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Research paper

Evaluation of the fentanyl patch-for-patch program in Ontario, Canada

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ABSTRACT

Background: Rising use of prescription opioids is a major public health concern associated with increased risk of mortality worldwide. Fentanyl, a synthetic opioid available in patch form, is particularly concerning given its high potency. To curb the misuse and diversion of fentanyl patches, a Patch-for-Patch (P4P) program was implemented in some counties in Ontario between 2012 and 2015. The program requires that patients prescribed fentanyl must return used patches to the pharmacy before receiving more patches.

Objective: To evaluate the impact of the P4P program on fentanyl and non-fentanyl dispensing and opioid-related hospitalizations and deaths.

Methods: We conducted a repeated cross-sectional time-series analysis among counties that implemented the P4P program using Ontario administrative claims data. Because intervention dates varied by county due to staggered program initiation, we aligned all intervention months and examined outcome rates in the 5 years preceding and 12 and 24 months following implementation. We explored the monthly rate of prescriptions dispensed for fentanyl and non-fentanyl opioids, opioid toxicity-related hospital and emergency department visits, and opioid-related deaths. We modeled each outcome using an interventional autoregressive integrated moving average (ARIMA) model and tested the impact of the P4P program using a ramp function.

Results: We analyzed 16 counties that implemented the P4P program and had at least 12 months of follow-up. The introduction of the P4P program was associated with a 30.5% decline in the volume of fentanyl patches dispensed at 24 months (from 1,277–888 patches per 10,000 population; $p = 0.04$). In contrast, there was no significant change in the rate of non-fentanyl opioid dispensing ($p = 0.32$), opioid toxicity related hospitalizations and emergency department visits ($p = 0.4$) or opioid-related deaths ($p = 0.96$) in the 12 months following implementation of the program.

Conclusions: We found that the implementation of a P4P program in select counties in Ontario was associated with a lower volume of fentanyl patches dispensed by pharmacies, without an increase in use of other opioids. The program had no measurable impact on rates of opioid toxicity-related hospital visits or deaths. Policymakers should consider the use of P4P programs as part of larger opioid strategy.

Background

Fentanyl is a synthetic opioid 80–100 times more potent than morphine that is available by prescription across North America, most commonly as a transdermal patch (Canadian Pharmaceutical Association, 2008; Trescot, 2016). Diversion of fentanyl patches is commonly reported as a significant source of illicit opioid use in Canada (Fischer, Vojtila, & Rehm, 2017; Young, Pirie, Buxton, & Hosein, 2015), and has led to considerable concern given rising rates of fentanyl-involved deaths across Ontario (938% rise from 34 to 353 deaths from 2003 to 2016) from both diverted and bootleg sources (Fischer et al., 2017; Public Health Ontario, 2017). Bootleg sources are defined as sources that are not derived from prescription, this often refers to fentanyl that is produced in illegal labs. In particular, given the high potency of fentanyl, and the fact that used patches retain up to 80% of their original dosage in the matrix, preventing the diversion of these

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products has become a priority (Ontario Association of Chiefs of Police – Substance Abuse Committee, 2014). In response to concerns regarding overdoses from misused or diverted fentanyl patches, one endorsed strategy has been the implementation of Patch-for-Patch (P4P) programs (Ontario Public Drug Programs Division, 2016).

P4P programs require that patients dispensed fentanyl patches must return their used patches to the pharmacy before receiving a refill of their prescription. If there is evidence that patches have been tampered with, or if the patient does not return the number of patches expected, the prescription must be altered according to the number of patches returned. In addition, the pharmacist must also notify the police and the prescriber. These P4P programs were first introduced in Nipissing County in Ontario in December 2013 as a collaboration between law enforcement, public health officials, and pharmacies (Ontario Association of Chiefs of Police – Substance Abuse Committee, 2014). The program later expanded to several other counties across the province (Chaudhry, 2017; Kim, 2018). The initial launch of the program did not mandate participation by pharmacies. Mandatory province-wide expansion of the P4P program was launched on October 1, 2016 (Ontario Public Drug Programs Division, 2016).

