Societal cost savings from abuse deterrent formulations for prescription opioids in Canada

Author
Brett J Skinner, Ph.D.

Publication Date
May 29, 2017.

Citation
Skinner BJ (2017). Societal cost savings from abuse deterrent formulations for prescription opioids in Canada. *Canadian Health Policy*, May 29, 2017. Toronto: Canadian Health Policy Institute. URL: www.canadianhealthpolicy.com

Summary

Introduction
Available evidence suggests non-medical use (NMU) of prescription opioids (RxO) in Canada is significant, and is partly facilitated by users who modify the drug product. Abuse deterrent formulations (ADF) exist but are not mandatory for all prescription opioids.

Objective
This study estimates the magnitude of the societal economic costs in Canada resulting from non-medical use of prescription opioids that could be avoided if all prescription opioids were mandated to be abuse deterrent formulations and were as effective as existing technology.

Data and Method
This paper builds on the methods and the data sources used in a 2012 study on the same topic: "Skinner BJ (2012). Net societal economic impact in Canada from withholding regulatory approval for generic OxyContin®. *Canadian Health Policy*, September 12, 2012. Toronto: Canadian Health Policy Institute." A literature review was conducted to update and summarize the state of evidence regarding the effectiveness of tamper resistant/abuse deterrent formulations for opioid products. A scan of related policy developments was conducted. New data and evidence were used to update from previous estimates of societal economic costs. Utilization data were obtained from QuintilesIMS.

Results
Estimated total societal economic costs from non-medical use of prescription opioids in Canada averaged about $4.3 billion per year. The four-year cumulative total was $17.1 billion from 2012 to 2015. The literature reviewed for this study found that existing ADF technologies were effective at reducing NMU rates. Estimates ranged from 3.3% to 98.8% effective at reducing the NMU rate. The median ADF effectiveness reducing NMU rates by between 45.1% and 64%. The range of the costs that could potentially have been avoided if ADF had been mandatory for all prescription opioids in Canada is determined by the effectiveness factored into each calculation. The four-year cumulative total from 2012 to 2015 ranged from $560 million to $16.9 billion (averaging from $140 million to $4.2 billion per year). The median estimate is about $9.3 billion for the entire period (averaging $2.3 billion per year).

Conclusions
The data suggest that the expected reduction in the NMU rate for RxO that would result from mandating adoption of ADF across all opioids, would very likely produce significant net societal cost savings.

Introduction

Medical experts and public health officials in Canada are concerned about the health and mortality risks associated with over-prescribing, long-term use and abuse or non-medical use (NMU) of prescription opioid drugs (RxO).[1,2,3,4]

Governments have recognized that prevention is an important element in mitigating the public health problems and social costs associated with non-medical use of prescription opioids in Canada. In December 2016, the federal government announced a new Canadian Drugs and Substances Strategy. The strategy is focused on several approaches including, "preventing problematic drug and substance use, supporting innovative approaches to treatment and rehabilitation, supporting measures that reduce the negative consequences of drug and substance use, addressing illicit drug production, supply and distribution."[5] Notably, the strategy omitted any mention of the potential for abuse deterrent formulations (ADF) to reduce the abuse of prescription opioids.

Many prescription opioid drugs are controlled release formulations that when taken as prescribed, allow higher dosage strengths to be administered safely to users over longer periods of time, providing extended pain relief. However, if the product is chewed, crushed for inhaling or dissolved in fluid for injecting, higher doses of the active ingredient are released immediately. The available evidence suggests that the non-medical use of prescription opioids in Canada is significant, and is partly facilitated by users who modify the drug product by "tampering with the medication or altering the route of delivery."[6]

Abuse deterrent formulations offer the potential to discourage abuse of prescription opioid drug products, while preserving normal availability for legitimate medical-use by patients. Abuse deterrent formulations exist and are in use for some products, but are not required for all prescription opioids.

RATIONALE

Medical experts and public health officials in Canada are concerned about abuse of prescription opioids.

Abuse deterrent formulations exist but are not mandatory for all prescription opioids.

This study estimates the magnitude of the societal costs that could be avoided if all prescription opioids in Canada were abuse deterrent formulations.

[1] Public Health Agency of Canada (2017). Statement from the Chief Public Health Officer: Pharmacists Help Address the Opioid Public Health Crisis in Canada. Ottawa, March 13, 2017. URL: https://www.canada.ca/en/public-health/news/2017/03/statement_from_thechiefpublichealthofficerpharmacistshelpaddress.html.

[2] Canadian Centre on Substance Abuse (2015). Canadian Drug Summary: Prescription Opioids. URL: www.ccsa.ca/.../CCSA-Canadian-Drug-Summary-Prescription-Opioids-2015-en.pdf.

[3] Pan-Canadian Public Health Network (2017). Special Advisory Committee on the Epidemic of Opioid Overdoses. Date modified:2017-02-20. URL: http://www.phn-rsp.ca/sac-opioid-gcs-opioides/index-eng.php.

[4] Kirkup, K (2016). Medical experts urge Canada to declare public emergency over opioid crisis. Globe and Mail, Nov 18, 2016. URL: http://www.cbc.ca/news/politics/opioid-crisis-meeting-1.3856740.

[5] Government of Canada, Health Canada (2016). Canadian drugs and substances strategy. URL: http://www.healthycanadians.gc.ca/publications/healthy-living-vie-saine/drugs-substances-strategy-2016-strategie-drogues-autre-substances/index-eng.php?_ga=1.239804163.1217760409.1486405524#_blank.

[6] Canadian Centre on Substance Abuse (2015).

Objective

This study estimates the magnitude of the societal economic costs in Canada resulting from non-medical use of prescription opioids that might potentially be avoided if all prescription opioids were abuse deterrent formulations.

The objective of this study follows the observations of Canada's health technology assessment agency, the Canadian Agency for Drugs and Technologies in Health (CADTH). In 2015 CADTH reviewed the existing evidence supporting the abuse deterrence impact of tamper resistant technology for extended release (ER) oxycodone concluding that,

> "All of the included studies examining the potential for misuse and abuse of ADF oxycodone suggest that there is reduced potential for misuse and abuse of tamper-resistant formulations. In some studies, this reduced misuse of ADF ER oxycodone was associated with an increase in demand for other prescription opioids that did not have tamper-resistant formulations (such as IR oxycodone and other ER opioids) and in others, it was associated with increased use of illegal opioids (such as heroin). It is likely that although ADF ER oxycodone has the potential to reduce abuse and misuse of ER oxycodone, a greater reduction in prescription opioid use will not be seen unless the majority of prescription opioids are available in tamper-resistant formulations. ADF oxycodone formulations may result in cost savings in the Canadian setting, however it is unclear how large those savings will be due to the lack of Canadian data. Tamper-resistant oxycodone is likely to be an effective contributor to a broad opioid abuse and misuse strategy."[7]

The paper builds on the methods and the data sources used in a 2012 study on the same topic.[8] A literature review was conducted to update the evidence on the effectiveness of abuse deterrent formulations for opioids. A scan of related regulatory policy developments was conducted.

New data and evidence were used to estimate the prevalence of non-medical use of prescription opioids and the associated societal economic costs. Canadian data were used when available, otherwise American data were used to extrapolate Canadian estimates. Canada's policy environment was compared to the USA to draw lessons about outcomes.

Policy Environment

The policy environment affecting ADF for prescription opioids has been distinctly different in the USA and Canada.

USA

The US FDA views the development of ADF for prescription opioids favourably and has taken regulatory actions to encourage their use and create incentives for further innovations that can deter abuse.

A 2016 FDA document states:

> "Prescription opioid analgesics are an important component of modern pain management. However, abuse and misuse of these drug products have created a serious and growing public health problem. One potentially important step toward the goal of creating safer opioid analgesics has been the development of opioid drug products that are formulated to deter abuse. FDA considers development of these products a high public health priority."[9]

Further, according to the FDA website:

> "The FDA is encouraging the development of opioid formulations with abuse-deterrent properties to help combat the opioid epidemic.

[7] CADTH (2015). Tamper-Resistant Oxycodone: A Review of the Clinical Evidence and Cost-effectiveness. Canadian Agency for Drugs and Technologies in Health. June 25, 2015.

[8] Skinner BJ (2012). Net societal economic impact in Canada from withholding regulatory approval for generic OxyContin®. *Canadian Health Policy*, September 12, 2012. Toronto: Canadian Health Policy Institute.

[9] US FDA (2016). General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products Guidance for Industry. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). March 2016: Generics.

