**Opioid Prescribing in Canada following the Legalization of Cannabis:**

**A Clinical and Economic Time Series Analysis**

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**Funding source:** Scientus Pharma Inc.

**Key words**: opioids, legalization, time series, Canada, cannabis

**Running title:** Opioid prescribing post cannabis legalization

**ABSTRACT**

**Rationale, aims and objectives**: Between January 2016 and March 2019, an estimated 12,800 Canadians died from an opioid-related overdose. A contributing factor has been the abuse of legally obtained prescription opioids. The use of plant derived cannabinoids for chronic pain has been growing in recent years. In October 2018, recreational cannabis became legal in Canada, which resulted in increased access and a reduction in the stigma associated with usage. The purpose of this study was to assess trends in the amount and total cost of opioid prescribing in Canada prior to and following cannabis legalization.

**Methods**: National monthly prescription claims data for public and private payers were obtained from January 2016 to June 2019. The drugs evaluated consisted of morphine, codeine, fentanyl, hydrocodone, hydromorphone, meperidine, oxycodone, tramadol and the non-opioids gabapentin and pregabalin. All opioid volumes were converted to a mean morphine equivalent dose (MED)/claim. Gabapentin and pregabalin claims data were analyzed separately from the opioids. Time series regression modelling was undertaken with dependent variables being mean MED/claim and total monthly spending. The slopes of the time series curves were then compared pre vs. post cannabis legalization.

**Results:** Over the 42-month period, the mean MED/claim declined within public plans (p < 0.001). However, the decline in MED/claim was 5.4 times greater in the period following legalization (4.1 vs. 22.3 mg/claim). Total monthly opioid spending by public payers was also reduced to a greater extent post legalization ($95,000 vs. $267,000 per month). The findings were similar for private drug plans; however, the absolute drop in opioid use was more pronounced (30.8 mg/claim pre vs. 76.9 mg/claim post). Over the 42-month period, gabapentin and pregabalin usage also declined.

**Conclusions**: Our findings support the hypothesis that easier access to cannabis for pain may reduce opioid use for both public and private drug plans.

**INTRODUCTION**

 One of the most serious public health crises over the past decade in Canada has been opioid addiction and abuse. Indeed, between January 2016 and March 2019, an estimated 12,800 Canadians died from an opioid-related overdose.1 A contributing factor has been the abuse of legally obtained prescription opioids.2 In one epidemiological study focusing on British Columbia and Ontario, the annual rate of fentanyl, hydromorphone, morphine and oxycodone prescribing (defined as the daily doses per 1000 population) was strongly correlated with mortality (based on provincial coroners' cause of death data).3 Death rates from opioid overdose were also significantly higher in jurisdictions with higher levels of opioid prescribing. The investigators concluded that new approaches and policies are needed to reduce opioid prescription volumes.3 This is particularly relevant to Canada from a public health perspective because on a per capita basis, Canadians are among the highest consumers of opioids globally, with approximately 595 prescriptions per 1,000 population.4 Therefore, medical opioid utilization should be limited and minimized to safer levels whenever possible and early alternatives explored. Particularly, patients with chronic pain may benefit from safer options with no or less addictive potential.

