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EVALUATING SLOW-RELEASE ORAL MORPHINE TO NARROW THE TREATMENT GAP FOR OPIOID USE DISORDERS

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North America is in the midst of an unprecedented public health crisis of opioid-related morbidity and mortality, fueled by the increasing contamination of the drug supply with illicitly manufactured fentanyl and related analogues (1). It is estimated that more than 2.5 million Americans have an opioid use disorder (OUD) and that more than 33 000 died from an opioid-related overdose in 2015—quadrupling the rates from 1999 (1). The scale and trajectory of the opioid overdose epidemic in North America underscore the need for an urgent scale-up and evaluation of science-driven solutions (2). Lessons drawn from the response to the HIV epidemic and, more recently, the Ebola virus outbreak show that prompt identification of and access to effective interventions are cornerstone elements in responding to any public health emergency (3, 4).

Fortunately, evidence-based treatments for OUD exist. However, despite the proven individual- and community-level benefits of opioid agonist therapy (OAT)—with buprenorphine or methadone (5, 6)—several health system and regulatory barriers to this treatment persist throughout North America, significantly undermining the population-level effect of these programs (6). In addition, buprenorphine and methadone may not be effective for all patients, with some studies indicating that fewer than 50% of persons who begin OAT with these medications are still receiving treatment at 6 months (7). The barriers to successful uptake and long-term engagement with OAT in the United States have resulted in a large unmet treatment need, leaving an estimated gap of up to 1 million persons with untreated OUD, who continue to be at risk for overdose, death, and other negative health and social outcomes (6). Besides continued efforts to increase access to and expand the capacity of existing treatment programs, alternative evidence-based treatment options are needed to better address the different needs of persons with OUD. Recent U.S. Food and Drug Administration (FDA) approvals of long-acting formulations of buprenorphine and naltrexone are important steps in that direction (2, 5, 6). However, the evidence base for these medications is somewhat limited, and their higher relative costs may pose an additional burden to the health system (5, 6). Moreover, experience with these medications has predominantly been with persons with more stable OUD (5, 6). Therefore, a critical knowledge gap remains regarding the optimal treatment approach for persons with less stable disease, including those who have not benefited from buprenorphine- or methadone-based OAT.

In this context, slow-release oral morphine (SROM) has emerged as a promising candidate for oral OAT. Existing studies suggest that OAT has efficacy rates similar to those of methadone in suppressing illicit opioid use and retaining patients in care, with a better safety profile and greater improvements in several patient-reported outcomes, including tolerability, treatment satisfaction, and mental symptoms, as well as alleviation of cravings and withdrawal symptoms (8). These findings are highly relevant, because research has indicated that failure to meet patients' self-perceived needs is an important contributor to the high attrition rates observed in traditional OAT programs, which, in turn, are associated with a high risk for relapse and death (5, 7). Moreover, the lower risk for drug–drug interactions with SROM may represent an additional safety advantage over methadone, given the high prevalence of comorbid conditions among persons with OUD (such as HIV, hepatitis C virus infection, and mental health disorders) that may require concomitant medications (5). Although in these studies SROM was generally well-tolerated and safe, like other full-opioid agonists, it has the potential for overdose. As such, appropriate measures should be taken to prevent diversion and ensure the safe delivery of SROM.

On the basis of this growing evidence base (8), SROM-based OAT is increasingly and successfully used in several European countries and has recently been incorporated in Canadian treatment guidelines (9). Although SROM shows promise, only 4 randomized clinical trials have been conducted to date (only 1 double-blinded); therefore, it has considerably less supporting evidence than other OATs (8). In addition, none of the existing trials was conducted among persons with a documented poor response to other OATs, and none involved persons using illicit fentanyl. Collectively, these findings highlight the urgent need for more rigorous research to assess the relative effectiveness, safety, and acceptability of SROM-based OAT compared with existing treatment options in persons who have not had success with other OATs. Co-formulations of SROM and naloxone may be particularly attractive candidates and should also be explored. Indeed, the identification of an effective and safe second-line oral OAT within a continuum of treatment intensity for OUD is among the most urgent clinical questions in the context of the escalating opioid epidemic in North America (5, 6). Although how SROM as OAT would be regulated in the United States presently is unknown, its current regulatory status (that is, FDA approved for pain management without the strict regulations that limit accessibility to methadone and available as an inexpensive generic product) provides a timely opportunity to confirm the earlier promising findings. If this attempt succeeds, it would be consistent with recent calls to repurpose existing drugs to treat OUD (2).