> The agency recognizes that opioids with abuse-deterrent properties (AD) are not abuse-proof, but are a step toward products that will help reduce abuse. The FDA fully supports efforts to better understand the impact of these products in the real-world setting and develop innovative formulations that have the potential to make abuse of these products more difficult or less rewarding. The FDA is working with many drug makers to support advancements in this area and help drug makers navigate the regulatory path to market as quickly as possible. In working with industry, the FDA is taking a flexible, adaptive approach to the evaluation and labeling of potentially AD products."[10]

Reformulated OxyContin was the first ADF prescription opioid approved by the FDA. OxyContin (oxycodone hydrochloride controlled-release) was first introduced in the USA during the mid-1990s as a high-dose, extended-release opioid. The manufacturer released a reformulated ADF version of the drug in 2010 and stopped selling previous versions.

In late 2012/early 2013, the FDA acted to effectively ban non-ADF generic versions of oxycodone HCL CR, by withdrawing its approval for the original version of OxyContin, leaving only the patented reformulated ADF version available, thus preventing generics from entering the market.[11]

In 2016, the FDA subsequently issued guidelines for all opioids requiring applicants for regulatory approval of generic versions to show that their products are no less abuse-deterrent than the original drug product.[12]

As of January 2017, the FDA has approved nine (9) extended-release/long-acting (ER/LA) opioids with labeling describing abuse deterrent properties consistent with the FDA's guidelines (OxyContin, Targiniq ER, Embeda, Hysingla ER, MorphaBond, Xtampza ER, Troxyca ER, Arymo ER, Vantrela ER).[13]

As of April 2017, there was only one immediate-release (IR) prescription opioid with labeling describing abuse deterrent properties consistent with the FDA's guidelines (RoxyBond [oxycodone hydrochloride]).[14]

There are currently no generic versions of any IR or ER prescription opioid with FDA-approved abuse deterrent labeling consistent with the FDA's guidelines.[15]

CANADA

In Canada, the manufacturer of OxyContin (oxycodone HCL CR) voluntarily withdrew the non-ADF product from the market, replacing it with the tamper resistant ADF reformulation (branded OxyNEO® in Canada) as of February 2012. The Canadian patent for the original non-ADF OxyContin expired on November 25, 2012.

Unlike the FDA, Health Canada approved generic versions of non-ADF oxycodone HCL CR. Non-ADF generic versions fully entered the market in 2013.

By May 2015, federal Health Minister Rona Ambrose had announced the Conservative government's intention to reverse its earlier approval of generic oxycodone HCL CR.[16]

Following the election of a Liberal government in October 2015, Health Canada published guidelines for tamper resistance efficacy claims in March

[10] US FDA (2017). FDA Facts: Abuse-Deterrent Opioid Medications. U.S. Department of Health and Human Services, Food and Drug Administration.

[11] US FDA (2017). Timeline of Selected FDA Activities and Significant Events Addressing Opioid Misuse and Abuse. U.S. Department of Health and Human Services, Food and Drug Administration.

[12] US FDA (2016).

[13] US FDA (2017). FDA Facts: Abuse-Deterrent Opioid Medications.

[14] News release (April 26, 2017). Inspirion Delivery Sciences Receives FDA Approval for RoxyBond™ (oxycodone hydrochloride) tablets CII, the First and Only Immediate Release Opioid Analgesic with Abuse-Deterrent Label Claims. Inspirion Delivery Sciences, LLC. PR Newswire: http://www.prnewswire.com/news-releases/inspirion-delivery-sciences-receives-fda-approval-for-roxybond-oxycodone-hydrochloride-tablets-cii-the-first-and-only-immediate-release-opioid-analgesic-with-abuse-deterrent-label-claims-300445964.html.

[15] US FDA (2017). FDA Facts: Abuse-Deterrent Opioid Medications.

[16] John Ivison (May 14, 2015). Federal government reversing its decision to allow generic OxyContin as addictions surge. National Post.

2016.[17] Health Canada subsequently published a regulatory update in April 2016 stating that proposed regulations requiring tamper resistance for generic versions of oxycodone HCL CR were cancelled.[18]

Meanwhile, in 2012 most of Canada's provincial governments acted to restrict or severely limit coverage of both the ADF and non-ADF versions of oxycodone HCL CR in public drug plans. As of March 2017, coverage in 9 provincial public drug plans remains very restricted for the ADF OxyNEO and is not available at all for non-ADF generic oxycodone HCL CR. By contrast, in Quebec non-ADF generic oxycodone HCL CR is reimbursable under the province's publicly funded drug plan. **[See appendix, Table 1]**

Non-ADF generic oxycodone HCL CR remains commonly reimbursable under private sector drug plans, and can also be accessed outside of a drug plan by out-of-pocket payment.

Prevalence of RxO Abuse

There are currently no reliable sources of national data on the overall prevalence of the non-medical use of prescription opioid drugs in Canada. Statistics Canada's Canadian Alcohol and Drug Use Monitoring Survey (CADUMS) asks questions to respondents about the use of "pain relievers to get high" (meaning prescription opioid abuse), but the most recent report (2011 data) states that, "the rate of abuse of opioid pain relievers is unreportable" due to "high sampling variability".[19]

However, there are administrative data available to measure all types of opioid poisonings that lead to hospitalization or emergency department (ED) visits and these statistics are now being publicly reported.

In 2016, the Canadian Institute for Health Information (CIHI) released a report focused on hospitalizations and ED visits due to opioid poisoning in Canada. The study found that: [20]

- "In 2014–2015, there were 4,779 hospitalizations due to opioid poisoning in Canada, an average of more than 13 hospitalizations a day, up from 3,357 in 2007–2008. From 2007–2008 to 2014–2015, the crude rate increased more than 30%, from 10.2 to 13.5 per 100,000 population."
- "The "other opioids" category (which includes oxycodone, morphine and hydromorphone, among others) accounted for more than half of all opioid poisoning hospitalizations in each year of the study (ranging from 55% to 59%). The rate of hospitalizations for opioid poisoning related to this group increased by more than 42% between 2007–2008 and 2014–2015 (from 5.8 to 8.2 per 100,000 population)."
- "Accidental opioid poisonings accounted for the highest proportion of hospitalizations, increasing from 40% (1,314) in 2007–2008 to 49% (2,291) in 2014–2015."
- "Intentional poisonings accounted for the second-highest proportion of hospitalizations, remaining stable at around 34% throughout the study period."
- "In contrast, the proportion of therapeutic poisonings (i.e., those that occurred when the drug was used as prescribed) decreased from 12% (407) in 2007–2008 to 6% (280) in 2014–2015."

Sources of national data on non-medical use of prescription opioids in the United States include the National Survey of Drug Use and Health (NSDUH) which reports detailed survey data on the non-medical use of prescription opioids in the American population.[21]

According to the 2015 NSDUH, 12.5 million Americans misused pain relievers in 2015. Of these,

[17] Health Canada (March 30, 2016). Guidance Document: Tamper-Resistance Formulations of Opioid Drug Products. Published by authority of the Minister of Health.

[18] Government of Canada (2016). Regulatory Update - Health Canada confirms proposed regulations requiring tamper resistance for Oxycodone will not move forward at this time. URL: http://news.gc.ca/web/article-en.do?nid=1045259. Date modified: 2016-04-04.

[19] Statistics Canada (2012). Canadian Alcohol and Drug Use Monitoring Survey (CADUMS). URL: http://www.hc-sc.gc.ca/hc-ps/drugs-drogues/stat/_2011/tables-tableaux-eng.php#t3. Date Modified: 2014-02-04.

[20] CIHI (2016). Hospitalizations and Emergency Department Visits Due to Opioid Poisoning in Canada. Canadian Institute for Health Information (CIHI).

[21] NSDUH (2016). Results from the 2015 National Survey on Drug Use and Health: Detailed Tables. Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. September 8, 2016.

2.1 million (16.8%) people aged 12 or older were recent initiates for pain reliever misuse (i.e., misused for the first time in the past year).[22]

The US Centers for Disease Control and Prevention (CDC), reports prescription opioid overdose data. According to the most recent data from the CDC:[23]

- "From 1999 to 2015, more than 183,000 people have died in the U.S. from overdoses related to prescription opioids."
- "Nearly half of all U.S. opioid overdose deaths involve a prescription opioid. In 2015, more than 15,000 people died from overdoses involving prescription opioids."

Societal Cost of RxO Abuse

The literature review did not find any national estimates for Canada of the societal-level economic cost of non-medical use of prescription opioids specifically. However, CIHI has published data that is a proxy for hospital related cost impacts associated with general opioid use, stating:[24]

- "With respect to health care resources, people admitted to hospital for an opioid poisoning remained for an average of 8.0 days, longer than the average total length of stay for those admitted for a heart attack (5.1 days), pneumonia (6.9 days) or hip replacement surgery (7.3 days)."
- "In 2014–2015, a total of 38,405 days of care were provided in Canadian hospitals to patients admitted with a diagnosis of opioid poisoning."