 The use of plant derived cannabinoids for medical purposes has been growing in recent years, particularly for the management of chronic pain. There are studies suggesting that cannabinoids can reduce pain intensity, improve quality of life and reduce or eliminate the need for opioid analgesics.5,6 In one prospective cohort study conducted in Israel by Abuhasira et al.,7 1186 elderly patients with chronic pain from various causes were started on medical cannabis and followed for six months. Data collection at baseline and at six months included pain medication, pain intensity measured on a numeric visual analogue scale (i.e. from 0 to 10), perception of the general effect of cannabis using a 7-point Likert scale (i.e. significant deterioration to significant improvement) and overall safety.6 At the end of six months, the investigators reported a statistically significant drop in pain intensity; from a median of 8 at baseline to 4 (p < 0.01). In addition, 66.8% of respondents reported a high pain intensity score (i.e. ≥ 8 units) at the initiation of cannabis compared to only 7.6% after six months (p < 0.01). Overall, 78.6% of patients had a moderate or significant improvement in their condition after six months of adjunctive cannabis therapy. Of equal importance, 14.4% of patients stopped using opioid analgesics and a further 3.7% reduced their dose. Other drugs eliminated included: other analgesics (7.3%), benzodiazepines (7.5%) and neuropathic pain drugs (4%).7 The retention rate of the initiated Cannabis therapy was high. Overall, 10.8% of patients discontinued their medical cannabis for various reasons, but only 1.4% was due to side effects. Abuhasira et al., concluded that medical cannabis was safe, effective and able to reduce or eliminate the need for opioid analgesics in some patients with chronic pain.7

 Other studies have suggested that the legalization of cannabis can reduce prescription drug use for a wide range of conditions such as anxiety, depression, nausea, seizures and especially chronic pain.8 One study from the United States reported a 13% reduction in prescriptions for pain drugs in those states with legalized medical cannabis when compared to those states where cannabis remained illegal (p < 0.01). This corresponded to an annual cost savings of approximately $500 million over the first four years post legalization.9 On October 17, 2018, recreational cannabis became legal in Canada, which resulted in increased access and a reduction in the stigma associated with its use. The impact of full cannabis legalization on the prescribing of opioids in Canada has not been formally evaluated. Therefore, the purpose of the current study was to assess trends in the amount and total cost of opioid prescribing in Canada prior to and following the legalization of cannabis. Our hypothesis was that cannabis legalization was associated with a statistically significant reduction in both the amount and total cost of opioid prescribing in Canada.

**METHODS**

Canada-wide monthly prescription claims data for both public and private drug plans were obtained from IQVIA PharmaStat for January 2016 to June 2019. The public data accounted for 100% of all opioid claims from all provinces, except for Alberta and Nova Scotia, where only 80% and 82% of the claims were available. In addition, no public payer data was available for the province of Prince Edward Island. With respect to private drug insurance coverage, the data covered approximately 82% of plans nationally. The data comprised of the number of prescription claims, units per claim and drug costs reimbursed per month. The agents consisted of morphine, codeine, fentanyl, hydrocodone, hydromorphone, meperidine, oxycodone and tramadol. The dosage forms were oral, rectal, injectable and transdermal. All opioid prescription volumes were then converted to a morphine equivalent dose (MED) per claim.10

Gabapentin and pregabalin are anticonvulsants but are often used to treat neuropathic pain.11 Claims data for gabapentin and pregabalin were also obtained to determine if any decrease in opioid prescriptions over the 42-month period was associated with an increase in gabapentin and pregabalin usage (opioid substitution). Separate analyses were performed for public and private claims. Gabapentin and pregabalin claim volumes and total costs were analyzed separately from the opioids.

All outcomes over the time period were presented descriptively as means and medians via time series plots. Time series regression modelling was undertaken with the opioid data. Dependent variables in the models were mean and median MED per claim and total monthly spending. The slopes of the time series curves were compared pre vs. post cannabis legalization. Any significant differences in the regression slopes would suggest that external factors were impacting opioid prescription volumes. With both the public and private data, Fitted Autoregressive Integrated Moving Average (ARIMA) models were then built using the 33-month claims data pre-legalization to forecast the mean and median MED per claim in the nine months that followed the legalization of cannabis,. The forecasts of MED per claim were then compared to what was observed (observed vs. expected). Monthly opioid expenditures were also compared for both public and private payers pre vs. post cannabis legalization.

For the gabapentin and pregabalin time series regression models, the dependent variable was mean monthly cost per claim over the 42-month time period. Changes in the mean monthly cost per claim pre vs. post cannabis legalization would be indicative of gabapentin and pregabalin drug volumes. A rise in the mean monthly cost per claim post legalization would suggest that at least some of the opioids presciptuions were being substituted by gabapentin and pregabalin. All of the statistical analyses were performed using Stata, release 11.0 (Stata Corp., College Station, Texas, USA).

