Identifying and evaluating patterns of prescription opioid use and associated risks in Ontario, Canada
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Citation for published version (APA):
Gomes, T. (2017). Identifying and evaluating patterns of prescription opioid use and associated risks in Ontario, Canada
Chapter 11: Impact of legislation and a prescription monitoring program on the prevalence of potentially inappropriate prescriptions for monitored drugs in Ontario: a time series analysis

Gomes T, Juurlink DN, Yao Z, Camacho X, Paterson JM, Singh S, Dhalla IA, Sproule B, Mamdani MM. Impact of legislation and a prescription monitoring program on the prevalence of potentially inappropriate prescriptions for monitored drugs in Ontario: a time series analysis. CMAJ Open. 2014. 2(4); E256-261.
Abstract

BACKGROUND
We assessed the impact of new legislation and a centralized prescription monitoring system (implemented November 2011 and May 2012, respectively), on the dispensing of prescriptions suggestive of misuse.

METHODS
We conducted a time series analysis of publically-funded prescriptions for opioids, benzodiazepines and stimulants dispensed monthly from January 2007 to May 2013. In the primary analysis, a prescription was deemed potentially inappropriate if it was dispensed within 7 days of an earlier prescription for at least 30 tablets of a drug in the same class and originated from a different physician and different pharmacy.

RESULTS
The prevalence of potentially inappropriate opioid prescriptions decreased by 13.2% after enactment of the new legislation (from 1.59% in October 2011 to 1.38% in April 2012; p=0.01). No further significant change in trend was observed after the introduction of the narcotic monitoring system (NMS) (p=0.78). By May 2013, the prevalence had dropped to 0.95%. Inappropriate benzodiazepine prescribing was significantly influenced by both the legislation (p<0.001) and the NMS (p=0.05), which together reduced potentially inappropriate prescribing by 57.5% between October 2011 and the end of the study period (from 0.40% to 0.17%). The prevalence of potentially inappropriate prescribing of stimulants was significantly influenced by the introduction of the NMS, falling from 0.68% in April 2012 to 0.27% in May 2013, following introduction of the NMS (p=0.02).

INTERPRETATION
For a select group of drugs prone to misuse and diversion, legislation and implementation of a prescription monitoring program dramatically reduced the prevalence of prescriptions highly suggestive of misuse.
Introduction

Misuse of drugs, including opioid analgesics, sedative-hypnotics and stimulants can have serious consequences, with more than 20,000 deaths in the US ascribed to prescription drug overdose each year.1 Furthermore, Canada has one of the highest opioid consumptions per capita in the world.2,3 Increased use of these prescription drugs, along with trends highlighting the substantial risks of overdose death among those receiving prescriptions for these medications in Ontario have led to considerable concern among physicians, public health officials and regulatory authorities. As governments attempt to curb inappropriate use of prescribed drugs, the regulation and monitoring of prescription medications has become increasingly important. Prescription monitoring programs that track detailed patient and prescriber information for controlled substances have been implemented in many jurisdictions across North America, with varying degrees of success.4-7 Although some studies suggest a significant impact of these programs on the supply of monitored drugs and rates of drug abuse and misuse8-10, their quality is variable, and their success relies on a variety of factors, including the accessibility of data to healthcare providers, pharmacist engagement, and the involvement of law enforcement.7,8,11,12

In November 2011, the Narcotics Safety and Awareness Act (NSAA) was implemented in Ontario, Canada, requiring that physicians identify themselves by their College registration number, and that pharmacists record and verify patient information (including name, address, age, gender, and government issued identification number) on prescriptions for all narcotics and other controlled substances dispensed in the province. Furthermore, this information must be disclosed to government officials upon request.13 Another key component of this legislation is the Narcotics Monitoring System (NMS), which captures prescriber, pharmacist and patient information for all narcotics and other controlled drugs dispensed in Ontario, regardless of payment type (e.g. cash, private insurance or public drug program). The NMS was created to provide provincial policy-makers with the tools to identify potentially inappropriate prescribing of monitored drugs. This information could lead to educational interventions, and the reporting of potential misconduct or criminal activity to regulatory and law enforcement agencies.14 Although full patient profiles for all prescriptions in the NMS system are accessible to physicians and pharmacists, pharmacists are now provided with more information in the Drug Utilization Review (DUR) messages (alerts) that includes the conflicting drugs,
quantities and other dispensing pharmacies. Pharmacies could begin submitting dispensing information through the NMS as of April 16, 2012, with full implementation on May 12, 2012.

