PUBLIC POLICY AND THE PRICE-ACCESSIBILITY OF PHARMACEUTICALS

THREE ESSAYS ON THE ETHICS AND EFFECTS OF PUBLIC POLICY ON THE PRICE-ACCESSIBILITY OF PHARMACEUTICALS

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Lay Abstract

The rising prices of some pharmaceuticals have made them inaccessible to patients and their families, who must make big financial sacrifices to afford the drugs they need. This thesis contains three studies on the impact of ethical pricing and public policy on the accessibility of pharmaceuticals. Its objectives are to develop definitions of fair pricing in terms of access, to analyze two public policies that sought to change the utilization of pharmaceuticals by changing the price people pay for them, and to elaborate on what these policies mean for the accessibility of these drugs. This thesis' contributions to the literature include novel theoretical models about pharmaceutical pricing and new evaluations of the effects, by sociodemographic category, of a policy designed to combat the ongoing opioids epidemic in Ontario, Canada, and the effects of OHIP plus on the emerging use of expensive oral-delivery cancer drugs in the same province.

Abstract

Pharmaceuticals have become, arguably, one of the fastest changing forms of health care. Advancements in pharmaceuticals are constantly bringing better treatments to illnesses previously untreatable. These advancements, however, come with a hefty price tag: In many countries they also represent the fastest growing source of health care expenditures. Innovative drugs often come to the market with high prices, and the prices of existing drugs can creep up if they are not reined in. These high prices can threaten patient access to the pharmaceuticals they need. Fortunately, there is a lot public policy can do, if it is designed to interact well with clinical, economic, and commercial factors, to safeguard this access.

This thesis contains three studies on the effects of public policy on the price-accessibility of pharmaceuticals. Its objectives are as follows: 1) To develop the definitions of a fair pricing of pharmaceuticals in terms of price-accessibility, 2) to present two case studies where public policy changes pharmaceutical prices and affects their utilization, and 3) discuss the significance of these case study policies on access to these drugs.

This thesis contributes to the existing body of literature by developing new theoretical models about what constitutes fair pricing of pharmaceuticals and about the relationships between the main parties responsible for making pharmaceuticals accessible to the people who need them. A new evaluation of the policy that delisted high-strength opioids from public formularies in Ontario is also presented with new regression models that allow the analysis of the ef-

fects of the policy across sociodemographic categories. Finally, this thesis also contains the first empirical analysis of OHIP plus, the policy that extended the public drug benefits to all individuals under 25 years of age; in this case, with the focus on oral chemotherapy drugs for cancer.

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I also want to thank my dad, my mom, and my sister. I love you. Thanks for being my original support network. We have been together through everything.

Dedicated to the loving memory of my mother

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List of all Abbreviations and Symbols

ABPI	Association of the British Pharmaceutical Industry
ASIR	Age-standardized incidence rates
CAD	Canadian dollars
CEO	Chief executive officer
CID	Corporation's Internal Decision (structure)
CMS	Centers for Medicare and Medicare Services (US)
DIN	Drug Identification Number (Canadian system)
DNA	Deoxyribonucleic acid
EAP	Exceptional Access Program
FDA	Food and Drug Administration
FSA	Forward Sortation Area
GBP	Pound sterling
HIV	Human immunodeficiency virus
IV	Intravenous
MME	Morphine milligram equivalent
MOHLTC	Ministry of Health and Long-Term Care (Ontario)
NHS	National Health Service
OAM	Oral anti-cancer medications
ODB	Ontario Drug Benefit
OECD	Organisation for Economic Co-operation and Development
OHIP-	'OHIP minus' (policy reference)
OHIP+	OHIP plus (policy)

OOP	Out-of-pocket (payment)
OPDP	Ontario Public Drug Programs
OUD	Opioid use disorders
Ped	'Pediatric' (patient category)
PMPRB	Patented Medicine Prices Review Board
QALY	Quality-adjusted life year
RD	Regression discontinuity
UK	United Kingdom
US	United States
USD	United States dollars
WHO	World Health Organization
YA	'Young adult' (patient category)

Chapter One: Introduction

This present chapter outlines the general theme and the objectives of this thesis. It also presents some overarching background on the subject, explains the rationale for this research, and the approaches taken in the three studies.

This thesis contains three studies on the effects of public policy on the price-accessibility of pharmaceuticals. Its objectives are as follows: 1) To develop the definitions of a fair pricing of pharmaceuticals based around the concept of accessibility; 2) to present two case studies where public policy changes pharmaceutical prices and affects their utilization; and 3) to discuss the significance of these case study policies on access to these drugs. The first objective is addressed in the first study, a theoretical ethics study, from now on referred to as the 'ethics study'. The second and third objectives are addressed in the two empirical studies, which follow.

The ethics study presents a critical analysis of ethical concepts around health care, access, and an overview of the facets of the pharmaceutical industry that can affect patient access. The second and third studies are empirical in nature, and are focused on case studies about the effects on utilization of two public formulary policies in the province of Ontario, Canada. The subject of the second study (from now on referred to as 'the opioids study') is the delisting of high-strength opioid products in January 2017. The third study (referred to as 'the cancer study') is focused on the extension of public formulary benefits to all people under the age of 25 (OHIP plus) in January 2018 and the ensuing redesign of the policy to retract these public benefits from people under 25

who have private prescription drug insurance, starting on April 2019 (Ontario Ministry of Health and Long-Term Care, 2019), which is informally referred to in this study as 'OHIP minus'.

Access to pharmaceuticals

Access is a complex and loaded term in healthcare. As Aday and Andersen (1974) point out, access has been "more of a political than an operational idea". It is often expressed as the implicit goal of health care policy, but it is seldom defined consistently at an operational level. Access has sometimes been equated to the sociodemographic characteristics of the people seeking health care or the availability of specific resources in a health care system. Other important factors are often ignored, such as the patients' willingness to seek health care (e.g. recognizing health problems, acknowledging the need for health care, confidence in the safety and effectiveness of health care). For practical purposes, access here is considered in terms of being able to obtain and use health care when it is needed (Aday & Andersen, 1974; Hurley, 2010).

In the pharmaceutical context, however, that patients who need pharmaceuticals can make use of them, might not paint a complete picture of access. Some patients might be paying prohibitively high prices relative to their income and wealth, for the drugs they need, so they do not have the same level of access as patients who pay nothing out-of-pocket (OOP) for the same medications. The concept of 'barriers to access' complements the notion of access as utilization according to need. The inability of an individual to recognize and accept their need for health care, their inclusion in the social structures that offer healthcare, the geographical distance to the closest health care provider, the requirement of getting a referral for a prescription drug from a physician, the

availability of said drugs, and their financial cost of a drug are examples of barriers to access (Gulliford et al., 2002).

The studies in this thesis are concerned with access at the level of utilization according to need and at the level of financial barriers to access, namely how much money patients and their families must pay to obtain the pharmaceuticals they are prescribed. The two empirical studies in this thesis measure utilization after changes in public formulary policy in Ontario. Higher utilization, however, is not equated automatically to better access. Some assumptions are made to discuss the changes in access based on utilization numbers, such as the putting aside of non-financial barriers to access. It is also assumed that different sources of payment for drugs always represent different degrees of financial barriers to patients: that the use of public subsidy for drug utilization presents a lower barrier than private insurance coverage, and that the latter does the same compared to paying for drugs completely out-of-pocket. Of course, this might not always be the case. Factors such as the amount of public subsidy, as well as private insurance co-payments play a role here. It might also be the case that because of indifference, convenience, or lack of knowledge, individuals might not always make use of a lowest-barrier source of payment available to them.

Other important factors not covered by the utilization numbers alone are also discussed in these studies: First, there is a degree of substitutability between drugs. Very often, there is more than one category of drugs that can fulfill specific health care needs. Second, that this substitutability gives place to drug preferences among patients and prescribing health care providers, who usually prefer the most effective and safest options.

The studies in this thesis make use of the concept of accessibility to explain what constitutes a fair pricing of pharmaceuticals. The case studies elaborate on what the changes in utilization produced by public policy can tell us about the financial accessibility of pharmaceuticals after changes in the prices people pay for drugs were implemented.

Pricing of pharmaceuticals in the Canadian context

Canada is in a peculiar position compared to the rest of the world when it comes to pharmaceutical pricing. By many measures, Canada pays among the highest prices for pharmaceuticals in comparison to other high-income countries (Lexchin, 2015). Among these countries, it is the only one whose universal health care system does not cover prescription drugs, except for those dispensed as part of hospital services (Morgan & Boothe, 2016). In Canada, territorial and provincial governments are responsible for paying for all the prescriptions drugs dispensed at health care centres. For outpatient prescriptions, however, each government can decide independently what prescription drugs to cover, how much, and for whom.

In Ontario, the largest public formulary is the Ontario Drug Benefit (ODB), although patients can apply on case-by-case basis for drugs outside of this formulary (Ontario Ministry of Health and Long-Term Care, 2020). Prior to January 2018, access to the ODB was given to individuals 65 years of age or older, enrolled in social assistance programs (e.g. Ontario Works, Ontario Disability Support Program), individuals in long-term care or receiving home and community care services, and households spending 4% or more of their after-tax income on prescription drugs (Government of Ontario, 2020). The two empirical studies in this chapter, however, are concerned with two public

formulary policies in Ontario. The subject of the opioids study is the delisting of high-strength opioid products in January 2017. The cancer study is focused on the extension of public formulary benefits to all people under 25 (OHIP plus) in January 2018. This policy was redesigned to retract these public benefits from people under 25 with private prescription drug insurance, starting on April 2019 (Ontario Ministry of Health and Long-Term Care, 2019). We have labeled this as 'OHIP minus'.

Rationale for this Research

The ethics study was born from an idea my supervisor, Dr. Christopher J. Longo, had to write a paper addressing where the ethical responsibilities of pharmaceutical companies lie, i.e., with the public or with the shareholders. I was inspired to take on this project, though I eventually took the project into a new direction when I began questioning what the basis was for the ethical notion of providing prescription drugs, or any form of health care, to those who cannot afford it. Was health care really 'a right' as many people say it is?

My life experiences exposed me to different perspectives on this issue. I have spent most of my life in three countries, where I was exposed to different perspectives about the ethical responsibility to answer this question. I grew up in Bolivia, a country without a universal health care system. Although the notion of health care as a right does not exist there, there are certainly calls for charitable contributions to pay for the treatment of low-income individuals. I also lived in the United States for ten years, where the expression 'right to health care' is politically loaded and polarizing. In Canada, however, there is legislation, the Canada Health Act, that uses ethical grounds to lay the foundations of a public universal health insurance system. My thesis chapter,

however, is based on a review of the ethics literature, not on political speech or legislation.

My initial attempts at finding the ethical basis for the provision of health care took me to discover the works of Daniels (1985) and Rawls (2005). That is when we recruited the help of Dr. Lisa Schwartz to become a member of my thesis committee. We determined that the best way to contribute to the body of literature with my thesis was to combine health care ethics with business ethics and keep the focus on the pharmaceutical pricing context. During a meeting with my supervisor the idea of the framework for an ethical pricing of pharmaceuticals, which combined health care ethics, business ethics, and health economic evaluations, was developed as the final product of my theoretical analysis. The organization of the ethics study, its overview of pharmaceutical pricing topics, and its development of the idea of accessibility in pricing served well in achieving the first objective of this thesis.

The two empirical studies in my thesis are the product of a growing interest of mine in the demand for pharmaceuticals and the role that their price plays. During the first year of my PhD I found several papers that analyzed the effects of natural experiments, such as delistings and changes in co-payments in public formularies, on the demand for prescription drugs. Effectively, delisting a drug from public formularies means that the people taking that drug will have to pay more, whether that is by private insurance co-payments or by paying the full price OOP. To the patients, their families, and prescribing health care providers, it constitutes a change in price, an increase, and a decrease in accessibility. One of these papers was particularly relevant as it analyzed a policy in the Canadian context, specifically Quebec, after the province changed

co-insurance provisions (Contoyannis, Hurley, Grootendorst, Jeon, & Tamblyn, 2005). At this time, we recruited the help of Dr. Paul Contoyannis, the main author of said paper, to become a member of my thesis committee.

We thought it would be interesting to look at the effects of price on the demand for life-saving drugs and for drugs that were not deemed life-saving but could greatly improve the quality of life of ill patients. Some examples my supervisor Dr. Longo, my friend James Spencer, and I thought of for the first group were antineoplastic (anti-cancer) drugs and anti-cholesterol drugs. The demand for antineoplastics could be expected to be less affected by price than anti-cholesterol drugs (i.e., a more inelastic demand), on the grounds that cancer treatment would commonly be perceived as more urgent, compared to cholesterol treatment. We also expected the demand for the life-saving drugs to change relatively little compared to the non-essential quality-of-life drugs and have a more inelastic demand. From a policy perspective, delisting drugs of inelastic demand could cause many patients to start paying OOP for the delisted drugs, bringing plenty of economic harm. On the other hand, drugs with a more elastic demand (i.e. those whose demand is less affected by price) could conceivably be delisted without the same economic repercussions. When it came to examples of non-essential, quality-of-life drugs, we identified opioids, antiemetics (commonly used to reduce nausea and vomiting among cancer chemotherapy patients), and antidepressants. Opioids were highly relevant given the ongoing opioid abuse epidemic in North America. The potential for addiction of these drugs added a layer of complexity to the effects of price on the demand for pharmaceuticals.

My supervisor, my friend James, and I worked with IQVIA on the specifica-

tions for the pharmaceutical sales data sets that were used on the empirical studies. Because of limitations in the data sets, certain research directions could not be explored, including those that required patient-level data and the empirical estimation of elasticities of demand. However, we were able to obtain data for all the drug categories requested. Serendipitously, I discovered that the ODB delisted high-strength opioids, and that it had happened during the period covered by our data set. James pointed out his interest in observing the effects of OHIP plus, and my supervisor has had a long history working in the cancer space. Measuring utilization of opioids and cancer drugs before and after the ODB delisting and OHIP plus tied very well with the theme of access in the ethics study. This is how the two empirical studies were conceptualized.

The opioids and the cancer study both constitute case studies of public formulary changes that target the price that is paid by patients and their families for specific drugs. In the opioids study, the policy seeks to decrease access to potentially harmful drugs (high-strength opioids) without restricting access to necessary pain management drugs. In the cancer study, OHIP plus seeks to facilitate access to oral cancer chemotherapy drugs through public drug subsidy for patients under 25. These case studies achieve the second objective of the thesis. Changes in utilization do not equate to changes in access, but the relevance of these price policies on patient access are discussed in each respective chapter, thereby achieving the third objective of the thesis.

