

Narrative Review


Prescription Opioid Related Misuse, Harms, Diversion and Interventions in Canada: A Review
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Disclaimer: The authors acknowledge research funding from the Canadian Institutes of Health Research (CIHR), specifically Team Grant #94814, supporting the development of this manuscript. Dr. Fischer furthermore acknowledges salary support from a CIHR/PHAC Chair in Applied Public Health. The authors have no conflicts of interest to declare.
Conflict of interest: None.

Manuscript received: 03/07/2012
Accepted for publication: 04/03/2012

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Background: The non-medical use of and harms related to prescription opioid (PO) analgesics – key medications to treat severe and chronic pain - are an emerging public health concern globally. PO use is proportionally highest in North America, where, consequently, nonmedical PO use (NMPOU) and morbidity/mortality are high and well documented for the United States. Canada is the country with the second highest PO consumption rate in the world – with steeper recent increases in PO use than the US - mainly driven by substantial increases in the use of strong opioids (e.g., oxycodone). Indications and select data of NMPOU and PO-related morbidity and mortality have emerged in recent years, yet a systematic and comprehensive collection of relevant data to characterize the phenomenon in Canada does not exist.

Objectives: This paper comprehensively reviews the available data in Canada regarding NMPOU, and PO-related harms, diversion, and interventions, and discusses implications for interventions and policy.

Study Design: Narrative literature/data review.

Setting: Canada.

Methods: Publicly available data and information – either from journal publications, “grey literature” (e.g., government/technical reports) or Web sites reporting relevant data on Canada - were searched and narratively reviewed.

Results: Indicators on NMPOU and PO-related harms in Canada are highly fragmented, and not nearly as systematic and comprehensive as they are in the US; virtually no national statistics/data are collected. Available –largely provincial/local - data indicate that PO misuse is increasingly common in key populations, including general adult and student populations, street-drug users, First Nations/Aboriginal Peoples, and correctional populations. Co-morbidities – e.g., pain, mental health problems, polysubstance use – among people reporting NMPOU appear to be high. Substance use treatment admissions for those with problematic PO use have risen substantially where reported. Opioid-related mortality (and oxycodone-related mortality, specifically) have increased considerably in Ontario where relevant data from the mid-1990s onward have been examined. In Canadian populations reporting NMPOU, sourcing of POs occurs through various diversion routes, including from family/friends, “double-doctoring,” or street drug markets. In addition, losses and theft/robberies from pharmacies and licensed medications dealers appear to be on the rise. Finally, interventions (i.e., provincial PO guidelines, prescription monitoring programs, substance use treatment services) are fragmented and inconsistently applied throughout the country, and currently fail to effectively address the growing problem of NMPOU and PO-related harms across Canada.

Limitations: This review did not rely on systematic review methodologies.

Conclusion: Corresponding to its increasing and high overall PO consumption levels, NMPOU and PO-related harms in Canada are high based on available data, and likely now constitute the third highest level of substance use burden of disease (after alcohol and tobacco). The data and monitoring situation in Canada regarding NMPOU and PO-related harms are fragmented, un-systematic, and insufficient. While major and concerted policy initiatives – primarily from the federal level - are absent to date, these urgently require vastly improved national data indicators and monitoring in order to allow for and evaluate evidence-based interventions on this urgent and extensive public health problem.

Key words: Prescription opioids, pain, non-medical use, epidemiology, public health, morbidity, mortality, treatment, policy, Canada

Pain Physician 2012; 15:-ES191-ES203

www.painphysicianjournal.com

In recent years, the misuse of prescription drugs has been emphasized as a major and “growing health problem” globally by leading international monitoring entities (1,2). This problem concerns primarily the misuse of prescription opioid analgesic drugs (POs) – i.e., pharmaceutical opioids designed and clinically used for the treatment of severe and/or chronic pain (SCP) (3-6) – the overall production and distribution of which has increased extensively in the past 20 years. For example, the global production of morphine worldwide has more than quadrupled from 168 tons in 1993 to a projected 788 tons in 2012; the global production of oxycodone rose by over 4,000% from about 6 tons in 1993 to an estimated 261 tons in 2012 (7,8). The primary focus and concern regarding PO misuse, and related harms, has been in North America, and specifically the United States, where data from the past decade have documented major increases in nonmedical PO use (NMPOU) in general (including adolescent student) populations; morbidity (e.g., PO-related admissions to emergency rooms and substance use treatment programs); and mortality (e.g., PO-related acute poisoning or overdose deaths) (9-12). According to recent data, 14,800 PO-related acute poisoning deaths occurred in the US in 2008, a figure that is greater than deaths from other drugs combined and a leading cause of unintentional death, second only to the number of deaths from motor-vehicle accidents (9,13,14).