The objective of this study was to evaluate the impact of the enactment of the NSAA and the implementation of the NMS on the rate of dispensing of monitored drugs among public drug plan beneficiaries in Ontario that was highly likely to represent misuse.

Methods
We conducted a population-based, cross-sectional time-series analysis of all publically-funded prescriptions dispensed in Ontario for drugs monitored by the NMS between January 1, 2007 and May 31, 2013. Ontario residents are eligible for public drug coverage if they are unemployed or disabled, have high prescription drug costs in relation to their net household income, receive home care, reside in a long-term care facility or are 65 years of age or older. All Ontario residents have universal access to hospital care and physician services. This project was approved by the Research Ethics Board of Sunnybrook Health Sciences Centre, Toronto.

DRUG EXPOSURE
We used the computerized records of the Ontario Public Drug Benefit Database to identify all prescriptions dispensed to Ontario public drug plan beneficiaries for drugs monitored by the NMS. This database contains information on the date, quantity and days supplied for each prescription, and encrypted patient, prescriber and pharmacy identifiers. It has an error rate of less than 1% and is regularly used to study drug utilization at the population level. To restrict to adults receiving these drugs in the community, we excluded prescriptions dispensed to residents in long-term care homes, and those younger than 18 years of age. We restricted our analysis to opioids, benzodiazepines, and stimulants monitored by the NMS, and excluded prescriptions with missing prescriber identifiers, and non-tablet formulations with the exception of fentanyl (full list available at http://www.health.gov.on.ca/en/pro/programs/drugs/monitored_productlist.aspx; June 14, 2013 edition). To test the robustness of our analysis, we also examined prescriptions for non-steroidal anti-inflammatory drugs (NSAIDs), which are not monitored by the NMS, reasoning that the rate of inappropriate prescribing of these medications should not change because they are not prone to abuse.
DEFINITION OF POTENTIALLY INAPPROPRIATE PRESCRIBING

We defined potentially inappropriate prescriptions of monitored drugs as those we believed were highly likely to represent misuse. This was measured in two ways. In our primary analysis, we defined a prescription as potentially inappropriate according to the following set of criteria, as done previously. We first identified all prescriptions for a monitored drug where at least 30 tablets (or 6 transdermal fentanyl patches) were dispensed. We then identified all prescriptions for drugs within the same drug class (e.g. opioid, benzodiazepine, stimulant or NSAID) that were dispensed in the 7 days following the initial prescription. This subsequent prescription was deemed inappropriate if it was issued by a different physician and dispensed at a different pharmacy than the initial prescription.

In a secondary analysis, we defined potentially inappropriate prescribing using the Drug Utilization Review (DUR) criteria incorporated into the NMS. These criteria warn pharmacists of potential multi-doctoring and poly-pharmacy based on prescription patterns over a 28 day period. Specifically, a prescription leads to a warning for multi-doctoring if a given patient obtains any combination of monitored drugs prescribed by 3 or more different physicians over a 28-day period. Similarly, the poly-pharmacy warning flags monitored drugs dispensed by 3 or more different pharmacies over 28 days. We defined potentially inappropriate prescriptions as those that would have led to the issuance of both a double-doctoring warning and poly-pharmacy warning.

In a sensitivity analyses, we broadened the definition in the primary analysis such that prescriptions were flagged as potentially inappropriate if they were issued by either a different doctor or a different pharmacy. All analyses were conducted at the prescription level, and therefore, if a patient was treated with drugs from multiple classes, (i.e. opioids, benzodiazepines, stimulants), all such prescriptions were considered separately.