Although the P4P program was designed with the expectation that reducing the diversion of fentanyl patches would lead to minimal availability in the illicit market, and therefore improved health outcomes, the impact of this program is unknown. We explored the impact of the P4P program implementation between February 2013 and September 2016 on opioid dispensing and toxicity events in participating counties in Ontario, Canada.

Methods

We conducted a population-based, cross-sectional time series analysis within counties participating in the early P4P program between Febuary 1, 2013 and September 30, 2016 in Ontario, Canada. This study was approved by the research ethics board of Sunnybrook Health Sciences Centre, Toronto.

Data sources

We used the Ontario Drug Benefit (ODB) claims database to identify all drugs dispensed to individuals eligible for public drug coverage through the Ontario Public Drug Programs. This data does not include prescriptions paid for out-of-pocket or by private insurers. We identified emergency department (ED) and hospitalizations visits using the Canadian Institute for Health Information's Discharge Abstract Database and National Ambulatory Care Reporting System, respectively. We used the Ontario Health Insurance Plan (OHIP) database to identify physician visits. Demographics, place of residence, and vital status information were obtained from the OHIP Registered Persons Database. Finally, we used the Drug and Drug/Alcohol Related Death database from the Office of the Chief Coroner of Ontario to identify all deaths investigated by provincial medical coroners that were determined to be opioid-related. Details of this data source have been published previously and are frequently used to study opioid overdoses in Ontario (Dhalla et al., 2009; Gomes, Mamdani, Dhalla, Paterson, & Juurlink, 2011). We used the Ontario Registered Persons Database (RPDB) to determine the demographic characteristics and identify location of residence of individuals. These databases, which are securely linked using unique, encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences (ICES, www.ices.on.ca), are routinely used to examine drug policy (Gomes, Juurlink, & Yao, 2014; Gomes, Martins, & Tadrous, 2017; Kwok, Khuu, & Fernandes, 2017; Piszczek, Mamdani, Antoniou, Juurlink, & Gomes, 2014).

Outcomes

Our primary outcome was the monthly rate of fentanyl patches dispensed. Secondary outcomes included the rate of non-fentanyl long-acting opioid volume dispensed, rate of hospital visits (inpatient hospitalization and ED visits) due to opioid toxicity, and rate of opioid-related deaths (overall, and deaths involving fentanyl). All outcomes were measured monthly. Location of residence was based on the individual's postal code. Hospital visits for opioid toxicity were defined as any ED visit or inpatient hospitalization with ICD-10 codes T40.0, T40.1, T40.2, T40.3, T40.4, or T40.6. Suspected diagnoses and those from planned hospital visits were excluded. Code T40.4 was used to define events related to synthetic opioids. Deaths were determined to have been the result of fentanyl toxicity if ruled as such by the coroner. All prescription outcomes were reported as rates per 10,000 active public drug plan beneficiaries, calculated as the total number of individuals dispensed any publically-funded drug in the year of interest. All rates of opioid-related hospital visits and deaths were reported per 10,000 population using Statistics Canada population estimates (Statistics C., 2019). We measured rates in a series of 30-day windows over the observation period, referred to as "months".

Analysis

We assigned each county an intervention date defined as the launch of the P4P program in that county (See Appendix). Launch dates were shared with us by the Ontario Provincial Police. The primary analysis combined information from all counties by zeroing the lookback and follow-up periods based on each county's intervention date. Only counties with sufficiently long follow-up were included in each analysis. Fentanyl and non-fentanyl dispensing rates were reported for counties with 12 (n = 14; 67%) and 24 (n = 4;19%) months of follow-up after the intervention date. Due to shorter data availability, opioid-related hospital visits and opioid-related deaths were reported among counties with 6 (n = 14; 67%) and 10 (n = 7; 48%) months of follow-up after the intervention date. Rates were reported for every month following the intervention date. All analyses were truncated at September 30, 2016 to avoid the confounding effects of the province-wide mandated P4P program, which was introduced October 1, 2016. Finally, we conducted an individual county-level analysis for fentanyl prescribing using all follow-up data available in each county. From these findings, we conducted a sensitivity analysis for all outcomes limited to counties in which a statistically significant reduction in fentanyl dispensing was observed following the introduction of the P4P program. This analysis was designed to explore whether there was a greater impact on outcomes in the regions in which the P4P had the largest influence on fentanyl dispensing patterns.