A previous review of the literature[25] revealed several studies that used American source data to specifically estimate the national societal-level economic burden from the non-medical use of prescription opioids. An updated review did not yield any newer studies. The most recent estimate of the societal level economic costs associated with the non-medical use of prescription opioids in the USA is a 2011 study that cites costs in 2009 $US at $55.7 billion.[26]

ADF Effectiveness

The potential of abuse deterrent formulations to avoid the societal costs of prescription opioid abuse depends on the technology's effectiveness. Studies of the effectiveness of existing ADF for prescription opioid drugs suggest a promising potential for these innovative technologies to reduce abuse.

In a 2015 study of nearly 11,000 American subjects, the effect of the 2010 introduction of the tamper resistant ADF version of oxycodone HCL CR (reformulated OxyContin) on drug-seeking behavior was examined. Reformulated OxyContin was associated with a significant reduction of past-month abuse after its introduction falling from 45.1% to 26.7%, four years after ADF entry. A small subset of subjects was interviewed about whether the ADF influenced their behaviour. Of those interviewed, 33.3% indicated that they switched to other non-ADF opioids, and 3.3% indicated that the ADF influenced their decision to stop abusing drugs altogether.[27]

Another 2015 American study, using national data from the from the 2010 NSDUH and DAWN surveys, examined the impact of the introduction of ADF on the non-medical use rates associated with ER oxycodone and ER morphine. The introduction of the tamper resistant ADF reduced the NMU rate for

[22] NSDUH (2016). Prescription Drug Use and Misuse in the United States: Results from the 2015 National Survey on Drug Use and Health. Authors - SAMHSA: Arthur Hughes, Matthew R. Williams, Rachel N. Lipari, and Jonaki Bose; RTI International: Elizabeth A. P. Copello and Larry A. Kroutil. September 2016. URL: https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR2-2015/NSDUH-FFR2-2015.htm.

[23] CDC (2016). Prescription Opioid Overdose Data. The US Centers for Disease Control and Prevention. URL: https://www.cdc.gov/drugoverdose/data/overdose.html.

[24] CIHI (2016). Hospitalizations and Emergency Department Visits Due to Opioid Poisoning in Canada. Canadian Institute for Health Information (CIHI).

[25] Skinner BJ (2012).

[26] Birnbaum, Howard G., Alan G. White, Matt Schiller, Tracy Waldman, Jody M. Cleveland, Carl L. Roland (2011). Societal Costs of Prescription Opioid Abuse, Dependence, and Misuse in the United States. Pain Medicine 2011; 12: 657-667.

[27] Theodore J. Cicero, Matthew S. Ellis (2015). Abuse-Deterrent Formulations and the Prescription Opioid Abuse Epidemic in the United States: Lessons Learned from OxyContin. JAMA Psychiatry. 2015;72(5):424-429. Published online March 11, 2015.

ER morphine by 45.1 to 98.8%; and for ER oxycodone by 15.4 to 64.0%.[28]

In an earlier experimental study abusers were tested on their ability to tamper with an abuse-deterrent formulation of oxymorphone and interviewed about the results. According to the study, "Most participants were not willing to snort (92%) or inject (84%) the tampered products."[29]

Another study surveyed a sample of opioid abusers in the United States, to collect survey respondents' assessments of the abuse-deterrent effectiveness following the introduction of the tamper resistant ADF for oxycodone HCL CR. The study found that, "...the selection of OxyContin as a primary drug of abuse decreased from 35.6% of respondents before the release of the abuse-deterrent formulation to just 12.8% 21 months later… Of all opioids used to "get high in the past 30 days at least once", OxyContin fell from 47.4% of respondents to 30.0% (P<0.001) ... Interviews with patients who abused both formulations of OxyContin indicated a unanimous preference for the older version… 66% indicated a switch to another opioid..."[30]

A 2015 study found that a formulation combining oxycodone with naloxone produced effects that could deter abuse. The drug worked as intended when taken as prescribed. However, the naloxone component caused acute withdrawal symptoms when the drug product was modified to be injected or snorted. The researchers concluded that the effect could act as a deterrent against non-medical use of the drug.[31]

Utilization

Regulatory policy differences between the USA and Canada could explain differences in utilization trends for prescription opioids in both countries. Similarly, differences in the public drug plan reimbursement environments across Canada's provinces might explain inter-provincial variation in utilization.

Dispensed prescription volumes were used as a proxy for utilization trends **[see Cautions and Limitations]**. Canadian and American data for prescription opioid utilization trends were provided by Purdue Pharma Canada and sourced from QuintilesIMS.[32] Canadian data covered the period from 2011 to 2015 and the American data covered the period from 2009 to 2016. The analysis focused on the post-ADF regulatory experience of oxycodone HCL CR because it was the first prescription opioid to be approved as an ADF in both the USA and Canada. The data period in both jurisdictions uses the year before the introduction of ADF in each market as the base year.

[Chart 1] displays the total volume of prescriptions dispensed for all opioids in the USA from 2009 to 2016. The chart indicates that total RxO volumes initially declined slightly following the first introduction of an ADF in 2010. In 2011 volumes spiked, but thereafter steadily declined through to the end of the period. By 2016, total RxO volumes were nearly 4% below 2009 volumes.

[Chart 2] displays the volume of prescriptions dispensed for oxycodone HCL CR in the USA over the same period. Prescription volumes for oxycodone HCL CR declined after the introduction of the ADF in 2010 falling 32% between 2009 and 2016.

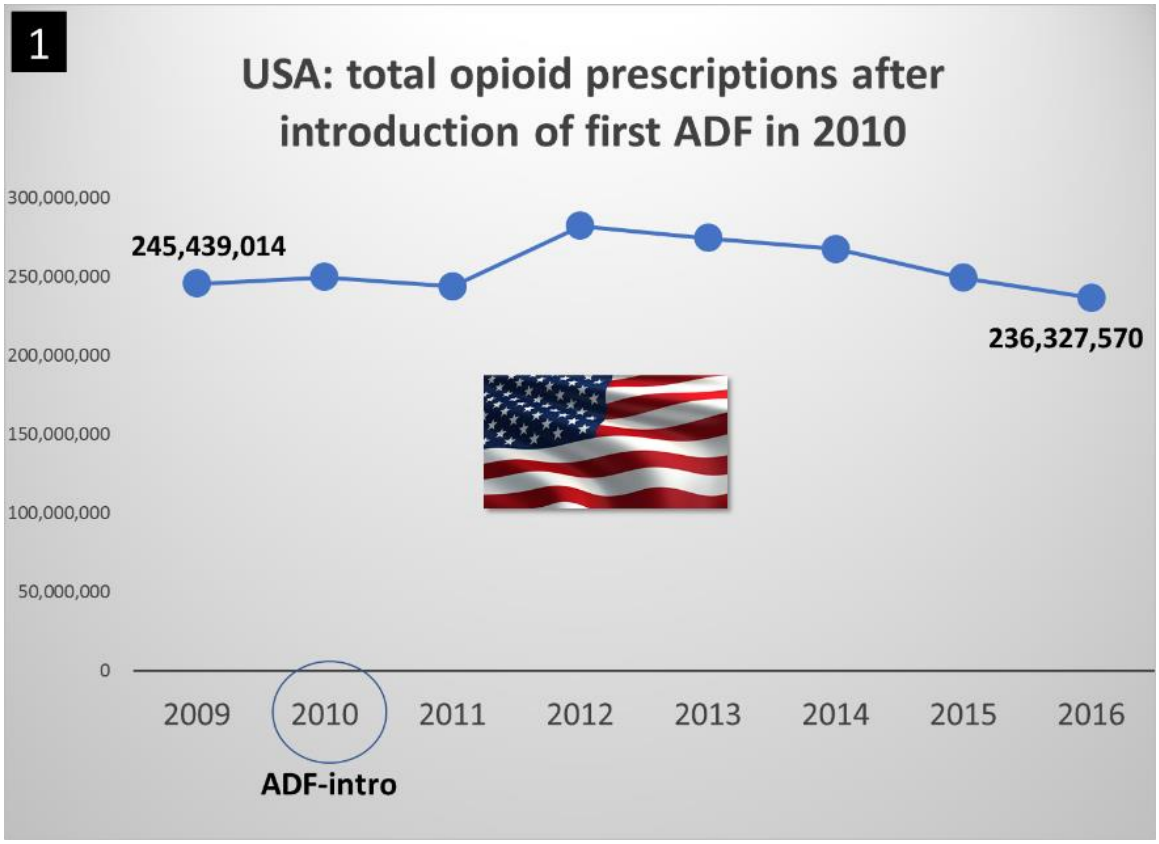
[28] Alan G. White, Joseph LeCates, Howard G. Birnbaum, Wendy Cheng, Carl L. Roland, Jack Mardekian (2015). Positive subjective measures in abuse liability studies and real-world nonmedical use: Potential impact of abuse-deterrent opioids on rates of nonmedical use and associated healthcare costs. Journal of Opioid Management 11:3, May/June 2015.

