Responses to the Opioid Crisis in the Presence of Substitutes:

Canadian Evidence from the Introduction of OxyNeo

by

Benjamin Lukenchuk

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Supervised by Dr. Chris Auld and Dr. Jill Horwitz
for
Dr. Martin Farnham, Honours Advisor
Dr. Elisabeth Gugl, Honours Advisor

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Abstract:

Rising rates of opioid-related morbidity and mortality have caused policymakers to declare opioid use a public health emergency (Heath Canada, 2017). Provinces have responded with multiple interventions. Here, I analyze the consequences of two supply-side interventions: 1) restricting access to a particular opioid through changes to the provincial formulary rules, and 2) replacing commonly abused drugs with tamper-deterrent formulations. To examine whether potential patients forgo opioid use altogether or substitute to other forms of opioids, I exploit variation in the regulation of the long-acting pain medication OxyContin and the introduction and regulation of OxyNeo, a tamper-deterrent reformulation of OxyContin introduced around 2012. Based on an original database identifying the dates that eight provinces listed OxyNeo and restricted the use of OxyContin and OxyNeo, I identify the effects of these supply-side restrictions on the rate of opioid poisoning hospitalizations. I find no effect on opioid poisoning hospitalizations from any of these restrictions. In additional analyses, I provide suggestive evidence that these hospitalizations do not decline in response to the supply-side interventions because consumers respond by using other legal or illegal opioids. These results suggest that supply-side restrictions on one particular drug without the introduction of other complementary interventions are insufficient to reduce negative opioid use outcomes.

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I. Introduction:

In 2016, there were over 2,800 opioid deaths in Canada and over 64,000 in the United States (GCDP, 2017). Two-thirds of drug overdose deaths in the United States involve an opioid (CDC, 2017). Between 1999 and 2017, the number of opioid-related deaths increased fivefold. Over the same period, the prescribing of opioids increased fourfold. Canada and the United States are the largest per-capita opioid consumers globally (GCDP, 2017). To put this in perspective, annually there is one opioid prescription written for every two Canadians (Robertson & Howlett, 2017). In response, Canadian provinces have declared the "Opioid Crisis" a public health emergency and have responded by limiting access to prescription opioids (Health Canada, 2017). In this paper, I study the efficacy of two types of supply-side restrictions on prescription opioids at reducing negative opioid use outcomes. I analyze the effect of 1) restricting access to a particular opioid through changes to the provincial formulary rules, and 2) replacing commonly abused drugs with tamper-deterrent formulations on opioid poisoning hospitalizations.

Extensive use of prescription analgesic opioids has come with substantial societal costs. Approximately 75% of opioid addictions begin with prescription opioid use as directed by a physician (Cicero, Ellis, Surratt & Kurtz, 2014). Diversion of prescription drugs is also cause for concern. For example, scholars have found that increasing the availability of opioids for Medicare-eligible individuals by 10% increases substance abuse treatment admissions by 7.4% and opioid-related mortality by 10% among people who are not eligible for Medicare (Powell, Pacula, & Taylor, 2015). This suggests that prescription opioids are being diverted for illicit use. In fact, Powell *et al.* (2015) suggest that prescription opioid diversion explains 73% of the growth in overdose deaths between 2000 and 2011 in the United States. In response, public health authorities have introduced policies that reduce the supply of prescription opioids. Examples include tamper-

resistant forms, prescription limits (rules limiting prescribed doses to less than a certain daily morphine equivalent), and prescription drug monitoring programs (electronic databases that allow prescribers and dispensers to survey a patient's previous prescriptions).

The intuition underlying these policies is that reducing supply will reduce harmful use. However, in the face of restrictions on any single opioid, there may be a substitution to other opioids. To assess whether people forgo opioid use or substitute to other opioids in the face of drug-specific reformulations and restrictions, I analyze a policy experiment related to the introduction of a new opioid in Canada.

Before 2012, the opioid OxyContin (the long-acting version of oxycodone) accounted for 30% of opioid prescriptions and 30%-50% of opioid misuse in Canada (Fischer, Vojtila, & Kurdyak, 2017). Some provinces responded to the risks of OxyContin by restricting it. In 2012, as the Canadian patent on OxyContin ended, Purdue Pharma replaced OxyContin with a tamper-deterrent formulation, called OxyNeo in Canada. This substitution occurred two years after Purdue made a similar substitution in the United States. Provincial drug plans responded to this reformulation by severely restricting or delisting OxyNeo from their formularies citing concerns around historically high rates of OxyContin misuse (CADTH, 2015). These restrictions on OxyContin and OxyNeo limited access to opioids and constituted a supply-side intervention. The timing of the restrictions varied by province.

I exploit this temporal variation in the coverage of OxyNeo by provincial drug formularies to identify the causal effect of reducing the supply of opioids on opioid misuse. This policy experiment allows me to assess the efficacy of a previously unstudied supply-side drug intervention. I use opioid poisoning hospitalizations as a measure of a negative opioid use outcome. Opioid-related hospitalizations likely give a fuller measure of the consequences of

excessive opioid use than mortality given that opioid-related deaths are comparatively rare (Unick & Ciccarone, 2017). I study both the effects of the reformulation of OxyContin and the introduction of OxyNeo and the regulation of both forms of the drug on provincial formularies. The formulary restrictions I study only apply to those who receive coverage under public drug plans (CADTH, 2015). Individuals who receive coverage under private drug plans may still access and receive coverage for a drug that is not listed on a provincial formulary if the private provider chooses.