Statistical analysis

We used interventional time series autoregressive integrated moving average (ARIMA) models to determine the impact of the introduction of the P4P program on each of our outcomes. Initial model selection was guided by visual inspection of correlograms. We used a ramp intervention function to assess the impact of the P4P program. We used the actual intervention date for the individual county-level analysis and the aligned intervention dates for the combined county analysis. To ensure model fit we examined the residual autocorrelation correlograms for model parameter selection and appropriateness. Stationarity and seasonality were assessed using the augmented Dickey-Fuller unit root test, autocorrelation plots and the Ljung-Box chi-square test for white noise.

Results

In our primary analysis of rates of fentanyl dispensing over a 12-month follow-up, we found that prior to the P4P program implementation, monthly rates ranged from 1023 patches dispensed per 10,000 eligible to 1229 patches dispensed per 10,000 eligible (Fig. 1).

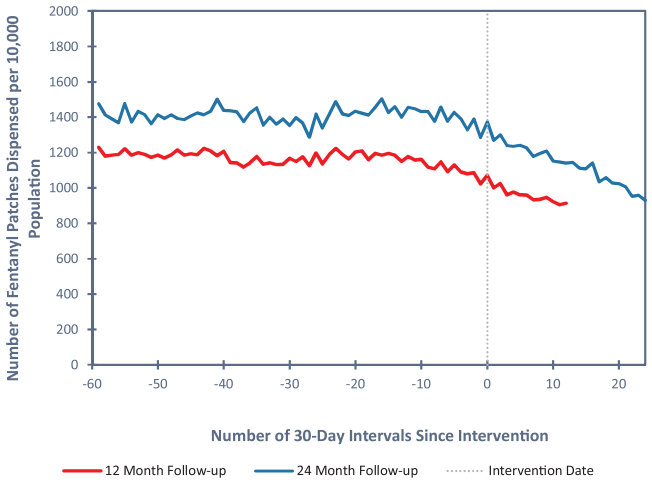

Fig. 1. Rate of prescription fentanyl patches dispensed by participating counties before and after the initiation of the P4P program at 12 and 24 months.
Note: 12 and 24 month follow-up above only include counties with sufficiently long follow-up. Dates were zeroed based on each county's intervention date.

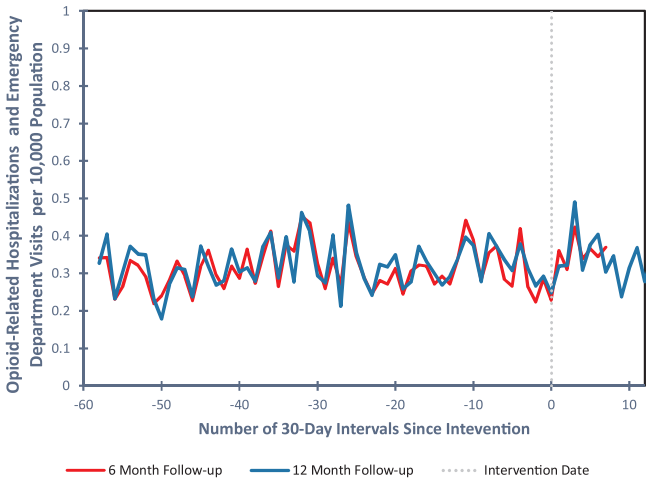

Fig. 3. Average rate of opioid-related hospital visits before and after the initiation of the P4P program at 6 and 12 months.
Note: 6 and 12 month follow-up above only include counties with sufficiently long follow-up.

