Safety and Use of Opioids

A summary of ODPRN research on prescription opioid use in Ontario

About the ODPRN

The Ontario Drug Policy Research Network (ODPRN) is a province-wide network of researchers who provide timely, high quality, drug policy relevant research to decision makers. The ODPRN’s core principles are quality, relevance, and timeliness.

We conduct research to determine real-world drug utilization, safety, effectiveness, and costs of drugs in Ontario, and have developed partnerships that allow us to engage in cross-provincial comparisons of drug safety and utilization.

Many of the studies reported here were supported by the Institute for Clinical Evaluative Sciences (ICES; www.ices.on.ca), a non-profit research institute sponsored by the Ontario MOHLTC. The design and conduct of the study; collection, management, analysis and interpretation of the data; and preparation of this report were conducted by the authors independently. No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred.

For more information about the ODPRN and the work we do, visit us on our website: www.odprn.ca or on twitter: @ODPRN_Research
Why study opioids?

Opioid analgesics are prescription painkillers used to treat various pain conditions; however the efficacy and safety of their use in treating chronic non-cancer pain is subject of considerable debate due to a lack of long-term studies in this area. Furthermore, with the availability of various opioid types and potencies on the market, and uncertainty on appropriate dosing, the safety of these drugs has been widely questioned. Canada and the United States have the highest consumption of opioids worldwide\(^1\), thus emphasizing the importance of exploring this issue further.

From 2008 - 2015, the ODPRN conducted several population-based studies using data from the Institute for Clinical Evaluative Sciences (ICES), IMS Health, and Ontario’s Office of the Chief Coroner to investigate the use of opioids in Ontario. The key objective of these studies was to provide evidence to inform discussions regarding the safe and appropriate use of opioids.

References

Summarizing the evidence

This document describes the ODPRN’s findings from studies on opioids from 2008-2015, summarized into four key themes of our research. It is intended for individuals and organizations engaged in policy and practice.

In each section, you will find key results as well as policy and practice implications of our findings.

1. Overall trends in opioid use
2. Safety of opioid use
3. Geographic variation in opioid prescribing, use and safety
4. Potential impact of policy and education interventions
Section 1
Overall trends in opioid use and dose

How has the use of opioids changed over the past 2 decades?

To answer this question, the ODPRN looked at opioid utilization and dosing patterns in Ontario and across Canada. In this section, we describe:

- Patterns of opioid use and dose in Ontario
- High dose opioid prescribing in Canada
- Implications for policy and practice

Patterns of opioid use and dose in Ontario

Over a 6-year study period from 2003 to 2008 in which data from Ontario’s public drug program beneficiaries aged 15 – 64 years were examined, the annual prescribing rate for opioids rose by 16.2% from 1848 per 1000 eligible in 2003, to 2148 per 1000 eligible in 2008. Additionally:

- Rates of long-acting oxycodone prescribing more than doubled, from 331 per 1000 to 675 per 1000 population.
- More than 1/4 of Ontario’s public drug beneficiaries received an opioid prescription

Furthermore, over this time, the prevalence of high dose prescribing rose among individuals treated with long-acting opioids (Figure 1). Specifically:

- By 2008, 26.8% of individuals prescribed long-acting opioids were treated with high daily doses (defined as >200 mg morphine or equivalent [MEQ]).
- This was most pronounced among those treated with long-acting oxycodone, where one-third (32.6%) of patients had daily doses exceeding 200 mg MEQ by 2008.
- As expected, high doses of immediate release opioids were uncommon.
There are also important gender differences in opioid prescribing and use. We looked at adults aged 15-64, over a 13 year time period (April 1, 1997 to December 31, 2010), who were eligible for Ontario Drug Benefits and receiving opioids for non-cancer pain. Most notably:

• 1 of every 45 men and 1 of every 70 women who received chronic opioid therapy escalated to a high dose therapy.²

• One of every 350 men and 1 of every 850 women receiving chronic opioid therapy died from opioid-related causes.²

• Individuals who escalate to high dose opioid therapy were nearly 24 times more likely to die from opioids than those who do not.²

• 3.8% of men and 2.2% of women prescribed > 200 MEQ per day later died of opioid-related causes.²

---

**High dose opioid dispensing in Canada**

“...high-dose opioid dispensing increased steadily in Canada between 2006-2008 before plateauing in 2009-2010, which aligns with the release of Canadian and American guidelines.”³

Mounting evidence shows that the prescription of opioids at high doses can be particularly dangerous⁴ (see **Box 1** for a definition of high dose prescribing). As a result, high dose formulations of opioids (e.g. tablets or patches that when used at the recommended frequency can lead to daily doses exceeding 200 mg MEQ) are cause for particular concern.