While the US, arguably, has the best available data on PO misuse and harms globally, there is wide consensus that the extensively high level of problems is distinctly associated with the uniquely high volume level of POs consumed in the US population, which is higher than anywhere else in the world (8,11,15). According to data from the International Narcotics Control Board (INCB), the US consumed 47,809 Standardized Defined Daily Doses (S-DDD) of POs in 2008-2010, a 112% increase from 22,524 S-DDD in 2000-2002 (8). Canada is home to the overall second highest level of PO use globally; total POs consumed in Canada increased from 8,713 S-DDD (2000-2002) to 26,380 S-DDD in 2008-2010 – a 203% increase, which is steeper than that observed in the US (8). Similarly, per capita spending on POs doubled from CDN \$7.00 (1998) to CDN \$14.70 (2007) (16). However, even countries like Australia – which features < 50% of Canada’s PO use rate – have reported recent increases in PO-related harms (e.g., increasing misuse and accidental deaths) (17). A recent analysis of provincial patterns of PO dispensing in Canada between 2005 and 2010 has demonstrated that there was

an overall substantial increase in PO use mainly driven by increased dispensing of strong opioids; however, PO dispensing levels – in both quantitative and qualitative patterns – varied considerably between provinces. For example, Ontario and Alberta dispensed 2.5 times as many POs compared to Quebec, whereas select POs (e.g., hydrocodone or meperidine), were consumed at high levels in some provinces but not in others (18). On this basis, there is good reason to systematically examine the situation and available indicators of PO misuse and harms in Canada, especially since no comprehensive review and synthesis of relevant indicators exist to date, yet are important both for guidance of domestic interventions as well as international comparison.

Importantly, problems of misuse and health harms related to POs need to be carefully examined in the wider context of the purpose for which these drugs primarily exist. Namely, POs are the primary medications for the treatment of SCP, a preeminent health problem – recently recognized as the “fifth vital sign” for which access to and quality of care has long been lacking (19-22). In Canada, some 15-29% of the general population are estimated to have SCP (23,24), however, access to specialist pain treatment is highly limited and inadequate. Studies of SCP patients have found extensive wait times for pain care; 50% of patients had to wait 6 months or more – often years in some settings – and large regions of Canada have no specialist pain care at all (25-27). While physician survey data from Ontario suggest that most general practitioners (95.4%) were currently involved in prescribing POs, a large proportion are hesitant or have concerns regarding PO prescribing. Their concerns include patients’ potential PO misuse and addiction, the lack of specialized pain and addiction treatment, as well as increasing government control dispositions that could quickly amplify and further negatively affect the delivery of pain care in response to indications of rising PO problems (28).

Based on the above, the principal objective of this paper is to provide a comprehensive review of available data on PO misuse, related harms (i.e., morbidity and mortality), diversion, and interventions in Canada.

METHODS

Publicly available data and information – either from journal publications, “grey literature” (e.g., government or technical reports) or Web sites reporting relevant content – were searched and reviewed. Relevant data and information were structured and are presented below.

DATA**Epidemiology of NMPOU****General Populations**

Recent estimations – by way of data triangulation methods – suggest that NMPOU is estimated to be the fourth most prevalent form of substance abuse (after alcohol, tobacco, and cannabis), in the general Canadian population, representing higher prevalence values than illicit drugs like cocaine and heroin (29,30). Specifically, some 500,000 – 1.25 million people are estimated to use POs nonmedically in Canada, of which 125,000 – 200,000 may be dependent (according to DSM-IV criteria) and are likely to be in need of treatment (30).

The only Canada-wide primary data on NMPOU in general populations come from the Canadian Alcohol and Drug Use Monitoring Survey (CADUMS), a representative annual general population telephone survey of adults 15 years and older, including items on PO use since 2008 (31). In 2010, one in 5 (20.6%) Canadians ($n = 13,615$) reported any PO use in the past 12 months; among those, 1.1% - or 0.2% of the total Canadian population - reported using them “for the feeling they caused” or “to get high” (32). The latter data represent slight declines from earlier years (e.g., 2008: 1.5%; 0.3%) (31). The Centre for Addiction and Mental Health’s “CAMH Monitor” (CM) – a representative telephone survey of the general population in the province of Ontario, aged 18 and older ($n = 2,037$) - found slightly higher values (21.1%/1.7%) for the same indicators in 2009 (33). Unfortunately, these survey indicators reflect suboptimal operationalizations of NMPOU (e.g., as compared to the National Survey on Drug Use and Health in the US) (34), and likely underestimate the extent of NMPOU (35). In 2010, the CM assessed NMPOU based on a modified question item (participants were asked whether they used POs in the last year without a prescription or a doctor telling them to do so) in a subsample ($n = 1,024$). This approach – more analogous to standard NMPOU items used in the US surveys - resulted in an NMPOU prevalence rate of 6.5% of the Ontario general population, thus highlighting the important role of NMPOU definitions in the assessment of this phenomenon (12,36,37).