Following the implementation of the P4P program, fentanyl dispensing rates decreased 16% from time zero to the end of follow-up; however this reduction did not achieve statistical significance ($p = 0.06$). When considering a 24 month follow-up, the fentanyl dispensing rate decreased significantly by 32% (from 1374 patches to 929 patches dispensed per 10,000 eligible; $p < 0.001$). Individual county-level analyses found large variations in the rates of fentanyl dispensing across counties, with Nipissing county having the highest rate of dispensing over the study period (average monthly dispensing of 1647 patches per 10,000 eligible) and Halton county consistently having the lowest rate of fentanyl dispensing (average monthly dispensing of 520 patches per 10,000 eligible) (**See Appendix**). Eleven ($n = 11$) of the 21 counties analyzed had a statistically significant reduction in the rate of fentanyl patches dispensed after the introduction of the P4P program (See Appendix).

Dispensing rates of non-fentanyl opioids did not appear to be impacted by the introduction of the P4P program ($p = 0.27$ and $p = 0.49$ at 12 and 24 months follow-up, respectively; Fig. 2**)**. Non-fentanyl opioid dispensing over a 12-month follow-up ranged from 91,907 units dispensed per 10,000 eligible to 101,212 units dispensed per 10,000 eligible. When considering a 24 month follow-up, the non-fentanyl opioid dispensing rate varied from 95,872 units to 106,410 units dispensed per 10,000 eligible. The monthly rate of opioid-related hospital visits was highly variable, ranging between 0.23 and 0.47 hospital visits per 10,000 population among counties with 6 months of follow-up and between 0.18 and 0.49 per 10,000 population among counties with 12 months of follow-up (Fig. 3). No statistically significant impact of the P4P program was found on rates of opioid-related hospital visits after 6 ($p = 0.30$) and 12 months ($p = 0.59$) of follow-up. Finally, the monthly rate of opioid-related deaths ranged between 0.02 and 0.08 deaths per 10,000 population among counties with 6 months of follow-up and 0.01 and 0.08 per 10,000 population among counties with 12 months of follow-up (Fig. 4). However, no statistically significant impact of the P4P program on rates of opioid-related deaths were found after 6 months ($p = 0.50$) and 12 months ($p = 0.96$) of follow-up. Similar results were found among fentanyl-related deaths, with no statistically significant impact ($p = 0.87$). All results remained consistent in the sensitivity analysis limiting analyses to counties with statistically significant reductions in the primary outcome of fentanyl dispensing (See appendix).

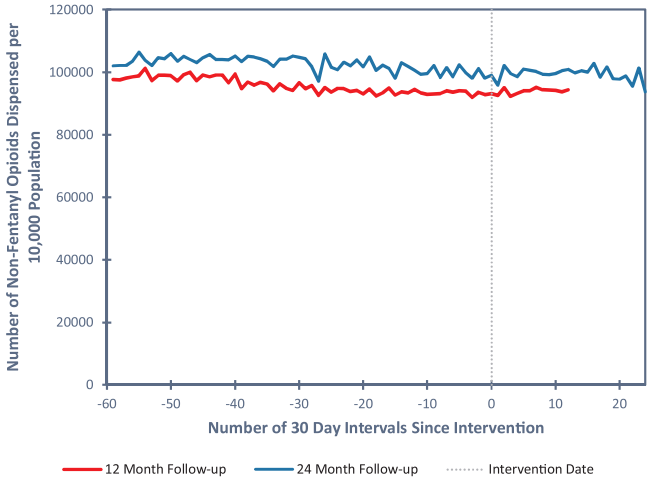

Fig. 2. Average rate of prescription non-fentanyl opioid units dispensed by participating county before and after the initiation of the P4P program at 12 and 24 months.
Note: 12 and 24 month follow-up above only include counties with sufficiently long follow-up. Dates were zeroed based on each county's intervention date.

