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Review

Pathways between COVID-19 public health responses and increasing overdose risks: A rapid review and conceptual framework

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**ABSTRACT**

**Background:** Emerging evidence indicates that illicit drug overdoses are increasing throughout the COVID-19 pandemic. There is a paucity of evidence on the causative pathways for this trend, but expert opinions, commentaries, and some reviews offer theoretical underpinnings.

**Methods:** In this rapid review, we collate the available published evidence, expert opinions, commentaries, and reviews on the unintended pathways between COVID-19 public health responses and increasing illicit drug overdoses. Using tenets of thematic analyses and grounded theory, we also offer a visual conceptual framework for these unintended pathways.

**Results:** Our framework focuses on five particular public health responses, namely social isolation/physical distancing/quarantine; staff/resource reallocations and reductions; closures of businesses and other places of employment; border closures and transportation restrictions; and the early release of people from prisons. As argued in the literature reviewed here, these public health responses have unintentionally created increased overdose risks by producing high risk use scenarios; increased risks of relapsing; disrupted addictions services and treatment; an increasingly toxic supply of drugs; and the risk of using with lowered tolerance.

**Conclusions:** Health care systems should respond to these pathways to mitigate the unintended consequences. Furthermore, the COVID-19 pandemic may represent an opportunity to enact proactive, progressive, and innovative solutions to an overdose crisis that will surely outlast the current pandemic.

**Introduction**

Since at least 2016, a deadly public health crisis of illicit drug overdoses has been spreading across North America. In the United States, drug overdose deaths rose from 52,902 for the 12-months ending in January 2016, to 65,571 in the 12 months ending in January 2017 (Vital Statistics Rapid Release–Provisional Drug Overdose Data, 2020). A similar trend occurred in Canada - there were 2825 opioid toxicity deaths reported in 2016, rising to 3914 reported in 2017 (Opioid- and Stimulant-Related Harms in Canada, 2020). In an effort to respond to the rise in cases, British Columbia (BC), the most impacted of the Canadian provinces, declared a public health emergency in 2016. The United States followed suit a year later.

These declarations enabled the expansion of public health and harm reduction services in an attempt to control the overdose crisis. In BC, this meant establishing a take home naloxone program, opening new supervised consumption sites, establishing a provincial Centre on Substance Use, and creating a new provincial Ministry of Mental Health and Addictions, to name a few (Joint Task Force on Overdose Prevention and Response, 2017). In the United States, this meant increased funding for opioid-related treatment, prevention, recovery, surveillance, and research (Division (DCD), 2018).

After several years, the efforts seemed to be paying off. The United States saw a decrease in drug overdose deaths, decreasing from 70,237 in 2017 to 67,367 in 2018 (Overdose Death Rates | National Institute on Drug Abuse (NIDA), 2020). In 2019, BC also saw a year-over-year reduction in overdose deaths - dropping from 1549 in 2018 to 984 in 2019 (Illicit Drug Toxicity Deaths in BC January 1, 2010–November 30, 2020).

In early 2020, the coronavirus disease 2019 (COVID-19) global pandemic emerged, prompting a second public health emergency to be declared not only in BC and the United States, but also in many other jurisdictions around the world. This shifted the focus of public health responses towards the management of COVID-19, with public health orders and recommendations that included physical distancing, business
closures, border closures, the redeployment of health care workers, and many others.

Unfortunately, the pandemic response may have undermined the progress that was previously made in regards to the overdose crisis. By the end of 2020, the BC Coroner Service had reported 1716 illicit drug toxicity deaths - the largest single year-over-year increase since 2010 (and a reversal of the progress made the year prior) (BC Coroner Service, 2021). Saskatchewan saw a doubling of fatal overdoses in 2020 (Saskatchewan’s Overdose Death Rate Doubles, Repeating a Fatal Pattern, 2021) and the United States saw its highest number of overdose deaths ever in a 12-month period, with 81,000 deaths by May 2020 (Overdose Deaths Accelerating During COVID-19, 2020). Primary data from the literature also corroborates similar increases in both fatal and non-fatal overdoses across other jurisdictions, including a 50% increase in fatal overdoses in a study from Kentucky (Slavova, Rock, Bush, Quesinberry, & Walsh, 2020); an increase of nearly 55% in the average daily fatal overdoses in San Francisco (Rodda, West, & LeSaint, 2020); and a 47% increase in overdose deaths found in Indianapolis (Glober et al., 2020).