With a more limited dataset, I am able to further assess the role of substitution in response to supply-side restrictions. Using data for Ontario, which records opioid mortality by drug, I test the relationship between the supply restrictions discussed above and mortality related to specific opioid drugs.

I find no change in opioid poisoning hospitalizations when provincial formularies restrict oxycodone products. This includes the effects of 1) restricting OxyContin, 2) restricting OxyNeo, and 3) the replacement of OxyContin with OxyNeo. Moreover, testing the same interventions in Ontario alone, I find statistically significant increases in the rates of fentanyl, hydrocodone, hydromorphone, and morphine related deaths in the period following OxyNeo's removal from Ontario's provincial drug formulary. The increase in the rates of death related to substitute opioids when OxyContin and OxyNeo are restricted suggests that the finding of no effect is being driven by consumers substituting to other opioids when the supply of one particular opioid is restricted.

II. Background:

OxyContin and the Opioid Crisis:

The "Opioid Crisis," as it is known today, is commonly traced to the introduction of OxyContin by Purdue Pharma in 1992 (Robertson & Howlett, 2016; Ubelacker, 2017). OxyContin is a slow release pain medication sold at the time as a safer and non-addictive alternative to previous opioid therapies. In Ontario alone, the rate of oxycodone prescribing grew by 850% between 1991 and 2007 (Dhalla *et al*., 2009). Despite the claims of its manufacturer, Purdue Pharma, OxyContin is highly addictive (Keefe, 2017). This resulted in a series of lawsuits against Purdue Pharma. In response, OxyContin was removed from the marketplace in March 2012 and replaced with a tamper-deterrent formulation called OxyNeo (Patented Medicine Prices Review Board, 2014). OxyNeo is the same medication as OxyContin but is more difficult to crush and forms a gel when added to water. These features prevent manipulating the medication to release the drug immediately in order to produce a euphoric high. There is nothing to prevent an individual from misusing OxyNeo by simply taking more of the drug.

In response to the reformulation, many provincial drug plans placed substantial restrictions on OxyNeo, citing concerns of historically high OxyContin use (CADTH, 2015). The view of policymakers was that making prescription opioids less accessible would correct for the high rates of abuse and misuse of the pain medications at the time (For example see Province of Manitoba, 2010; Nova Scotia Health and Wellness, 2012). While a reduction in the prescribing of oxycodone products did occur, the overall quantity of opioids dispensed remained largely unchanged (Gomes *et al*., 2017). Just after reformulation, illicit and highly potent fentanyl started becoming available in Canada, potentially amplifying the crisis (Robertson & Howlett, 2017).

Provincial Formulary Coverage of OxyNeo:

The response to OxyNeo's introduction varied by province. I develop an original database that determines the timing and nature of provincial formulary restrictions on oxycodone products (OxyContin, OxyNeo, and generics) from the second quarter of 2007. I present this in Appendix 1. Most provinces follow a similar pattern of coverage. OxyContin required some special authorization prior to March 2012 and then, upon reformulation, OxyNeo was only available to cancer and palliative care patients. There are three notable exceptions to this pattern. Alberta never places restrictions on OxyContin or OxyNeo and lists it as a full benefit throughout the study. Manitoba restricts OxyContin to cancer patients and patients with specific chronic conditions in 2010 prior to reformulation. This restriction extends to OxyNeo. Saskatchewan lists OxyContin as a full benefit prior to March 2012 and then restricts the drug to cancer and palliative care patients post-reformulation.

Unlike in the United States, where the Federal Drug Administration banned generic versions of OxyContin (Wilson, 2013), Health Canada did approve generics[1](Gomes *et al.*, 2018). Nova Scotia and Quebec were the only two provinces that elected to cover generic forms. This should not negatively affect my results, as Quebec does not report in my dataset and Nova Scotia constitutes a small number of the recorded hospitalizations.

III. Relevant Literature:

Research related to my question follows three major strands. The first addresses the conditions that affect opioid dispensing and use. The second addresses how crime responds to

[1] In 2015, however, the federal health minister announced that all oxycodone products would need to be tamper-deterrent within three years (Ivison, 2015).

prescription opioid restrictions. The third addresses the efficacy of policy interventions on misuse and how consumer substitution between opioids limits the effectiveness of policies that seek to reduce opioid misuse. Many of the relevant papers use the term opioid "misuse." This is because many use data from the National Survey of Drug Use and Health (NSDUH)[2]. This survey uses the terms "substance use" and "substance misuse."

The first strand of the existing literature has measured the effect macroeconomic conditions have on opioid use and dispensing. Economic downturns, measured as the rate of unemployment, are accompanied by an increase in opioid-related hospitalizations and opioid use (Hollingsworth, Ruhm, & Simon, 2017; Carpenter, McLellan, Rees, 2017). Carpenter *et al.* (2017), who control for individual characteristics, suggest that the increase in opioid use during economic downturns is driven by white males with low levels of education.