One of the most dramatic trends observed in recent years has been the rise of high dose opioid prescribing. As described earlier in this report, in 2008, roughly one-third of Ontarians using long-acting oxycodone had daily doses that exceeded thresholds outlined clinical guidelines.¹ Moreover, nationally, between 2006 and 2011:

• The rate of prescribing of high dose opioid formulations rose 23% in Canada, with more than 30 million tablets or patches of high dose opioids dispensed annually.³

• Provincial differences were observed in both the **prevalence** of high dose formulation prescribing and the **types** of opioids prescribed at high doses (Figure 2). For example:
  ○ High-dose opioid dispensing rates varied more than 3-fold by province.
  ○ Ontario and Alberta had the highest prescribing rates for high-dose oxycodone compared to other Canadian provinces. However, Ontario also had one of the highest rates of high dose fentanyl prescribing while Alberta had among the lowest rates in the country.
  ○ Two of the highest rates of high-dose hydromorphone dispensing were found in Saskatchewan and Nova Scotia, two of the provinces with the lowest rates of high-dose oxycodone prescribing.

---

**Box 1: How high is too high?**

• Until recently, guidelines did not provide a recommended daily dose threshold for opioids, and these drugs were initially marketed as having no upper dose threshold¹.

• Currently, the Canadian National Opioids Use Guidelines for chronic non-malignant pain classifies any dose higher than 200 mg/ day of morphine (or equivalent) as a high or ‘watchful’ dose.⁵ Other guidelines suggest dose thresholds ranging between 50 and 200 mg MEQ.

• Morphine equivalents (or “MEQ”) are used to convert the various strengths of different opioids into one consistent value. This allows us to to compare overall volume of opioids dispensed, regardless of opioid type over time and between people and jurisdictions.

---

[303x24]6

[61x579]High dose opioid dispensing in Canada

[61x554]“…high-dose opioid dispensing increased steadily in Canada between 2006-2008 before plateauing in 2009-2010, which aligns with the release of Canadian and American guidelines.”³

Mounting evidence shows that the prescription of opioids at high doses can be particularly dangerous⁴ (see **Box 1** for a definition of high dose prescribing). As a result, high dose formulations of opioids (e.g. tablets or patches that when used at the recommended frequency can lead to daily doses exceeding 200 mg MEQ) are cause for particular concern.

One of the most dramatic trends observed in recent years has been the rise of high dose opioid prescribing. As described earlier in this report, in 2008, roughly one-third of Ontarians using long-acting oxycodone had daily doses that exceeded thresholds outlined clinical guidelines.¹ Moreover, nationally, between 2006 and 2011:

• The rate of prescribing of high dose opioid formulations rose 23% in Canada, with more than 30 million tablets or patches of high dose opioids dispensed annually.³

• Provincial differences were observed in both the **prevalence** of high dose formulation prescribing and the **types** of opioids prescribed at high doses (Figure 2). For example:
  ○ High-dose opioid dispensing rates varied more than 3-fold by province.
  ○ Ontario and Alberta had the highest prescribing rates for high-dose oxycodone compared to other Canadian provinces. However, Ontario also had one of the highest rates of high dose fentanyl prescribing while Alberta had among the lowest rates in the country.
  ○ Two of the highest rates of high-dose hydromorphone dispensing were found in Saskatchewan and Nova Scotia, two of the provinces with the lowest rates of high-dose oxycodone prescribing.

---

**Box 1: How high is too high?**

• Until recently, guidelines did not provide a recommended daily dose threshold for opioids, and these drugs were initially marketed as having no upper dose threshold¹.

