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Correlations between population-levels of prescription opioid dispensing and related deaths in Ontario (Canada), 2005–2016

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ABSTRACT

Canada is experiencing an ongoing opioid-related public health crisis, including persistently rising opioid (e.g., poisoning) mortality. Previous research has documented marked correlations between population-levels of opioid dispensing and deaths. We examined possible correlations between annual population-level dispensing of specific opioid formulations and related poisoning deaths in Ontario (Canada), for the period 2005–2016. Annual coroner statistics-based numbers of poisoning deaths associated with six main opioid formulations (codeine, fentanyl, hydromorphone, methadone, morphine, and oxycodone) for Ontario were converted into annual death rates (per 100,000 population). Annual dispensing data for the opioid formulations under study were based on commercial retail-sales data from a representative, stratified sample of community pharmacies (IMSQuintiles/IQVIA CompuScript), converted into Defined Daily Doses (DDD/1,000 population/day). Possible relationships between the annual death and dispensing rates were assessed by Pearson's correlation coefficient analyses. Death rates increased for almost all, while dispensing rates increased for half of the opioid categories. A significant positive correlation between death and dispensing rates was found for hydromorphone ($r = 0.97$, 95% CI: 0.88–0.99) and oxycodone ($r = 0.90$, 95% CI: 0.68–0.97) formulations; a significant negative correlation was found for codeine ($r = -0.78$, 95% CI: −0.93 to −0.37). No significant correlations were detected for fentanyl, methadone, and morphine related deaths. Strong correlations between levels of dispensing and deaths for select opioid formulations were found. For select others, extrinsic factors – e.g., increasing involvement of non-medical opioid products (e.g., fentanyl) in overdose deaths – likely confounded underlying correlation effects. Opioid dispensing levels continue to influence population-level mortality levels, and need to be addressed by prevention strategies.

1. Introduction

In North America, high levels of opioid-related mortality (e.g., accidental overdose deaths) continue to contribute to an extensive disease burden on what is characterized as the 'opioid crisis', now in its second decade (Fischer and Rehm, 2017; Fischer et al., 2017a; Kolodny et al., 2015; Samet and Kertesz, 2018). Due to the persistently high burden from both opioid-related mortality and morbidity, which includes measurable reductions in life expectancy in sub-groups of the United States (US) population, public health emergencies have been declared in select Canadian provinces and the US nationally (BC Centre for Disease Control, 2017; Case and Deaton, 2015; Wetter et al., 2018). Concretely, there was a record-level of 37,273 opioid-related deaths in the US in 2016 (including 14,487 deaths related to natural and semi-synthetic opioids [e.g., oxycodone]; 3,373 methadone-related deaths; and 19,413 deaths related to synthetic opioids [e.g., fentanyl or fentanyl analogs]), constituting an approximately eight-fold increase since 2000 (Hedegaard et al., 2017). In Canada, there were a total of 2,946

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opioid-related deaths in 2016 (PHAC, 2018); this number has further steeply increased to 3,987 in 2017. While different in total numbers, the opioid-related mortality toll is similar in the US and Canada if measured on a per capita basis. While dispensing-levels of medical opioids (i.e., prescription opioid [PO]) consistently rose in North America for many years to global record levels, these recently (e.g., post-2012) plateaued or even decreased in select jurisdictions (International Narcotics Control Board, 2014, 2018). Yet, continuous increases in levels of opioid-related deaths in North America have, partially, been fueled by increasing availability and use of clandestine and highly potent opioid products (e.g., synthetic fentanyl or analogs, but also heroin) (Dart et al., 2015; Fischer et al., 2017b; Gladden et al., 2016; Rudd et al., 2016). However, large proportions of opioid-related mortality in both Canada and the US continue to be associated with various PO analgesics originally dispensed by medical sources.

A series of studies — involving various population-level data from different North American jurisdictions covering assessment periods up to about 2010 — have demonstrated correlations between population-levels of specific PO formulations dispensed and corresponding opioid-related mortality (Fischer et al., 2013, 2014b; Gomes and Juurlink, 2016; Modarai et al., 2013). These included instances where levels of opioid-related dispensing varied substantially over-time. In essence, these data collectively corroborated that general population-levels of exposure to specific types of opioids are a main driver of related mortality outcomes which, consequently, can be reduced by (measured) reductions in exposure or dispensing. Since then, further studies have added to this body of evidence. For example, Bohnert et al. (2014) ascertained moderate correlations between the average proportion of patients receiving methadone (Poisson regression coefficient (β) = 0.63, 95% Confidence Interval (CI): 0.37–0.90) and non-synthetic opioids (β = 0.53, 95% CI: 0.35–0.70) and rates of opioid-related overdoses among Veterans Health Administration patients (2001–2009) (Bohnert et al., 2014). Sauber-Schatz et al. (2013) found significant associations between the rates of opioid and oxycodone medication units dispensed and corresponding death rates at the county-level in Florida in 2009 (Sauber-Schatz et al., 2013). Gladstone et al. (2015) determined significant correlations between opioid dispensing and opioid-related mortality levels in 89 small geographic regions in British Columbia (Canada) from 2004 to 2013, despite major inter-regional variations (Gladstone et al., 2015).