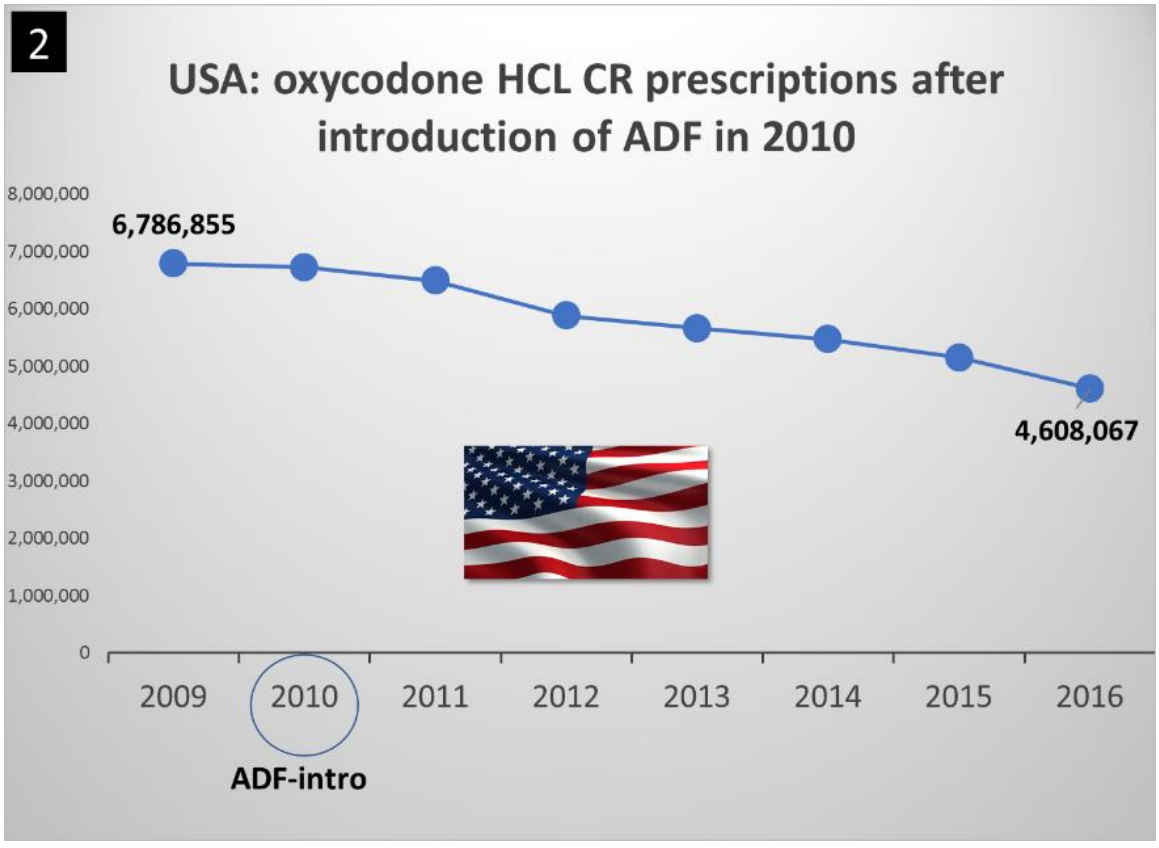
[29] Vosburg, SK., JD Jones, JM Manubay, JB Ashworth, IH Benedek, SD Comer (2012). Assessment of a formulation designed to be crush-resistant in prescription opioid abusers. Drug and Alcohol Dependence, June 19, 2012 (Epub ahead of print).

[30] Cicero TJ, Ellis MS, Surratt HL (2012). Effect of Abuse-Deterrent Formulation of OxyContin. New England Journal of Medicine, 367;2 July 12, 2012.

[31] Wong A, Macleod D, Robinson J, Koutsogiannis Z, Graudins A, Greene SL (2015). Oxycodone/naloxone preparation can cause acute withdrawal symptoms when misused parenterally or taken orally. Clin Toxicol (Phila). 2015;53(8):815-8.

[32] Canada data from Compuscript and Canadian Drug Store & Hospital Purchases Audit (CDH)database. USA data from NPA and NSP databases.


1
USA: total opioid prescriptions after introduction of first ADF in 2010
300,000,000
250,000,000
200,000,000
150,000,000
100,000,000
50,000,000
0
245,439,014
236,327,570
2009
2010
2011
2012
2013
2014
2015
2016
ADF-intro


2
USA: oxycodone HCL CR prescriptions after introduction of ADF in 2010
8,000,000
7,000,000
6,000,000
5,000,000
4,000,000
3,000,000
2,000,000
1,000,000
0
6,786,855
4,608,067
2009
2010
2011
2012
2013
2014
2015
2016
ADF-intro

[Chart 3] displays the total volume of prescriptions dispensed for all opioids in Canada from 2011 to 2015. The chart indicates that total RxO volumes increased every year during the period despite the introduction of an ADF version of oxycodone HCL CR (OxyNEO) in 2012. By 2015 total RxO volumes were nearly 8% above 2011 volumes.

[Chart 4] displays the volume of prescriptions dispensed for brand and generic versions of oxycodone HCL CR in Canada from 2011 to 2015. After the introduction of the ADF version prescription volumes for OxyContin/OxyNEO declined continuously, falling 54% by 2015 versus the base year of 2011. The overall market for oxycodone HCL CR in 2015 also declined by 40% versus 2011 despite the entry and growth of non-ADF generic versions in significant volumes. By 2015, non-ADF generics represented 22% of the total volume of prescriptions dispensed for oxycodone HCL CR in Canada.

[Table 2] displays the utilization trends at the provincial-level[33] for ADF and non-ADF oxycodone HCL CR following entry of the ADF in 2012. From 2012 to 2015 the total volume of ADF and non-ADF prescriptions dispensed in every province declined, except in Alberta (+3%) and Nova Scotia (+9%). The change in volumes ranged from +9% in Nova Scotia to -43% in British Columbia.

There is significant variation in the change in utilization of ADF oxycodone HCL CR across provinces over this period. The only province to show growth was Nova Scotia (+4%). In every other province utilization of the ADF version declined. By the end of 2015, prescription volume changes versus 2012 ranged from +4% in Nova Scotia to -63% in Quebec.

There is also significant variation in the change in utilization of non-ADF oxycodone HCL CR across provinces from 2013 (the first full year that generics were available) to 2015. Non-ADF volumes increased across all provinces, ranging from +26% in British Columbia to +208% in Saskatchewan.

[Chart 5] displays the non-ADF percentage of the total volume of prescriptions dispensed for oxycodone HCL CR by the end of the period in 2015. The non-ADF share of the total ranged from 2.3% in Saskatchewan to 52.3% in Quebec.

Avoidable Societal Costs

The literature review did not find any national estimates of the economic cost or prevalence of non-medical use of prescription opioids for Canada. Therefore, to estimate total potential societal economic costs from non-medical use of prescription opioids in Canada it was necessary to extrapolate findings from American studies that have produced societal estimates for the United States.