Secondary Students

Several provincial Canadian surveys have assessed NMPOU among secondary (i.e., high school) student populations. In the Ontario Student Drug Use and Health Survey (OSDUHS) – a representative survey of

grade 7 – 12 students ($n = 9,288$) collected from October 2010 through June 2011 14.0% of Ontario students reported NMPOU (defined by “use without a doctor’s prescription”) in the past year; this rate constituted a statistically significant decrease from 2009 (17.8%). No significant difference in use was found between male and female students in 2009; however, use increased with grade level, peaking at 18.0% among 11th-graders (38). In 2007, a question similar to the OSDUHS item was included in the Atlantic Provinces Survey (i.e., Nova Scotia, New Brunswick, Newfoundland, and Prince Edward Island), where 17%-20% of students indicated PO use; however, these data did not exclusively refer to nonmedical usage only (39,40). Among British Columbia (BC) students in grades 7 – 12 reviewed by the BC Adolescent Health Survey, the proportion who had ever used prescription pills (no further specification on drug type) without a doctor’s consent increased from 9% in 2003 to 15% in 2008 (41).

Street Drug Users

A recent triangulation of secondary data - based on overdose death, key informant, and survey data – estimated that the prevalence of nonmedical use of POs among street drug users had increased by approximately a quarter (24%) in Canada’s most populous provinces between 2002 – 2005 (42). Several Canadian street-involved drug user surveys have assessed NMPOU in their target populations. The OPICAN study – a multi-site study of street-involved illicit opioid and other drug users ($n = 585$) conducted in 7 Canadian cities between 2001 and 2005 – found that the prevalence of heroin use in the past month decreased and that the use of POs increased significantly, surpassing the rate of heroin use, in 5 of the 7 urban samples over the study period. In 2005, the main PO drugs reported for use by the total OPICAN sample were Dilaudid (37.4%), Tylenol 3 or 4 (29.4%), Percocet/Percodan (25.0%), and Morphine/MSContin and OxyContin (both 22.4%); in comparison, 29.9% reported heroin use. However, the prevalence of using individual POs was reported to vary greatly among study sites. For example, Dilaudid (hydromorphone) use was reported by 5.0% in Vancouver, BC and 91.5% in Fredericton, New Brunswick (43). PO use was more prevalent than heroin use in all study sites in 2005 except for Vancouver BC and Montreal, Quebec (44).

The Public Health Agency of Canada’s I-Track Survey, a surveillance study (2003 – 2005) to monitor risk behaviors among injection drug users (IDUs) recruited

from needle exchange programs in 7 Canadian cities (n = 3031) (45) found that several POs were reported among drugs injected in the past 6 months in the total sample, including morphine (45.9%), hydromorphone (32.9%) and oxycodone (17.1%). However, the prevalence of these drugs varied considerably between local sites, e.g., oxycodone ranged from 0.4% in Victoria (British Columbia) to 58.7% in Sudbury (Ontario). Correspondingly, POs were commonly reported among drugs not taken by injection in the past 6 months. Specifically, 51.5% reported the use of codeine, morphine (31.5%), oxycodone (27.8%), and hydromorphone (23.6%) (45); these rates also differed substantially by site. Data from the SurvUDI, an epidemiological surveillance study among IDUs in the province of Quebec (n = 4,956) conducted between 1995 and 2008, also found that heroin use had decreased, and the injection of POs – e.g., hydromorphone – had increased substantially among IDUs, from 25% in 2003 to 42% in 2007 (46). Self-reporting of lifetime PO use by participants was 66.3% (47).

First Nations/Aboriginal People

There have been mounting indications that NMPOU occurs at disproportionately high levels in First Nations/Aboriginal People's (FNAP) communities in Canada, although data are sparse. In some of the FNAP communities in the Nishnawbe-Aski Nation (NAN) in Northern Ontario, it has been estimated that up to 50%-75% of the adult population, and up to half of high school students, are involved in misusing POs; many of them have severe problems or dependence (48). A recent survey conducted in Matawa First Nations (constituting 9 NAN communities) estimated that 1,888 individuals – or an average prevalence of 37.6% – in these FNAP communities are addicted to POs, mainly to oxycodone (49). On this basis, it has been estimated that some 9,000–10,000 FNAP in the NAN region (with a total population of 45,000) are addicted to POs (49). This situation, together with the extensive health and social harms experienced in NAN communities, has prompted the NAN First Nations Chiefs-in-Assembly to declare a “state of emergency” with regards to the problem of PO misuse in 2010 (48). Recent data from the FNAP Non-Insured Health Benefits Program reported that 898 PO prescriptions were dispensed per 1,000 individuals in Ontario FNAP regions (Moose Factory Zone, Sioux Lookout Zone, Southern Ontario Zone, and Thunder Bay Zone) in 2007; the rate was 119/1,000 for oxycodone formulations alone. On this basis, PO prescription rates in these

FNAP regions were much higher than elsewhere in Canada (50).