The second strand of the existing literature studies the effect prescription opioid restrictions have on crime. Mallatt (2017) uses the implementation of prescription drug monitoring program databases to measure the effect of decreasing the availability of opioids on heroin-related crime rates. Given that heroin is an inexpensive substitute for prescription opioids (see for example Cicero and Ellis, 2015), one might expect a decrease in the availability of opioids due to a policy intervention to increase heroin demand and thus increase heroin-related crime. Mallatt (2017) finds that prescription drug monitoring programs caused an 8% drop in oxycodone shipments and 87% increase in heroin-related crime in the most opioid dense counties.

[2] This American survey is administered by the Substance Abuse and Mental Health Services Administration. Seventy-thousand people are randomly selected for an in-person interview across all states and the District of Columbia, and responses are confidentially recorded. Interviewees are asked about their drug use in the past month and year, about their mental health, and about mental health services accessed in the last year. No equivalent survey exists in Canada.

The third strand assesses the efficacy of public policy responses. There are two types of drug policy responses discussed in the literature: demand and supply-side. Safe injection sites and addiction treatment are examples of demand-side interventions. Any policy that attempts to reduce the availability of a drug is considered a supply-side intervention. Examples of supply-side interventions include tamper-deterrent formulations, prescription limits (rules limiting prescribed doses to less than a certain daily morphine equivalent), and prescription drug monitoring programs. Prescription drug monitoring programs are costly and have attracted substantial research attention (Meara *et al.*, 2016; Buchmueller & Carey, 2017; Mallatt, 2017). No consensus has emerged as to their efficacy at reducing negative opioid use outcomes. Tamper-deterrent formulations, like OxyNeo, have been found to be ineffective at reducing negative opioid use outcomes (Alpert, Powel, & Pacula, 2017; Evans, Lieber, & Power, 2017). Studies that examine the reformulation of OxyContin in the United States find a post-reformulation reduction in OxyContin misuse accompanied by a strong substitution toward heroin. More importantly, they find no reduction in net mortality. These findings suggest that consumer substitution toward heroine undid the effect of any reduction in the misuse of OxyContin.

I study the effect of the reformulation of OxyContin itself on opioid misuse, as has been done in the literature to date, but my focus is on measuring the effect of eliminating coverage for oxycodone products from public drug plans. This has not been studied to date. Since some provinces freely substitute coverage of OxyContin for OxyNeo in their formularies, my experiment offers a more accurate representation of how negative opioid use outcomes respond to opioid availability than studies that examine tamper-deterrent formulations alone.

The OxyContin reformulation and opioid prescribing more generally has also been studied in the medical literature. For example, Butler *et al*. (2013) find declines in oxycodone misuse post-

reformulation in the United States. Fischer, Jones, and Rehm (2014) find reductions in oxycodone dispensing post-reformulation in Canada. A widely cited paper by Cicero and Ellis (2015) reports the results of a structured survey of patients with an opioid use disorder. They report anecdotal evidence of individuals substituting to other opioids after the introduction of tamper-deterrent oxycodone in the United States. A number of studies link an increase in opioid dispensing in a region with an increase in opioid-related mortality (see for example Fischer *et al*., 2013a; Fischer *et al*., 2013b). Other studies have examined how dispensing and prescribing changes in the presence of policy interventions (See for example Gomes *et al*., 2017; Fischer, Jones, & Rehm, 2014). Gomes *et al*. (2017) use a time-series approach to study the introduction of OxyNeo in Canada. They find that after the introduction of OxyNeo, oxycodone dispensing fell by 46.4% but hydromorphone (a substitute, long-acting pain medication) dispensing increased by 47.8%. Their findings not only support the consumer substitution found in other papers but also suggest a substitution on the part of prescribers. Addressing this latter finding is beyond the scope of this paper.

IV. Data:

I use opioid poisoning hospitalizations to measure a negative opioid use outcome. I use data from the Discharge Abstract Database managed by the Canadian Institute for Health Information. This data is publically available for all provinces excluding Quebec at the annual level. As the result of a custom data request, I use data reported by province and by calendar quarter. My observations range from the second quarter of 2007 to the first quarter of 2017. Only confirmed hospitalizations identified by ICD-10-CA codes T40.0 to T40.4 and T40.6 in acute care facilities are counted. T40.0 measures poisoning due to opium. T40.1 measures poisoning due to

heroin. T40.2 measures poisoning due to "other opioids" such as codeine or morphine. This category includes oxycodone products. T40.3 measures poisoning due to methadone. T40.4 measures poisoning due to "other synthetic narcotics." T40.6 measures poisoning due to "other and unspecified narcotics." The coding of a diagnosis is based on a patient's chart documentation. There is the potential for human error. The data only accounts for treatment in acute care settings and does not account for treatment in other settings. Thus, any results are likely attenuated. Observations less than five are suppressed, requiring me to drop Prince Edward Island from my analysis. I also drop the aggregate "Territories" series given recent data limitations in Nunavut. Eight provinces remain and are used in my analysis: Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Nova Scotia, Ontario, and Saskatchewan. I report summary statistics by province in Table 1. I also report summary statistics pre and post-OxyNeo's introduction in Tables 2 and 3. I plot the log of hospitalizations by province in Figure 1. The vertical line indicates the introduction of OxyNeo in quarter 1 of 2012.