• Currently, the Canadian National Opioids Use Guidelines for chronic non-malignant pain classifies any dose higher than 200 mg/ day of morphine (or equivalent) as a high or ‘watchful’ dose.⁵ Other guidelines suggest dose thresholds ranging between 50 and 200 mg MEQ.

• Morphine equivalents (or “MEQ”) are used to convert the various strengths of different opioids into one consistent value. This allows us to to compare overall volume of opioids dispensed, regardless of opioid type over time and between people and jurisdictions.
Figure 2. High-dose opioid dispensing rate (number of units per 1000 population), by province and opioid type: Rates are calculated as the average rate of dispensing between 2006 and 2011 (reproduced from Gomes et al.3)

**Implications**

Opioid prescribing and dose have risen significantly over the past several decades, and over one-quarter of individuals treated with opioids in 2008 had daily doses exceeding thresholds now established in Canadian guidelines. Changes to clinical practice and policy could help improve safe prescribing of these drugs.

**Policy**

- Policy makers may want to consider:
  - Strategies that restrict high dose opioid use to select patients in whom other alternatives have been ineffective.
  - A national strategy to promote safe opioid prescribing. However this strategy must be flexible to address specific opioid prescribing issues at the provincial and local levels.

**Practice**

- Physicians should exercise caution when prescribing opioids - particularly in high doses - and carefully consider other drug and non-drug treatment options for pain.

**References**


What are some of the potential harms of opioid use?

The ODPRN conducted multiple studies to investigate opioid-related deaths and other potential adverse effects of opioid use in Ontario (note that these are not the only ways in which opioids can cause harm). In this section, we describe:

- Overall burden of opioid-related mortality
- Relationship between escalating opioid dose and adverse events
  - Opioid overdose death
  - Injury in motor vehicle accident
- Implications for policy and practice
- Sex differences in dose and usage

Overall burden of mortality

“In 2010, approximately 1 of every 170 deaths (in Ontario) was related to opioids.”

The rise in the use of opioids has contributed significantly to drug-related deaths in Ontario. Since the early 1990s, the annual rate of opioid related deaths has increased 3-fold in Ontario, from 12.2 deaths per million in 1991 (127 deaths annually) to 41.6 deaths per million in 2010 (550 deaths annually (Figure 3).
In our research, we uncovered key factors related to opioid-related mortality:

- **Age**: Among young adults in particular, opioid-related deaths contribute significantly to overall death rates; in 2010, 1 in 8 deaths among young adults aged 25-34 were related to an opioid (Figure 4).\(^1\)
- **Sex**: Opioid-related death occurred in 1 of every 350 men and 1 of every 850 women receiving chronic opioid therapy.\(^2\)

![Figure 4. Proportion of all deaths that are opioid-related, by age group during the years 1992, 2001, and 2010 (reproduced from Gomes et al.\(^1\))](image)

- **Burden of early loss of life**: The mean age at time of opioid-related death is 42 years. This clustering of opioid-related deaths in younger individuals translates to a considerable burden due to early loss of life. By 2010, the Person Years of Life Lost attributable to opioid-related deaths exceeded that attributable to influenza, pneumonia, and HIV/AIDS.\(^1\)
- **Physician prescribing patterns**: Doctors who prescribe opioids more frequently are also more likely to issue final prescription before a patient’s death (Figure 5).\(^3\)

![Figure 5. Rate of opioid prescribing and final prescriptions before death, by physician prescribing frequency: The dashed line represents the number of final opioid prescriptions before death issued by physicians in each quintile (reproduced from Dhalla et al.\(^3\))](image)
Relationship between escalating opioid dose and adverse events

“People prescribed high doses of opioids may be up to 3 times more likely to die from opioid-related overdoses compared to those treated with lower doses”.4

Although recent clinical guidelines have provided recommendations relating to upper or watchful doses of opioids, these thresholds have generally relied on expert clinical opinion. The ODPRN conducted two studies to investigate the potential association between escalating opioid dose and risk of 1) opioid-related death, and 2) being injured in a motor vehicle accident.