Correctional Populations

Data from a sample of male offenders (n = 1,272) enrolled in methadone maintenance treatment (MMT) within the federal Correctional Service of Canada (CSC) inmate population between 2003 and 2008 assessed changes in PO use prior to the offenders' most recent correctional admission and by region. Overall, PO use – principally morphine/hydromorphone and oxycodone – increased during this period, from 47.4% to 55.0% for morphine/hydromorphone and 10.3% to 21.0% for oxycodone; heroin use declined (from 67% to 44%) over the study period. Past-year PO use (morphine/hydromorphone) was found to be highest among inmates in the Atlantic (83%) and Prairie (77%) regions (51).

PO-Related Morbidity

PO use can be associated with a number of morbidity indicators, e.g., PO use can lead to problematic use or dependence – and consequentially require treatment – or be related to other health problems or consequences, such as pain, mental health problems, or infectious diseases. A recent review found disproportionately elevated levels of pain and mental health comorbidity indicators associated with PO use in different populations (52). Several recent US studies have found substantive increases in both PO-related substance use treatment and emergency department admissions in the past decade (9-11). Unfortunately, little such data are systematically documented for Canada, either because they are not consistently or comparably documented across provincial jurisdictions, or not routinely collected at all.

Treatment

The demand for PO problem-specific treatments appears to have increased in Canada in recent years. Specifically, the number of individuals enrolled in MMT in Ontario has risen substantially from approximately 7,800 in 2001 to 35,228 in 2011; these major increases in MMT admissions are considered to be largely driven by individuals with problematic PO use (32,53,54). Notably, evidence of substantial additional PO prescriptions and use among MMT patients in Ontario has been identified. Of the 18,759 patients (aged 15-64) who received at least 30 days of MMT between 2003 and 2010 (as covered by the Ontario Drug Benefit plan), 18.4% also received at least one non-methadone opioid prescription

of more than 7 days' duration, primarily in the form of codeine or oxycodone prescriptions (55). While some of these MMT patients may require additional PO prescriptions for severe/chronic pain care, others do likely not have an immediate clinical need and may utilize these drugs for misuse or diversion.

In addition, based on data collected from the Drug and Alcohol Treatment Information System (DATIS), PO-related admissions to publicly funded substance use treatment services (not including opioid substitution, e.g., MMT) in Ontario rose by 129% between 2004/05 and 2010/11 (from 8,886 to 20,374); their prevalence in the total caseload increased correspondingly, from 9.0% to 18.6% in this period (56). The annual proportion of oxycodone-related admissions into one of the largest urban opioid detoxification programs in Toronto increased substantially from 3.8% in 2000 to 55.4% in 2004 (57). Furthermore, a retrospective review of PO-dependent patients (n = 178, including patients with pain who meet DSM-IV criteria for opioid dependence) newly admitted to one of Toronto's largest MMT programs between 1997 - 1999, found that 83% had been using POs (either with or without heroin); PO users reported regular use of POs at much higher than therapeutic dosages (a mean daily consumption of 21 ± 3 oxycodone-containing tablets) (58).

NMPOU-associated Co-substance Use and Other Co-morbidities

Like other forms of psychoactive substance use, a substantive extent of NMPOU – regardless of population - co-occurs with other substance use, much of which is likely to be problematic and/or in need of treatment. For example, 74.5% of clients (compared to 46.5% of the total) admitted for substance use treatment due to PO-related problems in Ontario in 2008/2009 reported co-occurring substance use problems, mostly with crack/cocaine (46.9%) (59). Of those participants in the OPICAN cohort who engaged in NMPOU in 2001, 54.6% were also current users of crack or cocaine in the past 30 days (43). Based on data from the 2008/2009 cycles of the CM (n = 2,030 adults in Ontario), NMPOU was found to be significantly higher among men who used tobacco (6.5%, 95% Confidence Interval [CI] 1.6-11.3 versus 1.2%, 95% CI 0.3-2.1) and cannabis in the past 12 months (8.6%, 95% CI 2.3-14.4 versus 1.0%, 95% CI 0.2-1.8) (60). Among offenders enrolled in the CSC's MMT program – with an increasing use history of POs rather than heroin – 77% also reported a history of

problematic cocaine use in 2008 (51).