To measure mortality by drug, I use publically available data from Public Health Ontario. It is based on the Ontario Opioid-Related Death Database published by the Office of the Chief Coroner for Ontario. Deaths "where an opioid was present at death" from 2005 to 2016 are recorded (Public Health Ontario, 2018, p.2). Inclusion does not necessarily imply it contributed to the death. Mortality due to codeine, fentanyl, heroin, hydrocodone, hydromorphone, methadone, morphine, and oxycodone are recorded separately. Data are reported as a count per year and is geocoded to the Public Health Unit and Local Health Integration Network where the decedent resided. The level of aggregation is at the Public Health Unit and Local Health Integration Network level. I increase this to the provincial level. Poly-drug deaths are recorded in multiple categories.

Deaths in which heroin and morphine were both present are coded solely as heroin deaths. I present a line graph of the data in Figure 2. The vertical line indicates the year of OxyNeo's introduction.

V. Methods:

I begin by determining whether the introduction of OxyNeo affected the rate of opioid poisoning hospitalizations per quarter. All specifications measuring hospitalizations use data from the Discharge Abstract Database. I undertake two break-point tests. In the first test, I assess if the introduction of OxyNeo resulted in a level shift in opioid poisoning hospitalizations. I estimate the following specification:

$$\log\left(hosp_{pt}\right) = \beta_1 + \beta_2 neo_t + \beta_3 t + \phi_p + \gamma_{pt} + \varepsilon_{pt} \quad (1)$$

where $hosp_{pt}$ is the count of opioid poisoning hospitalizations in province *p* and quarter *t.* neo_t is an indicator variable that is coded 1 after OxyNeo is introduced in the first quarter of 2012 and 0 before the first quarter of 2012. *t* is the time trend. ϕ_p is a full set of province fixed effects. γ_{pt} is a full set of quarterly fixed effects by province. I estimate this specification using a feasible generalized least squares regression permitting each province to follow a distinct first-order autoregressive model. Reported standard errors are corrected for serial correlation in this fashion. The coefficient of interest is β_2 and can be interpreted as the percentage change in opioid poisoning hospitalizations per quarter associated with OxyNeo's introduction. If the effect of OxyNeo's introduction in Canada reflects the effect in the United States, we should expect this coefficient to be statistically equivalent to zero.

In the second test, I assess if the introduction of OxyNeo resulted in a trend break for opioid poisoning hospitalizations per quarter. I estimate the following specification separately for each province:

$$\log\left(hosp_t\right) = \beta_1 + \beta_2 t + \beta_3\left(t - 2012\right) \times D_{Neo} + \varepsilon_t \quad (2)$$

where $hosp_t$ is now the count of opioid poisoning hospitalizations in quarter *t. t* is the time trend. D_{Neo} is an indicator variable that is coded 1 after OxyNeo is introduced in the first quarter of 2012 and 0 prior to the first quarter of 2012. I estimate this specification using an ARIMA regression that permits the province to follow a first-order autoregressive model. Reported standard errors are corrected for serial correlation in this fashion. The coefficient of interest is β_3 and can be interpreted as the percentage change in the rate of opioid poisoning hospitalizations per quarter associated with OxyNeo's introduction. If the effect of OxyNeo's introduction in Canada reflects the effect in the United States, we should expect this coefficient to be statistically equivalent to zero.

I proceed by determining the effect of provincial formulary restrictions on oxycodone products. I exploit the variation in the timing of oxycodone restrictions across provinces to identify the causal effect of the formulary restrictions. I estimate the following difference-in-differences specification:

$$\log\left(hosp_{pt}\right) = \beta_1 + \beta_2 restrict + \beta_3 t + \phi_p + \varepsilon_{pt} \quad (3)$$

where $hosp_{pt}$ is the count of opioid poisoning hospitalizations in province *p* and quarter *t*. restrict is an indicator variable that is coded 1 if oxycodone products are restricted on a province's formulary and 0 if oxycodone products are available as a full benefit (i.e. not restricted). This indicator variable is based on my original data set of formulary restrictions in Canada. *t* is the time trend. ϕ_p is a full set of province fixed effects. I estimate this specification using a feasible generalized least squares regression permitting each province to follow a distinct first-order autoregressive model. Reported standard errors are corrected for serial correlation in this fashion.

β_2 is the coefficient of interest and the difference-in-differences estimator. It can be interpreted as the causal effect of introducing formulary restrictions on opioid misuse measured as

the percentage change in opioid poisoning hospitalizations per quarter. The identifying assumption is that in the absence of oxycodone restrictions on the provincial formularies, differences across provinces would have continued along the same trends.

I show that my results are robust to alternative oxycodone product restriction dates. Specifically, I separately test if moving the restriction date later in British Columbia (Equation 4), Ontario (Equation 5), and New Brunswick, Nova Scotia, and Newfoundland & Labrador (Equation 6) affects the estimates in Equation 3. This testing is largely done to account for assumptions made early in the study period for the original database of formulary restrictions.

