Canadian Psychiatric Association
Association des psychiatres du Canada

Perspective

The Canadian Journal of Psychiatry / La Revue Canadienne de Psychiatrie
1-5

DOI: 10.1177/07067437231188202
TheCJP.ca | LaRCP.ca
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A Call for an Evidence-Based Strategy Against the Overdose Crisis

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Keywords
safe supply, overdose crisis, evidence-based medicine, substance use disorders, mortality

Introduction

The current overdose crisis is one of the most devastating public health challenges in the field of mental health and substance use disorder care in history. Globally, about 1 in 5 deaths is attributable to substance use, with more than 70% attributable to opioids.[1] The dramatic increase in mortality in Canada and the USA since 2015 is primarily due to changing drug markets and related patterns of substance use, and an ill-prepared system of care.[2] In the USA, the economic cost of drug abuse is estimated to be $193 billion dollars annually, which includes healthcare costs, loss of productivity and criminal justice costs.[3]

Fentanyl now dominates the pattern of use in most regions of North America and has become the drug of choice among many people who use drug (PWUD).[4] This shift towards high-potent synthetic opioids has not stopped at fentanyl, with ultra-potent synthetic fentanyl derivatives such as carfentanil as well as non-fentanyl-derived ultra-potent synthetic opioids such as Nitazene now becoming readily available.[5,6] The latter, from a drug class known as benzimidazole-opioids, is several times more potent than fentanyl and is undetectable using currently available fentanyl test strips.[5]

As a result, the climb in overdose deaths in North America have been dramatic, and one that is seemingly impervious to previous response measures developed by public health agencies.[7] For instance in BC, there were 2,306 and 2,272 overdose deaths in 2021 and 2022, respectively, almost 25% more than the previous record set only in 2020 (1,774).[8] These numbers have set off alarms among healthcare leaders in the province, leading to the adoption of initiatives intended to mitigate the harms associated with the illicit toxic drug supply. The most recent has been the provision of a 'safe supply' – the prescription of high-potent psychotropic substances outside of a therapeutic context in the hope of reducing overdose risk due to increased toxicity of the illicit drug supply.[9] While the logic of providing 'clean' drugs to protect PWUD from exposure to a 'tainted' illicit drug supply is irrefutable, the 'devil' is very much in the details. Should this approach be viewed simply as a short-term intervention or as a strategy that over the long-term will curb mortality significantly? In the latter case, how will safe supply be integrated into a long-term therapeutic context in contrast to defaulting into a stand-alone option? A vigorous debate over these questions, along with concerted and well-supported research efforts to secure much needed objective data, remains the only evidence-

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based approach to develop a clear path forward devoid of wishful thinking borne out of desperation.

The Current State of Care for Substance Use Disorders

While these changes in drug supply are of critical importance, other factors are also to blame. Significant gaps in the Canadian and American healthcare system, such as lack of access to proven clinical treatment options, also contribute significantly to the current unsuccessful response to the overdose crisis.[10] For instance, long waiting lists for opioid agonist treatment (OAT), low retention rates due to the quality of care, and insufficient access to mental healthcare and psychosocial interventions, which are evidence based and can significantly increase retention in OAT programmes, are concerning realities.[11]

When compared to Europe, treatment access and coverage in North America is significantly worse, and is far below the World Health Organization OAT coverage target of 40%.[12] Only a very small proportion of individuals with opioid use disorder (OUD) are receiving OAT, and access remains a challenge in many parts of Canada, particularly in rural and remote areas.[10,13] This is devastating given that evidence has shown that OAT can decrease the risk of overdose death by 50% to 80%.[14] Similarly, across 6 healthcare systems in the USA, the prevalence of receiving medication for OUD among patients with documented OUD varied between 3% and 36%.[15]