Approaches

The ethics study investigates the following research question: 'When are pharmaceuticals priced fairly?'. It is a critical review of relevant literature on the areas of the ethics of health care provision, business ethics, and the pharmaceu-

tical industry. The first of these three areas is developed in a section concerned with the 'social perspective' of what constitutes a fair pricing of pharmaceuticals. This first section proposes an ethical objective centred on the idea of equality of access, which applied specifically to the pricing of pharmaceuticals, is focused on the concept of 'accessible pricing'.

The areas of business ethics and the pharmaceutical industry are reviewed in the second section, the 'business perspective' of fair pricing. The study applies the ethical concept of accessible pricing to the pharmaceutical pricing context. From this synthesis, the concept of 'justifiable pricing' is defined as the ethical objective for pharmaceutical companies in the pricing of their products.

The social and the business perspectives converge in an organizational framework, graphically represented by a two-by-two matrix illustrating four scenarios for the ethicality of drug prices. The review is complemented with a stakeholder model on the subject, pricing policy examples, and theory from health economics.

The approaches taken for the opioids and the cancer studies have many points in common. Both make use of the same data set provided by IQVIA, where pharmaceutical sales are used as proxy for utilization. The changes in utilization for specific groups of drugs and sectors of the public, before and after their policy subjects are characterized descriptively, and statistically. The latter analysis was made with regression discontinuity (RD) models, where the effect at the start of the policy is the treatment effect of interest, and change in utilization at the time of the start of the treatment is considered a product of the respective policies. The results of these statistical analyses are combined with qualitative knowledge of the policies to discuss their effect on the

accessibility of the drugs.

Conclusions

This thesis contains three studies on the effects of public policy on the accessibility of pharmaceuticals. The ethics study contains a literature review of topics in health care ethics, business ethics, and the pharmaceutical industry. It lays the foundations of what constitutes fair pricing of pharmaceuticals in terms of price-accessibility. The opioids and the cancer studies take two public formulary policies in Ontario as case studies. They analyze the changes produced by these policies on drug utilization through changes in the public formulary. For specific drugs and sectors of the population, this effectively changed the amount of money patients and their families need to pay to obtain prescription drugs. The observed changes in utilization are used to comment on the effect that these policies have had on the accessibility of drugs.

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Chapter Two: When Are Pharmaceuticals Priced Fairly?: A Framework for an Ethical Pricing of Pharmaceuticals

Preface

This thesis chapter is based on work authored by me, Dr. Lisa J. Schwartz, and my supervisor Dr. Christopher J. Longo; and first published online on March 30, 2020 in *Health Care Analysis* under the title 'When Are Pharmaceuticals Priced Fairly? An Alternative Risk-Sharing Model for Pharmaceutical Pricing'.

The published version of this work emphasizes more the development of a model for the relationship between the main stakeholders involved in the price setting and purchasing of pharmaceuticals (the pharmaceutical companies, third party payers, and the public). The thesis version of this work emphasizes more the literature review of health care ethics and business ethics. A copy of the published version of this work was adapted to conform with the formatting requirements for a thesis. It follows this preface and it is placed before the chapter developed for this thesis.

I am the main author of both, the published version and the thesis chapter. This work started as a research idea by my thesis supervisor, but it changed direction during development under my leadership of the project. The two-by-two matrix of the framework for the ethical pricing of pharmaceuticals was conceptualized jointly by my supervisor and myself as the convergence of a social and a business perspectives of the subject and the application of the cost-effectiveness plane used in economic evaluations. My supervisor and Dr. Schwartz contributed in the design of this research and the revision of the

manuscripts.

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When Are Pharmaceuticals Priced Fairly? An Alternative Risk-Sharing Model for Pharmaceutical Pricing (Published Version)

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Abstract

The most common solutions to the problem of high pharmaceutical prices have taken the form of regulations, price negotiations, or changes in drug coverage by insurers. These measures for the most part transfer the burden of drug expenditures between pharmaceutical companies and payers or between payers. The aim of this study is to propose an alternative model for the relationship between the main stakeholders (the pharmaceutical companies, third party payers, and the public) involved in the price setting and purchasing of pharmaceuticals, one that encourages a more cooperative approach. We draw from principles of ethics and health economics and apply them to the context of the pharmaceutical industry. The model prioritises two objectives, (1) to make drugs financially accessible to the patients who need them, and (2) to keep pharmaceutical companies viable and profitable. It is centered around the sharing of financial risk between the main stakeholders, which we describe as 'enlightened risk sharing'. After establishing the foundations of this model, we expand on the type of policies that can follow these principles with current day examples.

Introduction

Pharmaceuticals are a central aspect of health care. That is why there is a general public concern when patients cannot access the drugs they need due to their pricing. The concern is not limited to the expenses incurred by patients and their families, but also includes the financial burden faced by those governments that cover drug expenses for their citizens. In their defense, pharmaceutical companies argue that high prices are necessary to cover the costs of Research & Development (R&D) activities and of an increasingly demanding

regulatory environment. Since pharmaceutical companies, third-party payers (public and private insurers), and the public make efforts to bring prescription drugs to the patients that need them, we understand the current relationship between these stakeholders as one where each party looks for their own financial bottom line. Each one has different motivations and mechanisms to transfer to other parties the financial burden of paying for drugs and avoid assuming too much of that burden. With multiple sides of the argument in mind, we set out to outline a new model among the main stakeholders affected by pharmaceutical pricing, what ethical principles it should be founded on, and what types of policies can follow this model.

This study has three objectives: (1) to propose criteria for when pharmaceutical pricing can be called 'ethically priced'; (2) to outline the current relationship between the main stakeholders; and (3) to apply our findings in an alternative model. We call this model "Enlightened Risk Sharing" because it is based on enlightened capitalistic decisions from the part of the pharmaceutical companies to maximize profits by procuring a wide consumer base through broad access to their drugs, and on a cooperative model of financial risk sharing among the main stakeholders.

For the methodology of this study, we drew the basis of our model from theoretical concepts in equity, business ethics, and stakeholder theory, which were then applied on the current business practice around pharmaceutical commercialization and pricing. We performed a review from the literature in ethics, business, and policy to support the theory with applications and examples. This is, however, not a formal systematic literature review. While we do provide background information on the stakeholders, our focus is on the re-

lationship between them and not on the detailed description of the social or economic context in which each one operates. Our analysis is most applicable to developed economies with some degree of pharmaceutical pricing regulation.

Ultimately, we would like the principles of this model to guide policy and interactions between the stakeholders, and we present examples of modern policies that could help shift towards this cooperative model. We do not expect a radical departure from a capitalistic model in which the industry operates, nor do we postulate that pharmaceutical companies become arm's length agencies for governments. We believe that all the parties involved can benefit from this new approach as they share the financial risks of making pharmaceuticals accessible.

What Constitutes an Ethical Price for Pharmaceuticals?

The intent of this section is to establish the ethical principles under which our stakeholder model should be constructed. We opt for the principles of accessible pricing and justifiable pricing, coming from a social and a business perspective respectively. By accessible pricing, we mean that the price should be one that aims for allowing everyone who needs medications to be able to make use of them, regardless of who pays for them. By justifiable pricing, we mean that the prices should correspond with the value they represent and at the same time allow a pharmaceutical company to continue conducting business in a viable and profitable manner.

Accessible Pricing: The Social Perspective

For many ethicists, the literary foundations for the ethical responsibility to provide access to health care, begin with Rawls' (2005) theory of distributive

justice. Daniels (1985) uses principles of distributive justice, especially that of an "equality of opportunity" in life, to affirm society's moral responsibility to provide health care services. Different theories have been postulated about what form this responsibility takes, such as the idea of a "right to health" (International Health Conference, 2002), "equality in health" (Chang, 2002), "right to health care" (Denier, 2005) or right to a "decent minimum of health care" (Buchanan, 1984). Ultimately, the principle of "equal access to health care" (Daniels, 1985; Green, 1976), and in particular equal access according to need (Aday & Andersen, 1974), circumvents the major problems of unfeasibility and ethical arbitrariness of other ideas and has become the standard of distributional equity (fairness) in health economics (Hurley, 2000). Gulliford et al. (2002) present a comprehensive definition of "access to health care", pointing out that it can be limited by factors such as the availability of health care resources (e.g. level of resources, allocation, geographical distribution), effectiveness of care, personal barriers (recognizing the need for health care), organisational barriers (need for referrals, wait lists, procedural inefficiencies, etc.), and financial barriers. Our focus is on this last type of barrier.

We posit that every normative claim on health care can be extended to pharmaceuticals, as they are part of health care. Pharmaceuticals are the central part of the treatment to many conditions, often irreplaceable with other forms of health care. Pharmaceuticals, as portable products, can be easier to replicate, distribute, and administer than health care services (e.g. surgeries, psychological therapy), in many cases being less resource-intensive for a society (Neumann, Sandberg, Bell, Stone, & Chapman, 2000).

Arguably, then, the equal access to health care principle translates into ac-

cessible pricing, more specifically, on access to medications regardless of the individual's ability to pay. An ethical pricing of pharmaceuticals, therefore, is one that allows for this to be possible. Notice that at this point we are not specifying who is supposed to pay for these drugs. Even though the ethical requirement is that patients be able to get the drugs they need, it is not necessary that the drugs be priced at a level that every patient can pay for on their own. We are not requiring, either, that drugs be free of charge, nor even that everyone pay the same price for drugs. Rather, we assert that making the pricing of pharmaceuticals accessible to the people who need them is a societal responsibility, particularly for the main stakeholders involved, pharmaceutical companies, third-party payers, and the public. The specifics of who should pay for these drugs, and the role of pharmaceutical companies in making drugs accessible are addressed in the next sections.

The Business Perspective

There are many choices that pharmaceutical companies make with respect to their products that affect their accessibility, such as distribution and supply, but the one we are going to focus on is pricing. Pricing is an active choice (often a part of a broader marketing strategy), but it is constrained by regulatory and market forces. By this we mean that a pharmaceutical company is not completely free to choose the price of a product, as the price has to comply with regulations (present in most developed countries), conform to the market it targets, and priced in a way that can also keep the company viable and competitive. Despite these other forces in play, the pricing of a product remains an economic and ethical choice taken by pharmaceutical companies that affect patients, third-party payers, and shareholders.

People are willing to pay high prices for the drugs they need (if necessary) before forgoing a purchase. This is an economic phenomenon known as inelastic demand, and numerous empirical studies suggest that this might be in fact what happens with pharmaceuticals (Gemmill, Costa-Font, & McGuire, 2007; Yeung, Basu, Hansen, & Sullivan, 2018). In real world scenarios, patients often cannot be expected to pay for their medications on their own, so they will demand that third-party payers cover the drugs that are too expensive for them to pay. Because of the inelastic demand, pharmaceutical companies know that they can increase their prices with a relatively low impact on the volume of drugs they sell and increase their profits overall. These conditions can lead to unjustified price hikes and scenarios some authors would call exploitation. Sandberg (2013) writes: "It may be thought that the worst kind of exploitation by vendors is their raising of prices whilst knowing that some people will be unable to bargain because they simply need the goods to survive". Under this reasoning, people who need life-saving medications will, presumably, pay any price to preserve their lives. A company with an active patent for a life-saving medication has great freedom to increase its price or to introduce it in the market at an exceedingly high price to generate great profit; all while a free-market system justifies the company's right to increase prices. But, are pharmaceutical companies morally responsible for pricing their products in a way that makes them accessible?

The business ethics literature is divided about the moral responsibility of private companies to provide or facilitate access to health care, and pharmaceuticals are no exception. Huebner (2014) argues that pharmaceutical companies are established with a profit-driven role that should not be confused with a

"special obligation of beneficence". Similarly, Friedman (1970) asserted that "the social responsibility of business is to increase profit" and not that of advancing other social goals, based on the ethically binding relationship of agency between the owners of a corporation, who typically seek profit maximization, and the decision makers (managers) who they trust with the resources of the company.

Contrary to these ideas, French (1979), affirms that corporations are "full-fledged moral persons" and "members of the moral community" with the same moral "privileges, rights, and duties" as biological moral persons. He argues that the moral personhood of the corporation originates in its internal decision structure, which makes it separate from that of the owners or managers. Thus, we could argue that being constituted as a profit-seeking enterprise, does not clear a pharmaceutical company from broader social ethical responsibilities.

Huebner (2014) also explains that there are other forms of healthcare (say physician services) that can solve the needs for necessary healthcare; and that there are other payers (such as governments) that could also play a role in making medications accessible. While there are other forms of healthcare, most of these cannot fully substitute for a pharmaceutical intervention. Indeed, health professionals could hardly do their jobs without medications. We also acknowledge that there are other payers involved in the ethical provision of healthcare (e.g. private and public insurers), but rather than clearing pharmaceutical companies from any ethical responsibility in the pricing of their products, this means that no single party, including the pharmaceutical companies, should assume all the burden of making medications accessible, but neither should companies aim for unreasonable profits.

If we pre-emptively impose on the pharmaceutical companies alone the condition that any new drug to be developed must be priced in a way that it is accessible to everyone, the development of new drugs could be thwarted (Maitland, 2002). R&D typically costs over one billion dollars and over two billion when opportunity costs are included (DiMasi, Grabowski, & Hansen, 2016), and it must be paid for by revenue brought in by sales (the major, if not the only, source of revenue for most companies). Of course, not all the company activities generate value for the patients, but the cost of these other activities must also be covered by sales. This includes the sunk costs of R&D of products that failed to pass clinical trials at any stage, fines for recalled products and regulatory violations, and patent disputes (Grootendorst, Bouchard, & Hollis, 2012). Promotion is probably the activity whose costs gets the most criticism: Many pharmaceutical companies invest more in promotional activities than in R&D, depending on the jurisdiction, according to some estimates (Gagnon & Lexchin, 2008). While some authors consider this type of spending excessive (Maitland, 2002), others explain that promotion and innovation are complementary, since promotion increases profits (which are used to finance R&D) and makes innovation more profitable (Lakdawalla, 2018).

