ABSTRACT

In Canada, a rise in opioid use disorder (OUD) and overdose has been linked to opioid prescriptions in a number of contexts. At the same time, relatively few patients prescribed opioids reportedly develop OUD. This combination of findings suggests a pressing need for research on specific avenues through which medically prescribed opioids (MPOs) influence OUD and overdose in Canada. In this commentary, we therefore discuss a few of the potential processes that might allow for MPOs to indirectly influence rising overdose rates, and the processes that might account for inconsistencies between large correlational research and studies of OUD incidence in opioid-prescribed patients.

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Canada is currently facing an opioid crisis, with 2,816 opioid related deaths in 2016, or the equivalent of approximately 8 deaths per day.[1] To date, a number of links have connected the rise of this crisis to an increase in opioid prescribing by Canadian physicians.[2] This includes findings that deaths from opioid overdose are more common in areas where opioids are more frequently prescribed, that physicians who prescribe more opioids are more likely to have prescribed the last opioid before an individual's overdose death, and that higher-level doses and durations are correlated with increased drug-related mortality and morbidity.[2]

On first glance, these numerous associations might suggest a 'direct' relationship, wherein a patient unwisely prescribed opioids then develops OUD and is placed at higher risk for overdose. Surprisingly, however, reported rates of OUD amongst patients receiving prescriptions are quite low. In a 2012 Cochrane review, opioid dependence was found to have an incidence of 0–24% (median=0.5%) among of all opioid-prescribed patients.[3] Other reviews of specifically opioid abuse or addiction have found incidences ranging from 0.05-12%.[4] While these broad ranges likely reflect large variation in populations and/or prescribing patterns between studies, the generally low overall incidence suggests that the previously mentioned 'direct' mechanism of prescribing-to-overdose cannot represent the whole picture. Increased opioid prescribing may be connected to a rise in Canadian overdose rates, but it remains unclear exactly what processes are linking them together. In other words, it is still unclear exactly *how* medically prescribed opioids (MPOs) influence rising rates of OUD and overdose. In this commentary, we therefore discuss a few of the potential processes that might allow for MPOs to indirectly influence the rising overdose and OUD rates in Canada, or the processes that might account for inconsistencies between the large correlational research and studies of OUD incidence in opioid-prescribed patients. While not entirely comprehensive, this piece seeks to highlight gaps in the current research on opioid

prescribing, and call for new studies that address less obvious ways in which MPOs influence OUD and overdose in Canada. It is important to note that throughout this commentary, only medically prescribed opioids are discussed, rather than illicit prescription opioids.

Why Correlation and Incidence Might Not Match Up

First, diversion likely plays a critical role in transporting MPOs to those that did not receive a prescription. 'Diversion', a term used broadly, can refer to sold or gifted prescription opioids, often between family members or friends. Occasionally, the term is also used to describe patients who seek opioid prescriptions from multiple doctors (also known as "doctor shopping") or to refer to stolen prescription medication. Though no estimate for the rate of diversion in Canada currently exists, in the U.S. it was found that the quarterly event rate of MPO diversion increased from 1.5 to 2.5 per 100,000 population between 2002 and 2013.[5] The important role of this mechanism is further exemplified by smaller Canadian studies that found that the majority of children using MPOs obtained them from home, and that a main source illicitly obtained MPOs by Canadian adults is fraudulent prescriptions.[6] It has also been reported that in 2010, over half a million MPO doses went missing from Canadian pharmacies, and stolen doses of oxycodone from licensed dealers increased 14 times from 2005–2010.[6] One recent study of community pharmacists in Manitoba found that only 16.2% felt adequately trained in managing patients at risk for drug diversion.[7] Diversion is therefore one possible mechanism by which opioid prescriptions may be linked to increased prevalence of opioid overdose and deaths even if the individuals who received the prescription are unlikely to develop OUD. However, little research has explored the relative prevalence of each of diversion's unique components (i.e., sold, gifted, or stolen medications), or the extent to which each mechanism contributes to OUD and overdose.