To provide suggestive evidence of consumer substitution, I use mortality data from the Ontario Opioid-Related Death Database and undertake a statistical breakpoint test. I test for a trend break in the annual mortality measure by opioid at the year of OxyNeo's introduction. I estimate the following specification separately for each of the opioids measured:

$$death_t = \beta_1 + \beta_2 t + \beta_3 \left(t - 2012\right) \times D_{Neo} + \varepsilon_t \quad (7)$$

where $death_t$ is the count of deaths involving the particular drug in year t. t is the time trend. D_{Neo} is an indicator variable that is coded 1 after OxyNeo is introduced in 2012 and 0 before 2012. I estimate this specification using an ARIMA regression that permits the trend of deaths related to the particular opioid to follow a first-order autoregressive model. Reported standard errors are corrected for serial correlation in this fashion. The coefficient of interest is β_3. Statistically significant positive coefficients indicate that deaths related to the particular opioid increased after the introduction of OxyNeo. This method suffers from a substantial temporal aggregation problem as treatment is at the monthly level but data is only available yearly.

VI. Results:

First, I provide evidence that the introduction of OxyNeo itself did not reduce opioid misuse in Canada. Second, I provide evidence that formulary restrictions on oxycodone products do not have a causal effect on opioid misuse. Third, I conduct a sensitivity analysis to ensure my results are robust to alternative oxycodone product restriction dates. Finally, I provide suggestive evidence that my findings are driven by consumer substitution to other opioids.

The Effect of OxyNeo's Introduction:

I show graphically that the introduction of OxyNeo did not appear to affect opioid poisoning hospitalizations. Figure 1 plots the log of quarterly opioid poisoning hospitalizations by calendar quarter for the eight provinces I study. The vertical line denotes the date of OxyNeo's introduction to the Canadian market. The trend appears constant on either side of the line. If OxyNeo's introduction had an effect, we would expect a change in the slope or a level break in the trend at the vertical line. This is not evident.

To formalize this graphical analysis, I estimate Equation 1 and Equation 2. I report coefficient estimates and standard errors in Tables 4 and 5 respectively. In Equation 1, the coefficient indicating the sign and magnitude of the level shift in the percent change in hospitalizations due to OxyNeo's introduction is statistically equivalent to zero. As observed graphically, there is no level shift in opioid poisoning hospitalizations due to OxyNeo's reformulation. I estimate Equation 2 once per province. In all provinces, the coefficient indicating the sign and magnitude of the trend break at the time of OxyNeo's introduction is statistically equivalent to zero. As observed, there is no change in the trend of each province's opioid poisoning

hospitalizations due to OxyNeo's reformulation. These results reflect the effect estimated in the existing American literature.

The Effect of Provincial Formulary Restrictions:

To determine the effect of provincial formulary restrictions, I estimate Equation 3. I code the indicator variable for the presence of oxycodone product restrictions according to the original database of formulary restrictions presented in Appendix 1. I report the regression output in Table 6. The difference-in-differences estimate can be interpreted as the percent change in opioid poisoning hospitalizations per quarter caused by the introduction of oxycodone product restrictions. The estimate of a decrease of 0.3% in opioid poisoning hospitalizations is statistically equivalent to zero and is not practically significant. Note that this is not a *tight* zero result. A 95% confidence interval permits both a decrease in opioid poisoning hospitalizations and an increase of a practically significant magnitude.

Sensitivity Analysis:

There are two errors that could bias the estimates from Equation 3. First, there are limitations to the original database of formulary restrictions early in the treatment window. I need to make plausible assumptions about the nature of restrictions early in the database. Second, there is some subjectivity in the coding of the indicator variable given that provincial restrictions are not directly comparable. Given this uncertainty, I test any assumptions I make to ensure the robustness of my results. I report the regression output in Table 7. The difference-in-differences estimate remains both statistically and practically insignificant across all specifications. This indicates that my assumptions are not driving my results.

Consumer Substitution

The introduction of OxyNeo, which coincided with the timing of most province's oxycodone product restrictions, was accompanied by a 46.4% decrease in oxycodone dispensing in Canada (Gomes *et al.*, 2017). Given that prior to reformulation, oxycodone products were responsible for 30% to 50% of misuse (Fischer, Vojtila, & Kurdyak, 2017), the finding that formulary restrictions do not affect misuse requires some explanation. Analysis of mortality by opioid in Ontario demonstrates that deaths due to substitute opioids increased after the restriction of oxycodone products on the provincial formulary. This is demonstrated graphically in Figure 2. In Figure 2, I plot annual drug mortality by year. The vertical line indicates the year of OxyNeo's restriction in Ontario. Post-2012, we observe an increase in deaths related to fentanyl, hydrocodone, hydromorphone, and morphine. To formalize this graphical analysis, I look for a trend break in 2012. I estimate Equation 7 for each drug that is counted separately. I report coefficients and standard errors in Table 8. This analysis provides purely suggestive evidence. It only examines one province and suffers from a substantial temporal aggregation problem. It is, therefore, most informative to look at the signs and statistical significance of the estimates as opposed to the magnitude. Doing this, my estimates confirm the graphical analysis as statistically significant trend increases are reported for fentanyl, hydrocodone, hydromorphone, and morphine. Together with the fact that overall opioid misuse did not respond to restrictions on oxycodone products, the increase in deaths related to substitute opioids to OxyContin and OxyNeo suggests that consumer substitution undoes any effect of formulary restrictions.