A specific case concerning possible correlation between population-level opioid exposure and related mortality involves methadone, a PO used for both the treatment of opioid use disorder (OUD) and pain (Chou et al., 2015; Schuckit, 2016; Veilleux et al., 2010). While few statistical correlation analyses exist, some empirical illustrations come from the US. For example, the total number of annual methadone-related deaths in Vermont rose 14-fold (from 2 in 2001 to 29 in 2006), with a 300% increase in the proportion of methadone of all overdose deaths during that period; this multifold increase has been explained with substantial expansions of methadone usage in addiction and pain care (Madden and Shapiro, 2011). Similarly, Green et al. (2011) observed a 379% increase in methadone-related deaths in Connecticut, from 14 (1997) to 67 (2007), explained by substantial parallel increases in methadone dispensing during this period (Green et al., 2011). Conversely, Strang et al. (2010) demonstrated that despite a 7- and 18-fold increase in methadone dispensing, methadone-related deaths decreased significantly ($p < 0.05$) in England and Scotland, respectively, between 1993 and 2008 (Strang et al., 2010). This inverse relationship has been explained with substantial changes in methadone provision practice (e.g., supervised consumption). In Ontario, methadone-based treatment for opioid disorder has been extensively expanded in recent years and increases in methadone-related deaths have been observed (Albion et al., 2010; Fischer et al., 2016a; Kurdyak et al., 2018; Leece et al., 2015).

Epidemiological data have demonstrated substantial increases in opioid-related mortality for Ontario – Canada's most populous province – in recent years, amounting to an extensive and rising disease burden (Fischer et al., 2015a; Gomes et al., 2017, 2014b). Based on recently available data, the present study's aim was to assess the correlation between the annual levels of dispensing of specific opioid formulations and related mortality in the general population of Ontario for the period 2005 to 2016.

2. Methods

For information on opioid-related deaths, we used statistical data from Public Health Ontario (the public agency mandated with surveilling and protecting public health in Ontario) reporting the annual number of opioid-related deaths in Ontario for the years 2003 to 2016, as compiled from the Office of the Chief Coroner of Ontario (Public Health Ontario, 2018a, 2018b). The identification of opioid-related deaths followed a definition recently harmonized by provincial coroners' services across Canada (Canadian Institute for Health Information, 2018). The numbers of opioid-related deaths reported were by opioid formulation category (here specifically for the present analyses: codeine, fentanyl, hydromorphone, methadone, morphine, and oxycodone). However, opioid categories identified to be implicated in deaths are not mutually exclusive and multiple drugs may have been present in a single death. We excluded available data on hydrocodone, as its use and related deaths in Ontario were limited compared to others.

For correlations with PO dispensing, we used commercially available data on annual retail dispensing of POs by opioid formulation in Canada, from 2005 to 2016. Data on PO product dispensing came from CompuScript, provided by QuintilesIMS (new name: IQVIA), which monitors prescription-based retail transactions for branded and generic medications, and has been used for previous analyses assessing PO dispensing in Canada (Canadian CompuScript, 2016; Fischer et al., 2011; Gomes et al., 2014c; IMS Brogan, 2016). Although the QuintilesIMS data did not include non-retail (e.g., hospital- or emergency care-based), dispensing sources, it captures the majority portion (about 80%) of overall POs dispensed by prescription by way of retail pharmacies in Canada (Fischer et al., 2011). The CompuScript panel is drawn from a representative, stratified sample (including a continuously refreshed sub-sample) of approximately 6000 retail pharmacies – representing about two-thirds of the total of retail pharmacies - in Canada based on the large majority of prescriptions occurring at the national level. Following quality control checks, the monthly sample data, based on patented geospatial projection methodology, is projected to the universe of pharmacies by province. Since the retail dispensing data's representativeness is high (given the sample approach described), the sample error is considered low (not exceeding 5–10% in select instances) (Canadian CompuScript, 2016; IMS Brogan, 2016).

Annual aggregate dispensing data were provided in monthly summary totals of both the number of opioid medication prescriptions and units dispensed by opioid-formulations (e.g., codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, and oxycodone), product name (including 173 products), strength and form, selected here specifically for Ontario only. Based on the World Health Organization's Anatomical Therapeutic Chemical (ATC) classification methodology, data for each of the PO formulations were converted to values of 'Defined Daily Doses per 1,000 populations per day (DDD/1,000 pop/day)' (WHO Collaborating Centre for Drug Statistics Methodology, 2017). DDDs are the assumed average dose for a drug used for its main indication for an average adult, and considered a standard measurement to examine and compare consumption of different PO types (WHO Collaborating Centre for Drug Statistics Methodology, 2017, 2018). Respective drug product and ATC classification information for conversion came from Health Canada (Government of Canada, 2010), with ATC codes as follows: Codeine combinations N02AA59; Fentanyl N02AB03; Hydromorphone N02AA03; Methadone N07BC02; Morphine N02AA01; and Oxycodone N02AA05. DDD values for each opioid