STATISTICAL ANALYSIS

We calculated the monthly number and prevalence of potentially inappropriate prescriptions (defined as the percentage of all prescriptions dispensed each month that were deemed to be inappropriate), by drug class. We used interventional autoregressive integrated moving average (ARIMA) models to examine the impact of the enactment of the Narcotics Safety and Awareness Act (November 2011) and the full implementation of the Narcotics Monitoring System (May 2012) on the prevalence of potentially inappropriate prescribing of monitored drugs in Ontario.
(Figure 11.1). The effects of the NSAA and NMS were assessed using a ramp intervention function in the ARIMA model. The autocorrelation, partial autocorrelation, and inverse autocorrelation functions were assessed for model parameter appropriateness and seasonality, and stationarity was examined using autocorrelation functions and the augmented Dickey-Fuller test. Finally, the presence of white noise was assessed by examining the autocorrelations at various lags with the use of the Ljung-Box chi-square statistic. Final model specifications can be found in the Table 11.1. All analyses used a type 1 error rate of 0.05 as the threshold for statistical significance and were performed using SAS statistical software (version 9.3; SAS Institute Inc, Cary, North Carolina).

![Study Design](image)

Figure 11.1: Study Design.

*Box 'A' represents October 2011, the month prior to the enactment of the Narcotics Safety and Awareness Act (NSAA)*

*Box 'B' represents April 2012, the month prior to the implementation of the Narcotics Monitoring System (NMS)**

*Box 'C' represents May 2013, the end of the study period*

To describe the impact of the NSAA, prevalence rates are compared between Boxes 'A' and 'B'. To describe the impact of the NMS, prevalence rates are compared between Boxes 'B' and 'C'.

Results

Over the 77-month study period, 49,578,359 opioid prescriptions, 21,469,883 benzodiazepine prescriptions and 1,066,834 stimulant prescriptions were dispensed to 1,706,502, 928,240, and 34,902 public drug plan beneficiaries, respectively. Of these, 801,882 (1.6%) of opioid prescriptions, 75,789 (0.4%) of benzodiazepine prescriptions, and 7,794 (0.7%) of stimulant prescriptions were deemed to be potentially inappropriate according to our primary definition.
Table 11.1: Details of Time Series Analyses

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Model Specification</th>
<th>R-Squared</th>
<th>Enactment of NSAA* (P-value)</th>
<th>Introduction of NMS** (P-value)</th>
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</thead>
<tbody>
<tr>
<td>Primary Analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioids</td>
<td>IAR (3,1,0)</td>
<td>0.98</td>
<td>0.01</td>
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<td>Benzodiazepines</td>
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<tr>
<td>Opioids</td>
<td>ARIMA (6,1,1)</td>
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<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>Benzodiazepines</td>
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<td>Stimulants</td>
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<td>Sensitivity Analysis</td>
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<tr>
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<td>0.02</td>
<td>0.22</td>
</tr>
</tbody>
</table>

*NSAA: Narcotics Safety and Awareness Act; November 2011
**NMS: Narcotics Monitoring System: May 2012

PRIMARY ANALYSIS

Prior to enactment of the NSAA (January 2007 to October 2011), a monthly average of 1.84% of opioid prescriptions, 0.92% of stimulant prescriptions, and 0.39% of benzodiazepine prescriptions were deemed potentially inappropriate according to our primary definition (Figure 11.2). The prevalence of potentially inappropriate opioid prescriptions decreased 40.3% between October 2011 (prior to any regulatory changes) and the end of our study period. In particular, this prevalence fell by 13.2% following the enactment of the NSAA, from 1.59% (N=12,346 prescriptions) in October 2011 to 1.38% (N=11,046 prescriptions) in April 2012 (p=0.01). Although the subsequent implementation of the NMS did not lead to any further statistically significant reduction in the rate of inappropriate prescribing (p=0.78), the prevalence of potentially inappropriate prescribing continued to fall another 31.2% between April 2012 and May 2013, reaching 0.95% (N=9,138 prescriptions) by the end of the study period. In comparison, the prevalence of potentially inappropriate prescriptions for benzodiazepines decreased significantly following both the enactment of the NSAA (p<0.001) and the implementation of the NMS (p=0.05). Overall, the prevalence of potentially inappropriate
benzodiazepine prescriptions decreased 57.5% between October 2011 (prior to any changes) and the end of the study period (from 0.40% in October 2011 to 0.17% in May 2013). Finally, the prevalence of potentially inappropriate stimulant prescriptions did not decrease significantly following the regulatory requirements imposed in November 2011 (p=0.06), but did significantly decrease following the implementation of the NMS (p=0.02). Specifically, the prevalence of potentially inappropriate stimulant prescriptions decreased 60.3%, from 0.68% (N=138 prescriptions) in April 2012 (prior to the implementation of NMS) to 0.27% (N=67 prescriptions) in May 2013.