With more Americans dying from accidental opioid-related overdoses than from motor vehicle accidents and homicides combined (1), it is clear that evidence-based solutions are urgently needed. Although expanding and facilitating access to current FDA-approved medications for treating OUD should remain a priority, evidence suggests that SROM may provide another valuable tool to narrow the OUD treatment gap. As we work toward evaluating and expanding treatment options for OUD, we also should draw on lessons about problematic regulatory burdens for methadone and buprenorphine and construct a more balanced regulatory framework for all OATs moving forward. The Canadian model, in which methadone is dispensed through daily witnessed ingestion in community-based pharmacies, could be adapted to the U.S. context (4). This approach might help expand

access to existing and future medications while preventing diversion and addressing overdose risk. Comparative effectiveness research in this area should be a key component of the public health response to the opioid overdose epidemic in North America.

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References

1. O'Donnell JK, Gladden RM, Seth P. Trends in deaths involving heroin and synthetic opioids excluding methadone, and law enforcement drug product reports, by census region—United States, 2006–2015. *MMWR Morb Mortal Wkly Rep*. 2017; 66:897–903. DOI: 10.15585/mmwr.mm6634a2 [PubMed: 28859052]
2. Volkow ND, Collins FS. The role of science in addressing the opioid crisis. *N Engl J Med*. 2017; 377:391–4. DOI: 10.1056/NEJMSr1706626 [PubMed: 28564549]
3. Gates B. The next epidemic—lessons from Ebola. *N Engl J Med*. 2015; 372:1381–4. DOI: 10.1056/NEJMp1502918 [PubMed: 25853741]
4. Williams AR, Bisaga A. From AIDS to opioids—how to combat an epidemic. *N Engl J Med*. 2016; 375:813–5. DOI: 10.1056/NEJMp1604223 [PubMed: 27579632]
5. Connery HS. Medication-assisted treatment of opioid use disorder: review of the evidence and future directions. *Harv Rev Psychiatry*. 2015; 23:63–75. DOI: 10.1097/HRP.0000000000000075 [PubMed: 25747920]
6. 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; 19:35.doi: 10.1007/s11920-017-0783-9 [PubMed: 28526967]
7. Timko C, Schultz NR, Cucciare MA, Vittorio L, Garrison-Diehn C. Retention in medication-assisted treatment for opiate dependence: a systematic review. *J Addict Dis*. 2016; 35:22–35. DOI: 10.1080/10550887.2016.1100960 [PubMed: 26467975]
8. Canadian Agency for Drugs and Technologies in Health. CADTH Rapid Response Report: Summary of Abstracts. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2017. Sustained Release Oral Morphine, Injectable Hydromorphone, and Prescription Diacetylmorphine for Opioid Use Disorder: Clinical and Cost-Effectiveness, and Guidelines. Accessed at <https://cadth.ca/sustained-release-oral-morphine-injectablehydromorphone-and-prescription-diacetylmorphine-opioid-0> [on 15 August 2017]
9. British Columbia Centre on Substance Use. A Guideline for the Clinical Management of Opioid Use Disorder. Vancouver, BC, Canada: British Columbia Centre on Substance Use; 2017. Accessed at www.bccsu.ca/wp-content/uploads/2017/06/BC-OD-UD-Guidelines_June2017.pdf [on 12 August 2017]