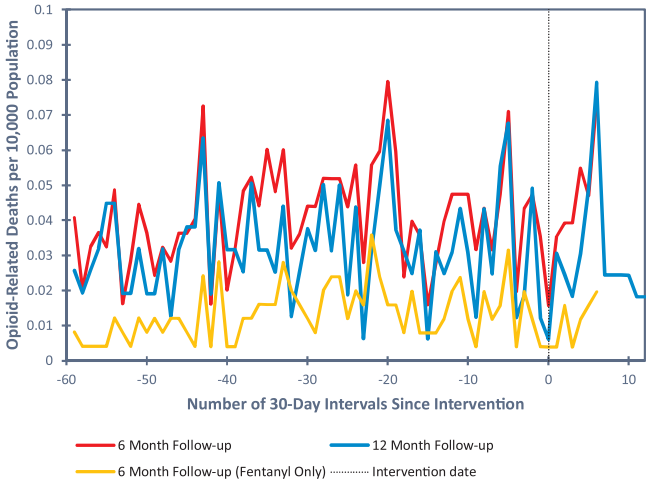

Fig. 4. Average rate of opioid-related deaths before and after the initiation of the P4P program at 6 and 12 months.
Note: 6 and 12 month follow-up above only include counties with sufficiently long follow-up.

Discussion

Our study assessed the impact of early fentanyl P4P programs introduced across 21 counties in Ontario, Canada. We found that the implementation of this program reduced the rate of fentanyl patch dispensing, with no significant impact on rates of other dispensed opioids, opioid-related hospital visits, or opioid-related deaths. These findings suggest that concerns that the introduction of P4P programs could possibly lead to changes in the dispensing patterns of non-fentanyl opioids and potentially lead to increased harms were unfounded. However, our results also suggest that P4P programs were not able to reduce the morbidity and mortality associated with opioid use, and should not be seen as a stand-alone solution.

The reduction in the dispensing of fentanyl patches in the 2 years following the implementation of P4P programs, did not significantly impact dispensing of non-fentanyl opioids. Therefore, the observed drop in dispensing rate of fentanyl patches, with no correlated increase in dispensing of non-fentanyl opioids, suggests that the program may have been successful at reducing dispensing of fentanyl patches that were diverted for sale on the illicit market. However, it is possible that some of the declining fentanyl dispensing may have impacted patients who used fentanyl patches for pain. This could occur when patches are lost, misplaced, or not returned using appropriate return-sheets. Future work should explore the implementation of the program and whether additional education or information could have improved the transition after the program's launch. Secondly, our finding of no change in measured harms may support the opinion that these programs are safe. This is important, since there has been concern that limiting access to fentanyl may turn some patients to illicit forms of opioids. Use of illicit forms of opioids, such as heroin or illicitly manufactured fentanyl products, have higher risks of overdose since they do not meet any manufacturing standards (Howlett, 2016; Young et al., 2015). The results of our study support use of similar P4P program in other jurisdictions as a means to potentially reduce diversion of patches. Inversely, the program did not reduce rates of overdoses, suggesting that the implementation of P4P programs are not a stand-alone solution to helping curb rising opioid-related harm. Therefore, it is imperative that P4P programs be integrated into larger multifaceted solutions that address a broad range of drivers of these harms.

Importantly, some P4P participating counties did not have a significant reduction in the rate of fentanyl patches dispensed. Given the voluntary nature of the initial phase of P4P programs, these findings could be due to a lower level of participation among pharmacies and prescribers, which would impact the county's ability to comprehensively implement the program. For example, counties with low levels of pharmacy participation may demonstrate little effect of the P4P program on fentanyl prescribing since individuals looking to by-pass the program can easily go to a non-participating pharmacy in the area. In contrast, Algoma county reported that in its major urban centre of Sault Ste. Marie they were able to recruit all but one pharmacy to participate in the program and demonstrated a statistically significant reduction in fentanyl dispensing ($p = 0.03$) (Kelly, 2015). Although more research is needed to directly link pharmacy participation rates with patterns of change, based on these findings, it is likely that any planned implementation of similar programs would be most impactful if introduced universally across a large geographic area.