It is also not enough for a pharmaceutical company to break even and be profitable in order to stay viable, but it also must remain competitive with respect to other companies in its industry. The pharmaceutical industry has certain expected profit margins. Company profits are a major selling point when a company competes against other ones for capital, especially investor capital. The climate of acquisitions and disputes for patent portfolio makes the competition for capital particularly intense in the pharmaceutical industry.

A company that cannot produce profits at the industry standard level will have a difficult time attracting investors, and with them, the capital needed for R&D, expansions, and other capital-intensive activities.

Justifiable Pricing

If pharmaceutical companies are entitled to profits, but not in a way that might affect the price-accessibility of drugs to the patients who need them, then how much should the pharmaceutical companies charge for their products before engaging in unethical pricing? Marckmann and In der Schmitten (2017) argue that a price is justified "only insofar as it allows the pharmaceutical company to recoup its R&D investments, including the cost of drug development failures, plus a reasonable profit". Also, a drug's price should reflect its "true benefit and societal and personal costs" (H. M. Kantarjian, Fojo, Mathisen, & Zwelling, 2013; Marckmann & In der Schmitten, 2017). Drugs can have different degrees of true benefit: Pharmaceutical companies sometimes present only marginal improvements over already existing products, such as sustained release, or slightly different formulation, meant to increase the effectiveness of the drug (Light & Lexchin, 2012), which hardly justify the price increases for the improvements. In other cases, there is a lot more merit from a social, scientific, clinical, and even commercial point of view when a breakthrough product (the first one in the market to treat a specific condition or one that is dramatically more effective than its competitors) is developed. By "societal and personal costs", Kantarjian et al. (2013) refer to how much a given society is capable and willing to pay to improve the life of a patient, in particular when many other healthcare needs must be fulfilled with limited resources. This indicates that the ethicality of the price of a drug also depends on the societal

context in which it is sold.

Bridging Social and Business Perspectives

By the interaction of accessibility and justifiability factors, the ethicality of the pricing of some pharmaceutical products can be categorized in one of the following quadrants, according to the framework in table 1.

Quadrant One: Accessible but Unjustifiable Pricing

Here fall products that are priced at a level where they can be relatively accessible to the people who need them, but whose pricing is too high given either their therapeutic value and/or the costs and efforts undergone by the companies that produce and commercialize these products. Arguably, examples of this category are some new generation of antipsychotics drugs (atypical antipsychotics) and newer oral hypoglycemics that usually are substantially more expensive compared to other available products, and for the most part show some increased effectiveness only in the more severe cases (Coyle, Palmer, & Tam, 2002; Percudani & Barbui, 2003; Stargardt et al., 2012; Tilden, Mariz, O'Bryan-Tear, Bottomley, & Diamantopoulos, 2007). Even if some of these drugs seem accessibly priced at first, their long-term funding could result in considerable financial burden for the payer. Governments might be able to fund these drugs, but an increase in their use or an increase in the expenditure in other drugs could compromise the sustainability of healthcare budgets.

Quadrant Two: Accessible and Justifiable Pricing

In this quadrant are found products sold at a price that is affordable and justifiable. Many generic drugs can be included in this area, as their loss of market exclusivity and competition between manufacturers bring down the

prices of such drugs. Several suppliers vie for market share, and they typically compete on price. From the perspective of access and justifications, these are cases of overall 'ethical' pricing. A drug going off-patent, however, is not a guarantee that its price will become more accessible. Some jurisdictions have policies that fail to curb generics prices as effectively as others (Law, 2013). Shortages (in some jurisdictions) and consolidation of generic manufacturers through acquisitions can also prevent the price of generics from going down (Alpern, Stauffer, & Kesselheim, 2014). There could be a few examples of branded drugs in this quadrant, but they are much less common.

Quadrant Three: Justifiable but Inaccessible Pricing

The drugs in this quadrant usually have a risky and costly development process or commercialization, or a small market. They also have a high therapeutic improvement over other competitors, which makes them valuable. In this case, companies can justify prices that allow them to cover such costs and that reflect the value of the product, even when their pricing might be relatively inaccessible; meaning that payers must incur great costs to supply them to the people who need them. Orphan drugs, for instance, target rare illnesses affecting < 1 in 2,000 people, most of them genetic in nature (McMillan & Campbell, 2017), although their definition might be different depending on the jurisdiction (Tambuyzer, 2010), and they typically have very high prices. For instance, Soliris, a drug that treats a rare blood condition, for example, can cost more than CAD 500,000 a year per patient (Fellows, Dutton, & Hollis, 2018). These drugs typically do not pass any of the common cost-effectiveness standards, and the decision of insurers to cover them usually depends on the effectiveness of the pressure exerted on them by patient advocacy groups and

manufacturers (Fellows et al., 2018; Handfield & Feldstein, 2013). In a similar way as quadrant one, the ethicality of these prices should be analyzed in a case by case basis, along with the possibility of sustainability of the funding for these products.

Quadrant Four: Unjustifiable and Inaccessible Pricing

In this quadrant are products with marginal therapeutic improvements that, nevertheless, demand considerably higher prices. In this category are also all the cases of unconscionable price hiking, when prices of a product are increased for no improvements in a product. From the accessibility and justification perspectives, these count as unethical pricing. A high-profile example of this happened when Mylan N.V. gradually hiked the price of EpiPen, their epinephrine autoinjector from $100 in 2009 to $600 in 2016 in the United States for a pack of two autoinjectors, the required dose for some patients (Lyon, 2016; Ramsey & Kiersz, 2016; Song, Brown, Karjalainen, Lehnigk, & Lieberman, 2018). The product did not present any added value, but Mylan increased its price capitalizing on two events, the enactment of the School Access to Emergency Epinephrine Act in 2013 in the US, which encouraged states to pass legislation requiring schools to maintain an emergency supply of epinephrine, and on Sanofi Pharma's voluntary recall of its own epinephrine autoinjector (Rubin, 2016).

The Relationships Between Stakeholders

In this section, we want to outline the relational dynamics between the main actors in the pricing and purchasing of pharmaceuticals and summarize them in a stakeholder model. We focus on the way each party assumes the burden of making pharmaceuticals financially accessible to patients (paying for them

or reducing their price) and how they can transfer their share of the burden to other parties, effectively putting pressure on them. In this analysis we want to highlight the contentious relationship among parties, where they seek to profit from pharmaceutical sales (in the case of companies) and to procure access to drugs without paying too much for them (in the case of the public and third-party payers). We later apply ethical objectives into these relationships to propose a new model of cooperation between the stakeholders.

For the sake of simplicity, we can consider that there are four parties that, we argue, should share the financial burden of making pharmaceuticals accessible: pharmaceutical companies, third-party payers (which includes governments, private insurers, and to a lesser extent charities), and the public. We include under the term 'public' patients, out-of-pocket (OOP) payers (whether this person is who ultimately consumes the medications or not), the physicians who make prescriptions in the best interest of patients, and patient advocacy groups. One additional stakeholder in this relationship are the stockholders (shareholders) of pharmaceutical companies (almost in their totality for-profit enterprises). Stockholders' demand for profitability and returns on their investments drives many of the decisions made by the upper management of the companies. Stockholders, however, do not directly make the pricing decisions. Their relationship with pharmaceutical companies are one-sided, and are for the most part shielded from direct interaction with the other stakeholders.

The motivation of pharmaceutical companies is to maximize profits and attract investment. More capital means growth and a greater chance of viability. Third-party payers want to improve financial access to drugs to the public. Of course, both public and private insurers have the incentive to fulfill the

public's demand at the lowest possible cost (operational efficiency). Finally, the public wants patients to have access to the drugs they need. They, too, want to pay as little as possible out-of-pocket and rely on third-party payers to cover most of the drug costs.

Because of inelastic demand, drug companies find that high drug prices will in many cases increase profits. They can justify these prices by bringing up the high costs of R&D and highlight their efforts in bringing innovative drugs to the market for the benefit of patients. Drugs can be priced out of the reach of the public as third-party payers, will be expected to pay for them. Governments will face political pressure from the public faced by governments to make drugs affordable, and then pharmaceutical companies can transfer the moral (and financial) responsibility of paying for drugs to the governments, all while feeling no pressure to lower their prices. But governments have other responsibilities that need funding that can be deemed equally as necessary as healthcare (defense, education, law enforcement, infrastructure, etc.). They can protect themselves and the public by regulating prices. Companies that do not abide by these prices will lose access to all the consumers in an insurance pool. Public and private insurers can also reduce their expenditures by terminating the coverage of drugs they find 'unaffordable' (delisting). In turn, a pharmaceutical company can push back by pulling individual products out of a market or withdraw from the market altogether if it finds the commercial and regulatory environment unfavourable or even unviable (an outcome the public and the insurers might find unfavourable). After all, the stockholders demand profits that are competitive with those from other companies in the industry.

The public also retains some power to reign in high drug prices by means of reducing their demand or seeking less expensive alternatives, as long as doing so will not make the sick sicker or increase the risk of death. They can also exert pressure on the governments (and private insurers) to pay for drugs or to keep high drug prices in check. Insurers can exact higher taxes, premiums, or copayments from the public to pay for drugs. These relationships are illustrated in Figure 2.

Besides the existence of these 'push back' mechanisms, there is another set of factors that prevents each party from transferring the financial burden to other parties. The consequences of a single party bearing too much of the cost are undesirable, and it could be considered a 'lose-lose scenario'. If patients are left on their own to pay for drugs, many will not have access to them, resulting in prolonged illness and possibly death. If governments are left to do all the effort, they might be unable to fund other important roles within healthcare or even outside of healthcare. If pharmaceutical companies are forced to curb their prices, cutting profits, just so that everyone can afford drugs, the development of new drugs might decrease significantly, although authors disagree on the magnitude of this effect (H. Kantarjian & Rajkumar, 2015; Vernon, 2005). In some cases, specific companies choose to withdraw specific products from the market when price regulation make them unprofitable, affecting patients' access to these drugs (Lyndon, 2003) or, in extreme cases, go out of business.

A similar analysis can be made centered around the concept of financial risk because it is in the uncertainty in paying for drugs and in securing a company's profitability that the problem of making drugs accessible starts. On the business side, companies incur great risks from the cost of R&D and the

other activities they engage in, plus the expectation of profitability from their shareholders. On the social side, illness and injury are unpredictable events (Hurley, 2010, p. 232)over which individuals have very little control. If individuals knew when they were going to get sick, they could budget for pharmaceutical (and other health care) costs in anticipation. Individuals run the risk of financial hardship if they have to pay out-of-pocket for medications for an unexpected sickness event. They might have to choose between paying for medications or for other necessary life expenditures (food, education, retirement, etc.). Because many drugs are priced too high for individuals to be expected to afford them is when governments and other insurers come in as third-party payers. In fact, the pooling of individuals' risks associated with health care expenditures is at the heart of the concept of health insurance (Hurley, 2010, p. 233). These insurers, however, run the risk themselves of paying more for drugs than they have budgeted for. While funding and the burden to pay are easier concepts to grasp and map than financial risk, we consider that the latter reflects the uncertainty that is ubiquitous in illness and health care spending. Finally, pharmaceutical companies run the risk of losing millions with failed R&D ventures, loss of patents (by legal challenge or expiration) (Grootendorst et al., 2012), product recalls, or pharmaceutical lawsuit damages and settlements. The overlying importance of financial risk is the reason we have decided to name our model around this concept. Deficits (and in some cases bankruptcies) are looming threats for each one of the main shareholders.

The Difficulty in Achieving an "Enlightened Capitalism"

It might seem strange that pharmaceutical companies do not initially choose to maximize their profits by pricing their products in an accessible way and

aiming to capture a large consumer base, while gaining the good will of society along the way. There are indeed economic models in the literature that suggest that decreases in price can result in an increase in profits under several scenarios (Longo, 2010). Companies could estimate a justifiable price level and work together with payers to ensure that very few who need for pharmaceuticals are priced out of the market. They might even benefit from making their drugs available to the largest number of people who need them. Instead of seeking this 'enlightened' capitalistic scenario, companies tend to opt first for higher prices to maximize their profits. In the case of drugs for rare diseases, low pricing is not even viable because of high R&D costs and small markets.

Companies can be highly strategic about their pricing, mostly with profitability rather than accessibility in mind. A penetration strategy, for instance, consists of introducing a product at a competitive or discounted price, compared to its competitors, with the hope of raising the price once market share is established (Lu & Comanor, 1998). When prices are increased that reliance (or dependence in some cases) to the drugs translate into higher profits. This is comparable to some sales strategies where companies offer free samples to doctors so patients can see the benefits of new drugs, which has been reported to be effective at influencing physicians' prescribing behaviour (Murshid & Mohaidin, 2017), but after a short period of free treatment, patients (or their insurers) must pay the full price to continue the treatment. Having to pay full price for a drug that patients have started relying on when it was priced for free can then lead to patient advocacy groups pressuring insurers to cover these new drugs. In skimming practice, a pricing strategy more common for drugs that offer significant advantages over its competitors, prices start high and are lowered

over time (Lu & Comanor, 1998). The high initial prices aim to capture the segment of the market willing to pay higher prices for a drug, recouping the costs of development more easily this way, and then lowering prices to capture other market segments, in a similar way of how most patented drugs are marketed first in the United States (more willing to pay high prices and with no price regulations), then expand to other high-income countries, and eventually reach lower income countries at a very low price (less ability to pay).

Glabau (2017) offers another explanation of why companies seem not to opt for accessible pricing aiming for a larger consumer base. She argues that pharmaceutical companies are treated as investments by their shareholders, who expect that the value of their investments will increase over time. In her view, prices communicate the success of a company and its profitability, and the financial market operates under these assumptions. She argues that the pricing of pharmaceuticals has lost much of its "underlying medical, technical, or social value" and become increasingly responsive to the expectations of the financial industry. She blames this shift on the "shareholder revolution", a change where larger stakes of ownership of a company are passing to external shareholders, such as banks and other financial institutions, solely concerned with investing capital (Glabau, 2017) where they might see the greatest returns, and wholly removed from the activities of a company. Then, she argues, these shareholders "exert pressure on actors within companies to reorganize their activities to prioritize raising share prices above all else" (Glabau, 2017). Finally, Friedman (1970) writes that it is immoral for a manager to pursue a public agenda, as the manager is appointed by shareholders to generate profit

for them, while the public elects officials to pursue the common good. By his own words, if business can automatically (and morally) be expected to maximize profit and only governments can be expected to look after the public, this can be interpreted as an invitation for adversarial regulation, which can result in an undesirable scenario for both parties. With this we move toward a potential solution to this dilemma in the alternate form of enlightened risk sharing.