In addition to access and capacity, the quality of care and diversity of treatment options is sub-standard. The rise in OAT coverage largely reflects an increase in the number of clients dispensed buprenorphine/naloxone, while methadone prescriptions remain stable relative to 2015.[16] Access to other treatment options, particularly slow-release oral morphine, hydromorphone and diacetylmorphine remain very low.[16] The disappointing slow uptake is difficult to reconcile with findings obtained from naturalistic and liberal OAT settings that fail to confirm reliance on single medication categories, encouraging instead choice of preferred opioid agonist from a range of options.[17] It is noteworthy that although in 2019 Health Canada approved injectable hydromorphone and diacetylmorphine as treatment for severe OUD in adults, the number of patients receiving injectable OAT (iOAT) is low.[16] Indeed, in an open-label phase 3 randomized controlled trial in Canada (NAOMI study), the rate of retention among individuals receiving diacetylmorphine was 87.8%, as compared with 54.1% among those receiving oral methadone.[18] In Europe, although methadone is the main medication prescribed, significant regional differences exist with slow-release oral morphine, codeine, dihydrocodeine, buprenorphine and diacetylmorphine also widely used.[19] In North America, careful consideration should be given to expanding access to a diverse range of medications for OUD, while also urgently improving treatment quality and integrating addiction and mental health counselling in primary care. Retention in OAT, as well as withdrawal management, are also matters of great concern, especially in an era in which fentanyl is broadly available. To date, only few attempts are being made to adapt treatment options to the challenges posed by the high potency of fentanyl relative to heroin.[20] This is due in part to legal restrictions and a perennial lack of resources, despite a prolonged public health crisis.

The Concept of 'Safe Supply'

The current situation thus constitutes a high-potent opioid problem in conjunction with a system of care problem. In response, a concept popularly known as 'safe supply' has been implemented in BC.[9] The aim of this public health intervention is to protect individuals from a toxic illicit drug supply, while also preventing overdose and other harms. Though the current provincial guidance on the treatment of OUD still recommends buprenorphine/naloxone and methadone as first-line treatment options, the Risk Mitigation interim clinical guidance recommends the prescription of oral hydromorphone or slow-release oral morphine to reduce an individual's reliance on the illicit drug supply and associated harms.[9,21] Using similar logic, dextroamphetamine or methylphenidate have been added as potential practice options for patients with stimulant use disorder.[22] Moreover, a novel programme (Safer Alternatives for Emergency Response; SAFER) also provides fentanyl as a direct substitute to the primary opioid in the local unregulated drug supply.[23] Various formulations are available, including injectable, sublingual, oral and transdermal formulations.[23]

However, this approach is not based on large-scale effectiveness studies which rely on the gold standards of clinical research, as was conducted for the introduction of heroin-assisted treatments (HAT) in Canada. Indeed, the evaluation and implementation of HAT in Canada followed a stringent scientific agenda.[24] The Canadian Health Research Institute (CIHR) funded an randomized controlled trial (RCT) for HAT called the NAOMI study.[18] A few years later, the CIHR and the provincial government of BC then supported another RCT to test the efficacy and safety of heroin and hydromorphone supported treatment in the SALOME trial.[25] These studies published in NEJM and JAMA Psychiatry proved objectively that HAT could be implemented successfully, with no severe adverse events. In addition, the trials found high retention rates and patient satisfaction. These HAT protocols remain in use but the capacity for such high-quality care remains very limited. Overall, what was originally deemed to be a risky controversial approach gained legitimacy due to the high standard of clinical research, which is now widely recognized as being amongst the best evaluated intervention in the treatment of severe opioid dependence.

On the other hand, growing political support for safe supply seems to be towards the less complicated approach of simply making pharmaceutical grade opioids available more widely outside of clinical settings. However, there has been no published systematic review of safe supply and a 2022 rapid review of 19 studies found no evidence of benefits from the provision of pharmaceutical opioids, heroin, crystal methamphetamine, cocaine or other substances to people who are dependent on these substances.[26] Finally, leading experts across the USA and Canada seem to express caution in their recommendations from the Stanford-Lancet Commission on the North American Opioid Crisis, when stating that 'the evidence clearly shows the folly of assuming that population health inherently improves when healthcare systems provide as many opioids as possible with as few possible regulatory constraints as possible. Policies that should attract scepticism include the dispensing of hydromorphone from vending machines and prescribing a range of potent opioids and other drugs (e.g., benzodiazepines, stimulants) to individuals with OUD, in hopes of creating a safe addictive-drug supply'.[7] Moreover, an approach akin to safe supply has not been implemented internationally leaving the current policy with no international benchmarks or comparator. The Stanford-Lancet Commission warns against policies that ignore the therapeutic and overall medical needs of people using drugs, particularly given that the overdose crisis, especially in the USA, has been attributed to expanded access to and over-prescription of opioids.