These studies found a significant dose-response relationship between escalating daily dose of opioid and risk of these outcomes. Specifically:

- Ontarians who were moderate (50-99 mg MEQ) or high (100-199 mg MEQ) dose users of opioids had an approximately doubled risk of opioid overdose death compared to users of low doses (<20 mg MEQ). Those who were very high dose (200+ mg MEQ) users of opioids had a threefold higher risk of overdose death.5
- Ontario drivers who were low (20-49 mg MEQ), moderate (50-99 mg MEQ), high (100-199 mg MEQ), and very high (200+ mg MEQ) dose users of opioids were 21%, 29%, 42%, and 23% more likely to visit the hospital with injuries from motor vehicle accidents than very low dose users (<20 mg MEQ), respectively.6
**Implications**

Opioid-related mortality has risen significantly over the past several decades, and these deaths have been associated with increased prescribed dose. Changes to clinical practice and policy could help reduce the overall burden of mortality.

**Policy**

- Given the observed relationship between escalating opioid dose and risk of adverse events, along with limited evidence of efficacy of long-term high dose opioid use to treat pain, policies designed to restrict widespread high dose opioid use may be warranted.
- Strategies to reduce opioid-related harm should include specific components designed to focus on those individuals who frequently prescribe opioids.
- The 2010 Ontario Narcotics Safety and Awareness Act was introduced in an effort to address appropriate use of opioids in Ontario. Canadian guidelines were also published in 2010, with specific recommendations around high dose opioid prescribing. The impact of this Act and the Canadian guidelines on opioid prescribing patterns and opioid-related deaths has yet to be examined.

**Practice**

- Physicians should be aware of potentially serious adverse effects of opioids, particularly when prescribing to the younger population.
- Prescribers and pharmacists should communicate the risk of these medications to patients, especially as they relate to overdoses and impacts on driving.
- Family physicians may want to reduce the risk of opioid-related harm in their patients by carefully considering the appropriateness of opioid prescribing in light of limited evidence of efficacy of opioids in treatment of chronic non-cancer pain.

**References**

Section 3
Geographic variation

How do opioid prescribing, use, safety, and mortality vary across Ontario?

The ODPRN conducted studies to assess differences in opioid prescribing and related harms across various regions of Ontario. In this section, we describe:

- Geographic variation in opioid prescribing and mortality
- Potential trafficking of opioids across the US-Canada border
- Implications for policy and practice

Geographic variation in opioid prescribing, hospital/emergency room visits, and mortality

The rate of opioid prescribing varies considerably across Ontario. According to data for Ontario residents aged 15 to 64 years receiving publicly-funded opioids between 2011 and 2013, several 'hot-spots' exist in Ontario where higher rates of opioid prescribing is prevalent (Figure 6).¹ Hospital visits related to opioid toxicity also increased across Ontario between 2006-2010 and 2011-2013 among both younger (15-64) and older (65+) individuals.¹

“During 2011-2013, there was an 11-fold variation in annualized rates of opioid prescribing and a 7-fold variation in annualized rates of opioid toxicity-related hospital admission between Ontario counties.”

Looking at the opioid related deaths in Ontario from 1991 to 2010 (figure 7)², there is a similar level of variation across the province. There are also some similarities between areas with high opioid prescribing and opioid-related mortality rate, such as Thunder Bay.

Figure 6. Annual opioid prescribing rate in Ontario between 2011 - 2013 (visit http://odprn.ca/ for interactive version of map)

Figure 7. Annual Opioid-Related Mortality Rates in Ontario, by County from 2006-2010 (visit http://odprn.ca/ for interactive version of map)
The top 5 highest opioid-related death rates and highest death counts by county.