Though it may appear the recent increase in overdoses is occurring in the context of the COVID-19 pandemic response, there is a paucity of primary data to support these causative linkages. Peer-reviewed and published expert opinions, commentaries, and review articles do reveal some anecdotal and theoretical underpinnings, but there have been no systematic reviews compiling them to date. In this study, we review the theoretical linkages made in these publications and provide a conceptual framework that links specific COVID-19 pandemic responses to the unintended pathways that generate increased overdose risks.

Methods

This study uses a modified version of Cochrane’s interim guidance for rapid review methods (Garritty, 2021). A rapid review uses components of systematic review processes, but simplifies or omits various components in order to produce information in a timely manner.

In this rapid review, a single reviewer searched MEDLINE and EMBASE databases (all via OVID) using the keywords “covid” OR 2019-nCoV OR sars-cov-” AND “overdose” on December 8 2020. Results were filtered to publications in 2020 only. Titles and abstracts were screened against the following predefined inclusion criteria: 1) English language; AND 2) expert opinion, commentary, or review articles with comments on how COVID-19 public health responses have led to increasing drug overdose risks OR 3) qualitative or quantitative studies regarding overdoses in the context of the COVID-19 pandemic. These qualitative or quantitative studies were included for full review in order to draw out any comments or conclusions made in their respective background and discussion sections. However, we only included the discussion of overdoses in the context of COVID-19, not the data in these articles. If any articles included for full-review did not provide comments related to inclusion criteria 2, they were excluded from the final analysis.

A total of 29 articles were included for final analysis (Fig. 1). Data from these articles were entered into a data-extraction form, the creation of which was informed by a pilot literature search the month prior. The data were coded and an iterative thematic analysis was performed, where emergent themes of unintended processes and consequences within the text were expanded and collapsed into one another until a final set of themes could no longer be intuitively combined. The themes of unintended processes and consequences were then grouped according to the public health responses in which they originated. Drawing loosely on the tenets of grounded theory, a framework of overdose risk due to COVID-19 public health responses emerged from this process. A further targeted search of the literature was used to inform the background and discussion sections. We opted to not perform a formal risk of bias assessment, as the majority of sources and data were expert opinions, commentaries, reviews, or anecdotal, which are typically accepted as lower quality evidence (What Is GRADE? | BMJ Best Practice, n.d.).

Results

29 studies from Canada, the United States, Australia, Ukraine, Spain, South Africa and the United Kingdom were included for final analysis. Our work reveals five overarching public health responses that led to an unintended increase in overdose risks. A visual framework and conceptualization of the unintended pathways can be seen in Fig. 2 and a table of the literature included in the analysis can be found in Supplementary Table 1.

Physical distancing, social isolation, or quarantine

Public health orders regarding physical distancing and social isolation are designed to enforce distancing between people to reduce transmission. These include keeping a minimum physical distance apart, banning indoor gatherings and social events, and guest policies in support-
ive housing, to name a few. Quarantining, or mandated periods of isolation when people become diagnosed with COVID-19 or come into contact with known COVID-19 cases, further forces the physical isolation of individuals.

These were the most discussed public health responses found in the literature and we identified several unintended processes leading to increased overdoses (see Fig. 2). More specifically, physical distancing and social isolation is believed to be forcing people to increase their use alone (Bao, Williams, & Schackman, 2020; Bonn et al., 2020; Friedman, Beletsky, & Schriger, 2020; Henry et al., 2020; Hsu, Ahern, & Suzuki, 2020; Khatri & Perrone, 2020; MacKinnon, Socías, & Bardwell, 2020; Ostrach et al., 2020; Rodda et al., 2020; Slavova et al., 2020; Stack et al., 2020; Tyndall, 2020). This is a risky use setting and one that is compounded by a decrease in bystanders that are able to intervene in witnessed overdoses (Henry et al., 2020; Khatri & Perrone, 2020; Rodda et al., 2020).