Current Pricing and Regulator Strategies Regarding Price Versus Enlightened Risk Sharing

The solution, rather than coming from an 'enlightened capitalism', might come in the form of an 'enlightened risk sharing'. We propose that this adversarial relationship can be replaced for one of cooperation between companies, payers, and the public. This model prioritises two objectives, (1) to make drugs financially accessible to the patients who need them, and (2) to keep pharmaceutical companies viable and profitable. Secondarily, the model proposes that the cost of making pharmaceuticals accessible be distributed between the three parties, so that no single party is left facing a disproportionate share of the costs. The price of a drug should depend on the extent that a drug demonstrates a therapeutic value and a price that reflects reasonable social and personal costs. Whenever possible, making a drug accessible and securing a wide consumer base can reduce financial risk for a company, and this is facilitated through third-party payers' market access. Additional incentives can be given to pharmaceutical companies to continue innovating while reducing their financial risk.

To implement this model, a close coordination between governments and drug

makers can ensure that population needs are met, prices are kept in check, and companies make a reasonable profit. Profit controls, for instance, can be set in place where companies pay the government if their profits exceed a certain percentage over their costs and can only increase prices if their profits fall bellow a reasonable percentage. An example of this is the Pharmaceutical Price Regulation Scheme agreed upon by the Department of Health in the United Kingdom and the Association of the British Pharmaceutical Industry (ABPI) (Association of the British Pharmaceutical Industry, 2014). Similarly, pharmaceutical companies can refund governments when public expenditures on a certain drug have exceeded a budget agreed upon by both parties. This is what Adamski et al. (2010) categorizes as price-volume risks-sharing agreements. Governments and pharmaceutical companies can also agree on the introduction of a drug at a discount to give it a wide access and "enhance the value of a drug", later increasing the probability that that government decides to cover that drug in public plans (patient access schemes), as well as plans where companies refund governments when their products fail to reach the desired therapeutic outcomes (performance based/outcome-based models) (Adamski et al., 2010).

Our model also calls for the application of proposed initiatives where governments, non-profit research institutions, and pharmaceutical industry consortia share the cost of the basic research that identifies and validates potential drugs for human use. The findings of this research would hypothetically be placed in the public domain, advancing scientific knowledge and making R&D efforts more efficient by avoiding duplication of effort and the legal fights over patent rights (Grootendorst, Hollis, Levine, Pogge, & Edwards, 2011). Such reform

could expedite drug discovery, keep the high reward for the development of breakthrough drugs, but reduce the risk (and lower the entry barriers) of R&D.

The financial risk of R&D faced by brand drug companies can be shared with the other parties of generic drug makers pay "royalties" for the sale of drugs to the companies that discovered and developed the drugs (Grootendorst et al., 2011) temporarily. While this approach could increase the price of generic drugs, it is likely to decrease the elevated price of patented drugs. It could also allow for a smooth (and possibly quicker) process by which drugs go off-patent, as it makes the time a new drug is on patent less critical for a brand company to cover its R&D costs.

Market access schemes can be used not only to reduce drug expenditures for third-party payers, but also to save companies money on promotion activities and commercial competition. The combination of drug companies bidding for access to an insurer's (be it private or public) market and royalties to drug innovators can make prices more accessible to the payers and to the public. Those companies awarded market access can spend less in product promotion, as their prescription would be more streamlined. While companies compete for manufacturing and commercialization efficiency, the companies that experience the greatest financial risk, brand companies, can continue recouping the cost of their R&D investment, even if generic versions of their drugs are the ones being sold. These companies could still get the incentive to achieve brand recognition and operational efficiency during their patent period to become the strongest bidder when their drugs become off-patent.

In this model, the three main parties would come to agree on pharmaceutical prices, budgets, and sale volumes that prioritize the two objectives. Companies

can lower their prices if they can count on having enough sales volume and if they can reduce some of their costs. Naturally, this works better with generic drugs than with patented drugs, and it is more difficult to apply for orphan drugs, which do not count with the markets to make them profitable. Just as with orphan drugs, however, regulatory and financial incentives can attract drug makers to these more difficult markets.

Conclusions

Pharmaceuticals are one of the fastest changing aspects of healthcare. With innovation, advancement, and increased demand prices have increased, and they currently are some of the main drivers of costs in heath care systems. Just as most governments and insurers have realized how critical it is to cover physician and hospital expenses for the public, ensuring patients have access to the drugs they need can save lives and relief pain. Paying to bring drugs to the patients, however can represent a big financial risk to governments, private insurers, and the public. Pharmaceutical companies are also exposed to big financial risk if they cannot cover their costs of operation, which includes R&D, with pharmaceutical sales. If the pressure to make prescription drugs available falls solely on them (through regulation, for instance), their viability and the important role they play is in peril. Consequences are equally dire if governments or the public are made solely responsible.

Even when companies could increase profits by making their drugs accessible to a wider consumer base, they face pressure (and incentives) on many fronts to increase drug prices. For this reason, rather than expecting an 'enlightened capitalism' to bring about greater access to pharmaceuticals, the solution might be in an 'enlightened risk sharing' as we have presented here.

As stated, this cooperative approach between companies, third-party payers, and the public has many positive aspects. In this arrangement, financial is risk is shared among these parties while prioritizing patients needs for drugs and ensure pharmaceutical companies remain viable and profitable. Incentives should be provided to pharmaceutical companies by which accessible pricing gives them access to a third-party payer's market.

When Are Pharmaceuticals Priced Fairly?: A Framework for an Ethical Pricing of Pharmaceuticals (Thesis Chapter)

Abstract

Public concern about high pharmaceutical prices has been well described in literature and media, but there is little consensus in the academic literature about what a fair drug pricing entails. Excessive pricing is undisputed for a handful of drugs, but little has been done to fully describe under which circumstances the pricing can be considered excessive. The matter is complicated even more when the perspective of pharmaceutical companies is factored into the discussion. To answer the question 'when are pharmaceuticals priced fairly?'; this chapter reviews the existing literature on ethical pricing from a social and a business perspective. The review is complemented with a stakeholder model in the subject, pricing policy examples, and theory from health economics. In doing so, this study proposes a conceptual two-by-two categorical framework outlining when pharmaceutical prices could arguably be considered 'fair' according to their accessibility and justifiability. In the conclusions, these concepts are applied in the proposal of a more collaborative approach on the relationship between pharmaceutical companies, third party payers, and the public.

Introduction

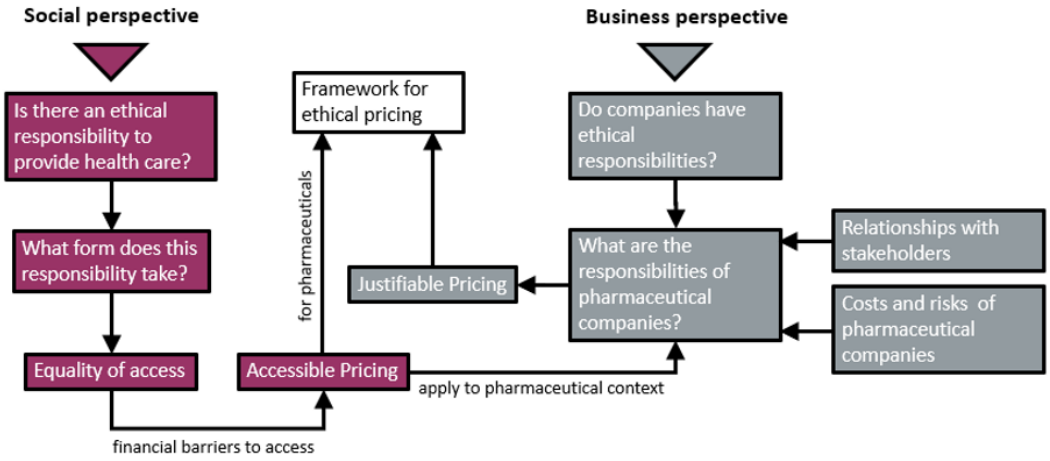
Pharmaceuticals are a central aspect of health care. For many conditions, drugs are either the central part of the treatment or an important complement to other forms of health care. There is, then, a general public concern when high drug prices mean that many people who need medications are unable to afford them. The concern is not only limited to the out-of-pocket payments

patients and their families must endure, but also includes the financial burden faced by those governments that cover drug expenses for their citizens. It is estimated that in Canada, 8.2% of patients using prescription drugs cannot fill their prescriptions due to costs, a situation more prevalent among women, young adults, indigenous peoples, people in poor health, low-income groups, and the uninsured. Also, that 4.73% of the population have to trade-off expenditures in other areas, from food and leisure to heat and housing to afford their medications (Law et al., 2018). Pharmaceutical companies argue that such high prices are necessary to cover the Research & Development (R&D) costs of innovative and better products. In fact, the World Health Organization (WHO) identified two main problems with pharmaceutical pricing: high prices that threaten the accessibility of drugs and low prices that lead to shortages. Even when low prices are not the only cause for drug shortages, "if prices are too low, production costs are not covered or potential return is insufficient, manufacturers may drop out of the market" (WHO, 2017a). The WHO also noted that the "different stakeholder groups have different priorities", but that there is a consensus around "the overall objective… that there should be effective care, accessible care and affordable care" (2017a), which includes essential medicines (2017b). With both sides of the argument in mind, this study sets out to find ethical grounds that could be used to assess when pharmaceuticals are priced fairly.

This study has three objectives: (1) to review the ethics literature and propose a cogent objective for the fulfillment of healthcare needs based on ethical grounds; (2) to identify the role that pharmaceutical companies must play in this ethical endeavour when it comes to pricing their products; and (3)

to apply our findings in a framework that can help governments, insurers, and pharmaceutical companies assess when pharmaceuticals are priced fairly. The first objective is addressed in the opening section of this study, which is called the 'Social Perspective' because the ethical goal proposed here is to be achieved by society in general, without assigning specific responsibilities. This study reviews the literature on the ethical responsibility to provide health care, as defined by various authors. An ethical objective is proposed, centred on the idea of equality of access, which, applied specifically to the pricing of pharmaceuticals, is focused on the concept of 'accessible pricing'. The second objective of this study is addressed in the subsequent section, which is identified as 'Business Perspective'. This section presents a review on the literature on business ethics. The situation of pharmaceutical companies with respect to their stakeholders, as it relates to the subject of pharmaceutical pricing is analyzed. Keeping in mind that pharmaceutical products are an integral part of health care, the study applies the ethical concept of accessible pricing to the pharmaceutical pricing context. From this synthesis, the concept of 'justifiable pricing' is defined as the ethical objective for pharmaceutical companies in the pricing of their products. The ethical objectives of accessible pricing and justifiable pricing are applied in the third section, 'A Framework for Ethical Pricing', thereby addressing the third and final objective of this study. The workflow of contents of this study is illustrated in Figure 1.

Figure 1: Diagrammatic representation of the workflow of the content and the argument



This study is applicable to capitalistic economies in high-income countries, which face higher pharmaceutical prices than low- and middle-income countries because they are targeted first by pharmaceutical companies to recoup the cost of their R&D investments. In these countries there are varying degrees of government involvement in the purchase of pharmaceuticals and price regulation; only privately-owned companies participate in the market and engage in R&D of new products and commercialization activities. Also, individuals and private insurers assume some share of the total pharmaceutical expenditures. There are varying degrees of competition between generic and brand products, but some products are unique in their effectiveness to treat certain conditions, becoming the only option for some patients. Patent regulations in these countries are well enforced, ensuring that market exclusivity is maintained for the full duration of the drug's patent.

This thesis chapter is based on work published by the author and two of the thesis committee members (Balderrama, Schwartz, & Longo, 2020), which is

attached to this thesis.

The Social Perspective: Accessible Pricing as an ethical objective

A big part of the debate about fair pricing of drugs is that people should not be priced out of the market for the care they need, nor be required to make excessive financial sacrifices just to afford their much needed treatments. But, can we make the ethical argument, that people should have the medication they need to save their lives or alleviate their suffering regardless of their ability to pay for them? If so, who should bear the cost of this ethical objective? The purpose of this section is to propose a definition of the pharmaceutical provisions to which individuals are entitled on ethical grounds. More specifically, the ethical concern is about the provision of pharmaceuticals to individuals who are unable to afford this care on their own. The analysis begins with a review of the moral responsibility around health care. After reviewing the relevant literature in ethics and health economics, the concept of 'equality of access' is put forward as the broader ethical objective in the provision of healthcare to be achieved by society in general. This analysis posits that every normative claim on health care can be extended to pharmaceuticals, as they are part of health care.

Many authors might be willing to recognize the ethical responsibility to provide health care, yet disagree on how this health care should be paid for. Even a staunch libertarian like Buchanan (1984) writes:

> There is a basic moral obligation […] to those in need. In a society that has the resources and technical knowledge to improve health or at last to ameliorate important health defects, the application of this requirement […] includes the provision of resources for at least certain forms of health care.

For many ethicists, the literary foundations for the ethical responsibility to provide access to health care, begin with Rawls' (2005) theory of distributive justice. The tenets of this theory hold that socioeconomic inequalities in things such as wealth and income are acceptable as long as all individuals receive a fair equality of opportunity in life to reach self-fulfillment (Rawls, 2005, p. 60-65). Having a good health status, regardless of how this standard is defined, is fundamental to this notion of fair opportunity, and access to health care is an important determinant of health. From a contractarian point of view (Rawls, 2005, p. 16) no socioeconomic system, can justify itself in front of the people who live in it if it denies to some people the minimum requirements that could make a fair chance in life while it favours other individuals. A system of such characteristics is likely to be the result of an imposition of the favoured groups of certain individuals over others. Daniels (1985) uses principles of distributive justice, especially that of an "equality of opportunity" in life, to affirm society's moral responsibility to provide health care services. Even though the ethical call to action to provide healthcare seems clear, it is more difficult to specify what must be done and who is responsible for it.

What form does this ethical responsibility to provide health care take?