The analysis conducted below uses the base data from the preceding sections of this paper to produce a Canadian estimate. The assumptions of the estimate are informed by the facts reviewed in the preceding sections. The estimate is adjusted where noted **[See Table 3]** using supplementary data as follows:

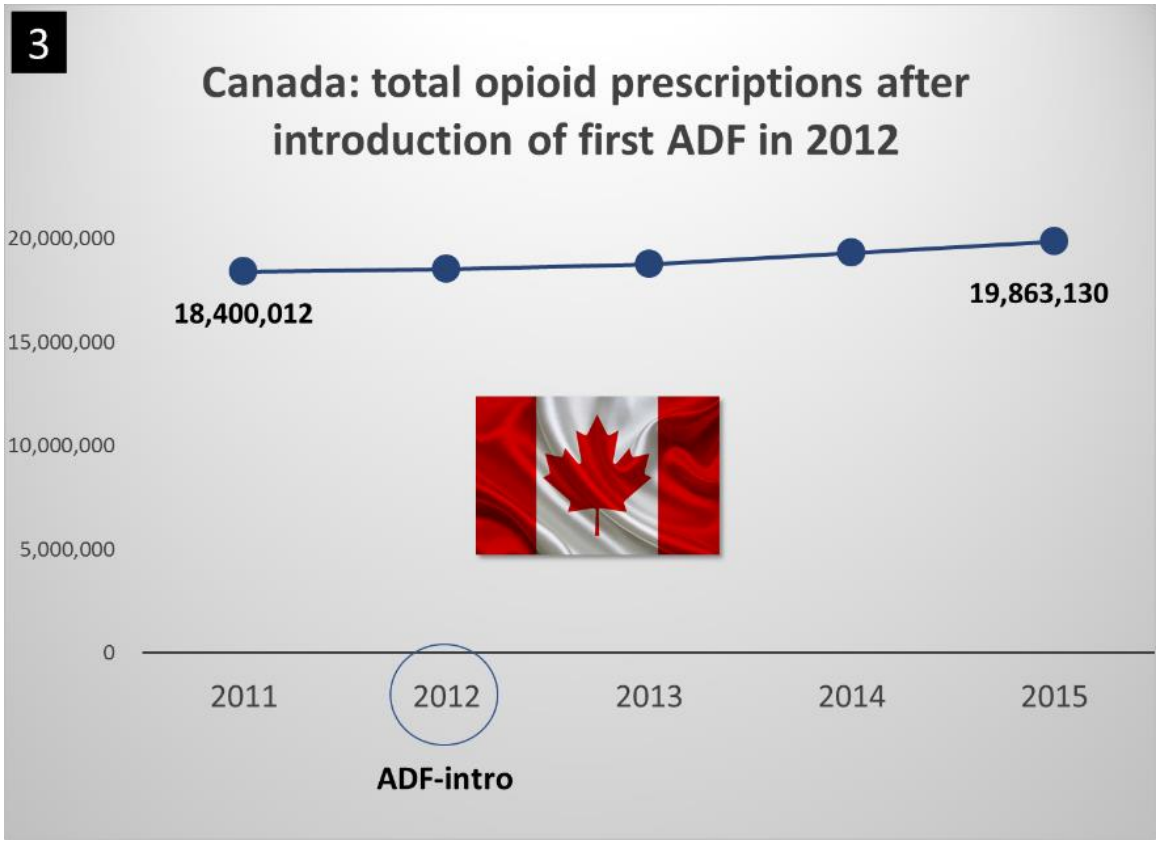
- USA costs adjusted for: Inflation (changes in CPI).[34] Changes in RxO volumes.
- CAN costs adjusted for: Changes in RxO volumes. Ratio of CAN/USA healthcare expenditures per capita.[35] CAN/USA dollar Market Exchange Rate ($MER).[36]

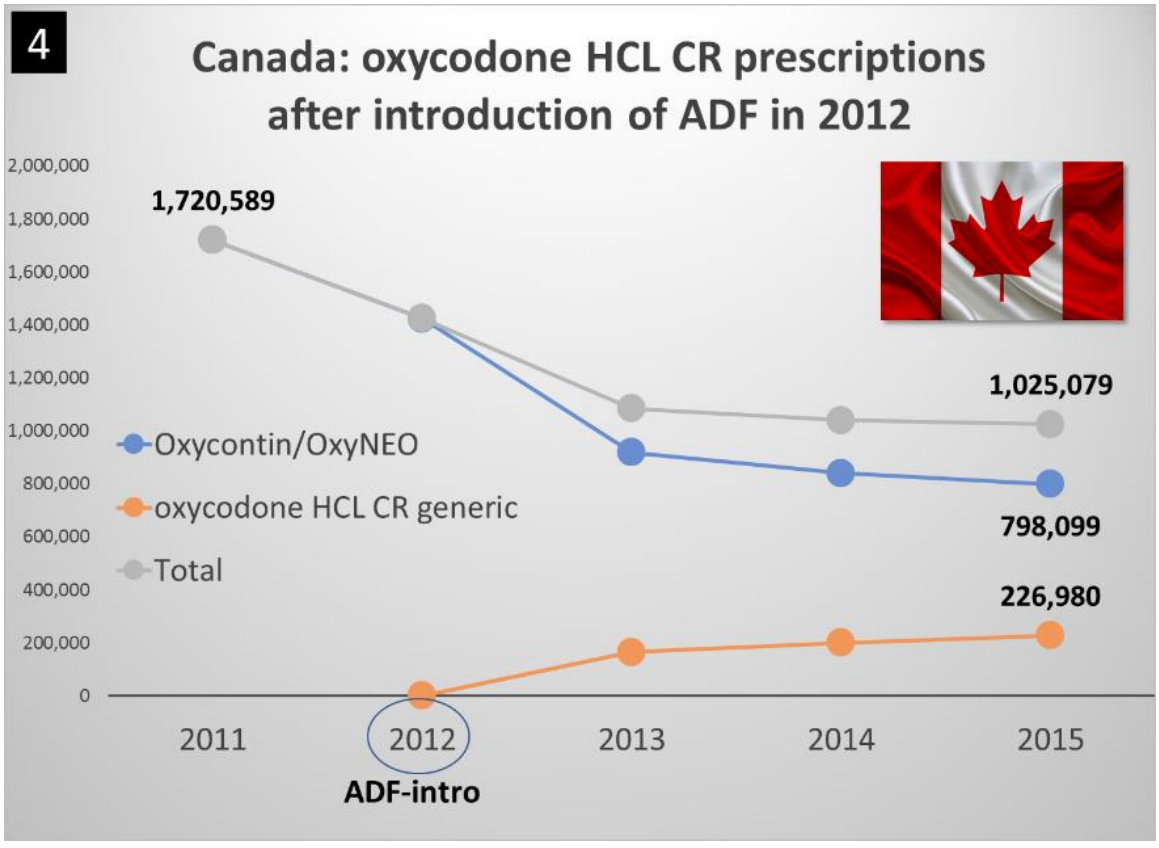
[33] Prince Edward Island and Newfoundland & Labrador are combined in the source databases.

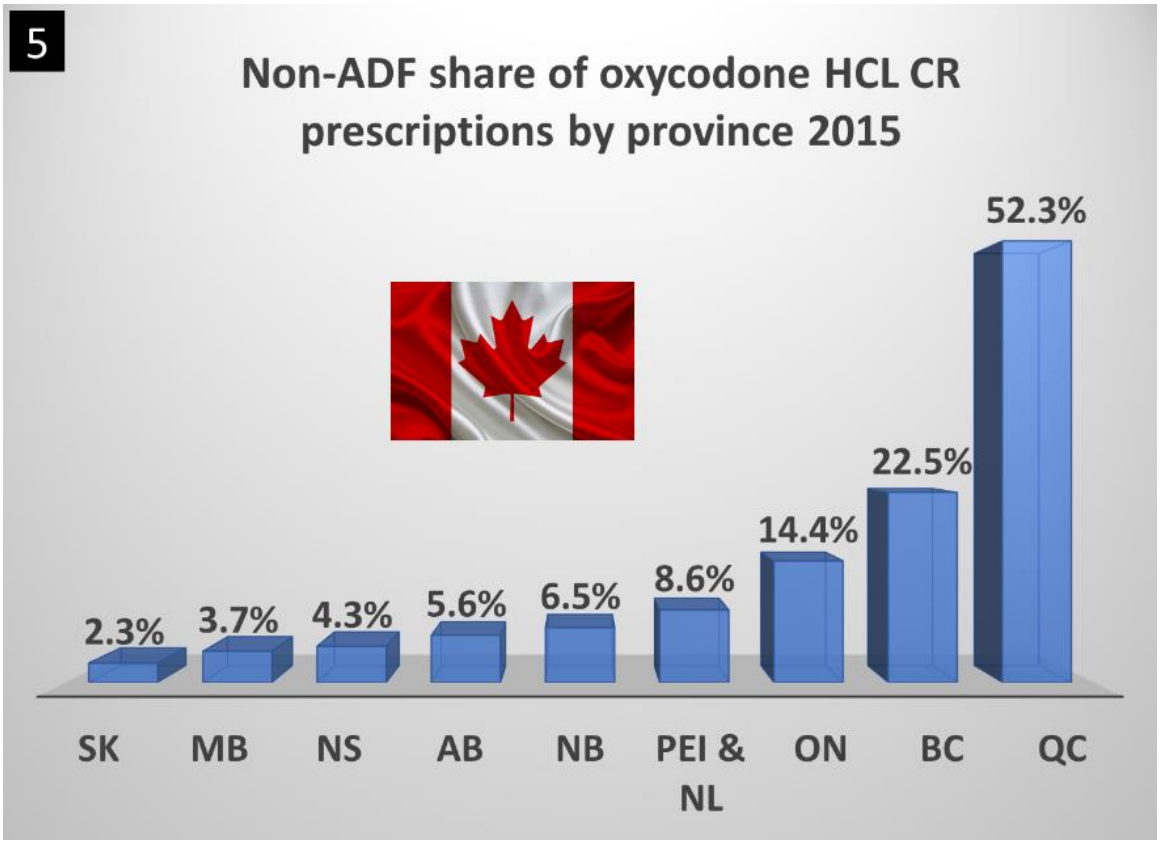
[34] U.S. Bureau of Labor Statistics (2017). CPI Inflation Calculator. URL: https://www.bls.gov/data/inflation_calculator.htm.

