The authors respond to letters on using prescribed psychostimulants to treat stimulant use disorder

We thank Bahji and colleagues,[1] Elefante and colleagues[2] and Morin and colleagues[3] for their comments regarding our article in *CMAJ*.[4]

Bahji and colleagues[1] commented that the meta-analysis by Tardelli and colleagues[5] concluded that evidence to support prescription psychostimulants "is lacking." However, Tardelli and colleagues' conclusion states that "prescription psychostimulants, particularly prescription amphetamines given in robust doses, have a clinically significant beneficial effect to promote abstinence in the treatment of individuals with psychostimulant use disorder, specifically the population with cocaine use disorder."[5]

We acknowledge the point made by Elefante and colleagues[2] regarding the distinction between studies on cocaine versus those on methamphetamine use disorder. The lack of conclusions drawn by Tardelli and colleagues regarding effectiveness of prescription psychostimulants for the latter is driven primarily by the small number of studies on prescribed psychostimulants to treat methamphetamine use disorder at the time of their evidence review.[5] Evidence is accumulating, however. For example, in Sweden, a population-level, nationwide cohort recently found that lisdexamfetamine was associated with decreased risk of hospital admission and all-cause mortality for people with amphetamine use disorder.[6] However, distinguishing between cocaine and methamphetamine use disorders might be challenging in practice, given variable patterns of stimulant use, based on preference, cost and availability.[7] Furthermore, prescription psychostimulant preferences may not map directly onto patterns of unregulated stimulant use, suggesting that the suitability of prescription psychostimulants for individual patients may be more complex than making a diagnosis based on the most frequently used psychostimulant.[8]

Although the level of evidence to support prescription psychostimulants has not reached that supporting medications for other substance use disorders, such as opioid use disorder, the level of evidence available for opioid agonist treatment (OAT) does not need to represent the benchmark for action on implementation of prescription psychostimulants.

Despite much evidence from clinical trials to support OAT, logistical and political barriers have continued to limit OAT access in Canada.[9] Furthermore, the lack of applicability of clinical trial data to real-world settings is often used to discount or limit implementation (e.g., injectable OAT), and there is no reason to expect that this same barrier will not apply to implementation efforts for prescription psychostimulants. Prescribers and patients can jointly monitor medication effects and discontinue prescription psychostimulants if the risks are deemed to outweigh the benefits.

We agree with Morin and colleagues[3] that implementation studies are needed to continue to build protocols for the provision of prescription psychostimulants to people with stimulant use disorder in real-world settings. Morin and colleagues[3] refer to a study that makes an important contribution.[10] The study matched case and control patients on age, sex and index date of prescribed stimulants. When making direct comparisons, it is important that selection of control patients considers characteristics that might be associated with the outcome of interest. It is reasonable to assume that baseline cocaine use will be associated with the outcome of a urine test positive for cocaine, and thus it is unclear why attempts were not made in that study to balance baseline cocaine use indicators between case and control patients (31% v. 20% of urine tests positive for cocaine at baseline). The lack of conclusive evidence on this important outcome (which is, arguably, the most conservative indicator of change in substance use) does not suggest no potential benefit of prescription psychostimulants, as the study's authors conclude. Prescription psychostimulants may have a range of positive effects even in the absence of abstinence, as evidenced by several studies, including reductions in cocaine or methamphetamine use, improvements in health, and reductions in morbidity and mortality.[5] In line with approaches to evaluation of other substance use disorders, evaluations of prescription psychostimulants should account for outcomes beyond abstinence,[11] in line with patient goals.

With respect to points raised about the appropriate duration of treatment with prescription psychostimulants and the need for implementation protocols, we agree with Morin and colleagues that these are important questions. We suggest continued prescription psychostimulant implementation, given the known harms (e.g., cardiovascular risk, overdose) of long-term exposure to illegal cocaine and methamphetamine.[12] Implementation would allow for these important questions to be evaluated, monitored, documented and translated into evidence in real-world implementation studies to advance access to care in a timely manner, in line with the urgency of the ongoing risk of harm of the unregulated stimulant supply.

Regarding risk of psychosis for people using methamphetamine, we agree with the content of the article cited by Bahji and colleagues, which discussed risk of psychosis from unregulated methamphetamine.[13] We did not intend to imply that prescription psychostimulants will protect against psychosis. However, the risk of possible harm from prescription psychostimulants, including the risk of psychosis, must be weighed against preexisting risks faced by those accessing the illegal stimulant supply. If a patient is already experiencing harm (e.g., methamphetamine-associated psychosis), considering the potential benefit offered by prescription psychostimulants is reasonable, given that clinical trials of these drugs focused on populations with psychosis have not been initiated, and may never be. This is why we speak to the need for a balanced approach when considering the

mental health of patients with psychostimulant use disorder who currently lack access to alternatives to the unregulated stimulant supply.

We did not, as Elefante and colleagues[2] suggest, characterize prescription psychostimulants as "not associated with adverse events," but note, as stated directly in a 2016 Cochrane review, that prescription psychostimulants have "not been associated with serious adverse events."[14] Furthermore, Tardelli and colleagues noted that previous reviews found "no medication and placebo difference in dropouts due to any adverse events, cardiovascular events or serious adverse events."[5]

We agree with Bahji and colleagues'[1] call for broader psychiatric supports, medical care, housing and psychosocial treatments for people with psychostimulant use disorder. Nevertheless, inequities have been worsening in North America recently[15] and, in this context, the need for stimulant use disorder services and care remains imperative.[16] Clinical and public health practitioners can play a role in advocating for policy interventions that can address the social determinants of health, but these are broad social issues that require systemic change and will not be resolved quickly.

Direct patient care is within the scope of practice for prescribers who have an opportunity to make immediate impacts on their patients' lives by providing interventions. The persistent inequities in access to broader medical care, psychosocial treatment and housing further reinforce the imperative to provide interventions for psychostimulant use disorder. Attention to all possible interventions that may provide benefit to such patients (including prescription psychostimulants) is needed in the context of widening inequities, where people needing interventions are most often the ones left behind.

Looking ahead, development of much needed evidence, and clinical protocols to outline where and how it may or may not be suitable to provide prescription psychostimulants, would help to advance care and minimize harm for a population already facing poor outcomes.

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