Attempts at defining the extent of this ethical responsibility have produced several possible claims on healthcare entitlements. Definitions centered around health equality, such as the 'right to health' put forward in the WHO Constitution (International Health Conference, 2002), are sometimes criticized for its vagueness and operational unfeasibility. 'Equality' in health is another concept that can be defined in empirical terms without touching on the nor-

mative system of values in the provision of health care. 'Equity', on the other hand, is an ethical principle; a normative concept (Chang, 2002) focused on "the distribution of resources and other processes that drive a particular kind of [unfair, systematic] health inequality […] between more and less advantaged social groups" (Braveman & Gruskin, 2003). As Braveman and Gruskin (2003) explain, not all health-inequalities are unfair. For instance, it is hard to argue that certain natural health inequalities based on age and biological sex are unfair (e.g., younger people are typically healthier than the elderly and women do not have prostate problems). We can easily say that it is unfair, however, that gender, race, or income should define the likelihood that an individual will receive appropriate medical attention. Hence, 'equity' provides a more appropriate ethical, rather than empirical focus than 'equality' for the matter at hand.

Among equity-based definitions, the claim that health care is a 'right' is attractiveness because it implies that it is a "collective moral obligation on the part of society" and a stringent one at that (Denier, 2005). Many authors, however, stop short of making this statement due to the ethical implications of calling health care a right (Buchanan, 1984; Daniels, 1985, pp. 4-9; Denier, 2005). It is controversial to describe healthcare as a right as a moral obligation (Denier, 2005) or as an entitlement enforceable even by means of coercion by an authority such as the government (Buchanan, 1984). Even those authors sympathetic to the idea of the most inclusive claims to healthcare rights recognize that this provision cannot be boundless. Denier (2005) writes:

> … the right to healthcare cannot be an unlimited right. It cannot be a right of everyone to have access to whatever healthcare services would be of net benefit to the individual. Rationing of healthcare

has to be a fact of life.

There are technological, clinical, and economic limitations that would make it impossible to fulfill every healthcare need or demand. The problem with upholding a right to health care as an ethical responsibility for society is that "providing health care for all disease-related disabilities will become a bottomless pit able to swallow all available resources and more" (Moskop, 1983). Ethicists have also debated the idea of limiting this scope to a "decent minimum" of health care goods and services that society is ethically responsible for providing (Buchanan, 1984; Daniels, 1985, p. 74). The problem with this definition, however, is that the content of this package could change depending on the resources available to society, or to some scheme of priorities where some services or goods are considered more basic than others (Buchanan, 1984). As Fried (1976) writes, "In the end, I will concede very readily that the notion of minimum health care, which it does make sense for our society to recognize as a right, is itself an unstable and changing notion". There is still a need for a healthcare theory based on ethics (Buchanan, 1984). The reality is that ethics must, at one point, meet scarcity and policy.

The principle of "equal access to health care" (Daniels, 1985, p. 7; Green, 1976) circumvents the major unfeasibility problem of the right to health care and the ethical arbitrariness of the right to a decent minimum. It does not require an equal allocation or consumption of healthcare, equal health outcomes, or an indefinite provision of healthcare that satisfies every need. Equality of access just requires "that everyone in society is equally able to obtain or make use of health care" (Hurley, 2000), so that whatever healthcare services are available to some must be available to everyone. An equal access to health

care also addresses, from an operational perspective, Braveman and Gruskin's (2003) concern about an "equal opportunity to be healthy" and systematic associations between social disadvantages and disparities in health.

From an ethical perspective, equal access should be achieved by broadening access to services that previously only the privileged could afford. Conversely, equal access could also be fulfilled by removing from the pool of resources those that are available only to the most privileged (Daniels, 1985, p. 7). The ethicality of this seemingly harmful principle, which has been called "strong equal access" (Buchanan, 1984) is somewhat unresolved, and increases the appeal of a guaranteed access to a decent minimum of health care, while leaving additional health care services and goods beyond this level to still be available (Buchanan, 1984). The Canadian health care system, for instance, is odd among OECD countries, in that the government holds a monopoly of the health insurance market for physician and hospital services for the purpose of preserving an equal access and the quality of the public system (Flood & Haugan, 2010). It also offers a first-dollar coverage ("Canada Health Act," 1985) to both the rich and the poor. Additionally, this strong equal access results on the inability for the wealthy to purchase better amenities in health care than what anyone else could receive. Pharmaceuticals, however, are not included in this minimum package, except for those dispensed as part of standard hospital services ("Canada Health Act," 1985), another feature that makes the Canadian health care system uncommon when compared to others (Morgan & Boothe, 2016). Another theoretical implication of the strong equal access is that both rich and poor should pay the same for health care. While this principle is theoretically sound, in practice it works against the viability of

public health care systems. Even if individuals usually face the same health care prices, regardless of their income (except in the case of social assistance) and first-dollar coverage policies eliminate these prices altogether, the financing of government health care systems depends largely on taxation regimes where individuals contribute according to their ability to do so, i.e., higher income individuals pay more in taxes than lower income individuals. Unequal contributions could then be considered necessary to achieve an equal access for all.

Accessible Pricing

An equal access according to need, in particular, is the standard of distributional equity (fairness) in health economics (Hurley, 2010), health care research, and ethics, requiring that health care can be obtained and used when it is needed (Aday & Andersen, 1974). It circumvents the major problems of unfeasibility and ethical arbitrariness of other definitions. Gulliford et al. (2002) present a comprehensive definition of "access to health care", pointing out that it can be limited by factors, such as the availability of health care resources (e.g., level of resources, allocation, geographical distribution), effectiveness of care, personal barriers (recognizing the need for health care), organisational barriers (need for referrals, wait lists, procedural inefficiencies, etc.), and financial barriers. The focus of the social dimension of analysis of ethical pharmaceutical pricing lies on this last barrier, more specifically, on access to medications regardless of the individual's ability to pay. An ethical pricing of pharmaceuticals, then, is one that allows for this to be possible. Notice that at this point it is not specified who is responsible for paying for these drugs. Even though the ethical requirement is that patients be able to get the drugs they need,

it is not necessary that the drugs be priced at a level that every patient can pay for on their own. It is not required, either, that drugs be free of charge, nor even that everyone pay the same price for drugs. The specifics, from an ethical standpoint, of who should pay for these drugs, are addressed in the next sections.

The Business Perspective: Justified Pricing as an Ethical Responsibility of Pharmaceutical Companies

This current section is devoted to providing an ethical explanation of the role pharmaceutical companies can be expected to play, with respect to the pricing of their products, to achieve the ethical objective proposed in the previous section. This section argues that a pharmaceutical company has the right to a fair compensation for the efforts and costs incurred while bringing a product to the market. However, it also has the ethical responsibility to price products in a manner that, in collaboration with other stakeholders, can make drugs accessible to patients across all income categories, even if that means they make less profit than what they could otherwise make without this stipulation. The pricing must be conducive to achieving equal access without placing an undue financial burden on a single party; meaning that neither the government, nor private insurers, nor patients should be left to pay excessive prices to ensure access. Pharmaceutical companies should not be expected to forgo all profits to achieve this societal objective, either.

Companies make a plethora of choices with respect to their products that affect their accessibility, such as distribution and supply, but the focus of this study is pointedly on pricing. Pricing is an active choice (often a part of a broader marketing strategy), but it is constrained by regulatory and market forces.

This means that a pharmaceutical company is not completely free to choose the price of a product, as the price has to comply with regulations (present in most developed countries), conform to the market it targets, and priced in a way that can also keep the company viable and competitive. Despite these other forces in play, the pricing of a product remains an economic and ethical choice taken by pharmaceutical companies that affect patients, third-party payers, and shareholders.

What does it mean for a corporation to be ethical?

Before focusing on the ethical responsibilities specific to pharmaceutical companies, it is necessary to address whether companies can be held ethically responsible for their actions. Can we expect a company's responsibilities to be any different than those of the individuals who own or manage the company? With whom do these responsibilities lie? It is important to clarify that throughout this chapter, the word 'manager' refers to any individual granted some agency in decision making in a corporation, either by direct appointment by the owners (as would be the case of a Chief Executive Officer, for instance), or hiring by other managers according to a hierarchical chain. Also, the term shareholder refers to the owners.

Corporations are based on the delegation of agency from the owners of the corporation to the managers and employees for the administration of the assets and resources of the corporation. The managers and employees, in return, are expected to act in the best interest of the owners, who remain largely absent from most of the decision-making (White, 1993). This does not warrant the owners exoneration of any ethical responsibilities simply because they are not

the ones making the decisions; neither can managers, under the pretence that they are mere agents for the company owners, who rake in all the profits for themselves. It makes no sense to say that owners and managers should have no responsibility to play, other than that of the average individual, given how their decisions can affect so many patients. Establishing a corporation should not be a way for individuals to waive all ethical responsibilities by giving away any pricing decisions to market forces and a profit-maximizing motive, yet reap benefits from these activities. French (1979) argues that a Corporation's Internal Decision (CID) structure, the chain of command that assigns authority to one or more individuals to make decisions for the company and to approve the decisions before their execution, is where corporate intentionality resides. This is where the corporation's ethical persona diverges from that of the biological individuals that own and manage it. Decisions produced by the CID structure are then considered company policy and not just the decisions of single individuals (French, 1979). The shareholders can change company policy through the CID structure, and it is the same structure that bestows managers some control over company decisions with ethical weight.

Even if we can agree that a corporation is an ethical person, we have not resolved what the ethical responsibilities of the corporation are. Milton Friedman (1970) emphasizes the agency relationship between the owners and the managers as the ethical raison d'être of the corporation. A manager's only responsibility, according to him, is advancing the shareholders' interests, which typically means maximizing profits for them. Society has publicly elected officials to advance social goals, making it unethical for a privately appointed manager to pursue social goals when they conflict with the shareholder's in-

terests. Other than profits, the only responsibility of a corporation is to abide by "the rules of the game", namely "engaging in open and free competition without deception or fraud".

Leisinger (2005) proposes a tiered system of corporate social responsibility where abiding laws and regulations are at an essential (must do) level, roughly equivalent to Friedman's idea of a "fair game". Next, there is an enlightened self-interest level, an "ought to do" level where companies respond to the spirit of the law and not only to the letter of the law. Finally, there is a "can do" level of desirable corporate actions that are "neither required by law nor standard industry practice" (Leisinger, 2005). While this moves beyond the agent-principal focus of Friedman, Leisinger only provides a 'fuzzy' idea of what the ethical responsibility of a corporation is, somewhere between legal requirements and "nice to have" philanthropy.

Because of the ethical importance of equity in health care, this chapter postulates instead for a social ethical objective to be shared among all actors in society, including the pharmaceutical companies. The next section develops the idea that pharmaceutical companies have a special role to play because of their health orientation.

Business ethics in the pharmaceutical context

Largely, people are willing to pay high prices for the drugs they need (if necessary) before forgoing a purchase. This is an economic phenomenon known as inelastic demand, and numerous empirical studies suggest that this might be in fact what happens with pharmaceuticals (Gemmill, Costa-Font, & McGuire, 2007; Yeung, Basu, Hansen, & Sullivan, 2018). In real world scenarios, patients

often cannot be expected to pay for their medications on their own, so they will demand that third-party payers (insurers) cover the drugs that are too expensive for them to pay. Because of the inelastic demand, pharmaceutical companies know that they can increase their prices with a relatively low impact on the volume of drugs they sell and increase their overall profits. These conditions can lead to unjustified price hikes and scenarios some authors would call exploitation. Sandberg (2013) writes: "It may be thought that the worst kind of exploitation by vendors is their raising of prices whilst knowing that some people will be unable to bargain because they simply need the goods to survive". Under this reasoning, people who need life-saving medications will, presumably, pay any price to preserve their lives. A company with an active patent for a life-saving medication has great freedom to increase its price or to introduce it in the market at an exceedingly high price to generate great profit; all while a free-market system justifies the company's right to increase prices.

In all fairness, it must be acknowledged that pharmaceutical companies do not always seek the highest prices the market can bear. Companies lose profits when the prices are so high that they become unaffordable to many payers. They might seek the highest market price that does not preclude the purchase of their products. However, people may be willing to pay exorbitant prices for life-saving medications. Yet, healthcare services and products cannot be marketed like any other commodity. People's willingness to pay more for medications originates from their urgent need for them, and it is ethically wrong to increase profits indiscriminately by exploiting these needs. But the question remains, are pharmaceutical companies morally responsible for pricing their

products in a way that makes them accessible?

Companies play an ethically consequential role because the choices they make in the pricing of their products affects access to necessary medications. Huebner (2014) argues against these types of claims by pointing out that pharmaceutical companies are established with a profit-driven role that should not be confused with a "special obligation of beneficence". This is similar to Friedman's (1970) assertion that "the social responsibility of business is to increase profit" and not that of advancing other social goals. Contrary to these ideas, French (1979), affirms that corporations are "full-fledged moral persons" and "members of the moral community" with the same moral "privileges, rights, and duties" as biological moral persons. Therefore, being constituted as a profit seeking enterprise (rather than one with a public mission) does not clear a corporation from ethical responsibilities.

Huebner (2014) also explains that there are other forms of healthcare (for instance physician services) that can solve the needs for necessary healthcare; and that there are other payers (such as governments) that could also play a role in making medications accessible. While there are other forms of healthcare, most of these cannot fully substitute for a pharmaceutical intervention. Indeed, health professionals could hardly do their jobs without medications. It is true that there are other payers involved in the ethical provision of healthcare (e.g., private and public insurers). This does not mean that pharmaceutical companies are absolved from ethical responsibilities when it comes to the pricing of their products. It means that no single party, including the pharmaceutical companies, should assume all the burden of making medications accessible, but neither should companies aim for unreasonable profits.

The Costs and Risks Incurred by Pharmaceutical Companies

Pharmaceutical companies perform many types of activities, the cost of which must be covered by the revenue brought in by sales (the major if not the only source of revenue for most companies). For brand companies (unlike generic companies), research and development of a product typically costs over one billion dollars and over two billion when opportunity costs are included (DiMasi, Grabowski, & Hansen, 2016). Once the drug is developed and approved, however, the marginal cost of manufacturing per unit (e.g. a single pill) of a drug is often just pennies (Hill, Barber, & Gotham, 2018). Brand companies depend on the temporary market exclusivity granted by patent protection, which helps a company recover the cost of R&D, by allowing it to charge higher prices than they otherwise could in a competitive market. These companies are in a position to charge particularly high prices for products that are the only ones that can treat a specific condition or are exceptionally effective in doing so when compared to any other treatment (breakthrough drugs) while they are protected by patents.