<table>
<thead>
<tr>
<th>NUMBER OF OPIOID-RELATED DEATHS (2006 - ‘10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toronto</td>
</tr>
<tr>
<td>Hamilton</td>
</tr>
<tr>
<td>Peel</td>
</tr>
<tr>
<td>Middlesex</td>
</tr>
<tr>
<td>Niagara</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RATE OF OPIOID RELATED DEATHS (2006 - ‘10)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thunder Bay</td>
</tr>
<tr>
<td>Manitoulin</td>
</tr>
<tr>
<td>Sudbury Regional Municipality</td>
</tr>
<tr>
<td>Algoma</td>
</tr>
<tr>
<td>Nipissing</td>
</tr>
</tbody>
</table>

*Annual standardized rate of death per 100,000 population

Potential trafficking of opioids across the US-Canada border

In August 2010, the US replaced the highly abused formulation of long-acting oxycodone – OxyContin® with an abuse-deterrent formulation (OxyContin-OP®). However, OxyContin® remained available in Canada until February 2012. The ODPRN sought to understand whether differences in the availability of OxyContin in the US and Canada may have led to drug-seeking behavior across the US-Canada border by measuring dispensing patterns at pharmacies close to the 5 border crossings in Ontario: Niagara Falls (2 border crossings [bordering Niagara Falls, N.Y.]), Windsor (2 border crossings [bordering Detroit, Mich.]) and Sarnia (bordering Port Huron, Mich.). We found that:

- In 4 of the 5 border crossings, no change in dispensing behavior was identified over the study period.
- Near the Detroit-Windsor Tunnel, there was a significant increase in dispensing of the original formulation of OxyContin in Ontario pharmacies following the introduction of OxyContin-OP in the US (from 505 tablets per 1000 population to 1969 tablets per 1000 population in February 2011; Figure 7).
- An immediate reduction in OxyContin dispensing occurred after a warning letter was issued to pharmacists and prescribers alerting them of potential drug seeking behaviour. In an eight month span after the letter was released (from March 2011 – November 2011) dispensing rates near the Detroit – Windsor Tunnel dropped to the lower levels of early 2010.
- Approximately 250,000 excess Oxycontin tablets were dispensed near the Detroit-Windsor tunnel during this time, and it is likely that many of these were trafficked across the border into the USA.
Implications

The geographic variation in prescribing and potential for drug-seeking behaviour across borders when inconsistent policies exist between jurisdictions should be considered in policy and practice.

Policy

- Given the regional variation in opioid prescribing patterns and related adverse events, public health interventions and education could be targeted to areas where opioid prescribing poses an especially large risk.
- Mechanisms should be developed to facilitate rapid notification of prescribers and pharmacists regarding potential drug-seeking behaviour near US-Canada border crossings in the future.

Practice

- Clinicians practicing in areas with high rates of opioid prescribing and related mortality should carefully consider their patients’ prescription needs and should speak with their patients about the risks of using opioids, their addictive properties, and alternative pain management strategies.
- Physicians and pharmacists should be aware of the potential for increases in drug-seeking behavior following policy changes related to the availability of opioids between jurisdictions.

References

3 Gomes T, Paterson JM, Juurlink DN, Dhallia IA, Mamdani MM. Reformulation of OxyContin and pharmacy dispensing patterns near the US-Canada border. Open Medicine 2012; 6 (4): 141-145
Section 4
Potential impact of policy and educational interventions

How effective are policies and interventions at changing physician prescribing behaviors?

Strategies to reduce opioid-related harms have been implemented at the policy level as well as through individual educational opportunities. The ODPRN examined the effects of policy and educational interventions on more appropriate opioid prescribing practices for physicians. In this section, we describe:

• Impact of a legislative intervention
• Effects of an education intervention
• Implications for policy and practice

Impact of a legislative intervention

The Narcotics Safety and Awareness Act (NSAA) was introduced in November 2011, followed by the implementation of the Narcotics Monitoring System (NMS) in May 2012 with the objective of promoting appropriate opioid prescribing and dispensing in Ontario. We evaluated the impact of these legislative interventions on potentially inappropriate prescribing behavior of monitored drugs in Ontario.1

From October 2011 (before intervention) to May 2013, inappropriate opioid prescribing had dropped from 1.6% (12,346 of 777,950 prescriptions) to 1.0% (9138 of 959,898 prescriptions).

