naloxone cannot be self-administered during an overdose, it is critical to expand low-barrier access to a safer supply of opioids. In particular, broad distribution of safer opioids is required to prevent overdose events when drugs are not being consumed in supervised locations (e.g., supervised consumption sites), and where structural barriers prevent access to overdose prevention interventions (e.g., rural communities). While taking steps to move in this direction, wider support from physicians, public health and medical leaders, and other key stakeholders for treating OUD with injectable/oral hydromorphone is imperative, and is a key step in tackling the overdose crisis.

Declaration of Competing Interest

The authors have no actual or potential conflict of interest to declare.

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