Reducing the market benefits of patent protection could, however, thwart the development of new drugs (Maitland, 2002). The same might happen if we pre-emptively impose on the pharmaceutical companies alone, the condition that any new drug to be developed must be priced in a way that it is accessible to everyone. Companies might also perceive a "perverse" incentive of forgoing research "not because [it] might fail, but because it might succeed" (Fried, 1976). Governments provide other incentives to pharmaceutical companies besides patent protection. Hence, we need a system that provides incentives to pharmaceutical companies to develop new drugs, while also making drugs

affordable, by a combination of responsible pricing and a shared burden by all payers. Some governments indirectly help fund R&D efforts with publicly funded basic research and education (Maitland, 2002), and sometimes directly through public subsidy of clinical trials (Grootendorst, Hollis, Levine, Pogge, & Edwards, 2011). These incentives have the purpose of promoting drug discovery or a domestic R&D industry, and the use of public funding is usually not binding to price constraints to make drugs affordable (Maitland, 2002).

Companies cover R&D costs with price discrimination and subsidies to a great degree. Some countries bear the burden of paying for pharmaceutical R&D more than others and benefit from R&D differently. High-income countries face higher prices than low- and middle-income countries. In the US, for instance, the public faces the highest pharmaceutical prices in the world, and access to medications is often based on the ability of patients to pay. At the same time, more than half of all new drugs are developed in the United States, and this country has benefitted economically from having the most vibrant R&D industry in the world and from being the first one to have access to most of all the newly developed drugs (Maitland, 2002). It is precisely the lack of pricing regulation and the size of the market, that has made the US the most profitable market for drug companies and, therefore, their preferred location for R&D. By starting in the US market, they can recover their R&D costs the fastest. On the other hand, in countries like New Zealand, regulatory and market forces have kept prices in check for most drugs, making them widely accessible to patients. This has made any pharmaceutical R&D effort prohibitive in this country, but not the sales of drugs. Pharmaceutical companies tend to market their products at low prices in developing countries only after they have covered

the R&D costs with sales in more developed economies. This is not due to price regulation, but to the ability of the markets to pay for pharmaceuticals.

Of course, not all the company activities generate value for the patients, but the cost of these other activities must also be covered by sales. This includes the sunk costs of R&D for products that failed to pass clinical trials at any stage, fines for recalled products and regulatory violations. Generic companies only manufacture and commercialize drugs whose patents have already expired, and do not face the cost of R&D of their products, although they engage in costly legal disputes around patents (patent challenges, extensions, etc.) with brand companies (Grootendorst, Bouchard, & Hollis, 2012). Promotion is probably the activity where costs face most criticism: Many pharmaceutical companies invest more in promotional activities than in R&D, depending on the jurisdiction, according to some estimates (Gagnon & Lexchin, 2008). While some authors consider this type of spending excessive (Maitland, 2002), others explain that promotion and innovation are complementary, since promotion increases profits (which are used to finance R&D) and makes innovation more profitable (Lakdawalla, 2018).

It was estimated that in 2004 pharmaceutical companies in the US spent USD 57.5 billion on promotion, versus USD 31.5 billion on R&D, a 1.83 spending ratio (Gagnon & Lexchin, 2008); while in Canada companies spend more in R&D than in promotion: CAD 918,200 in R&D, versus CAD 697,000 in promotion, a 1.32 spending ratio in the opposite direction in 2016 (Lexchin, 2018). Some countries have taken measures to curb pharmaceutical promotion: Canada has restricted direct-to-consumer advertising (Gardner, Mintzes, & Ostry, 2003), and gifts made to physicians by pharma sales representatives. The ethicality of

such practices, however, is not the subject of our analysis. As Maitland (2002) points out, such practices are probably "wasteful and borderline corrupt", but the right solution to them is most likely to come from changes in the way the industry markets its products rather than on price restraint.

It is also not enough for a pharmaceutical company to break even and be profitable to stay viable, but it also must remain competitive with respect to other companies in its industry. The pharmaceutical industry has certain standards of profit margins. Company profits are a major selling point when a company competes against other ones for capital, especially investor capital. The climate of acquisitions and disputes for patent portfolios makes the competition for capital particularly intense in the pharmaceutical industry. A company that cannot produce profits at the industry standard level will have a difficult time attracting investors, and with them, the capital needed for R&D, expansions, and other capital-intensive activities.

Justifiable pricing

If pharmaceutical companies are entitled to profits, but not in a way that might affect the price-accessibility of drugs to the patients who need them, then how much should the pharmaceutical companies charge for their products before engaging in unethical pricing? Marckmann and In der Schmitten (2017) argue that a price is justified "only insofar as it allows the pharmaceutical company to recoup its R&D investments, including the cost of drug development failures, plus a reasonable profit". Also, a drug's price should reflect its "true benefit and societal and personal costs" (Kantarjian, Fojo, Mathisen, & Zwelling, 2013; Marckmann & In der Schmitten, 2017). Drugs can have different degrees of

true benefit: some present only marginal improvements over already existing products, such as sustained release, or slightly different formulation, meant to increase the effectiveness of the drug (Light & Lexchin, 2012), which hardly justifies the price increases for the improvements. In other cases, there is a lot more merit from a social, scientific, clinical, and even commercial point of view when a breakthrough product (the first one in the market to treat a specific condition or one that is dramatically more effective than its competitors) is developed. By "societal and personal costs", Kantarjian et al. (2013) refer to how much a given society is capable and willing to pay to improve the life of a patient, in particular when many other healthcare needs must be fulfilled with limited resources, implying that the ethicality of the price of a drug also depends on the societal context in which it is sold.

Some jurisdictions apply profit controls to curb pharmaceutical expenditures already and require that companies disclose financial indicators, such as their rate of return on capital invested and certain types of costs incurred (including R&D, marketing, information, and fixed costs). However, some companies tend to engage in "creative compliance", reporting finances in a way that complies with the letter rather than the spirit of the law (Bradley & Vandoros, 2012). Also, different quantitative economic evaluation methodologies have been developed that capture the benefits and costs of drugs (and other forms of treatments), at the levels of clinical performance, personal preferences, and at a societal level (Drummond, Sculpher, Claxton, Stoddart, & Torrance, 2005). Different jurisdictions have already applied therapeutic improvement in the economic evaluation of new pharmaceutical products. The Patented Medicine Prices Review Board (PMPRB) in Canada, for instance, categorizes

new drugs into one of four groups by these criteria: those that present "slight or no improvement", "moderate improvement", "substantial improvement", and "breakthrough" drugs (Patented Medicine Prices Review Board, 2017). This classification has weight in the recommendation the agency makes regarding product pricing to public insurers.

How the Financial Burden of Making Pharmaceuticals Accessible is Shared: A Stakeholder Model

As some of Huebner's (2014) claims suggest, an analysis of fair pricing cannot be complete without including the dynamics between the companies that decide the prices and the multiple parties in society that would also be assuming the responsibility of making pharmaceuticals accessible. These dynamics are complicated by some of the features of the pharmaceutical market like regulation, negotiation, and insurance. This section outlines these relational dynamics and summarizes them in a stakeholder model. We focus on the way each party assumes the burden of making pharmaceuticals financially accessible to patients (paying for them or reducing their price) and how they can transfer their share of the burden to other parties, effectively putting pressure on them. This analysis highlights the contentious relationship among parties, where they seek to profit from pharmaceutical sales (in the case of companies) and to procure access to drugs without paying too much for them (in the case of the public and third-party payers). The ethical, social, and business objectives are later applied into these relationships to propose a new model of cooperation between the stakeholders.

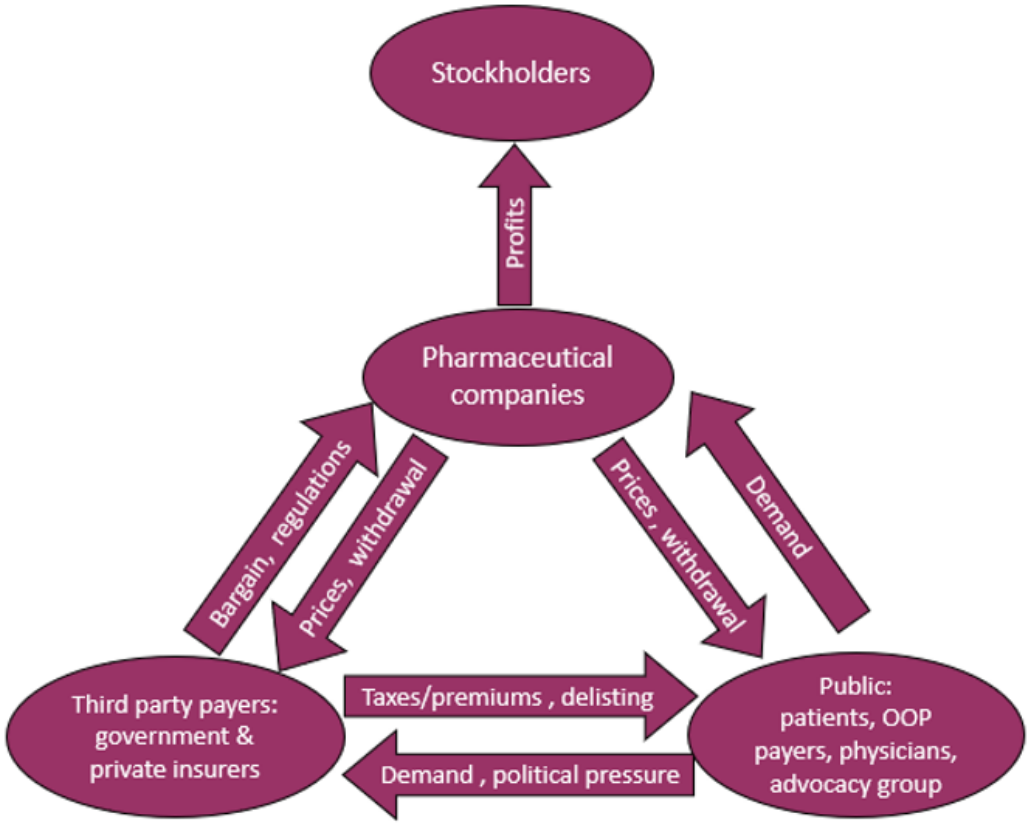
For the sake of simplicity, we can consider that there are four parties that should share the financial burden of making pharmaceuticals accessible: phar-

maceutical companies, third-party payers (which includes governments, private insurers, and to a lesser extent charities), and the public. Here, the term 'public' refers to patients, out-of-pocket (OOP) payers (whether this person is who ultimately consumes the medications or not), the physicians who administer prescriptions in the best interest of patients, and patient advocacy groups. One additional stakeholder in this relationship are the stockholders) (shareholders) of pharmaceutical companies (almost in their totality for-profit enterprises). Their demand for profitability and returns on their investments drives many of the decisions made by the upper management of the companies. Stockholders, however, do not directly make the pricing decisions. Their relationship with pharmaceutical companies is one-sided, and they are for the most part shielded from direct interaction with the other stakeholders.

Many drugs are priced so high that individuals in the public cannot be expected to pay for their treatments alone. Kalydeco, for instance, is a "breakthrough" drug, the first drug to treat the underlying causes of cystic fibrosis, but it is one of the most expensive drugs on the market (Rachul, Toews, & Caulfield, 2016), priced at CAD 400 a pill or about CAD 300,000 per patient per year (CBC News, 2013). This is where governments and other insurers come in as third-party payers. Among them, private insurers and charities are different from public payers (governments). Although they may also insure a great number of individuals and purchase large volumes of pharmaceuticals, they have greater freedom to stop paying for drugs they deem too costly. Also, they lack the regulatory power of governments, and, depending on the jurisdiction, they might have less bargaining power when it comes to negotiating prices with manufacturers.

Drug companies sometimes take advantage of the political pressure from the public, faced by governments, to make drugs affordable. They can highlight their efforts in bringing better and innovative drugs to the market for the benefit of patients and then transfer the moral responsibility of paying for drugs to the governments, all while feeling no pressure to lower their prices. But governments have other responsibilities that need funding that can be deemed equally as necessary as healthcare (defense, education, law enforcement, infrastructure, etc.). Governments can protect themselves and the public by making use of price regulations as a way of limiting a drug company's price-setting power. In turn, a pharmaceutical company can pull individual products off the market or leave a country altogether if it finds the commercial and regulatory environment unfavourable or even unviable. After all, the stockholders demand high returns for their investments in the form of profits. Nevertheless, the public, which includes consumers and physicians, retain some power to reign in high drug prices by means of reducing their demand or seeking less expensive alternatives, if doing so will not make the sick sicker or die. Patient advocacy groups can also exert pressure on the governments (and private insurers) to pay for drugs or to keep high drug prices in check. Private and public insurers can stop covering (delist) drugs if their expenditures are too high. They can also exact higher taxes, premiums, or copayments from the public to pay for drugs. These relationships are illustrated in Figure 2.

Figure 2: Interactions between payers and stakeholders



It is very unlikely that a single party could be made solely responsible for making pharmaceuticals accessible. Each one of them can exert pressure on the other parties. If too much financial burden falls on one party, it can relieve itself of some of that burden by exerting pressure on the other parties, through the mechanisms described above. Besides the existence of these 'push back' mechanisms, there is another set of factors that prevents each party from transferring the financial burden to other parties. The consequences of a single party bearing too much of the cost are undesirable. If patients are left on their own to pay for drugs, many will not have access to them. If governments are left to do all the effort, they might be unable to fund other important roles within

healthcare or even outside of healthcare. If pharmaceutical companies are forced to cut their profits so that everyone can afford drugs, the development of new drugs might decrease significantly, although authors disagree on the magnitude of this effect (H. Kantarjian & Rajkumar, 2015; Vernon, 2005). In some cases, specific companies choose to withdraw specific products from the market when price regulations make them unprofitable, affecting patients' access to these drugs (Lyndon, 2003) or, in extreme cases, go out of business.

A similar analysis can be made centered around the concept of financial risk because it is in the uncertainty in paying for drugs and in securing a company's profitability that the problem of making drugs accessible begins. From a business perspective, companies incur great risks from the cost of R&D and the other activities they engage in, plus the expectation of profitability from their shareholders. From a social context, illness and injury are unpredictable events (Hurley, 2010, p. 232) over which individuals have very little control. If individuals knew when they were going to get sick, they could budget for pharmaceutical costs (and/or other health care needs) in anticipation. In fact, the pooling of individuals' risks associated with health care expenditures is at the heart of the concept of health insurance (Hurley, 2010, p. 232). These insurers, however, run the risk themselves of paying more for drugs than they have budgeted for.