While the prevalence of pain co-morbidities among NMPOU populations has been reported to be relatively high (52,57,61), Canadian data is limited. In the OPICAN cohort – indicating high but not exclusive PO use – 15.2% reported at least moderate pain (43). Similarly, little data exists on co-occurring mental health problems. Some 64.5% of the total OPICAN cohort sample indicated mental health problems, with most (49.2%) reporting mood disorder, or depression problems (43). Among inpatients receiving detoxification treatment for problematic PO (i.e., oxycodone) use in Toronto between 2000 and 2004 (n = 428), 53% reported depressive symptoms and 25% reported anxiety, levels clearly above the general population average (57). Finally, a main co-morbidity concern for opioid use – especially in marginalized populations – is blood-borne-viruses (BBV), e.g., HIV or Hepatitis C Virus (HCV) transmission or infection (61). Substantial HIV (up to 20.3%) and HCV (up to 66.3%) infection rates have been determined in the PO use involved street drug user populations listed above (43,62). However, no systematic analyses have been conducted as to how the primary use of PO – e.g., as compared to other opioids/nonopioids – may predict or influence BBV transmission dynamics, e.g., by way of lesser injection use, or other risks of harms (43). Qualitative or narrative data from Canadian study samples have suggested evidence for possible associations in both directions, i.e. higher levels of PO use may be associated with either elevated or lowered risk for BBV transmission. Specifically, data conducted with PO users in recent years from Montreal and Toronto suggested that both the limited availability or affordability of certain POs on street markets, together with complicated preparation processes for use, may result in higher use frequency or risk, e.g., through increased injection equipment sharing and thus higher risk for BBV transmission (46,63,65).

Finally, a recent study has provided evidence for high levels of PO-related pregnancy problems among FNAP women. A study assessing 482 live births at the Sioux Lookout Meno-Ya-Win Health Centre, Northern Ontario, found that the incidence of PO abuse among the pregnant women there had increased from 8.6% in 2009 to 17.2% in 2010. Nearly a third, 29.5%, of neonates exposed to POs in utero had neonatal abstinence syndrome at birth; neonatal abstinence syndrome was observed among 66.0% of newborns whose mothers had used POs daily (66).

PO-Related Mortality

Unlike in the US – where accidental poisoning death data are documented nationally by the Centers for Disease Control and Prevention – such data are only collected provincially (by provincial coroners' services) in Canada. Moreover, provincial data analysis and documentation standards vary considerably among jurisdictions and hence only fragmented and inconsistent data regarding PO mortality are available in Canada. Select local – yet unsystematically documented – spikes in PO-related deaths, for example in Newfoundland, have been observed over the past decade (18,67). The sporadically available indicators suggest that PO-related deaths have consistently increased, and have been crudely estimated to now contribute to 30% – 50% of drug-related deaths in Canada (33,68).

A systematic study covering from 1991 through 2004 ($n = 3,406$ death cases) and based on coroners' data, documented that opioid-related deaths (e.g., morphine, heroin, oxycodone, codeine, methadone, fentanyl) doubled in the Ontario population, from 13.7 per million to 27.2 per million (67). Notably, other non-opioid depressants (e.g., benzodiazepines or alcohol) were involved in 92% of the observed opioid-related deaths in Ontario (67). Increases in opioid-related mortality in Ontario were found to be associated with the addition of long-acting oxycodone to the provincial drug formulary in 2000, as a disproportionate increase (of 416%, $P < 0.01$) in oxycodone-related mortality was observed between 1999 and 2004; overall opioid-related mortality increased only by 41% ($P < 0.02$) in the same period (68). More recently, based on coroners' data, opioid-related deaths in Ontario increased from 250 in 2005 to 325 in 2009 (a 30% increase); deaths related to oxycodone specifically rose by 49%, from 96 to 143 (69). Two retrospective studies examined the toxicological characteristics of 112 fentanyl (2002-2004) and 251 hydromorphone (1985-2003) death cases which occurred in Ontario (70,71). Both investigations found that the majority of deaths occurred in conjunction with other psychoactive drugs and/or by way of non-medical administration (e.g., injection).

A recent case-control study conducted in the Ontario population aged 15-64, found that the daily dose of POs (morphine, codeine, oxycodone, hydromorphone, meperidine, fentanyl) prescribed to those with non-malignant pain was strongly associated with risk for opioid-related mortality. Specifically, 1,463 individual death cases (out of a cohort of 607,156 prescribed least one opioid from 1997 through 2006) were identi-

fied; an average daily dose of > 200 mg of morphine equivalent was associated with nearly a 3-fold increase in the risk of opioid-related mortality (72). The prescribing patterns of opioids varies widely among family physicians in Ontario and opioid-related mortality has been found to be concentrated among those treated by physicians who prescribe opioids more frequently (72).