[35] Health, United States, 2015. Centers for Medicare & Medicaid Services. Table 93 and National Health Expenditures 2015 Highlights. | National Health Expenditure Database, 1975 to 2016, Canadian Institute for Health Information. Table A.3.1.3 Total Health Expenditure by Use of Funds, Canada, 1975 to 2016—Current Dollars (per capita).

[36] Bank of Canada. CAD/USD Exchange Rate Lookup. Average of the annual low and high.


3
Canada: total opioid prescriptions after introduction of first ADF in 2012
20,000,000
15,000,000
10,000,000
5,000,000
0
18,400,012
19,863,130
2011
2012
2013
2014
2015
ADF-intro


4
Canada: oxycodone HCL CR prescriptions after introduction of ADF in 2012
2,000,000
1,800,000
1,600,000
1,400,000
1,200,000
1,000,000
800,000
600,000
400,000
200,000
0
1,720,589
1,025,079
798,099
226,980
Oxycontin/OxyNEO
oxycodone HCL CR generic
Total
2011
2012
2013
2014
2015
ADF-intro

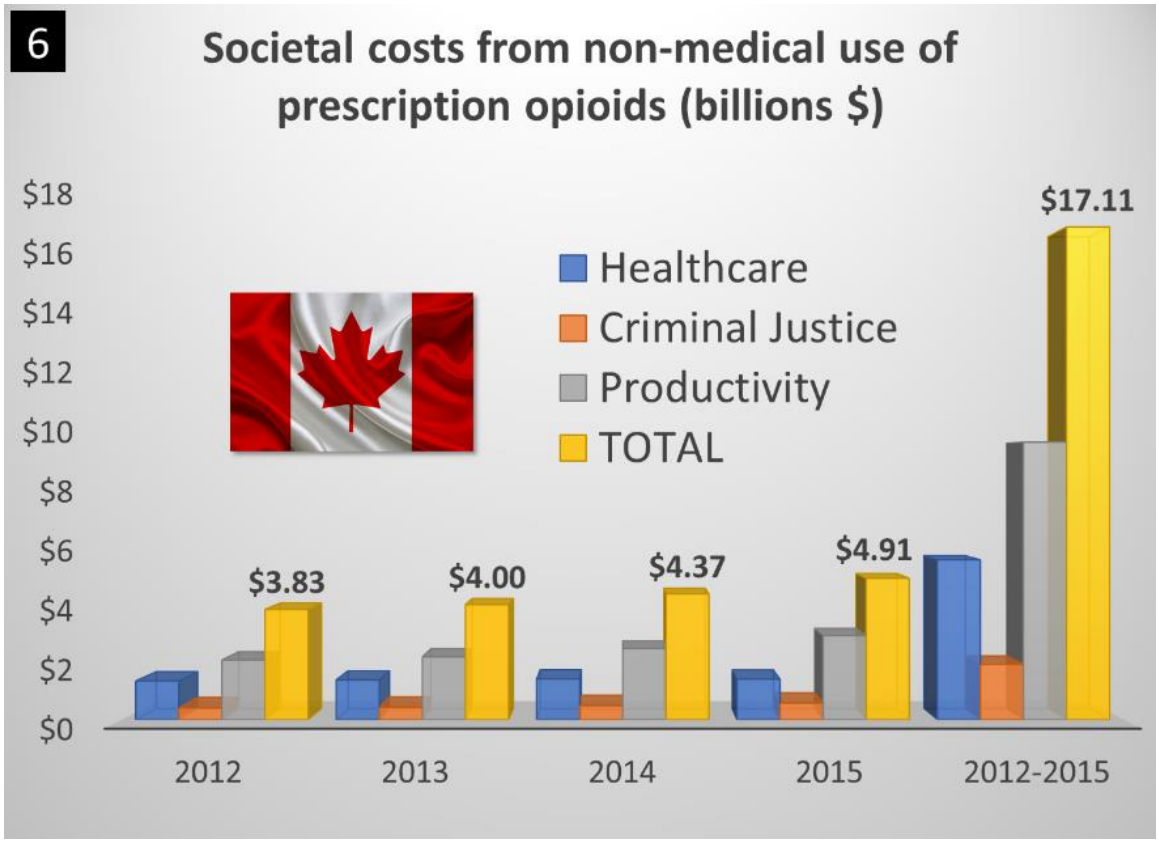


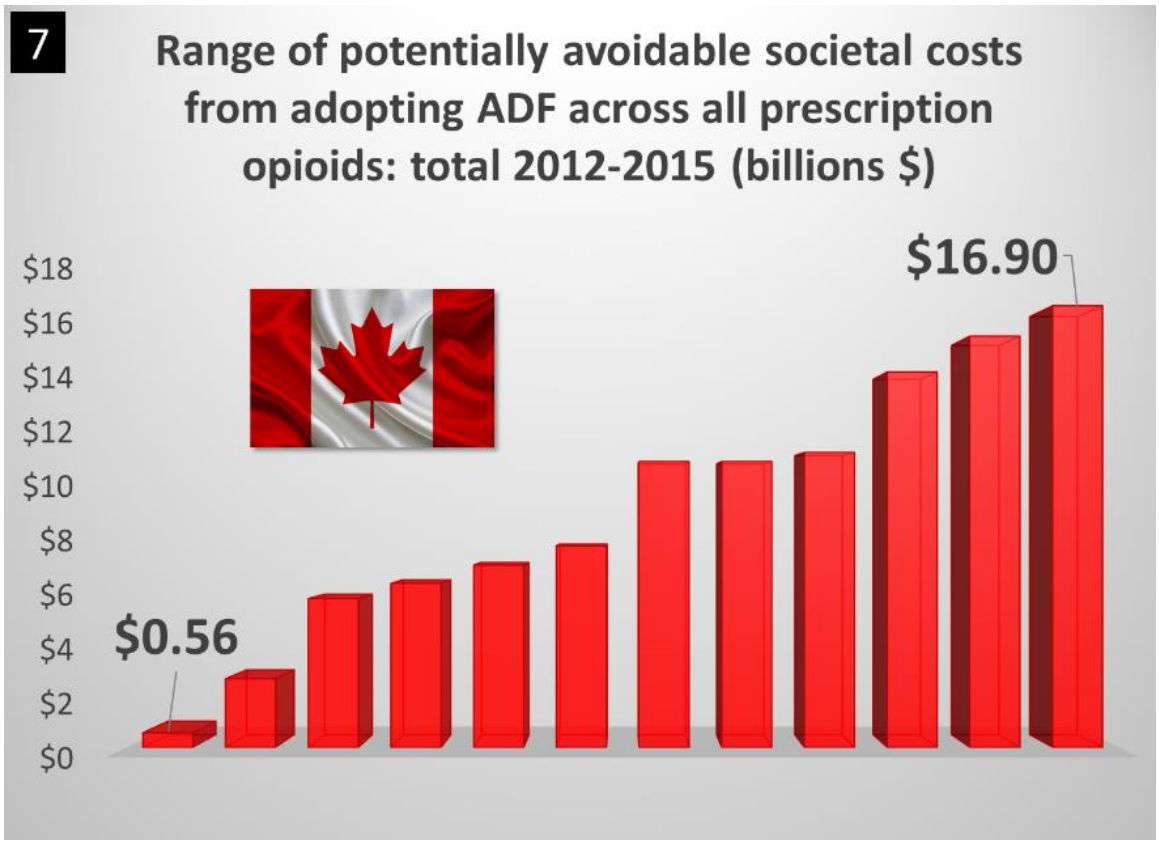
[Table 3] displays the American source data followed by the extrapolated Canadian estimates for the total societal economic costs associated with the non-medical use of prescription opioids in each country. The bottom of the table shows the calculated costs of non-medical use that could potentially have been avoided if ADF had been mandatory for all prescription opioids in Canada from 2012 (the first year it was available for oxycodone HCL CR) to 2015. The data are shown by year and as a cumulative total for the whole period.