VII. Conclusion:

As the opioid crisis deepens in North America, health policymakers will be under continued pressure to act. It is important that any responses to the crisis do not unintentionally push consumers of opioids to more harmful substitute opioids. In this paper, I study two supply-side drug restrictions. I find that restricting access to a particular opioid through changes to the provincial formulary rules and replacing commonly abused drugs with tamper-deterrent formulations are ineffective at reducing opioid poisoning hospitalizations. I show that this is likely due to consumer substitution to other drugs. My results suggest that supply-side restrictions on one particular drug without the introduction of other complementary interventions are insufficient to reduce negative opioid use outcomes. I also contribute to further research by constructing an original database of oxycodone product restrictions in Canada on provincial formularies.

Given my findings, suggesting an alternative response for health policymakers is important. The solution may come as a result of another unrelated policy goal. More U.S. states are legalizing marijuana (Robinson, Berke, Gould, 2018) and Canadian Prime Minister Justin Trudeau's looming July 1st deadline to legalize marijuana is fast approaching (Tasker, 2018). It is possible that legalization efforts may in fact also address the opioid crisis. Powell, Pacula, & Jacobson (2015) find a 31% reduction in opioid overdoses and a 53% reduction in opioid addiction treatment admissions for states with medical marijuana laws and legal protection for dispensaries. Data will soon be available to study the introduction of recreational marijuana in Colorado and Washington state. This should be the subject of future research. While legalizing marijuana is not risk-free, it appears that the cheap, effective, and politically feasible solution is already in the works.

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Appendix 1: Coverage of OxyContin and OxyNeo on provincial formularies in Canada, 2007Q2 – 2017Q1

Province	Rule – OxyContin	Rule - OxyNeo	Special Rule – OxyNeo
Alberta	Regular benefit until October 1, 2012	Freely substitutable from March 1, 2012, on Alberta Health and Wellness Drug Benefit List	0
British Columbia	April 1, 2011 – 5-80mg Limited Coverage requiring special authority approval; also covered by Palliative Drug Benefit (I assume this extends to the start of the study period) Pharmacare Coverage effectively discontinued March 8, 2012 (5 mg through 80 mg). Note: BC Pharmacare removed OxyContin from Palliative Drug Benefit on December 5, 2014. This is purely an administrative change with no practical significance for this study.	As of March 8, 2012, OxyNeo is only available on a case-by-case basis. Covered by Palliative Drug Benefit. Listed Feb 25, 2012. Special Authority must be renewed.	Patients with current annual special authority approval for OxyContin will continue coverage for OxyContin and OxyNeo until their special authority approval ends. Patients with current indefinite special authority approval will be granted 12-month transitional coverage until Feb. 28, 2013, for OxyContin and OxyNeo to allow time for them to work with their physician to assess their pain management treatment.
New Brunswick	September 1, 2001 – special authorization required for treatment of cancer or chronic pain. Never a regular benefit drug. Delisted February 29, 2012	February 9, 2012 - OxyNeo will not be listed on the provincial formulary.	Those who received continue within the previous 3 months prior to March 1, 2012, could get OxyNeo. A new prescription for OxyNeo required.
Nova Scotia	Effective March 1, 2012, no new starts.	Effective March 1, 2012, no new starts.	Those who received OxyContin within the previous 3 months prior to March 1, 2012, could get

	Prior, 5-80mg available as exception status drug "for the treatment of moderate to severe chronic pain syndromes, as an alternative to morphine or hydromorphone" (I assume this extends to the beginning of the study period)	Palliative and cancer pain assessed on a case-by-case basis.	OxyNeo. A new prescription for OxyNeo required.
Ontario	Coverage withdrawn on March 2, 2012. Prior to this, OxyContin required a Limited Use Form. Clinical criteria for use was "For the treatment of chronic pain in patients who cannot tolerate, or have failed treatment with a listed long-acting opioid." (I assume this extends to the beginning of the study period)	Effective February. 29, 2012 Oxy Neo considered through Exceptional Access Program for treatment of cancer or palliative pain and only if patient experiences intolerance of at least one other long-acting opioid. OxyContin and OxyNeo are not interchangeable. Never a regular benefit.	Existing Ontario Drug Benefit recipients who had a claim for OxyContin within 6 months prior got automatic coverage for OxyContin for 1 month Feb 29, 2012, to April 2, 2012. After April 2012, could get OxyNeo for one year ending Feb 28, 2013. Exceptional Access Program after that.
Saskatchewan	On Formulary as Full Benefit Dec 1, 2000.	Added to formulary February 29, 2012, under Exception Drug Status Program for "treatment of pain in palliative and cancer patients." OxyNeo and OxyContin not interchangeable. A new prescription is required.	Beneficiaries who have filled a benefit prescription for OxyContin in the three months prior to February 29, 2012 will have Exception Drug coverage for OxyNeo.

Manitoba	Effective March 26, 2010 OxyContin and generics moved from Part 1 to Part 3 Exception Drug Status.	Exception Drug Status once OxyContin removed from the market.	Substitutable for a valid script
Newfoundland and Labrador	No new starts Feb 20, 2012. Prior, OxyContin was available by Special Authorization for "persistent pain." (I assume that this extends to the beginning of the study period)	Feb 13, 2012. OxyNeo not considered for coverage. OxyContin and OxyNeo are not interchangeable. A new prescription needed. No new Special Authorization is needed.	Patients who received coverage between December 1, 2011, and March 1, 2012, are eligible for coverage.