A Framework for an Ethical Pricing of Pharmaceuticals

With the interaction between stakeholders in mind, and with the accessibility and justifiability concepts in pricing, the following framework can help categorize the ethicality of the pricing of pharmaceutical products. When pharmaceuticals are priced in a way that the joint efforts on the part of pharmaceutical

companies and payers can ensure that patients can procure and make use of prescription drugs, this is accessible pricing. On the business side of the argument, justifiable pricing happens when the prices reflect the therapeutic value of the drug and the costs and risks undertaken by the pharmaceutical companies at the research, development, manufacturing, and commercialization of a drug. The interactions between these two concepts is at the root of the framework proposed here.

The framework illustrates some of the complexity of pricing decisions, by bringing together these two perspectives: The justifiability dimension in this framework addresses the interests of the pharmaceutical companies; while the affordability dimension, that of the stakeholders (patients, public, payers). Ultimately, neither interest (companies nor stakeholders) can be served on its own without the other. Accessibility can only be achieved in a sustainable way, by including the perspective of the pharmaceutical companies into our ethical analysis of pricing: their incurred risks, costs, and their need to remain competitive to achieve long-term viability. By the interaction of accessibility and justifiability factors, in this framework the ethicality of the pricing of a pharmaceutical product can fall into one of the following areas, described here as quadrants, and summarized in Table 1.

Table 1: Summary of the framework

		Justifiable Pricing	
		Justifiable	**Unjustifiable**
Accessible pricing	**Accessible**	**Q II** Accessible and sold at a moderate profit by the manufacturer Example: Generic drugs	**Q I** Affordable, but sold at an unreasonable profit by the manufacturer given the costs of developing and manufacturing Example: Atypical antipsychotics
	Non-accessible	**Q III** Risky and costly development, commercialization, small market, or application. Possibly high therapeutic improvement. Yet, the pricing is justifiable given these risks and benefits. Example: Orphan drugs	**Q IV** Unjustifiably high pricing for limited therapeutic improvement, given the development and/or low R&D risks. Unjustified price increases Example: EpiPen (US), many cancer drugs, hepatitis C drugs

Quadrant one: Accessible but unjustifiable pricing

Here fall products that are priced at a level where they can be relatively accessible to the people who need them, but whose pricing is too high, given their therapeutic value and/or the costs and efforts undergone by the companies that produce and commercialize these products. Arguably, examples in this category are some new generation of antipsychotics drugs (atypical antipsychotics) and oral hypoglycemics that usually are substantially more expensive

as other products available, and for the most part show some increased effectiveness only in the more severe cases (Coyle, Palmer, & Tam, 2002; Percudani & Barbui, 2003; Stargardt et al., 2012; Tilden, Mariz, O'Bryan-Tear, Bottomley, & Diamantopoulos, 2007). The overall ethicality of this pricing or the decision to fund these products should be assessed with other factors in mind, such as long-term sustainability. Even if some of these drugs seem accessibly priced at the beginning, their long-term funding could result in considerable financial burden. Similarly, governments might be able to fund these drugs, but an increase in their use or an increase in the expenditure in other drugs could compromise the sustainability of healthcare budgets.

Quadrant two: Accessible and justifiable pricing

In this quadrant are found products sold at a price that is affordable and justifiable. Many generic drugs can be included in this section, as their loss of market exclusivity and competition between manufacturers reduce their prices. From the perspective of access and justifications, these are cases of overall 'ethical' pricing. Due to the competitive nature of the generic market this will always be true since several suppliers are vying for market share, and they typically compete on price. A drug going off patent, however, does not guarantee that its price will become more accessible. Some jurisdictions have policies that fail to curb generics' prices as effectively as others (Law, 2013). Shortages (in some jurisdictions) and consolidation of generic manufacturers through acquisitions, can also prevent the price of generics from decreasing (Alpern, Stauffer, & Kesselheim, 2014). There could be a few examples of branded drugs in this quadrant, but they are much less common.

Quadrant three: Justifiable but inaccessible pricing

The drugs in this quadrant usually have a risky and costly development process or commercialization, or a small market. They also have a high therapeutic improvement over other competitors, which makes them valuable. In this case, companies can justify prices that allow them to cover such costs and that reflect the value of the product, even when their pricing might be relatively inaccessible; meaning that payers must incur great costs to supply them to the people who need them. Orphan drugs, for instance, target rare illnesses, affecting less than 1 in 2,000 people, most of them genetic in nature (McMillan & Campbell, 2017). Orphan drugs might be defined differently depending on the jurisdiction (Tambuyzer, 2010), and they typically have very high prices associated with them. Soliris, a drug that treats a rare blood condition, for example, can cost more than CAD 500,000 a year, per patient (Fellows, Dutton, & Hollis, 2018). Manufacturers justify these prices by arguing that R&D costs have to be covered by sales among few patients. This is a reasonable argument, but the prices leave public and private insurers flummoxed (Fellows et al., 2018), as these drugs typically do not pass any of the common cost-effectiveness standards, and the decision of insurers to cover them usually depends on the effectiveness of the pressure exerted on them by patient advocacy groups and manufacturers (Fellows et al., 2018; Handfield & Feldstein, 2013). The ethicality of these drugs' pricing is further complicated because governments already provide economic incentives to companies for the research and development of these drugs, such as those outlined in the US Orphan Drug Act in 1983 (Tambuyzer, 2010). Similar to quadrant one, the ethicality of these prices should be analyzed on a case-by-case basis, along with the possibility of sustainability

of the funding for these products.

Quadrant four: Unjustifiable and inaccessible pricing

In this quadrant are products with marginal therapeutic improvements that, nevertheless, demand considerably higher prices. Captured within this category are also all the cases of unconscionable price hiking, when prices of a product are increased for no improvements in a product. From the accessibility and justification perspectives, these are regarded as unethically priced. A high-profile example of this happened when Mylan N.V. gradually hiked the price of EpiPen, their epinephrine autoinjector, from USD 100 in 2009 to 600 in 2016, in the United States for a pack of two autoinjectors; the required dose for some patients (Lyon, 2016; Ramsey & Kiersz, 2016; Song, Brown, Karjalainen, Lehnigk, & Lieberman, 2018). As Rubin (2016) quotes: "People are upset about the idea that a 40-year-old technology using a 100-year-old drug can cost $600". Heather Bresch, CEO of Mylan, blamed the price increase on the insurance industry, the supply chain, and a slow regulatory system (Mangan, 2017, March 3). Rubin (2016) tells a different account: Bresch was considering selling EpiPen to other companies until she decided to capitalize on US President Barack Obama's enactment of the School Access to Emergency Epinephrine Act in 2013, which encouraged states to pass legislation requiring schools to maintain an emergency supply of epinephrine and on Sanofi Pharma's voluntary recall of its own epinephrine autoinjector. These circumstances allowed Mylan to increase the price of EpiPen until it agreed to a settlement of USD 465 million with the US Department of Justice and introduced a generic version of EpiPen at half the price (USD 300), in response to a lawsuit filed by Sanofi on behalf of the US federal government (Department

of Justice, 2017; Lyon, 2016).

Similarities with a cost-effectiveness analysis

This framework draws from a modified version of the cost-effectiveness plane. This is an economic tool that maps graphically the quantitative measures of the costs and the benefits of a health strategy (such as a new drug therapy), compared to another standard of care (e.g., an already available drug or another form of treatment) and compares both treatment options. The framework, in contrast, provides a categorical organization of drugs across similar dimensions. The benefits of a drug in our analysis are in part captured by the dimension of price justifiability, which includes, conceptually, a measure of the therapeutic value and the costs and risks in the development of a drug. Similarly, the costs of a drug (from the perspective of the payer) are captured in the price accessibility dimension of the framework. The cost-effectiveness plane maps the strategies being tested into quadrants where they can be easily categorized as dominant (more effective and cost-saving compared to the standard of care), dominated (less effective and cost-increasing), or require an estimation of the trade-off between effectiveness and cost-saving (Cohen & Reynolds, 2008). In a similar way, two of the quadrants in the framework can suggest that the pricing of a product can be easily categorized as ethical (if prices are justifiable and accessible, as in quadrant two), unethical (unjustifiable and inaccessible pricing in quadrant four), or instances when a judicious analysis with other criteria, such as long-term budgetary sustainability, might be required (as in quadrants one and three).

The difficulty in achieving an 'enlightened capitalism'

It might seem peculiar that pharmaceutical companies do not initially choose to maximize their profits by pricing their products in an accessible way and aiming to capture a large consumer base, while gaining the good will of society along the way. There are indeed economic models in the literature that suggest that decreases in price can result in an increase in profits under several scenarios (Longo, 2010). Companies could estimate a justifiable price level and work together with payers to ensure that very few who need pharmaceuticals are priced out of the market. They might even benefit from making their drugs available to the largest number of people who need them. This section intends to explain why the behaviour in quadrant two is not observed as often as this hypothetical scenario suggests. Instead of seeking this 'enlightened' capitalistic scenario, pharmaceutical companies tend to opt first for higher prices to maximize their profits. In the case of drugs for rare diseases, low pricing is not even viable because the market for rare diseases is so small that high prices are needed to recover the costs and risk of R&D and commercialization.

Companies can be highly strategic about their pricing, mostly, it would seem, with profitability rather than accessibility in mind. A penetration strategy, for instance, is commonly used to introduce products that represent only a marginal improvement over other ones already in the market. It consists of introducing a product at a low price and raising that price later. Low prices encourage the use of these drugs and makes the party responsible for the purchasing decisions rely on these drugs (Lu & Comanor, 1998). When prices are increased, that reliance (or dependence in some cases) to the drugs translates into higher profits. This is comparable to some sales strategies where

companies offer free samples to doctors so patients can see the benefits of new drugs, which has been reported to be effective at influencing physicians' prescribing behaviour (Murshid & Mohaidin, 2017), but after a short period of free treatment, patients (or their insurers) must pay the full price to continue the treatment. Having to pay full price for a drug that patients have started relying on when it was priced for free can then lead to patient advocacy groups pressuring insurers to cover these new drugs.

Another common pricing strategy is that of skimming, which is more suitable for drugs that offer significant advantages over its competitors. In skimming pricing, prices start high and are lowered over time (Lu & Comanor, 1998). The high initial prices aim to capture the segment of the market willing to pay higher prices for a drug, recouping the costs of development more easily this way. They then lower prices to capture other market segments, in a similar way of how most patented drugs are marketed first in the United States (more willing to pay high prices and with no price regulations). They then expand to other high-income countries, and eventually reach lower income countries at a very low price (those less able to pay).

Glabau (2017) offers another explanation of why companies seem not to opt for accessible pricing and aim for a larger consumer base. She postulates that pharmaceutical companies are treated as investments by their shareholders, who expect that the value of their investments will increase over time. In her view, prices communicate the success of a company and its profitability, and the financial market operates under these assumptions. She argues that the pricing of pharmaceuticals has lost much of its "underlying medical, technical, or social value" and become increasingly responsive to the expectations of

the financial industry. She blames this shift on the "shareholder revolution", where larger stakes of ownership of a company are passing to external shareholders, such as banks and other financial institutions. These shareholders are concerned solely with investing capital (Glabau, 2017) where they might see the greatest returns, and wholly removed from the activities of a company. Then, she argues, these shareholders "exert pressure on actors within companies to reorganize their activities to prioritize raising share prices above all else" (Glabau, 2017).

Sometimes, policies to curb prices and reward innovation with higher price allowances can create incentives to comply with the letter of the law instead of the spirit of the law. For instance, in health economic evaluations, the therapeutic improvement of a drug is sometimes reported in quality-adjusted life-years (QALYs), a unit that combines measures of how much a treatment option (say, a drug) can extend the life of a patient and at what relative level of quality of life it offers, compared to another treatment option (say, another drug available in the market, or an absence of treatment). Some policymakers rely on arbitrary thresholds, whereby, for example, only drugs that cost CAD 50,000, USD 50,000 or GBP 30,000 per QALY or less, depending on the jurisdiction (Grosse, 2008), can receive public funding. Instead of preventing drug companies from proposing prices over this threshold, these policies have incentivized companies to frame their drugs as capable of producing a high number of QALYs and to price them just below the threshold.

Conclusions

The framework proposed here offers a way to assess, from a social and a business perspective, when pharmaceuticals can be considered fairly priced. We

reviewed the literature on the ethical responsibility to provide health care and focused on 'equal access' as a social ethical objective. On the business side, we reviewed the composition of a corporation and the relationship between a pharmaceutical company and its main stakeholders when it comes to drug pricing. With this in mind, we defined justifiable price as one that reflect the risks and costs that companies take in developing their products, as well as the therapeutic improvement they bring. Access to pharmaceuticals cannot be achieved without considering the viability of the companies, and at the same time, accessibility must be a guiding principle in the justification of prices. As much as risk-taking and innovation should be rewarded, they cannot be a carte blanche for high prices. At the same time, society cannot impose the onus of making drugs accessible on the companies alone. The WHO reiterates that fair pricing is not the same as low pricing, but is one that "allows for a reasonable return on investment in exchange for an affordable price, which is to say one that does not bankrupt health systems and other payers" (2017a).

Milton Friedman (1970) wrote that it is immoral for a manager to pursue a public agenda, as the manager is appointed by shareholders to generate profit for them, while the public elects officials to pursue the common good. By his own words, if business can automatically (and morally) be expected to maximize profit and only governments can be expected to look after the public, this can be interpreted as an invitation for adversarial regulation, which can result in an undesirable scenario for both parties. The importance of bringing together the social and the business perspectives in this ethical assessment is clear. As Aneurin Bevan, founder of the National Health Service in the UK said, "Illness is neither an indulgence for which people have to pay, nor

an offence for which they should be penalised, but a misfortune the cost of which should be shared by the community" (Cook, 2018). A fair pricing of pharmaceutical products, based on the principles developed in this study is key to ensuring access to prescription drugs without any single party facing a disproportionate share of the costs. But another important part might be the rethinking of the relationship between companies, payers, and the public. The solution, rather than coming from an 'enlightened capitalism', might come in the form of a change in the relationship between, where they can see each other as stakeholders with two goals in mind: that people who need medications can have access to them and that companies can remain viable and competitive. This relational model, dubbed "enlightened risk sharing" is the focus of the published version of this work (Balderrama et al., 2020).