Physical distancing/social isolation orders may also lead to a decrease in people able to access addictions services and treatment, such as harm reduction and opioid agonist therapy (OAT) (Bao et al., 2020; MacKinnon et al., 2020; Sun et al., 2020; Vasylyeva, Smyrnov, Strathdee, & Friedman, 2020), supervised consumption sites (MacKinnon et al., 2020), or recovery meetings (Hochstatter et al., 2020). This is not only done in an attempt to adhere to public health orders, but also to personally avoid COVID-19 infections (Bao et al., 2020). Without access to harm reduction resources or OAT treatment, people will increasingly use in riskier settings or will be at an increased risk of relapsing. It may also become difficult for service providers to perform outreach and provide services to those who are isolating (Collins, Ndoye, Arene-Morley, & Marshall, 2020).

The experience of quarantining and isolation itself also leads to worsening mental health, increased stress, and feelings of anxiety, despair, and depression, all of which potentiate the risk of relapse and substance use (Henry et al., 2020; Khatri & Perrone, 2020; Lapeyre-Mestre et al., 2020; MacKinnon et al., 2020; Metelliuk et al., 2020; Slavova et al., 2020; Stack et al., 2020; Walters, 2020). Vasylyeva et al. (2020) also suggests that social isolation may lead people to stockpile their drugs, while a study by Glober et al. (2020) suggests that use during isolation may become intensified. This is worsened if regular dealers are also isolating, forcing people to procure an illicit supply from untrusted and potentially more toxic sources (Ostrach et al., 2020).

In contrast, for those isolating and intending to decrease their use or become abstinent, tolerance will begin to wane and overdoses may
occur when people relapse into regular use patterns (Stowe, Scheibe, Shelly, & Marks, 2020; Vasylyeva et al., 2020). This may especially be difficult for those forced to isolate in shelters or housing that puts them into proximity with people who use drugs, increasing the risk of relapse (Hochstatter et al., 2020).

**Staff or resource reallocations, reductions and changes**

Another public health response frequently discussed in the literature were staff and resource reductions, often due to reallocations in order to focus on responding to the COVID-19 pandemic (Villarin, Gao, & McCann, 2020). This has the result of decreasing the availability of services and treatments that prevent overdoses, such as harm reduction services/resources, supervised consumption sites, overdose outreach and prevention programs, recovery programs, peer support programs, withdrawal management programs, and OAT (Bandara, Kennedy-Hendricks, Merritt, Barry, & Saloner, 2020; Bonn et al., 2020; Collins, Ndoye, Arene-Morley, & Marshall, 2020; Collins, Beaudoin, Samuels, Wightman, & Baird, 2020; Dunlop et al., 2020; Halpern, 2020; Hsu et al., 2020; Khatri & Perrone, 2020; Lapeyre-Mestre et al., 2020; MacKinnon et al., 2020; Slavova et al., 2020; Sun et al., 2020). For those currently receiving treatment, the reduction in service availability can also lead to premature OAT discontinuation, increasing the risk of relapse and overdose if regular use patterns resume (Dunlop et al., 2020; Sun et al., 2020).

The International Society of Addictions Medicine surveyed 177 addictions medicine professionals across 77 countries and reported that harm reduction services were reduced in 41% of countries that responded. Overdose prevention services were impacted in 57% of countries and outreach services were impacted by 81% of countries, all due to the COVID-19 pandemic (Radfar et al., 2020). These reductions in treatments, resources, and services may also be exacerbated in particular settings, such as in rural areas (Ostrach et al., 2020).