The analysis calculated the potentially avoidable costs according to the findings of various studies that have tested the abuse deterrent effectiveness of existing ADF technology already in use for opioids. The analysis assumes that if ADF was mandatory for all prescription opioids, that the ADF technologies would be of similar effectiveness to those already in use.

[Chart 6] shows the results of the extrapolated estimates for the total societal economic costs associated with the non-medical use of prescription opioids in Canada ($C). The results are shown by year and as a cumulative total for the whole period, and displayed by separate bars for the various components. Annually, total societal economic costs from non-medical use of prescription opioids in Canada averaged about $4.3 billion per year. The four-year cumulative total was $17.1 billion from 2012 to 2015.

[Chart 7] shows the range of the calculated costs of non-medical use that could potentially have been avoided if ADF had been mandatory for all prescription opioids in Canada. The estimates vary according to the effectiveness factored in to each calculation which is based on the findings of the literature review. The four-year cumulative total from 2012 to 2015 ranged from $560 million to $16.9 billion (averaging from $140 million to $4.2 billion per year). The median estimate is about $9.3 billion for the entire period (averaging $2.3 billion per year).


6
Societal costs from non-medical use of prescription opioids (billions $)
$18
$16
$14
$12
$10
$8
$6
$4
$2
$0
Healthcare
Criminal Justice
Productivity
TOTAL
$3.83
$4.00
$4.37
$4.91
$17.11
2012
2013
2014
2015
2012-2015


7
Range of potentially avoidable societal costs from adopting ADF across all prescription opioids: total 2012-2015 (billions $)
$18
$16
$14
$12
$10
$8
$6
$4
$2
$0
$0.56
$16.90

NMU Initiation Rate

ADF might be particularly successful at reducing the initiation rate of new non-medical users of prescription opioids. This could produce cumulative savings over time by avoiding the compounding of downstream societal costs.

The literature review did not find any Canadian sources of national data that estimates the initiation rate of new non-medical users of prescription opioids. Assuming that the Canadian NMU initiation rate is the same as in the USA, the proportionally attributable societal economic costs can be extrapolated by applying the American NMU rate to the Canada/USA prescription opioid utilization ratio.

As shown earlier in this paper, 12.5 million Americans misused pain relievers in 2015. Of these, 2.1 million (16.8%) people aged 12 or older were recent initiates for pain reliever misuse (i.e., misused for the first time in the past year). NMU initiates therefore accounted for 16.8% of the $62.43 billion in societal economic costs from non-medical use of prescription opioids in the USA in 2015.

Based on the data available to this study, prescription opioid utilization in Canada was 7.98% of utilization in the USA during 2015. Applying this to the American data above produces an estimate of potentially 997,500 non-medical users of prescription opioids in Canada in 2015, of which 16.8% or 167,580 were new initiates, proportionally accounting for between $29 million (= $0.16b * 16.8%) to $815 million (= $4.85b * 16.8%) of the potentially avoidable costs associated with non-medical use of prescription opioids in 2015.

Discussion

US Regulatory Support for ADF

Regulatory policy divergence between Health Canada and the US FDA is associated with divergent utilization trends for prescription opioids, of which non-medical use is assumed to be proportionally associated.

The US FDA's encouragement for ADF through its regulatory policies has coincided with a greater availability of ADF across multiple opioid products, and this has also coincided with a decline in the total utilization of prescription opioids in the USA over time as the ADF technology has proliferated across products.

By contrast, Health Canada's regulatory policies have coincided with lesser availability of ADF across opioid products, while the utilization of prescription opioids in Canada has steadily increased over time.

This suggests that the American regulatory policies offer incentives to develop and proliferate ADF, and that such incentives are absent in Canada's policy environment. The combination of allowing non-ADF generics on the market, and restricting public drug plan coverage for ADF products, is probably discouraging the proliferation of socially beneficial ADF technology in Canada.

Avoidable Costs v. Generic Savings

Presumably, one of the main policy considerations to allow non-ADF opioids to enter the market (or allow existing non-ADF opioids to remain available for sale to consumers) is to capture the savings from lower prices for generic drugs.

Previous research has shown that even at low levels of effectiveness at reducing overall non-medical use of opioids, ADF technologies can avoid a greater magnitude of costs at the societal level than can be saved from paying lower generic prices in drug plans.

According to the 2012 study that this analysis is based on, mandating ADF for OxyContin needed to reduce abuse by as little 18% to 30% for the trade-off to be economically neutral.[37]

[37] Skinner BJ (2012).

The literature reviewed for this study found that existing ADF technologies were effective at reducing NMU rates. Estimates ranged from 3.3% to 98.8% effective at reducing the NMU rate. The median ADF effectiveness reducing NMU rates by between 45.1% and 64%.

The data suggest that the expected reduction in the NMU rate for RxO that would result from mandating universal adoption of existing ADF technology across all opioids, would very likely produce significant net societal cost savings.

Cautions and Limitations

This study relies on the accuracy and completeness of the data supplied by Purdue Pharma which was sourced from QuintilesIMS.

The analysis of utilization assumes comparability between prescription sizes as a unit of measure between Canada and the USA, and constancy of prescription sizes within each market over time. This was a requirement of available data. However, it is known that prescription sizes vary between markets and within markets over time. Caution is advised when interpreting utilization trends based on variable units of measure.

The analysis of avoidable costs assumes that a person who is deterred from abusing prescription opioids by the ADF will not substitute other illicit drugs for abuse. It is unlikely that all the societal economic costs attributable to RxO abuse will be eliminated to exactly the same degree that tests on specific opioids have found. However, as this study has shown, the ADF need only eliminate a small percentage of overall drug abuse to produce significant societal cost savings.

This study assumes that the potential, if not the actual prevalence of RxO abuse is proportionally similar in Canada and the United States. The available evidence generally supports this assumption.

The extrapolated data have been adjusted for differences in per capita health costs between Canada and the USA. However, extrapolations of other societal economic costs have not been adjusted for potential cross-national differences. Other adjustments have been made (noted in the text and tables) to mitigate for known divergence between Canada and the USA.

ADF offer the potential to deter abuse of prescription opioid drug products, while preserving normal availability for legitimate medical-use by patients. Using restricted access policies to reduce the costs of opioid abuse must be weighed against the socio-economic costs resulting from the loss of health benefits to the vast majority of the user population that makes legitimate medical use of opioids as pain relievers. The potential loss of health benefits caused by restricted access is not part of the analysis.

Author

Dr. Brett J Skinner is the Founder and CEO of Canadian Health Policy Institute (CHPI) and the Editor of CHPI's online journal *Canadian Health Policy*. Dr. Skinner was previously Executive Director Health and Economic Policy at Innovative Medicines Canada; and he was also previously CEO and Director of Health Policy Studies at Fraser Institute. Dr. Skinner has a B.A. from the University of Windsor, an M.A. through joint studies between the University of Windsor and Wayne State University (Detroit), and a Ph.D. from Western University (aka University of Western Ontario, London), where he has lectured in both the Faculty of Health Sciences and the Department of Political Science.

Acknowledgements

The analysis, conclusions and opinions expressed in this paper are the author's own independent research and ideas, and do not necessarily reflect the views of the author's employers or any affiliated organizations. The author is the sole guarantor of the integrity and originality of the work contributed to this research paper.

This study is based in part on data sourced from QuintilesIMS Inc. The statements, findings, conclusions, views, and opinions contained and expressed herein are not necessarily those QuintilesIMS Inc. or any of its affiliated or subsidiary entities.

Free public access to this study was made possible by funding provided by Purdue Pharma Canada Inc. As a courtesy, the sponsor was given an opportunity to preview and comment on this paper prior to its publishing.