Second, it is possible that studies of OUD incidence among those prescribed opioids often do not capture some patients at high risk of overdose, particularly when overdose is not preceded by OUD. In West Virginia (where prescription opioids contributed to 93 percent of overdose deaths), it was found that relatively few of the MPO-related deaths were preceded by iatrogenic addiction.[8] Overdose without the presence of OUD can occur when overly high dosages accompany improper MPO use, when there is a switch between MPOs of different potencies (e.g. methadone to oxycodone), or when MPOs are rapidly tapered off. For example, in Ontario, approximately five per cent of overdose deaths from 2006 to 2008 were preceded by a recent change in MPO,[9] and it is not unusual for patients suspected of aberrant drug-related behaviors to be quickly discharged from opioid therapy programs in North America before tapering can be properly managed.[10,11] Studies that seek to assess overdose risk by examining DSM or ICD diagnoses for OUD might therefore miss certain patients who might be at risk of sudden overdose. Likely due to methodological difficulty, little research to date has examined the risk of overdose without the presence of OUD.

Third, polydrug use involving MPOs likely plays a role in connecting medically prescribed opioids to overdose. For example, in the U.S. it was found that from 2001 to 2013, there was a sharp rise in the combined use of POs and benzodiazepines.[12] As above, it is possible that these patients are sometimes not captured by reviews of OUD incidence, however, it is more likely that polydrug use simply has not been examined in enough isolation to determine its effect. Because many physical symptoms of OUD are not considered pathological in the context of opioid therapy, diagnosing OUD in patients prescribed opioids can be difficult. Thus, studies of opioid misuse in pain management programs frequently use urine drug screens to measure aberrant drug-related behaviors (ADRBs).[10,11,13,14] In this case, polydrug use may be measured, but it is often confounded

with other ADRBs, such as failed pill counts or requesting opioids from multiple doctors. Thus, it remains unclear to what extent polydrug use really contributes to prescription-OUD in Canada.

Finally, the confusion regarding MPOs and OUD incidence could be a result of incorrectly equating drastically different definitions of OUD and populations under study. For example, many of the studies examining OUD incidence in pain care involve shifting definitions of "addiction" and unreliably include designations such as "dependence", "abuse", "misuse", or "problematic use" of MPOs.[2] Likewise, as might be suggested by the large variation in estimated incidence of OUD among opioid-prescribed patients,[4] there could be large variation between the different populations examined in these studies. Thus, it is possible that certain high-risk groups account for much of the influence of MPOs on rising overdose rates, but the effect remains uncaptured by studies of incidence since the inclusion of lower-risk populations and overly-broad definitions of opioid misuse are muddying the waters.

Though all of these factors (and potentially other social-structural determinants) undoubtedly play some role in connecting MPOs to the Canadian opioid epidemic, research has not adequately examined what these impacts are, or the optimal strategies with which to address them. In order to properly address these gaps, large prospective studies are needed to investigate the primary ways in which MPOs drive OUD in specific cases or high-risk populations, enter and influence the lives of those who are not prescribed opioids, and affect those who might overdose yet never get labelled as having OUD. As well, studies that specifically examine polydrug use with MPOs and estimate the rate of MPO diversion in Canada are needed. It is also essential that we examine more closely the tools that may allow physicians to assess the risk of patients developing prescription OUD (e.g. the Opioid Risk Tool), diverting, combining, or improperly using MPOs. Presently, there is no

fully validated screening tool for OUD risk-assessment[1], no gold standard for determining equianalgesic doses of different POs, and little evidence to guide physicians when initially prescribing opioids.[15] Finally, it is important to highlight the necessity of improved overdose prevention and OUD treatment in Canada. Despite the breadth of research and media attention on MPOs, the gaps in our understanding of the mechanisms through which they impact the opioid epidemic are alarmingly large. Only once we understand how a reduction in opioid prescribing functions to reduce the opioid crisis can we most effectively make that reduction happen.

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