**Border closures and transportation/travel restrictions**

Many countries have implemented border closures and transportation/travel restrictions in an attempt to minimize the importation or exportation of infectious COVID-19 cases (Kang et al., 2020). However, this may be leading to a number of unintended processes related to increasing overdoses. For one, it is believed that this has created an increasingly toxic and erratic supply of illicit drugs (Bonn et al., 2020; Khatri & Perrone, 2020; Ostrach et al., 2020; Tyndall, 2020; Wakeman, Green, & Rich, 2020). Toxic supplies can increase the risk of overdose by being contaminated with higher potency substances that are cheaper to make or by adding different classes of drugs, such as benzodiazepines (MacKinnon et al., 2020), while an erratic supply can lead to fluctuations in prices.

If prices increase due to difficulties with importation, affordability may become an issue and people may begin to decrease their use or even become abstinent (Stack et al., 2020), causing tolerance to wane and the risk of overdosing once regular use resumes (Wakeman et al., 2020). Increased prices may also push people to switch to other substances that are more affordable. In these cases, low tolerance and unfamiliarity to new substances may also put people at an increased risk of overdosing (Ostrach et al., 2020; Wakeman et al., 2020).

Conversely, prices may decrease due to an overabundance of supply from reduced purchasing (Stack et al., 2020). It is also believed that these erratic supply issues may encourage people who use drugs to stockpile, especially in rural areas (Stack et al., 2020).

**Closures of businesses and other places of employment**

The ordering of certain businesses and places of employment to be closed is another common public health response. Some businesses have also been forced to close due to an inability to adhere to social distancing guidelines or from being unable to survive the ensuing recession. Large amounts of the population have, therefore, suddenly become unemployed, many of whom are now experiencing financial hardships. As concluded by the authors, this has the effect of increasing stress, anxiety, depression, and other mental health exacerbations which potentiate the risk of relapse and substance use (del Pozo & Rich, 2020; Halpern, 2020).

**Early release of people from prison**

Another public health response often discussed in the literature is the early release of people from prisons in order to avoid the heightened risk of infection found in institutions known to have poor ventilation, poor access to healthcare, overcrowding, and congregation (Dutheil, Bouillon-Minois, & Clinchamps, 2020). Indeed, by December 8th 2020, there were over 312,000 COVID-19 cases amongst people in prison and prison staff in the USA (A State-by-State Look at Coronavirus in Prisons, 2020), and approximately 170,000 people in prison had early releases by October 2020 (Mass Release of U.S. Inmates Sets Up Test of “Decarceration” Movement, 2020). It has also been estimated that up to 65% of people in US prisons have active substance use disorders (National Institute on Drug Abuse, 2020).

Unfortunately, with mass early releases in the context of the COVID-19 pandemic, many people from prison are having difficulty connecting with community-based addictions services (Bandara et al., 2020; Khatri & Perrone, 2020). This has the dual impact of not only discontinuing treatment (such as OAT) that was received in prison, but also increasing the risk of relapse in the context of waned tolerance and abstention while in prison (Stowe, Scheibe, Shelly, & Marks, 2020; Tyndall, 2020).

**Discussion**

Emerging evidence indicates that illicit drug overdoses are escalating during the COVID-19 pandemic (Glober et al., 2020; Redda et al., 2020; Slavova et al., 2020), with some jurisdictions, such as British Columbia, now seeing its largest year-over-year increase in illicit drug toxicity deaths since 2010 (BC Coroners Service, 2021). In this review, we have summarized the ways in which research and expert opinion have identified the ways in which COVID-19 public health responses have undermined the previous progress made on the overdose epidemic. We have also synthesized a conceptual framework that links specific COVID-19 public health responses to increased overdose risks.

