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## CAN EXTENDED-RELEASE INJECTABLE MEDICATIONS HELP CURB UNITED STATES AND CANADA'S OPIOID OVERDOSE EPIDEMIC?

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### Abstract

Settings throughout the United States and Canada continue to face escalating overdose epidemics. Notably, history of overdose is associated with increased risk of fatal overdose. Unfortunately, despite frequent contact with health services and the well-known mortality benefits of medications for opioid use disorder (MOUD), only a fraction of overdose survivors is successfully linked to addiction care after leaving the emergency department. This may be partially explained by well-documented challenges of oral MOUD, including the need for frequent visits to the pharmacy to receive their medications, which may limit the flexibility to acquire or sustain employment, and therefore contribute to high rates of opioid addiction care discontinuation. This commentary discusses the potential fit of different extended-release injectable MOUD to circumvent limitations of oral formulations, and thereby improve linkage and retention in care of high-risk populations, such as opioid-overdose survivors.

### Keywords

buprenorphine; extended-release; medication for opioid use disorder; naltrexone; opioid use disorder; overdose

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Settings throughout the United States and Canada are facing an unprecedented and escalating public health epidemic of opioid-related morbidity and mortality. In 2018, over 52,000 lives were lost as a result of opioid overdose across these 2 countries, driven largely by an increase of illicit fentanyl in the street drug supply.<sup>1,2</sup> Of concern, a significant proportion of individuals who experienced a fatal overdose had had contact with health care services in the preceding year, yet a substantial proportion of these individuals left acute care settings without being seen, suggesting a critical missed opportunity for overdose prevention and linkage to addiction care.<sup>3,4</sup> Such dynamics raise questions about what is currently being done, and what ought to be done, to address this public health crisis.

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Despite the well-known mortality benefits of oral medications for opioid use disorder (MOUD, eg, buprenorphine, methadone),<sup>5</sup> only a fraction of people who present with a nonfatal overdose to emergency departments are successfully linked to addiction care. For example, a recent study from Massachusetts found that of the more than 17,000 individuals who survived a nonfatal overdose, less than one-third initiated MOUD in the 12 months after the overdose event.<sup>4</sup> Among those who did initiate oral MOUD, the median duration of treatment was less than 6 months. This is concerning given recent research demonstrating that a history of overdose is associated with an increased risk of a future fatal overdose,<sup>6</sup> with one recent study demonstrating 10% of overdose survivors will die within 1 year.<sup>7</sup> Sadly, these findings are not entirely surprising given that the barriers to access and retention in oral MOUD programs are well-documented.<sup>8</sup> Among these, common programmatic requirements including the need for frequent visits to receive their medication can limit the flexibility to acquire or sustain employment or facilitate ongoing education.<sup>9</sup> Additionally, significant costs are associated with existing oral MOUD programs, including both direct (eg, frequent pharmacy dispensation fees) and indirect (eg, travel, lost productivity/wages, childcare) costs. Together, these challenges contribute to low rates of MOUD initiation and/or high rates of attrition after oral MOUD initiation, placing individuals at increased risk for future overdose, and highlighting the need for innovative and tailored interventions for this high-risk population.

In this context, extended-release injectable MOUD formulations have generated clinical interest because of their potential to attract and retain high-risk individuals with opioid use disorder (OUD) in treatment, for whom daily adherence to a medication may be a challenge. Currently, extended-release injectable formulations exist for naltrexone and buprenorphine. While a priori, all extended-release MOUD have the potential to circumvent some of the traditional limitations of existing oral products, due to differences in their pharmacological and clinical profile, not all subpopulations of people with OUD will benefit equally from all of them.<sup>10</sup>

For instance, although research has shown that once initiated, extended-release naltrexone (XR-NTX, available as a once-monthly intramuscular injection) has similar effectiveness as oral buprenorphine, few patients are actually successfully induced onto this medication due to the need to be fully detoxified from opioids before the first injection.<sup>10</sup> In addition, there is concern about XR-NTX not being equally effective in preventing overdoses as opioid agonist MOUD, and a potential higher risk of overdose after discontinuation due to loss of opioid tolerance.<sup>11</sup> Likewise, the first buprenorphine extended-release formulation to be marketed, a 6-month sub-dermal implant, requires a surgical procedure and it is only indicated for patients with a long period of clinical stability on relatively low doses of sublingual buprenorphine (<8 mg/d), and for a maximum duration of 12 months.<sup>10</sup> These characteristics of XR-NTX and the buprenorphine implant suggest that neither of them may be the best option for most individuals presenting after a non-fatal overdose for whom relapse to opioid use may be associated with significant overdose risk, particularly in the fentanyl era.

More recently, 2 buprenorphine subcutaneous depot injection products were developed, one available as a once-monthly injection, and the other also incorporating a weekly dosing