Elsewhere in Canada, data from the British Columbia's Coroner's Service indicate that 140 to 180 deaths annually were caused by prescription drugs from 2000 through 2010 (73).

PO Diversion

A review of data on PO sourcing for NMPOU purposes in North America revealed that sourcing occurs via various key routes and diversion mechanisms, including: "double doctoring," prescription fraud/forgery, street drug markets, thefts and robberies, and Internet purchases, making it a complex target for interventions (15). Importantly, US surveys have found that the majority of individuals in the general population engaging in NMPOU source their PO drugs informally from family or friends (15,75).

Data from 624 Ontario students in grades 7-12 (based on the 2007 OSDUHS) who had engaged in NMPOU in the past year showed that 72.4% sourced their drugs from home, while $< 0.5\%$ reported obtaining POs on the street (39). Other data suggest that while the main source of POs in Canada appears be fraudulently obtained prescriptions (or via "double doctoring"), street-drug markets may play a substantive role in supplying POs for NMPOU purposes (57). Based on data from a sample of 499 individuals admitted for opioid detoxification between from 2000 through 2004, 37% had sourced their POs from doctors' prescriptions, with other main sources being street (21%) or a combination of these sources (26%). The likelihood of obtaining POs from the street was found to decrease with age, while obtaining POs from doctors' prescriptions increased with age (57).

Different NMPOU subpopulations have reported different PO sourcing pathways. Between 8% and 40% of street drug users in the local OPICAN cohort sources (assessed in 2001; $n = 679$) reported sourcing POs from physicians, while 13%-45% reported obtaining POs from regular drug dealers (76). An exploratory Canadian study of nonmedical PO users in Toronto ($n = 43$) and Victoria ($n = 39$) in 2007 found that 79.1% in Toronto and 35.9% in Victoria used regular sources to obtain POs, indicating potentially differentiated patterns of PO sourcing

and relevant drug market cultures in Canadian cities (77). A qualitative study conducted between 2007 and 2009 among street-PO users in downtown Montreal (n > 60) recently documented that PO sales occur directly and easily on the street in a relatively “relaxed” environment, with less perceived violence commonly seen associated with street drug market activities (64). More than a decade ago, Sajan et al (78) already documented a high availability of prescription drugs – including POs – on street markets in Vancouver. Data from several local street drug user cohort studies – specifically, the Vancouver Injection Drug Users Study (VIDUS), the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS), and the At-Risk Youth Study (ARYS) – have assessed temporal changes in the availability of POs in street-level drug markets more recently from 2006 through 2010 (47). Data from these cohorts (n = 1,871) found that the immediate street drug market availability (i.e., available in < 10 minutes) of all POs examined (e.g., common hydromorphone, oxycodone, morphine, and codeine formulations) increased during this period. Availability increases for oxycodone and hydromorphone formulations were the most pronounced, with increases from 11% (2006) to 38% (2010) for oxycodone, and 22% to 41% for hydrocodone.

PO losses from thefts, break and entries, and armed robberies are a substantive yet often neglected pathway of PO diversion (79). Based on federal government data, 215,000 doses of codeine (compared to 234,210 doses in 2005), 61,362 doses of morphine (104,118), and 296,251 doses of oxycodone (340,328) went missing from Canadian pharmacies in 2010. Conversely, losses and thefts of POs from “licensed dealers” (i.e., manufacturers, wholesalers, importers) appear to be on the rise. Most notably, 168,420 doses of oxycodone were stolen or lost from licensed dealers in 2010, a 14-fold increase from 2005 (12,375 doses). In 2010, over 300,000 doses of oxycodone were lost as a result of either armed robbery or break and entry from both pharmacies and licensed dealers; 58,551 doses were pilfered by employees and 29,376 lost doses of oxycodone were “unexplained” (80).

Interventions for NMPOU

The room for interventions aimed at NMPOU is shaped by distinct jurisdictional parameter boundaries in Canada, namely that pharmaceutical drug approval and psychoactive drug control (including POs), e.g., through the Controlled Drugs and Substances Act (CDSA), are based in the federal domain – yet matters

of health care, pharmaceutical drug coverage, medical practice and professional regulation are provincial domains (18,81,82). In addition, the medical profession – i.e., physicians – have retained a rather pronounced status of self-regulation, mainly organized via the provincial Colleges of Physicians and Surgeons at arm’s-length from undue state interference (83,84).