Our results parallel other evaluations of policies and programs designed to reduce the misuse of controlled drugs. Research on opioid-related interventions has suggested that policies and programs are often able to significantly impact drug utilization, but have limited impact on harms (Gilson, Fishman, Wilsey, Casamalhuapa, & Baxi, 2012; Gomes, Juurlink, & Yao, 2014; Pradel, Frauger, & Thirion, 2009; Reifler, Droz, & Bailey, 2012). These findings across studies suggest that the broad availability of both prescription and illicit opioids allows people to seek alternatives when changes to access are introduced. Further, as the supply of diverted prescription opioids decreases, the demand for opioids remains unchanged. This can lead to an increase in the value of these products. Therefore, it is important that these programs are accompanied by improved, rapid access to treatment for opioid use disorder and harm-reduction strategies. Furthermore, healthcare workers, such as pharmacists, need to be trained to both enforce policies and triage patients wishing to access harm-reduction programs and treatment for opioid use disorders. This alignment of interventions and programs is likely to have the largest impact on reducing opioid-related harms.

Our study has limitations that warrant discussion. First, during the study period, the P4P program was not mandatory. Therefore, pharmacies were participating in the program voluntarily and not all pharmacies in a county were required to participate. Therefore, the full impact of the P4P program may not have been observed in some regions due to low pharmacy participation rates. However, the sensitivity analyses limited to counties that had a statistically significant reduction in fentanyl dispensing, demonstrated consistent findings to our primary analysis and suggests that this limitation did not greatly influence our overall interpretation. Second, not all counties initiated P4P programs at the same time, and individuals may have gone to pharmacies in neighboring counties where no program was present to obtain fentanyl for the purposes of misuse and diversion. Third, our analysis was limited to only publically-funded prescription drugs and does not account for shifts in the use of opioids paid for by other means (cash and private insurance) or use of illicit forms of opioids. It is important to note that this policy was applied to all fentanyl patches regardless of payer and so we would not anticipate any differences by payer. Fourth, this analysis only evaluated opioid prescribing outcomes, opioid-related hospital visits and deaths. Therefore, it may not account for other risks and benefits of the program such as other healthcare utilization, use of other pharmacologic agents, and uptake of opioid maintenance therapy. The use of administrative claims data also limits our ability to assess important factors such as quality of life. Additionally, we were unable to assess if patients had an increase in their utilization of short-acting opioids often used in an as needed basis. Finally, it is possible that these programs have a longer-term clinical harms beyond our 12 month follow-up period. Future work could measure longer-term impacts of these programs, but would have to consider the influence of the province-wide implementation of P4P in October 2016.

Conclusion

The findings of our study support the perception that P4P return programs are generally safe. The P4P program appears to have helped reduce the dispensing of fentanyl patches, which may in turn have reduced diversions. Our findings are important to policymakers given concerns that reduced access to fentanyl could lead those dependent on opioids to turn alternative, non-prescribed opioids with higher risks of harm. Importantly, the initiation of P4P programs cannot be seen as a singular solution to reducing opioid-related harms. Clinicians need to be trained to both enforce policies and triage patients to harm-reduction programs and treatment for opioid use disorders. Future research should study the long-term impacts on patient outcomes broadly and any fentanyl-patch related consequences specifically. Overall, the early initiation of the P4P program appears to have reduced the dispensing of fentanyl patches that may have been diverted, without measurable adverse consequences. Policymakers should consider the use of P4P programs as part of larger opioid strategy.

Disclosures

Dr Muhammad Mamdani has received honoraria from *Novo Nordisk, Allergan, and Celgene*. David Juurlink has received payment for presentations and expert opinions involving opioids, including fentanyl, but engages in no instances with pharmaceutical companies. No other authors have any conflicts of interest to declare.

Prior presentations

This work was presented at the International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Montreal, Canada, August 2017. It was presented at "Canadian Association of Population Therapeutics Conference, October 2018, Toronto, Canada". It is also presented as part of a Public Safety Canada report.

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All authors were involved in the design, interpretation of results, writing, conceptualization of recommendations, and revision of the manuscript (MT, SG, DM, KN, SS, MMM, DNJ, TG). MT, SG, KN, DM, and TG, were involved in the implementation of the study. MT is the guarantor of the content of the manuscript, including the data and analysis.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugpo.2019.01.025.

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