Note 1: Data assembled by author.
Note 2: Quebec, Prince Edward Island, and the Territories omitted due to data limitations.

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Figure 1:

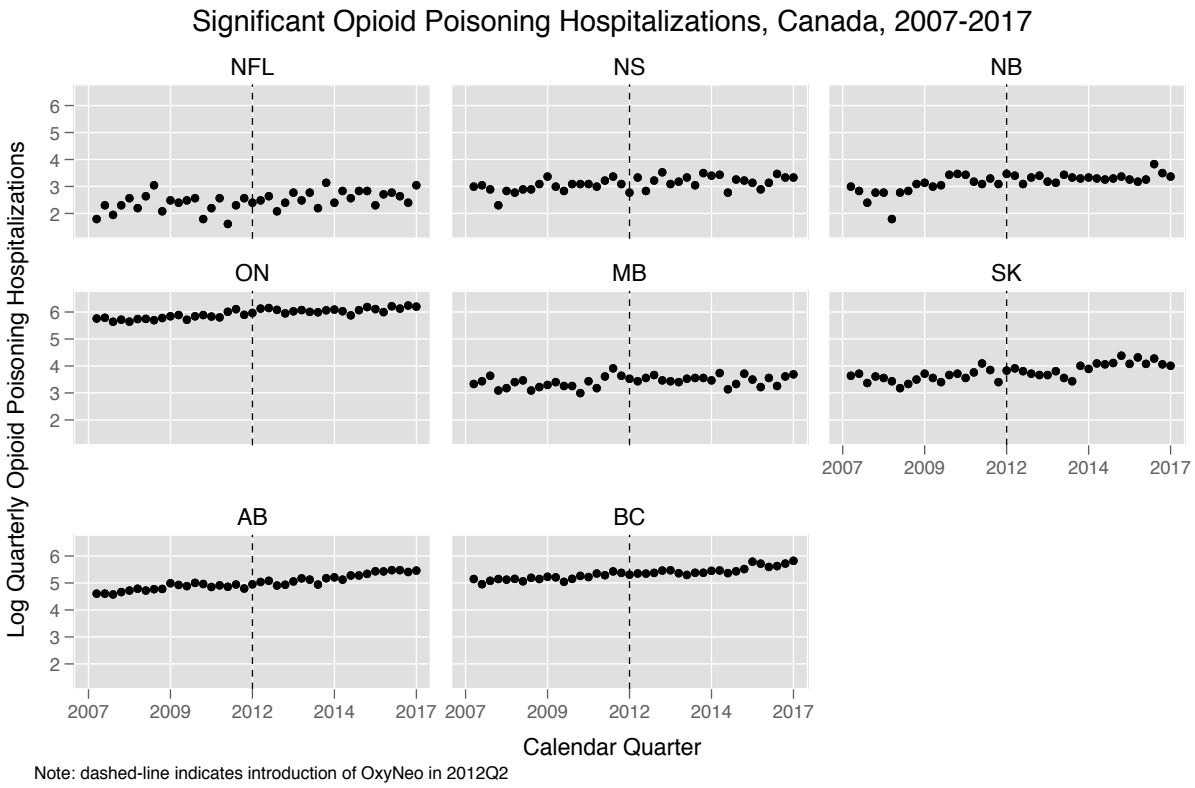
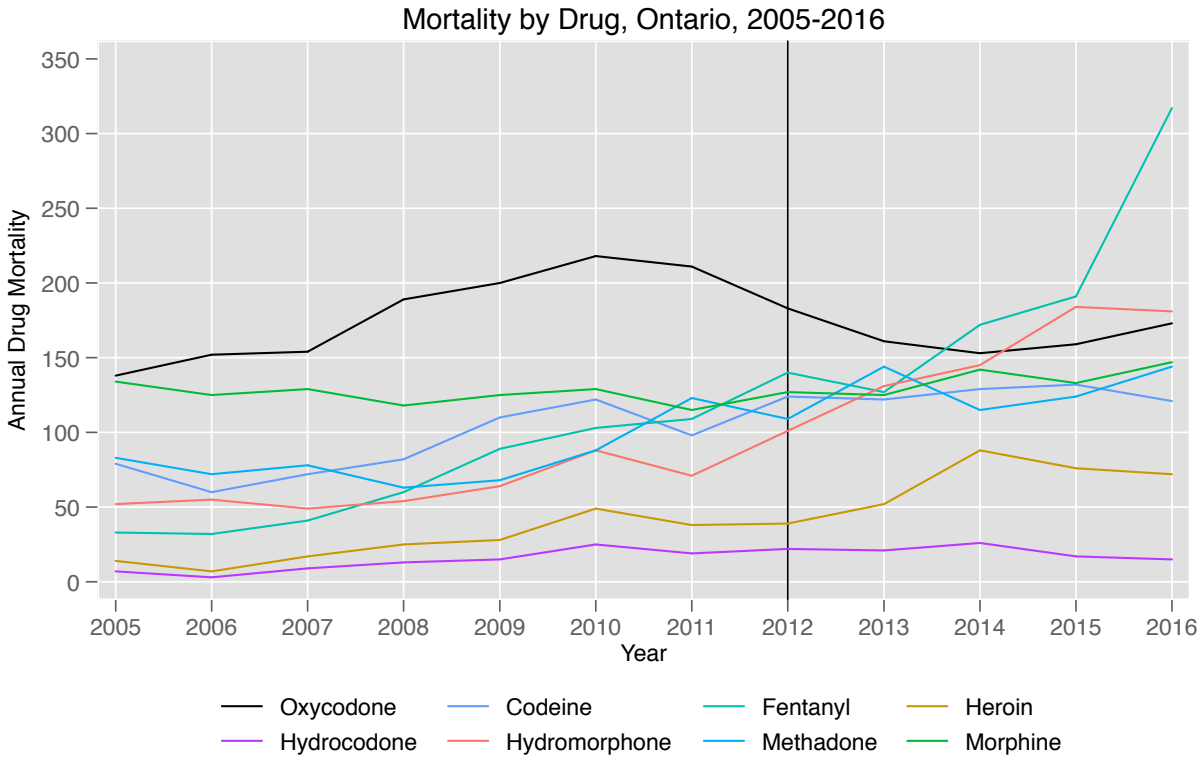