It is presumably for these reasons that, to date – and different from other countries, e.g., the US or Australia – virtually no recent concerted federal interventions or policy measures aimed at NMPOU have been implemented in Canada (30). While federal policy initiatives exist in the realms of alcohol, tobacco and illicit drugs – i.e., in the form of the National Anti Drug Strategy – NMPOU, or prescription drug abuse in general – has not been embraced by any explicit or designated federal initiative. Experts have criticized this absence of federal leadership in this problem realm, given the evidently clear need for comprehensive and concerted efforts to deal with the major problem of NMPOU and PO related harms (30,85,86).

There are 3 main strands of interventions primarily rooted in provincial levels aiming at NMPOU: 1) PO prescription guidelines; 2) prescription monitoring programs (PMPs); and 3) substance use treatment services for POs. Medical practice guidelines for clinical PO use in the context of SCP have existed in several provinces for quite some time (e.g., Alberta, Nova Scotia, Quebec, and Ontario) as typically produced by the respective Colleges of Physicians and Surgeons or related medical professional bodies (e.g., the Canadian Pain Society) (87,88). National iterations of medical PO use guidelines from leading nongovernmental entities, e.g., the guidelines for the Use of Opioids in the Treatment of Chronic Non-Cancer Pain (89) and, more recently, the Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain, aiming for reduced pain and improved functioning in pain patients on the basis of PO-based care while reducing undue risks, misuse and harms, have also been developed (90,91). However, all of these guidelines are suggestive and nonbinding, and their impact upon medical practice regarding POs, or NMPOU, remains unassessed.

PMPs exist mainly in the US and are promoted as an effective tool to reduce the misuse and harms from controlled prescription drugs; there is evidence that they reduce overall use levels of controlled prescription drugs, although the evidence for their overall beneficial impact on harms and problems is mixed (92-94). In Canada, PMPs exist in the majority (i.e., 7) but

not all Canadian provinces; however these programs differ considerably in terms of design and operations between provinces (18). Specifically, existent provincial PMPs in Canada rely on either electronic systems or multiple prescription copy programs to track controlled drugs (95). One of the most comprehensive examples of electronic prescription monitoring is British Columbia's PharmaNet system, which feeds and links prescription information on all controlled substances to a central data system providing information to pharmacists, medical professionals, and hospitals with the aim to prevent prescription fraud, accidental duplication, and hazardous drug interactions (96,97). Similar electronic systems are run in Alberta (Netcare), Manitoba (DPIN), and Nova Scotia (NSPMP) (with Newfoundland & Labrador and Prince Edward Island [PEI] in developing stages of implementing Pharmacy Network databases) where erratic prescribing or dispensing patterns are identified and investigated (95,98,99). The province of Alberta currently also still operates a paper-based triplicate pad PMP; both Ontario and New Brunswick plan to see electronic PMPs covering POs implemented in the near future; and Quebec also plans on creating a drug information system with electronic health records, although currently no PMP exists in Quebec or PEI (95).

There is little systematic evidence on the impact of PMPs, on either medical PO use or PO misuse and harms, in Canada. There is some suggestive indication that overall PO use and NMPOU problems may be higher in provinces without any/electronic PMPs (e.g., Ontario, Alberta), although the lowest levels of PO use are found in the province of Quebec which does not operate a PMP. A recent analysis of temporal changes in overall PO use levels by province also did not find change differences associated with the existence of PMPs (18).

Substance use treatment interventions – when publicly provided – for PO-related problem drug use (e.g., dependence) are largely offered and covered by provincial programs and funds (exceptions are FNAP living on reserve communities and federal correctional populations which are covered by federal health care programs). As shown, treatment demand for PO-related problems in Ontario has risen substantially in recent years (53,56-58). Across most of Canada, the number of people enrolled in Opioid Substitution Treatment (OST) – MMT and increasingly buprenorphine/suboxone based treatment – has increased substantially, i.e., more than doubled in the past decade to > 50,000 (30,54,100). In Ontario alone, there are currently > 35,000 patients enrolled in MMT (54,101). Without exact data available,

it is estimated that the vast majority of these increases in OST utilization are related to and driven by problematic PO (rather than heroin) use.

Select Canadian law enforcement agencies have devoted increasing attention, efforts, and resources towards PO diversion and illegal supply. The Criminal Intelligence Service Canada (CISC) recently reported that although the level of organized crime activity around POs appears to be small, the majority of groups operate in the Atlantic provinces, and oxycodone and hydromorphone are the most commonly seized POs in Canada (102). Ontario has seen a substantial increase in the number of POs seized by law enforcement in recent years, notably oxycodone, during heightened vehicle and home inspections; in Ontario's Northern FNAP communities specifically, there were 180 drug investigations and a seizure of 8,500 oxycodone tablets in 2010 alone. The Nishnawbe Police Services have reported a steady rise in police calls, most likely linked with increased oxycodone use, from 13,437 calls in 2005 to 20,325 calls in 2010 (48). Despite the increasing attention by enforcement agencies in Canada to reduce PO diversion, the extent of these activities and their impact is difficult to assess. Notably, and despite the above developments, the most recent (103) Drug Situation Report of the Royal Canadian Mounted Police (RCMP) – the Canadian federal police force tasked with drug law enforcement – does not address or mention PO diversion or illicit supplies (while maintaining a detailed focus on drugs like heroin and opium).