**RESULTS**

 Over the 42-month evaluation period, visual inspection of the time series graphs revealed a steady decline in amount of opioids prescribed (presented as a median MED per claim) for both public and private drug plans in Canada (Figure 1). The mean and median declines were obtained from the slopes of the time series regression lines. A negative slope would be consistent with a reduction in the MED and cost per claim. When the slopes were quantified respectively over the entire time period, the mean and median decline in the MED per claim for public drug plans was 5.7 and 5.2 mg morphine equivalent. Similarly, the mean and median decline in the MED per claim for private drug plans was 39.6 and 4.7 mg morphine equivalent respectively (Table 1). However when the time series regression slope was determined from January 2016 to September 2018 (the time period before cannabis legalization) and then compared to the slope from the months after legalization, the rate of decline in the MED per claim for both public and private drug plans was accelerated (Table 1). For public payers, the mean decline in the MED per claim was 4.1 mg pre legalization compared to 22.3 mg post legalization (an 18.2 mg absolute or 82% relative reduction in the MED per claim post legalization). The decrease in opioid utilization for private drug plans was even more pronounced. The mean decline in the MED per claim pre legalization was 30.8 mg compared to 76.9 mg post legalization – an absolute reduction of approximately 46.1 mg in the MED per claim post legalization (Table 1).

 For public payers, the decline in the utilization of opioids after October 2018 also resulted in cost savings. The monthly decline in opioid spending before cannabis legalization was approximately $95,140 per month. However, after legalization, the monthly decline in spending became even more pronounced at $267,253 per month, representing an additional cost savings of $172,113 per month (Table 1 and Figure 2). Cost savings post cannabis legalization were also observed for private drug plans. The monthly reduction in opioid expenditures before cannabis legalization was approximately $76,111 per month. However, after legalization, the monthly decline in expenditures increased to $142,276 per month, an additional cost savings of $76,245 per month (Table 1).

 ARIMA models were constructed with the public and private payer time series data from January 2016 to September 2018 only. The models were then used to forecast the median MED per claim in the nine months that followed the legalization of cannabis, and these were compared to what was observed. If the legalization of cannabis had no impact on the mean and median MED per claim, then the observed values should have been comparable to the forecasted estimates. Two ARIMA models were built and, in both cases, the model predicted forecasts for median MED per claim were greater to what was observed in the nine months following legalization (Figure 3). Indeed, these data suggest that external factors contributed to a decline in opioid volumes from October 2018 until June 2019, the end of the evaluation period.

 One factor could be a reduction in the national prevalence of chronic pain. However, a recently published study used Community Health Survey data to measure the prevalence of chronic pain in Canada. The prevalence of chronic pain in general Canadian population increased in all provinces, in all age groups and also among people with no other chronic medical problems. At a national level, there was an 5.7% increase in chronic pain, from 16.3% in 2000 to 21.0% in 2014.12 Therefore, it is unlikely that decreases in the prevalence of chronic pain post legalization are responsible for the drop in overall opioid consumption.

 If the prevalence of chronic pain is on the rise in Canada, then patients may be receiving alternative agents such as gabapentin and pregabalin. To test this hypothesis, prescription claims data for both public and private payers were evaluated over the same 42-month period. Gabapentin and pregabalin utilization were expressed as a median cost per claim. The findings revealed that the utilization of both gabapentin and pregabalin, within both public and private payers, also declined (Figure 4). Therefore, it does not appear that gabapentin and pregabalin were being substituted for opioids to a large extent.