Significant Opioid Poisoning Hospitalizations, Canada, 2007-2017
NFL
NS
NB
ON
MB
SK
AB
BC
Log Quarterly Opioid Poisoning Hospitalizations
Calendar Quarter
2007
2009
2012
2014
2017
Note: dashed-line indicates introduction of OxyNeo in 2012Q2

Figure 2:



Note: The vertical line denotes the year of Oxy Neo's introduction.

Table 1: Summary Statistics: Quarterly Opioid Poisoning Hospitalizations, by province, 2007Q2 – 2017Q1

	N	Min	Max	Mean	Median	SD
NL	40	5	23	12.4	12	4.1
NS	40	10	34	22.9	22	5.5
NB	40	6	46	24.8	26	6.9
ON	40	281	514	388.3	395	65.7
MB	40	20	50	31.5	31	6.4
SK	40	24	80	45.2	41	13.6
AB	40	97	239	156	142	42
BC	40	142	338	214.2	211	46.8

Table 2: Summary Statistics: Quarterly Opioid Poisoning Hospitalizations, by province, prior to 2012Q1

	N	Min	Max	Mean	Median	SD
NL	19	5	21	10.6	10	3.7
NS	19	10	29	20.4	20	4.4
NB	19	6	32	20.7	21	6.7
ON	19	281	449	334.8	326	41.6
MB	19	20	50	29.5	28	7.3
SK	19	24	60	36.7	35	8.1
AB	19	97	149	123.5	121	16.3
BC	19	142	228	180.4	173	21.7

Table 3: Summary Statistics: Quarterly Opioid Poisoning Hospitalizations, by province, after 2012Q1

	N	Min	Max	Mean	Median	SD
NL	21	8	23	14	14	3.8
NS	21	16	34	25.1	25	5.5
NB	21	22	46	28.4	28	4.9
ON	21	357	514	436.7	434	40.9
MB	21	23	42	33.2	34	5.1
SK	21	31	80	53	55	13
AB	21	135	239	185.3	177	36
BC	21	200	338	244.8	233	42.1

Table 4: Breakpoint Test A - Level Shift Regression Output (Equation 1)

	(1) Log(Hosp)
β_2	0.023 (0.05)

Standard errors in parentheses. Adjusted to allow for each province to have a distinct AR(1) process.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 5: Breakpoint Test B – Trend Break Regression Output (Equation 2)

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
	NL	NS	NB	ON	MB	SK	AB	BC
β_3	0.012 (0.02)	-0.014 (0.01)	-0.034 (0.02)	-0.009 (0.00)	-0.013 (0.01)	0.014 (0.01)	0.011 (0.01)	0.007 (0.01)

Standard errors in parentheses. Adjusted for an AR(1) process.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 6: Formulary Restriction Difference-in-Differences Regression Output (Equation 3)

	(1) Log(Hosp)
β_2	-0.003 (0.07)

Standard errors in parentheses. Adjusted to allow for each province to have a distinct AR(1) process.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 7: Formulary Restriction Difference-in-Differences Sensitivity Analysis Regression Output (Equation 3-6)

	(3)	(4)	(5)	(6)
	Log(Hosp)	Log(Hosp)	Log(Hosp)	Log(Hosp)
β_2	-0.003 (0.07)	0.012 (0.06)	-0.003 (0.06)	0.011 (0.05)

Standard errors in parentheses. Adjusted to allow for each province to have a distinct AR(1) process.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 8: Breakpoint Test: Ontario Mortality by Drug Regression Output (Equation 7)

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
	Oxycodone	Codeine	Fentanyl	Heroin	Hydrocodone	Hydromorphone	Methadone	Morphine
β_3	-0.036 (0.04)	-0.020 (0.01)	0.062* (0.03)	0.008 (0.01)	-0.014*** (0.00)	0.050*** (0.01)	0.003 (0.03)	0.018*** (0.00)

Standard errors in parentheses. Adjusted for an AR(1) process.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$