option.<sup>10,12,13</sup> Before starting these injections, patients should receive at least one dose of oral buprenorphine to assess tolerance, though up to 7 days may be required. Some potential benefits of the 2 monthly injectable buprenorphine formulations include opioid blockade effects with just 1 injection, higher plasma buprenorphine levels, and prolonged therapeutic levels (up to 12–20 weeks) after the last injection once the steady state is achieved. This is particularly relevant given the higher mortality risk in the first 4 weeks of treatment of OUD, or in the four weeks immediately after leaving treatment.<sup>5</sup> These characteristics, in turn, make them attractive candidates for opioid overdose survivors. However, the evidence to support the use of buprenorphine depot injections is limited. There is only one randomized clinical trial evaluating the efficacy and safety of each intervention, of relative short duration (24 weeks), with one of the products having been only compared to placebo.<sup>12,13</sup> Of note, although the number of overdose events in these pivotal efficacy studies was small, none of them occurred in the experimental arms. Accordingly, a critical need exists for further research to confirm the potential of these novel treatment approaches in real-world settings and populations, including in overdose survivors. Fortunately, a number of clinical studies are currently underway to try to address some of these research gaps. These include the evaluation of the safety and tolerability of faster initiation schedules, the effectiveness and safety of extended-release injectable buprenorphine formulations among overdose survivors, those using highly potent synthetic opioids (eg, fentanyl), pregnant women, and individuals released from correctional settings or discharged from hospital. Alongside clinical research, there is a need for more qualitative studies to improve our understanding of patients' preferences and perceptions that may influence acceptability and uptake of these novel medications in different settings.<sup>14,15</sup> Given current higher costs of extended-release buprenorphine compared to available oral formulations, this information will be key for health care programming, and allow for targeting of those who might benefit the most from these innovative treatment options.

Despite substantial efforts to expand access to MOUD, naloxone and other harm reduction interventions across Canada and the United States, the opioid overdose epidemic remains one of the most pressing public health issues of modern times. To tackle this worsening crisis, there is a need for a more comprehensive response, including addressing its socio-economic drivers, continuous scale-up of evidence-based interventions, and implementation and evaluation of novel approaches. Although extended-release MOUD may not fully address existing access barriers to OUD care, given the potential benefits of extended-release injectable buprenorphine products, their role in the response to the North American's overdose epidemic should be further explored.

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## REFERENCES

1. Special Advisory Committee on the Epidemic of Opioid Overdoses. National report: Apparent opioid-related deaths in Canada (January 2016 to March 2019). Web Based Report. Public Health Agency of Canada. Published September 2019. Updated September 15, 2019. <https://>

- [health-infobase.canada.ca/datalab/national-surveillance-opioid-mortality.html](https://health-infobase.canada.ca/datalab/national-surveillance-opioid-mortality.html). Accessed September 26, 2019.
2. Ahmad F, Escobedo L, Rossen L, Spencer M, Warner M, Sutton P. Provisional drug overdose death counts. National Center for Health Statistics. Published 2019. <https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm>. Accessed September 2, 2019.
  3. Otterstatter MC, Crabtree A, Dobrer S, et al. Patterns of health care utilization among people who overdosed from illegal drugs: a descriptive analysis using the BC Provincial Overdose Cohort. *Health Promot Chronic Dis Prev Can*. 2018;38(9):328–333. [PubMed: 30226726]
  4. Larochelle MR, Bernson D, Land T, et al. Medication for opioid use disorder after nonfatal opioid overdose and association with mortality: a cohort study. *Ann Intern Med*. 2018;169(3):137–145. [PubMed: 29913516]
  5. Sordo L, Barrio G, Bravo MJ, et al. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. *BMJ*. 2017;357:j1550. [PubMed: 28446428]
  6. Caudarella A, Dong H, Milloy MJ, Kerr T, Wood E, Hayashi K. Non-fatal overdose as a risk factor for subsequent fatal overdose among people who inject drugs. *Drug Alcohol Depend*. 2016;162:51–55. [PubMed: 26993373]
  7. Weiner S, Baker O, Bernson D, Schuur J. One-Year Mortality of Opioid Overdose Victims Who Received Naloxone by Emergency Medical Services. Washington, DC: ACEP Research Forum; 2017.
  8. Sharma A, Kelly SM, Mitchell SG, Gryczynski J, O'Grady KE, Schwartz RP. Update on barriers to pharmacotherapy for opioid use disorders. *Curr Psychiatry Rep*. 2017;19(6):35. [PubMed: 28526967]
  9. Richardson L, Wood E, Montaner J, Kerr T. Addiction treatment-related employment barriers: the impact of methadone maintenance. *J Subst Abuse Treat*. 2012;43(3):276–284. [PubMed: 22301085]
  10. Institute for Clinical and Economic Review. Extended-Release Opioid Agonists and Antagonist Medications for Addiction Treatment (MAT) in Patients with Opioid Use Disorder: Effectiveness and Value. 2018. Published December 3, 2018. [https://icer-review.org/wp-content/uploads/2018/04/ICER\\_OUD\\_Final\\_Evidence\\_Report\\_120318.pdf](https://icer-review.org/wp-content/uploads/2018/04/ICER_OUD_Final_Evidence_Report_120318.pdf). Accessed October 7, 2019.
  11. Morgan JR, Schackman BR, Weinstein ZM, Walley AY, Linas BP. Overdose following initiation of naltrexone and buprenorphine medication treatment for opioid use disorder in a United States commercially insured cohort. *Drug Alcohol Depend*. 2019;200:34–39. [PubMed: 31082666]
  12. Lofwall MR, Walsh SL, Nunes EV, et al. Weekly and monthly subcutaneous buprenorphine depot formulations vs daily sublingual buprenorphine with naloxone for treatment of opioid use disorder: a randomized clinical trial. *JAMA Intern Med*. 2018;178(6):764–773. [PubMed: 29799968]
  13. Haight BR, Learned SM, Laffont CM, et al. Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2019;393(10173):778–790. [PubMed: 30792007]
  14. Neale J, Tompkins CNE, Strang J. Prolonged-release opioid agonist therapy: qualitative study exploring patients' views of 1-week, 1-month, and 6-month buprenorphine formulations. *Harm Reduct J*. 2019; 16(1):25. [PubMed: 30943990]
  15. Saunders EC, Moore SK, Walsh O, et al. Perceptions and preferences for long-acting injectable and implantable medications in comparison to short-acting medications for opioid use disorders. *J Subst Abuse Treat*. 2020;111:54–66. [PubMed: 32076361]