Our framework summarizes that COVID-19 public health responses, especially a) physical distancing, social isolation, or quarantine; b) staff or resource reallocations, reductions, and changes; c) border closures and transportation/travel restrictions; d) closures of businesses and other places of employment; and e) the early release of people from prison are ultimately creating increased risks of illicit drug overdoses. This impact is mediated by multiple unintended pathways, particularly by: increasing use in riskier settings (such as using alone, increasing usage, or stockpiling of drugs); worsening mental health, unemployment, and other processes that increase the risk of relapse; disrupting the access of both treatment and harm reduction services (such as supervised consumption sites); creating an increasingly toxic supply of drugs; and lowering tolerances while at risk of relapsing to regular use.

As suggested by Grebely, Cerdá, and Rhodes (2020), when considering the potential effects of COVID-19 public health restrictions on the health of people who use drugs, our framework contributes to a body of literature that situates the health of people who use drugs (PWUD) within the context of the environment. In the case of our study, we have revealed how psychosocial, economic, and political dimensions intersect to create a “risk environment” of increasing illicit drug overdoses (Rhodes, 2002).

At the time of writing, many countries have recently approved COVID-19 vaccines, including in Canada, the United Kingdom, and the United States. It is hoped that immunization will create a pathway towards normalcy and that the rollback of public health responses and restrictions can slowly begin. However, the overdose crisis will likely per-
sist and last beyond the resolution of this pandemic unless mitigating actions are taken now. Indeed, multiple scholars, advocates, and agencies have been calling for action since the pandemic began and some have even provided specific recommendations (Alexander, Stoller, Haffajee, & Saloner, 2020; Bao et al., 2020; Buxton, Moe, Papamihali, & Kuo, 2020; Dunlop et al., 2020; Khatri & Perrone, 2020; MacKinnon et al., 2020; Mental Health in Canada: Covid-19 & Beyond: CAMH Policy Advice, 2020; Volkow, 2020; Wakeman et al., 2020).

In some ways, the pandemic has allowed governments, public health institutions, and the health care system to think outside the box - to respond in nimble and innovative ways. We are at a moment in time where there has been an alignment of context, content, and the willingness of actors in Walt and Gilson’s health policy triangle (1994) - an alignment that enables favourable health policy changes.

One such example of a nimble policy change to address the unintended consequences is in British Columbia, Canada, where in response to COVID-19, guidance was released that allows the prescription of pharmaceutical-grade opioids and other restricted drugs in order to avoid the increasingly toxic illicit supply (Ahmad et al., 2020). Guidance was also released that encouraged relaxed OAT prescribing, such as encouraging carries and longer take-home intervals (British Columbia Centre on Substance Use, 2020). In addition to this, on September 16, 2020, British Columbia’s provincial health officer issued an order that enabled registered nurses and registered psychiatric nurses to also prescribe these controlled substances (Health, 2020).

How effective these interventions are from a public health perspective are yet to be seen, but the authors report anecdotal experiences of appreciative patients. While this initial change in regulation may be welcomed by some providers and patients, it is unknown whether any changes made during the COVID-19 public health emergency will be sustained into the future. Indeed, we need more proactive, sustainable, and long-term solutions to ensure that the vulnerabilities and inequities highlighted by the COVID-19 pandemic are addressed both now and long after the acute public health response to this pandemic ends.

### Next steps

This study uses expert opinions, anecdotes, commentaries, reviews, and published discussions to draw theoretical conclusions. There is a lag in primary linking the COVID-19 pandemic to increased overdoses - research should therefore be undertaken to provide higher quality evidence of the experiences highlighted in this study. Future studies should also validate the framework synthesized in this paper. A study collating recommendations from experts may also prove useful. Any recommendations made should have acceptability and feasibility evaluated for local applicability, and must include the perspectives of people with living or lived experiences of substance use in order to effectively address their needs (Ti, Tzemis, & Buxton, 2012).

### Limitations

Limitations to this study include the fact that the majority of sources were expert opinions, commentary, or reviews, which are typically accepted as lower quality evidence. We did not do a review of primary data or epidemiological studies. Thus, our study provides a theoretical framework, offering what Grebely et al. (2020) terms as “indicators of possibility in an unfolding adaptive situation... momentary cases of 'emergent causation'”. In this sense, we agree when Grebely et al. (2020) state that “it is important to recognize the uneven and uncertain nature of currently available data.”