The safe supply model largely advocates for the provision of take-home psychoactive substances. This bears a close resemblance to the drastic increase in access to addictive prescription drugs at the turn of the century, which led to increased harms through diversion, misuse, overuse, and thousands of overdose deaths.[7] Historically, North America has routinely failed to guard against misuse, diversion, addiction and death when providing increased access to addictive prescription drugs.

Integration of Pharmacotherapy and Psychosocial Care

Crucially, it is imperative that health and social care systems make an enduring commitment to provide services for PWUD that are fully integrated with mainstream care, accessible to all and target a range of outcomes. Portugal and Switzerland both successfully addressed their historic public health crises of the 1990s and 2000s, respectively, without resorting to the use of safe supply. Portugal decriminalized personal substance use and made it an administrative offence allowing in-person assessment, housing support, medical care, substance treatment, and vocational rehabilitation. Since then, rates of drug-related deaths and diseases have plummeted.[27,28] Switzerland decreed a new national drug policy in the 1990s which introduced harm reduction as a 4th pillar besides prevention, treatment and law enforcement. The medical prescription of diacetylmorphine to individuals with OUD in a regulated and controlled environment was the most controversial element of the new Swiss drug policy. Combined with other innovations such as overdose prevention sites (safe injection rooms), integrated basic healthcare, infection screening and social services, the overdose deaths in the country decreased by 50%, HIV infections decreased by 65%, and new heroin users decreased by 80%.[28,29] Both countries showed convincingly, that any successful model must also consider important medical and social issues (e.g., mental health, homelessness, incarceration, debt, etc.) that cannot be solved by use of medications alone.[7] This is in contrast to BC which has focused largely on harm reduction only, at the detriment of the other pillars. Supervised injection sites, safe snorting sites and kits, and now safe supply were 'firsts' in North America but the current numbers of overdose deaths in BC clearly shows the impracticality of harm reduction as the primary strategy without also focusing on the other dimensions.

The Lessons From COVID-19

The COVID-19 pandemic has proven the important role that clinical research and high-quality evidence can play in prevention and treatment during a public health crisis. Armed with clinical and epidemiological research from the beginning, the pandemic has shown that when all aspects of care are combined in a complementary manner, mortality is reduced and severe suffering diminished. The COVID-19 vaccine is a prime example, estimated to have prevented 14.4 million deaths from COVID-19 in the first year of vaccination.[30] This strategy was even more effective when combined with complementary public health policies like mask wearing, social distancing, public hygiene, adaptation of hospitals for the infected, etc. These assessments were based on science, and allowed for ongoing adaptations.

With the overdose crisis, decision-makers seemingly chose a different way. After criticizing the over-prescription of opioids in pain treatment as the main reason for initiating the crisis, which was and is being followed by lawsuits against the pharmaceutical industry, similar drugs are now being distributed as 'safe supply' without the supporting evidence from clinical studies. The need for an evidence-based approach advocated here, must be based on scientific principles. Simple beliefs are insufficient to justify the risk of adverse events, cost and structural decisions in healthcare. Clinical practice is trying to cope with these challenges but that is not a replacement for a systematic evidence-based, study-driven approach that informs decision making.

The development of effective treatments that is based on evidence (e.g., HAT) along with better prevention strategies and increased safety in a comprehensive system of care must be a priority. Despite the obvious appeal of

ensuring access to uncontaminated sources of opioids from regulated suppliers, coupled with the removal of unsafe products from the open market, it would be a grave mistake to lose sight of the many harms that would accompany unsupervised access to powerful synthetic opioids. As the old saying goes, if something sounds too good to be true, then it probably is.

Declaration of Conflicting Interests

MV has received consultation and speaker fees from Camurus. AP holds a US patent entitled "Tetrahydroprotoberbine Compounds and Uses Thereof " in the Treatment of Neurological, Psychiatric and Neurodegenerative Diseases (United States, US20150306092) and holds shares in Resilience Biosciences Inc., Canada, focused on tetrahydroprotoberberine drug development. MI declares receiving honoraria for presenting (BCCSU, WCAF, Indivior), receiving VCHRI Team Grant (Fentanyl Cohort Study), receiving CSAM grant (Development of Stigma Series), being awarded the UBC/VGH Foundation BMO Capital Markets Innovators Challenge (Clinical Application of a Compact, Quantitative, and Inexpensive Opioid Detector), receiving research stipend (BCCfE The Hope to Health Research & Innovation Centre) and participating in a regional consult meeting for Otsuka and Lundbeck. The other authors declare no conflict of interest.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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