The prevalence of potentially inappropriate NSAID prescribing was low over the entire study period, with a monthly average of 0.11% (range 0.09% to 0.14%). As expected, we found no change in rates of inappropriate NSAID prescribing following the introduction of both the NSAA and the implementation of the NMS (Figure 11.2; p=0.29 and p=0.94, respectively).
SECONDARY ANALYSIS: DUR WARNINGS

The findings of a secondary analysis of the prevalence of prescriptions triggering DUR warnings for both poly-pharmacy and multi-doctoring were generally consistent with our primary analyses. Overall, the prevalence of opioid prescriptions that would have triggered both DUR warnings decreased 19.0% following the enactment of the NSAA, from 2.1% (N=16,060 prescriptions) in October 2011 to 1.7% (N=13,420 prescriptions) in April 2012 (p<0.001). This prevalence dropped a further 31.1% following the implementation of the NMS, to 1.2% (N=11,062 prescriptions) in May 2013 (p<0.001; Figure 11.3). Similarly, the 36.5% reduction in benzodiazepine prescriptions that would have triggered both DUR warnings (from 0.8%, N=2,312 in October 2011 to 0.5%, N=1,609 prescriptions in May 2013) was driven by both the enactment of the NSAA (19.1% reduction from October 2011 to April 2012; p=0.01) and the implementation of the NMS (21.5% reduction from April 2012 to May 2013; p=0.02). Finally, the

**Figure 11.3:** Prevalence of warnings for both poly-pharmacy and multi-doctoring among monitored drugs

*Proportion of all publically-funded prescriptions for opioids, benzodiazepines and stimulants that would have triggered both a poly-pharmacy and multi-doctoring Drug Utilization Review warning in Ontario, Canada. January 2007 to May 2013.*
prevalence of stimulant prescriptions that would have triggered both DUR warnings decreased 41.8% following the regulatory changes in November 2011 (from 2.8%, N=546 in October 2011 to 1.7%, N=334 in April 2012; p=0.04), but was not affected by the implementation of the NMS (prevalence 1.4%; N=354 in May 2013; p=0.13).

SENSITIVITY ANALYSIS

In our sensitivity analysis, we loosened the criteria on potentially inappropriate prescriptions to require only double doctoring or polypharmacy. Using these loosened criteria, 2.8% of opioid prescriptions, 1.0% of benzodiazepine prescriptions, and 1.2% of stimulant prescriptions were deemed potentially inappropriate over the study period. For both opioids and benzodiazepines, the results were consistent with the primary analysis. Among opioids, we found a significant reduction in the proportion of potentially inappropriate prescriptions following the enactment of the NSAA (5.6% reduction from October 2011 to April 2012; p=0.03), but no further significant reduction after the implementation of the NMS (p=0.44). Similarly, among benzodiazepines, we found a significant reduction in the proportion of potentially inappropriate prescriptions after both the enactment of the NSAA (12.5% reduction from October 2011 to April 2012; p<0.001) and the implementation of the NMS (19.8% reduction from April 2012 to May 2013; p=0.03). However, among stimulant prescriptions, the sensitivity analysis found a significant impact of the enactment of the NSAA (28.0% reduction from October 2011 to April 2012; p=0.02), but no further impact of the NMS (p=0.22). This is in contrast to the primary analysis, where the NSAA had a marginally non-significant impact, and the NMS had a significant impact on reducing potentially inappropriate prescribing.