In our study, a prescription was deemed potentially inappropriate if it was dispensed within 7 days of an earlier prescription for a drug in the same class (where that earlier prescription included at least 30 tablets or 6 transdermal fentanyl patches) and if it originated from a different physician and different pharmacy. We found that enactment of the NSAA led to a 12.5% reduction in the prevalence of potentially inappropriate opioid prescribing in the subsequent 6 months. Between October 2011 (prior to any legislative changes) and May 2013, the prevalence of potentially inappropriate opioid dispensing had dropped from 1.6% (12,346 of 777,950 prescriptions deemed inappropriate) to 1.0% (9138 of 959,898 prescriptions deemed inappropriate).1
Potential effects of an education intervention

“...regulation might have a substantially greater effect than education on physicians’ opioid prescribing”

Education interventions are often used as strategies for targeting behaviour change; however, the effectiveness of education strategies on opioid prescribing behaviours is still unclear. We assessed the effect of a 2-day course run by the College of Physicians and Surgeons of Ontario (CPSO) designed to promote appropriate opioid prescribing habits (Box 2). It was found that:

- Voluntary enrollment in the course was not shown to decrease opioid prescribing rates during the two-year period following course attendance.²
- However, if a physician was referred to attend the course by CPSO (e.g., following a complaint), there was a marked decrease in opioid prescribing following referral by the CPSO, but prior to the prescriber completing the course (Figure 8).

The findings of this study suggest that the course itself had little effect on opioid prescribing, whereas prescriber notification by the CPSO had a considerable effect.²

Box 2: CPSO’s Education Intervention.

- The 2-day course involved presentations, case discussions, standardized patients, a written test, and a follow-up telephone conference after the course was completed.²
- The College of Physicians and Surgeons of Ontario (CPSO) is a medical regulator, who provides education on opioid prescribing to those who voluntarily want to attend, but also enforces mandatory education as part of a set of regulatory actions for those physicians who have had a complaint made against them and have been found to inappropriately prescribe opioids.

---

<table>
<thead>
<tr>
<th>Quarter</th>
<th>Amount of opioids prescribed, mg ME</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>0</td>
</tr>
<tr>
<td>C</td>
<td>0</td>
</tr>
<tr>
<td>D</td>
<td>0</td>
</tr>
</tbody>
</table>

ODB-Ontario Drug Benefits, mg ME-milligrams of morphine equivalent.

Figure 9. Total amount of opioids prescribed by physicians per quarter pre/post course completion (reproduced from Kahan et al.²)
Implications

Policy regulation may be an effective tool to change prescribing habits for physicians, especially for opioids specifically, but more research is still warranted. Despite the need for more evidence in this area, these studies offer important policy and practice implications.

Policy

- The components of an educational initiative designed to promote safe prescribing of opioids require further exploration.
- Although the recent legislative changes in Ontario have successfully reduced inappropriate opioid prescribing, policy-makers may want to consider how the Narcotics Monitoring System could be improved to further reduce inappropriate prescribing of prescription drugs prone to abuse. This may include providing prescribers with access to real-time data on patient prescribing history to allow them to more readily identify drug-seeking behavior.

Practice

- Considerations should be made to ensure that information learned in course-based interventions is incorporated into practice and that changes to prescribing behaviours are sustained.
- Physicians should continue to be vigilant in attempts to identify drug-seeking behavior in patients.

References


Key Messages

Overall, the key findings of our research to date demonstrate that opioids are widely prescribed by physicians to manage chronic non-cancer pain in Ontario, and therefore policy and practice considerations should be made to encourage safe use of these drugs.

1. There is an overall trend of increasing opioid use in Ontario, particularly at doses that exceed guideline recommendations.
2. Opioid use – particularly at high doses – is related to serious adverse events, including risk of overdose death and road trauma.
3. Geographic variation opioid prescribing, dose and mortality and related mortality is apparent and should be considered when designing public health and policy initiatives.
4. Inappropriate prescribing is a multi-faceted issue that can’t be addressed with only one strategy. It will require a combination of regulatory/legislative changes, as well as patient and clinician education to respond to this ever-shifting prescribing environment.

On the forefront of knowledge on opioids

The ODPRN continues to generate research on the important issue of opioids as it pertains to policy and practice. To stay up-to-date on our research findings, visit our website: www.odprn.ca or follow us on Twitter: @ODPRN_Research