**DISCUSSION**

 The findings of this 42-month time series analysis (which included the month when cannabis was legalized) revealed a steady and statistically significant decline in the mean and median MED per claim for public payer drug plans. However, when comparing the pre vs. post legalization time periods, the decline in the mean MED per claim was 5.4 times greater in the period following legalization (4.1 vs 22.3 mg per claim). In addition, total public payer monthly opioid spending reductions averaged $95,000 per month before October 2018 compared to $267,000 per month following the legalization of cannabis. Similar findings were also observed within private drug plans, but the absolute magnitude of the decline in opioid use was more pronounced (30.8 vs 76.9 mg per claim) post legalization. Gabapentin and pregabalin usage were also reduced over the same time period, suggesting that these agents were not used in place of opioids. Therefore, the legalization of cannabis coincided with a marked drop in opioid volumes prescribed in Canada.

 As reported in other studies,8,9,13,14 our findings support the hypothesis that easier access to cannabis for chronic pain may reduce opioid use and reduce drug costs for both public and private payers. In one investigation conducted in the United States, Carroon et al.,15 surveyed 2774 people across all 50 states, 1248 (46%) reported substituting cannabis for prescription drugs. Respondents indicated the most common drug classes to be substituted were opioids (35.8%), anxiolytics (13.6%) and antidepressants (12.7%).15 Of relevance to the current study, Carroon et al.,15 determined that respondents were substituting cannabis for prescription drugs, independent of whether or not they identified themselves as medical users or not. Furthermore, cannabis was most commonly being substituted to concomitantly manage the triad of pain, anxiety and depression. The investigators concluded that approximately 46% of respondents surveyed were discontinuing FDA approved prescription drugs in place of cannabis, without medical guidance and despite the fact that cannabis remained illegal in some US states.15 Similar findings have also been reported in studies conducted in Canada.16

 The legalization of cannabis in Canada may have even broader implications. Cannabis legalization may have a direct impact on the Canadian opioid dependence crisis. One study from the Unites States examined medical marijuana policies and hospitalizations related to marijuana and opioid use for pain.17 Hospital admission and discharge records from 1997 to 2014 were examined from 28 states that had legalized medical marijuana. The analysis determined that the legalization of medical cannabis was associated with a 23% (p = 0.008) reduction in hospital admissions for opioid dependence and a 13% reduction in admissions for overdoses (p = 0.025). Furthermore, there was no evidence to suggest that cannabis legalization lead to an increase in marijuana-related hospitalizations.17

 In another study, Bachhuber et al., used time series analysis to compare opioid analgesic overdose death rates between 13 states with legalized medical cannabis to states where medical cannabis remained illegal.18 Overall, states with legalized medical cannabis had a 24.8% lower annual opioid overdose mortality rate (95%CI: −37.5%to −9.5%; p = .003) relative to states without legal medical cannabis laws.18 Therefore, the published data suggest that cannabis legalization in Canada may provide benefits beyond opioid prescription volume decreases and cost savings to public and private payers.

 There are several limitations in the current study that need to be addressed. Firstly, even though the time series analysis revealed that the legalization of cannabis coincided with a marked decrease in prescription opioid use across Canada, it does not imply causation. Other factors such as a heightened awareness by Canadian physicians of the risks associated with overprescribing opioid analgesics for patients with chronic pain may have contributed to the decline in use. However, it is important to recall that a steady decline in the MED per claim was observed from January 2016 until September 2018 and the decline became more pronounced after October 2018. Cannabis prescribing data post legalization was not available for comparison, nor did we survey patients who were receiving opioid analgesics for chronic pain. Therefore, it is unknown which agents were substituted for opioids in such patients post legalization. Opioid prescription claims data were not complete. Only 80% and 82% claims data were available for public payers in Alberta and Nova Scotia. In addition, no public payer data were available for the province of Prince Edward Island and private payer data covered only 82% of plans nationally. Opioid prescription claims data were only evaluated for 8 months post legalization. Longer follow up data is required to determine if the rate of the MED decline per claim is sustained. Pain, anxiety and depression often present as a medical triad; however, we did not evaluate the prescribing patterns of anxiolytics and antidepressants over the 42-month evaluation period.