Discussion

In this population-based study, we found that both a legislative intervention and the introduction of a prescription monitoring program specifically developed for opioids and controlled substances resulted in significant reductions in the prevalence of potentially inappropriate prescribing of monitored drugs in Ontario, ranging between 40% and 60%. Due to our strict definitions of misuse, the monthly prevalence of potentially inappropriate prescriptions rarely exceeded 2%. However, more than 70 million prescriptions for monitored drugs were dispensed over the 6.5 year study period; of these, almost 1 million were deemed highly likely to represent misuse. Given our conservative definitions, the true number of inappropriate prescriptions is likely to be even higher. As a result, despite the relatively small absolute prevalence of inappropriate prescriptions observed in this study, the public health impact of
reductions in this prevalence is likely substantial. These findings demonstrate the potential for regulatory interventions driven by policy-makers to influence prescribing and dispensing patterns of controlled substances, and suggest that the impacts of these interventions can be quickly realized.

The findings of this study align with another Canadian study that used similar methods to assess the impact of the implementation of British Columbia’s (BC) PharmaNet system in 1995 on inappropriate prescribing. Although the BC PharmaNet system captures all drugs (compared to the limited list of drugs monitored by the Ontario NMS), Dormuth et al. reported a 33% reduction in inappropriate opioid prescribing and a 49% reduction in inappropriate benzodiazepine prescribing, which is consistent with, but slightly lower than our findings of 40% and 58%, respectively. This suggests that, although the products available and the rates of use and abuse of these drugs (particularly opioids) have changed substantially since that time, the value of prescription monitoring programs that allow pharmacists access to real-time data on patient prescribing history remains high.

Several limitations of the analyses merit emphasis. First, our findings are limited to publically funded prescription drugs (which accounts for approximately 43% of all drug costs in Ontario), and may not be generalizable to the entire population. However, because the NMS tracks prescriptions for all monitored drugs dispensed in Ontario, it is likely that these findings also extend to those paying through private insurance or out of pocket. Regardless, because we only identify publically-funded prescriptions, the number of potentially inappropriate prescriptions estimated in this study is likely a substantial underestimate of the true number of inappropriate prescriptions dispensed in Ontario, highlighting the public health importance of these findings. Second, defining inappropriate prescriptions using administrative databases can be difficult, and it is possible that some prescriptions defined as inappropriate were caused by appropriate switching of medications. However, we expect that this would apply equally prior to, and following the implementation of the NMS. Therefore, this limitation will not likely influence the trends observed in this study. We developed two definitions of potentially inappropriate prescribing that incorporated early prescription refills, multi-doctoring, and poly-pharmacy. These definitions were designed to be conservative and specific, and are likely to misclassify prescriptions of shorter duration, or those that met only one of the multi-doctoring or poly-pharmacy requirements. Furthermore, our study excluded prescriptions with missing prescriber identifiers, which may be more likely to be inappropriate. Therefore, our
study likely underestimates the true prevalence of inappropriate prescribing of monitored drugs in Ontario. However, the consistency of findings between the two definitions of potentially inappropriate use, along with the null finding among our tracer drug class (NSAIDs) suggest a true association between regulatory and prescription monitoring changes in Ontario and reductions in inappropriate prescribing. Third, due to the small number of stimulant prescriptions identified in this analysis, there is considerable variation in estimates of potentially inappropriate stimulant use over time. Despite this, we were able to specify robust time series models that evaluated the impact of the policy interventions in our analysis. Finally, we did not assess whether these changes in prescribing patterns resulted in fewer hospitalizations or deaths related to drug overdoses. Studies evaluating the impact of the legislation and NMS on patient outcomes should be done as soon as sufficient data are available.

Conclusions
The enactment of legislation requiring patient identification on prescriptions for monitored drugs, and a prescription monitoring program providing real-time data access to pharmacists led to significant reductions in the prevalence of prescriptions for opioids and controlled substances that were highly likely to represent misuse. Given that hundreds of thousands of inappropriate prescriptions for these drugs are dispensed each year in Ontario, these findings highlight the potential impact that drug policy decision makers, legislators and front-line healthcare professionals can have in reducing harmful prescribing behaviors.

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