While the federal government has issued documents aimed at aiding physicians and pharmacists on how to recognize prescription shoppers (102,104,105), key basic prevention measures for POs are notably absent or neglected in Canada (30). For example, safe drug storage requirements to reduce theft are currently poorly outlined (106). Canada lags behind in terms of pharmaceutical drug return and recycling efforts and has no formal or nationwide programs in place (107). Although the amount of pharmaceutical medication returned in BC between 2004 and 2010 has reportedly quadrupled, these amounts only represent a small proportion of prescription drugs dispensed, and do not provide specific data on POs (108,109).

CONCLUSION

In the context of recent recognition of PO misuse and related harms emerging as a major health problem globally, there are clear indications from numerous empirical sources that this phenomenon – while

perhaps on a somewhat lesser scale, similar to recent developments in the US – currently constitutes a major and acutely rising substance use and public health crisis in Canada (2,30,110). In fact, based on estimations of data available, the overall burden of disease related to PO misuse and harms appears second only to alcohol and tobacco (i.e., it is larger than that from illicit drugs) (30). These assessments – as shown – to a large extent need to rely on the synthesis of many sporadic, provincially/locally restricted or nonlongitudinal indicators in regards to NMPOU, and PO-related morbidity, mortality, and diversion in Canada; extensive temporal or jurisdictional data gaps exist (77). For example – and very different from the US – no reliable and systematic national data on NMPOU, PO-related morbidity or mortality in the Canadian general population exist (29,35,68). Given the severe extent and impact of the PO crisis issue, as well as the length of time for which its signals have been on various “radar screens,” this is an untenable situation, and ought to be considered a severe neglect of key substance abuse related health indicators monitoring in one of the wealthiest industrialized countries in the world. This situation urgently needs to be changed and ameliorated. Such systematic data monitoring is urgently required to inform, guide and evaluate policy and other intervention initiatives, especially on the national level.

It is equally surprising that very little – if anything – in policy initiatives or strategies to concertedly intervene vis-a-vis the substantive PO misuse problem has occurred yet in Canada. Especially from the federal government level – home jurisdiction of the country’s psychoactive drug control legislation, the CDSA and related regulatory authorities regarding prescription medication, the national public health authority (‘Public Health Agency of Canada’), as well as a richly resourced “National Anti-Drug Strategy” (which does not include prescription drug misuse in its scope) together with standing federal institutions (e.g., the Canadian Centre on Substance Abuse (CCSA) mandated to facilitate substance use policy – the nonexistence of a targeted interventions plan or program is perplexing.

Both the US and Australia have federal strategies and policy programs concerning PO misuse and harms in place (2,111). Given the extent and impact of the PO problem on rational (e.g., burden of disease) scales – also compared to other substance use problems actively – as well as the complex landscape of jurisdictional and other (e.g., professional) stakeholders in Canada, a federal policy strategy or program aimed at PO misuse and related harms is urgently needed in Canada.

There clearly is a sizeable amount of knowledge yet to be developed and considered with regards to effective interventions – both on the micro and macro level – towards reducing the prevalence and harms of PO misuse and harms. For example, there is little and insufficient information on the basic motives for and pathways into NMPOU in general and other populations (112,113). Very few prevention or treatment interventions have been specifically developed or assessed for problematic PO use; in the area of treatment – e.g., opioid substitution treatment – the system relies mainly on evidence originally generated for heroin dependence treatment (114-116). On a population level, specifically in the disproportionately “PO rich environments” of North America, it seems unquestionable that a reduction in PO misuse and related harms likely ought to come with an overall volume reduction of POs dispensed in the general population (18). This premise, of course, points to one of the fundamental challenges for policy and interventions implementation in the realm of PO misuse and harm – namely to avoid major “collateral damage” or “chilling” effects for the availability and quality of SCP care as an undesirable side effect of efforts to better control the availability and use of POs in the population (22,94,117). Specifically in Canada, where professional pain care is severely lacking for many of those who need it, this must be avoided (25,27,118).

At the same time, by all accounts, Canada is facing a major public health crisis related to PO misuse and harms, and better data to both more accurately assess the problem as well as to guide the implementation and monitor the impact of acutely needed interventions are urgently required.

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