 Notwithstanding these limitations, our study results are encouraging as they seem to reflect behaviour change in opioid prescribing and utilization. We strongly recommend further clinical studies and educational programs in large well-defined medical populations to monitor the benefits of cannabis for specific medical conditions and to educate patients, with the ultimate goal being to offer patients in need alternatives to opioids.

**Conclusions**

The findings of this study are compelling and add to the growing body of evidence that easier access to cannabis for patients with chronic pain can substantially reduce opioid use and save drug costs for both public and private drug plans.

**Disclosure**

LM and BPE are employees of Scientus Pharma Inc. All authors had full access to the data, participated in the design of the study, interpretation of the results and preparation of the final manuscript. There are no other conflicts of interest to declare.

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# LIST OF TABLES

1. Opioid MED and cost per claim pre vs. post cannabis legalization.

**Table 1.** Opioid MED and cost per claim post vs. pre cannabis legalization.

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| --- | --- | --- |
| **Outcome [Mean, (SE)]** | **Public Payers** | **Private Payers** |
| Monthly decline in MED (mg) per claim from January 2016 - June 20197,8Monthly decline in MED (mg) pre legalization6Monthly decline in MED (mg) post legalizationDifference in MED monthly decline per month(post vs. pre) | 5.7 (0.70)14.1 (0.92)122.3 (5.5)218.2 | 39.6 (8.2)130.8 (13.1)376.9 (17.2)446.1 |
| **Outcome (Median, SE)** | **Public Payers** | **Private Payers** |
| Monthly decline in MED (mg) per claim from January 2016 - June 20197,8Monthly decline in MED (mg) pre legalizationMonthly decline in MED (mg) post legalizationDifference in MED monthly decline per month(post vs. pre) | 5.2 (0.42)15.0 (0.60)110.3 (4.2)55.3 | 4.7 (0.44)15.2 (0.64)17.6 (3.7)62.4 |
| **Total Opioid Spending per Month** | **Public Payers** | **Private Payers** |
| Monthly decline in total spending over entire time periodMonthly decline in spending pre legalizationMonthly decline in spending post legalizationDifference in total opioid spending per month(post vs. pre) | $108,929 (7407)1$95,140 (59863)3$267,253 (10195)1$172,113 | $84,467 (4392)1$76,111 (6114)1$142,276 (41831)1$76,245 |

Abbreviations: SE = standard error, MED = morphine equivalent dose

1p < 0.001, 2p = 0.005, 3p = 0.003, 4p = 0.025, 5p = 0.047, 6p = 0.081. The p values are associated with the slopes of the time series regression line.

7The mean and median declines were obtained from the slope of the time series regression line. A negative slope was consistent with a reduction in the MED and cost per claim

8Cannabis received full legalization in Canada in October 17, 2018.

**LIST OF FIGURES**

1. Median morphine equivalent dose (mg) per claim for Canadian public and private drug plans.
2. Total monthly cost of opioid prescriptions for Canadian public and private drug plans.
3. ARIMA model forecasts on the median MED per claim for the nine months following cannabis legalization: observed vs. expected.
4. Median cost per claim for gabapentin and pregabalin for Canadian public and private drug plans.

**Median MED per claim**

Cannabis legalization

**Figure 1**. Median morphine equivalent dose (mg) per claim for Canadian public and private drug plans. Cannabis received full legalization in Canada in October 17, 2018.

Cannabis legalization

**Figure 2.** Total monthly cost of opioid prescriptions for Canadian public and private drug plans. Cannabis received full legalization in Canada in October 17, 2018.

**Median MED per claim**

**Figure 3**. ARIMA model forecasts on the median MED per claim for the nine months following cannabis legalization: observed vs. expected.

**Cost per claim**

**Figure 4.** Median cost per claim for gabapentin and pregabalin for Canadian public and private drug plans.