Table 1. Reimbursement status of non-ADF OxyContin, ADF OxyNEO and generic non-ADF oxycodone HCL CR on provincial public drug plans.[38]

	OxyContin (Sept/11)	OxyNEO (Mar/17)	Generic non-ADF oxycodone HCL CR (Mar/17)
BC	Restricted benefit[1]	Not listed; case-by-case approval[8]	Not listed
AB	Open benefit	Open benefit	Not listed
SK	Open benefit	Restricted benefit[9]	Not listed
MB	Part III	Part III[10]	Not listed
ON	Limited Use[2]	Not listed – on EAP[11]	Not listed
QC	Open benefit	Restricted access[12]	Restricted access[12]
NB	Restricted benefit[3]	Not listed	Not listed
NS	Restricted benefit[4]	Not listed; case by case for cancer and palliative care	Not listed
PEI	Restricted benefit[5]	Not listed	Not listed
NL	Restricted benefit[6]	Not listed	Not listed
NIHB	Limited Use[7]	Not listed – case by case	Not listed

Reimbursement Conditions

1. Pain management in cancer, palliative care and chronic pain PLUS for patients who are unable to tolerate or receive an adequate response to either the regular release dosage forms of oxycodone or the sustained release preparations of morphine.
2. For the treatment of chronic pain in patients who cannot tolerate, or have failed treatment with a listed long-acting opioid.
3. For the treatment of moderate to severe cancer-related or chronic non-malignant pain.
4. For treatment of moderate t severe chronic pain syndromes, as an alternative to morphine or hydromorphone. For patients with persistent pain* who have been stabilized on a titrated dose of an oral short-acting oxycodone product OR whose pain is not adequately controlled or who are intolerant to an oral sustained-release morphine product despite dose titration and adjuvant antiemetics and laxatives. *Please note: in order to assess requests for coverage in the treatment of non-malignant pain the Department will require the following information: a) results of any xrays/CT scans/MRIs; b) information relating relating to any consultations completed and their recommendations (ie surgical, orthopaedic and/or physiotherapy consultations);c) surgical history; d) past analgesic use and response; current analgesic use, dosage, and assessment of current level of pain control, e) any other information you feel is pertinent to the request.
5. For treatment of severe chronic pain that is not well controlled by short and long-acting morphine and hydromorphone products. For treatment of: moderate to severe cancer pain in patients who cannot tolerate or who have failed treatment with at least one other long-acting opioid (such as sustained-release morphine or controlled-release hydromorphone). b) For treatment of moderate to severe non-cancer chronic pain in patients who cannot tolerate or who have failed treatment with at least one other long-acting opioid (such as sustained-release morphine or controlled-release hydromorphone). Day supply limit per dispense will be 30 days.
6. No criteria are provided.
7. Palliative care and cancer pain only.
8. Cancer pain and unable to tolerate or inadequate response to IR oxycodone or SR morphine or SR hydromorphone OR non-cancer chronic pain and unable to tolerate or inadequate response to IR oxycodone or SR morphine or SR hydromorphone.
9. Intolerance or failure of an adequate trial (e.g., 3 months) of ≥1 listed CR opioid (10, 15, 20, 30 & 40 mg).
10. Failure/intolerance/contraindication of 2 other opioids.

[38] Sources: OxyContin from historic views of the provincial drug plan formularies; OxyNEO and generic oxycodone CR from current provincial drug plan formularies. Courtesy of Kristin Beard, BScH, MSc, PhD, Manager, Reimbursement Strategy, Purdue Pharma (Canada).

Table 2. Prescriptions dispensed for ADF v. non-ADF oxycodone HCL CR by Province, percentage change v. base year.

	AB				
	2012	**2013**	**2014**	**2015**	**% Change**
ADF	156,445	142,791	149,551	151,733	-3%
Non-ADF	-	5,564	7,442	8,928	60%
TOTAL	**156,445**	**148,355**	**156,993**	**160,661**	**3%**
Non-ADF % Total		3.8%	4.7%	5.6%	

	BC				
	2012	**2013**	**2014**	**2015**	**% Change**
ADF	110,157	64,845	53,120	48,725	-56%
Non-ADF	-	11,175	12,660	14,129	26%
TOTAL	**110,157**	**76,020**	**65,780**	**62,854**	**-43%**
Non-ADF % Total		14.7%	19.2%	22.5%	

	MB				
	2012	**2013**	**2014**	**2015**	**% Change**
ADF	31,255	25,220	24,979	24,486	-22%
Non-ADF	-	736	1,196	946	29%
TOTAL	**31,255**	**25,956**	**26,175**	**25,432**	**-19%**
Non-ADF % Total		2.8%	4.6%	3.7%	

	NB				
	2012	**2013**	**2014**	**2015**	**% Change**
ADF	27,182	22,588	21,528	20,690	-24%
Non-ADF	-	1,120	1,611	1,434	28%
TOTAL	**27,182**	**23,708**	**23,139**	**22,124**	**-19%**
Non-ADF % Total		4.7%	7.0%	6.5%	

	NS				
	2012	**2013**	**2014**	**2015**	**% Change**
ADF	12,592	11,392	12,565	13,115	4%
Non-ADF	-	296	423	586	98%
TOTAL	**12,592**	**11,688**	**12,988**	**13,701**	**9%**
Non-ADF % Total		2.5%	3.3%	4.3%	

	ON				
	2012	**2013**	**2014**	**2015**	**% Change**
ADF	715,670	439,918	396,456	382,447	-47%
Non-ADF	-	47,737	59,275	64,236	35%
TOTAL	**715,670**	**487,655**	**455,731**	**446,683**	**-38%**
Non-ADF % Total		9.8%	13.0%	14.4%	

	PEI & NL				
	2012	**2013**	**2014**	**2015**	**% Change**
ADF	24,400	23,858	19,220	21,600	-11%
Non-ADF	-	876	1,708	2,045	133%
TOTAL	**24,400**	**24,734**	**20,928**	**23,645**	**-3%**
Non-ADF % Total		3.5%	8.2%	8.6%	

	QC				
	2012	**2013**	**2014**	**2015**	**% Change**
ADF	327,967	174,163	148,209	122,510	-63%
Non-ADF	-	97,923	116,082	134,380	37%
TOTAL	**327,967**	**272,086**	**264,291**	**256,890**	**-22%**
Non-ADF % Total		36.0%	43.9%	52.3%	

	SK				
	2012	**2013**	**2014**	**2015**	**% Change**
ADF	18,404	14,243	14,160	12,793	-30%
Non-ADF	-	96	222	296	208%
TOTAL	**18,404**	**14,339**	**14,382**	**13,089**	**-29%**
Non-ADF % Total		0.7%	1.5%	2.3%	

Table 3: Potentially avoidable societal costs from adoption of ADF for all RxO.

	2012	2013	2014	2015	
USA societal costs from non-medical use of RxO:		(billions $US)			**TOTAL**
Healthcare adjusted for change in CPI, RxO volume	$30.75	$30.34	$30.04	$28.02	**$119.14**
Criminal Justice adjusted for change in CPI, RxO volume	$6.27	$6.19	$6.13	$5.72	**$24.31**
Productivity adjusted for change in CPI, RxO volume	$31.49	$31.06	$30.76	$28.69	**$122.00**
TOTAL	**$68.52**	**$67.58**	**$66.91**	**$62.43**	**$265.44**

	2012	2013	2014	2015	
CAN societal costs from non-medical use of RxO:		(billions $C)			**TOTAL**
Healthcare adjusted for CAN/USA: RxO volume, healthcare costs and $MER	$1.35	$1.38	$1.41	$1.41	**$5.55**
Criminal Justice adjusted for CAN/USA: RxO volume, healthcare costs and $MER	$0.41	$0.43	$0.49	$0.58	**$1.92**
Productivity adjusted for CAN/USA: RxO volume, healthcare costs and $MER	$2.07	$2.18	$2.47	$2.92	**$9.64**
TOTAL	**$3.83**	**$4.00**	**$4.37**	**$4.91**	**$17.11**

	2012	2013	2014	2015	
Potential avoidable CAN societal costs from adoption of ADF for all RxO:		(billions $C)			**TOTAL**
(Cicero 2015) ADF:					
deterred all abuse among NMUsers 3.3%	$0.13	$0.13	$0.14	$0.16	**$0.56**
induced drug switch among NMUsers 33.3%	$1.28	$1.33	$1.46	$1.63	**$5.70**
reduced NMUsers seeking treatment by 40.8%	$1.56	$1.63	$1.78	$2.00	**$6.98**
(White 2015) ADF reduced NMU rate by:					
oxy. 15.4%	$0.59	$0.62	$0.67	$0.76	**$2.63**
morph. 45.1%	$1.73	$1.80	$1.97	$2.21	**$7.71**
oxy. 64%	$2.45	$2.56	$2.80	$3.14	**$10.95**
morph. 98.8%	$3.79	$3.95	$4.32	$4.85	**$16.90**
(Vosburg 2012) ADF reduced tampering:					
inject by 84%	$3.22	$3.36	$3.67	$4.12	**$14.37**
snort by 92%	$3.53	$3.68	$4.02	$4.51	**$15.74**
(Cicero and Surratt 2012) ADF:					
reduced NMU rate by 36.7%	$1.41	$1.47	$1.60	$1.80	**$6.28**
reduced drug as primary choice for NMU by 64%	$2.45	$2.56	$2.80	$3.14	**$10.95**
induced drug switch among NMUsers 66%	$2.53	$2.64	$2.88	$3.24	**$11.29**