Secondly, we did not identify any positive consequences of COVID-19 public health responses through our search strategy, though evidence exists that some programs have started allowing take home dosing of OAT or the advent of mobile solutions (Stowe et al., 2020). This may reflect how the existing drug and drug policy literature tends to focus on negative outcomes rather than positive ones.

Thirdly, due to limited research capacity, this project did not assess the grey literature (such as government sources), from which there may be additional knowledge and data available, such as evidence that border closures have also disrupted supply chains of precursor chemicals (Canadian Centre on Substance use and Addiction, 2020). Finally, there may be other reasons that overdoses are increasing in 2020, unrelated to COVID-19. Our search strategy did not capture non COVID-19-related possibilities.

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### Ethical approval

Ethical approval was not obtained for this study, as it is a rapid review of the published literature.

### Declarations of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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### Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.drugpo.2021.103236.

### References

A State-by-State Look at Coronavirus in Prisons. (2020, May 1). The Marshall project. https://www.themarshallproject.org/2020/05/01/a-state-by-state-look-at-coronavirus-in-prisons.

Ahmad, K., Bach, P., Brar, R., Chow, N., Coll, N., & Compton, M. (2020). Risk mitigation: In context of dual public health emergencies. Alexander, G. C., Stoller, K. B., Haffajee, R. L., & Saloner, B. (2020). An epidemic in the midst of a pandemic: Opioid use disorder and COVID-19. Annals of Internal Medicine, 172(1), 57-58. 10.7326/m20-1141.

Bandara, S., Kennedy-Hendricks, A., Merritt, S., Barry, C. L., & Saloner, B. (2020). Early effects of COVID-19 on programs providing medications for opioid use disorder in jails and prisons. Journal of Addiction Medicine Publish, Ahead of Print. 10.1997/ADM.0000000000000718.

Bao, Y., Williams, A. R., & Schackman, B. R. (2020). COVID-19 could change the way we respond to the opioid crisis—For the better. Psychiatric Services. 10.1176/ps.ps20200026.

BC Coroners Service. (2021). Illicit drug toxicity deaths in BC January 1, 2020—December 31, 2020. BC Coroners Service. https://www2.gov.bc.ca/assets/gov/birth-adoption-death-marrige-and-divorce/deaths/coroners-service/statistical/illicit-drug.pdf.

Bons, M., Palayew, A., Bartlett, S., Brothers, T. D., Touennard, N., & Tyndall, M. (2020). Addressing the syndemic of HIV, hepatitis C, overdose, and COVID-19 among people who use drugs: The potential roles for decriminalization and safe supply. Journal of Studies on Alcohol and Drugs, 81(5), 556-560. 10.15288/jsad.2020.81.556.

British Columbia Centre on Substance Use. (2020). COVID-19: Information for opioid agonist treatment: Prescribers and pharmacists. British Columbia Centre on Substance Use. https://www.bccentre.ca/wp-content/uploads/2020/03/COVID-19-Bulletin-March-19-2020.pdf.

Buxton, J., Moe, J., Papamihali, K., & Kuo, M. (2020). The physician’s role in supporting people who use substances in a dual public health emergency. British Columbia Medical Journal. BCMJ, 62(6), 207–208.

Canadian Centre on Substance use and Addiction. (2020). CCENDU alert: Changes related to COVID-19 in the illegal drug supply and access to services, and resulting health harms. Canadian Centre on Substance Use and Addiction. https://www.ccasa.ca/sites/default/files/2020-05/CCSA-COVID-19-CCENDU-Illlegal-Drug-Supply-Alert-2020-en.pdf.
Clinicians need to be aware of the potential for drug use to be a trigger for overdose-related harms. Programmatic and policy-level approaches to enhance overdose-related harms are necessary to mitigate the negative impacts of the COVID-19 pandemic on drug use and overdose risk.