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Chapter Three: Changes in Prescription Opioid Utilization After the Public Delisting of High-strength Products in Ontario, by Sociodemographic Category and Funding Source

Abstract

To stem the abuse and overdose of prescription opioid drugs, the province of Ontario delisted twenty high-strength products from its public formulary in January 2017. Among them are fentanyl patches and hydromorphone, morphine, and meperidine pills. A net decrease in publicly funded opioids dispensation of some of these opioids has been reported in the province, suggesting this policy achieved its intended objective. It is unclear, however, whether private funding for these drugs is compensating for the decrease in public subsidy, possibly working against the intended objective of the policy. It is also unclear which sectors of society have actually lowered their consumption of opioids and which have only shifted the source of funding from public to other sources. For this reason, this study answers two questions: 1) whether the overall utilization of the targeted categories of opioid products decreased after the Ontario Drug Benefit (ODB) plan delisting, and 2) whether all sociodemographic categories were affected equally. This study makes use of pharmacy sales data and regression discontinuity models for its analysis. The results show an overall decrease in the consumption of the opioid drugs, except for meperidine, while a decrease in the number of prescriptions is found only for morphine. Private insurance and out-of-pocket payments partially replaced public funding for some of these drugs in specific sociodemographic categories, especially for products with low substitutability. Opioid utilization among

higher income groups has been less affected by the policy.

Introduction

Canada has the highest consumption of opioids per capita in the world after the United States and is the largest consumer overall when morphine milligram equivalents (MMEs), a standardized measure of opioid dose, are used in the metrics (Donroe, Socias, & Marshall, 2018; Fischer, 2015). The Public Health Agency of Canada estimates that there were more than 17,000 suspected opioid overdoses and 14,700 apparent opioid-related deaths between January 2016 and September 2019 in Canada (Special Advisory Committee on the Epidemic of Opioid Overdoses, 2020).

In July 2016, the Ontario Public Drug Programs (OPDP) announced the delisting of high-strength opioid products from the main provincial public formulary, the Ontario Drug Benefit (ODB) Program (2016a). This policy was part of a multi-pronged strategy to address the ongoing epidemic of opioid use disorders (OUDs). The wider strategy was announced in October 2016 by the Ontario Ministry of Health and Long-Term Care (MOHLTC) and included the development of evidence-based standards for opioid prescriptions, the establishment of new chronic pain clinics, the increasing of access to naloxone and Suboxone™ [1], a stricter control on the prescription and dispensation of fentanyl patches, along with the aforementioned delisting of high-strength opioid products (Ministry of Health and Long-Term Care, 2016). This strategy was informed by

[1]Naloxone can prevent or reverse the effect of opioids, causing withdrawal. Buprenorphine is used in opioid substitution therapy and produces less physical dependence than other opioid drugs. However, it can be misused and abused intravenously. Suboxone™ is a buprenorphine/naloxone combination in a 4:1 ratio. It acts like buprenorphine when taken sublingually, as indicated, but when injected, it can precipitate withdrawal. It has the added benefit of preventing the intravenous misuse of the buprenorphine among opioid addicts (Orman & Keating, 2009).

the recommendations of the final report of the Methadone Treatment and Services Advisory Committee (2016), which was tasked by the MOHLTC with reviewing best practices, recent evidence, and expert reports and providing recommendations for the treatment of OUDs (Ministry of Health and Long-Term Care, 2016). The delisting policy, in particular, was informed by the recommendations of the Pain Medication Formulary Subcommittee assembled by the OPDP (Ontario Public Drug Programs [OPDP], 2016b).

The policy came into effect on January 31, 2017. It included twenty high-strength opioid products, where a product is defined by its assignment of a unique Drug Identification Number (DIN), in four drug categories: Fentanyl patches, morphine tablets, hydromorphone capsules, and meperidine tablets (OPDP, 2016a, 2017). These products, however, would still receive public funding for palliative care patients. A detailed list of the delisted products is shown in Table 1.

Table 1: Delisted products

Product	DIN	Manufacturer
Ms Contin 200 Mg Sr Tab	2014327	Purdue Pharma
Novo-Morphine Sr 200 Mg	2302802	Novopharm
M-Eslon 200 Mg Er Cap	2177757	Ethypharm Inc.
Hydromorph Contin 24 Mg	2125382	Purdue Pharma
Hydromorph Contin 30 Mg	2125390	Purdue Pharma
Fentanyl Transdermal Patch 75 Mcg	2314657	Apotex
Fentanyl Transdermal Patch 75 Mcg	2386887	Cobalt
Fentanyl Transdermal Patch 75 Mcg	2396734	Mylan
Fentanyl Transdermal Patch 75 Mcg	2341409	Pharmascience
Fentanyl Transdermal Patch 75 Mcg	2330148	Ranbaxy
Fentanyl Transdermal Patch 75 Mcg	2327155	Sandoz
Fentanyl Transdermal Patch 75 Mcg	2282976	Teva
Fentanyl Transdermal Patch 100 Mcg	2314665	Apotex
Fentanyl Transdermal Patch 100 Mcg	2386895	Cobalt
Fentanyl Transdermal Patch 100 Mcg	2396742	Mylan
Fentanyl Transdermal Patch 100 Mcg	2341417	Pharmascience
Fentanyl Transdermal Patch 100 Mcg	2330156	Ranbaxy
Fentanyl Transdermal Patch 100 Mcg	2327163	Sandoz
Fentanyl Transdermal Patch 100 Mcg	2282984	Teva
Demerol 50 Mg Tab	2138018	Sanofi Aventis Pharma

This 2017 delisting was preceded by the 2012 delisting of another opioid, OxyContin™ (oxycodone) (OPDP, 2012), which was associated with a high number of opioid-related deaths and health harms (Fischer, Rehm, & Tyndall, 2016). Studies indicate, however, that "although well intended", the delisting of oxycodone from the ODB caused "supply gaps" that were filled by other high-strength drugs, such as fentanyl, hydromorphone, and the illicit use of dangerous analogs, such as carfentanyl. This emphasizes the difficulties in foreseeing the "consequences on the growing population of opioids users [...] and the volatile and hazardous dynamics of opioid supply" (Fischer, Pang, & Tyndall, 2019; Fischer et al., 2016).

In fact, an early evaluation by Guan et al. (2018) of the 2017 delisting shows that there was a shift in utilization from high-strength fentanyl and hydromorphone products to lower-strength formulations with public funding. They also show the expected decrease in publicly funded dispensation of the delisted products (by 98%), and a decrease in the overall public dispensation of fentanyl patches, hydromorphone capsules, and morphine tablets in all the available strengths. Some of the limitations of this study is that the authors included only opioid products dispensed through the public drug program (public payer) and that sociodemographic information for variables such as sex, age (Guan et al., 2018) and income levels were not captured. This additional demographic analysis and the inclusion of private sources of funding are precisely the contributions of the present study.

This study answers two questions: 1) whether the overall utilization of the targeted categories of opioid products decreased after the ODB delisting, and 2) whether all sociodemographic sectors were affected equally. The objectives

of this study are to 1) 'characterize the utilization of these opioid categories across sociodemographic variables and sources of funding', 2) 'detect if there were statistically significant changes in the overall utilization of these products', and 3) 'detect whether each of the sociodemographic categories experienced significant changes in utilization'.

Understanding the heterogeneous effects of delisting on sociodemographic categories is necessary for designing policies that can address the type of opioid consumption that leads to OUD. It is also desired that these policies minimize economic harm to patients who need opioids, by removing subsidies for necessary products for pain management that were previously subsidized. Delisting policies must also avoid causing a shift in consumption towards equally or even more dangerous drugs.

By delisting these products, the product price faced by patients effectively goes up. Predicting the changes in utilization of opioids brought about by this type of policy is further complicated because of the high rates of addiction these drugs can cause and by how much they can improve the quality of life of patients who require pain management, both acute or chronic. This suggests that opioids have an inelastic demand, that some patients might choose to pay out-of-pocket (OOP) for drugs previously funded by the government, and that these patients might be economically harmed by this policy. Another factor to keep in mind is the substitutability of the delisted products by other prescription opioids or even the substitution of medically prescribed opioids with illicitly acquired ones.

Throughout this study the term 'overall' refers to the utilization of an opioid category, aggregating all the sociodemographic categories and sources of

funding. The term 'sociodemographic variable' refers to variables such as age group, and a sociodemographic 'category' refers to a category within a variable (e.g. the pediatric age group).

Regression discontinuity models were used to analyze statistical changes in the utilization of opioids before and after the delisting. Pharmaceutical sales data is used as a proxy for utilization.

Methodology

Data

Time points: Monthly data for prescription opioid drug sales in Ontario was acquired from IQVIA (https://www.iqvia.com/). The time period included in this analysis spans from August 2015 (earliest available) to December 2017. The final time point was selected to isolate better the effects of the opioid delisting policy from another important policy affecting the Ontario public formularies, OHIP Plus, which came into effect on January 2018. In our analysis, opioid sales data is used as a proxy for utilization.

Coverage: The data set recorded point-of-sale (pharmacy) data of prescriptions purchases made in retail pharmacies across Ontario participating in IQVIA's data acquisition network. In Ontario, the coverage is for 42.5% of all the pharmacies in the province, but it includes most of the largest stores, accounting for a considerably greater percentage of all the prescriptions in the province. The data does not include dispensations made at health care centres. Data from pharmacies out of the network was estimated by IQVIA using geospatial projections, based on store size, number of stores, and distance (IQVIA, personal communication, April 14, 2020); see the *Dependent variables* section below for more details.

Age group and gender: The data includes sociodemographic categorical variables about the individuals filling their prescriptions, including gender and age group. The age group variable was re-categorized in the following manner:

- Pediatric (Ped): ages 0 through 14
- Young adult (YA): ages 15 through 24
- Adult: ages 25 through 59
- Senior: ages 60 and over

Income: A categorical income level variable was acquired by using Forward Sortation Area (FSA) codes of the pharmacies where the purchases were made as proxy for the income level of the prescription user. Data for the national distribution of the mean household income after-tax, per FSA, was acquired from the 2016 Canadian Census (Statistics Canada, 2017) and used to map geographic drug sales data with income levels. The national quintile distribution of household income was used, resulting in five income categories: low income, low-middle, middle, middle-high, and high income, for their respective quintiles.

Opioid products: This study included those products directly affected by the policy, marked as *Delisted*. Products were categorized as *Delisted* even in time periods before the policy came into effect. Prescription opioid products that were not delisted but have the same active molecule and form of administration as delisted products (e.g., orally administered hydromorphone) were included and classified as *Substitute* products, regardless of their brand or generic status. These products were typically lower-strength formulations of delisted products. This was considered a suitable criteria that physicians and patients might use in choosing products to change their prescriptions to in case of events like public

delistings. Any other product was considered unaffected by the policy and excluded from the analysis. Sales of products within each category (Delisted and Substitute) were aggregated. Unless otherwise specified throughout this study, both delisted and substitute (but not unaffected) products are analyzed together. The categorization and the analysis were repeated separately for each opioid product category (fentanyl patches, oral morphine, oral hydromorphone, and oral meperidine).

Payer type: The sale of opioid products was analyzed according to the primary source of payment: public insurance, private insurance, or OOP. Combined sales from all three sources are also analyzed in this study.

Unit of observation: The unit of observation in this study is the aggregation of prescription sales according to the combination of the following categorical variables: *time point*, *gender*, *age group*, *income level*, and *payer type*, as explained above. This organization is derived from the structure of the IQVIA data set acquired. The following is an example of a uniquely identified unit of observation: *Fentanyl patches category - January 2016 - Female - Adult - Low-middle income - public payer.* The unit of observation was initially specific to each individual pharmaceutical product (as defined by a single DIN), but these observations were aggregated by opioid product category and product status (delisted or substitute). It was considered that working at the individual product level would be of limited value in analyzing the effects of the policy. An analysis of publicly funded prescriptions for delisted and substitute products, separately, was already reported by Guan et al. (2018).

Dependent variables: The number of prescriptions and the total drug quantity sold at each time point were used as separate dependent variables. Drug

quantities were measured in an IQVIA proprietary unit, named "extended units", that can be used across similar products (same molecule and form), equivalent to the smallest common unit (e.g. a pill, tablet, or a patch) of a product regardless of strength (IQVIA, personal communication, August 16, 2019). These variables were used to calculate the dose of opioid products sold in each observation in morphine milligram equivalents (MME) with the following formula:

$$\begin{array}{l}\text{Extended}\\ \text{units}\end{array} \times \begin{array}{l}\text{Product}\\ \text{strength}\end{array} \times \begin{array}{l}\text{MME conversion}\\ \text{factor}\end{array} = \begin{array}{l}\text{Dose}\\ \text{(in MMEs)}\end{array} \quad (1)$$

Where product strength is typically given in micrograms per hour for fentanyl and milligrams for the other drugs, and the MME conversion factors used were 7.2 MMEs/day per each microgram/hour strength in fentanyl patches, 4 MMEs per each milligram of strength in oral hydromorphone, and 0.1 MMEs per milligram of strength in oral meperidine, as outlined by the US Centers for Medicare and Medicare Services (CMS) (2017). Naturally, morphine has an MME conversion factor of one (1).

The number of prescriptions dispensed for each unit of observation was also used in the statistical analysis. For each pharmacy not participating in IQVIA's network, the drug quantity and the number of prescriptions were projected using geospatial statistics, based on data reported by the closest two to ten participating pharmacies. The reported data was factored by the geographical distance to the non-participating pharmacy and weighted for differences in store size between them (IQVIA, 2018). A potential source

of error introduced was that the projected number of prescriptions for non-participating pharmacies was rounded down to the closest integer, unlike the projected drug quantity (IQVIA, personal communication, November 9, 2018). To reduce this error, any observations showing a non-zero drug quantity, but a zero number of prescriptions had the number of prescriptions rounded up to one. It is estimated that this change could only affected 1.76% of all the prescriptions in the data set. The dose quantities were not affected by this error.

Descriptive Statistics and Naïve Estimates

The utilization of opioids by delisting status in number of products, average dose per month, and number of prescriptions per month was analyzed. The purpose of this analysis was to produce a simple estimate of the difference in the utilization of delisted and substitute products for each product category before and after the delisting.

Naïve estimates of the changes in overall utilization and by sociodemographic categories were also prepared. These naïve estimates compare the average utilization per month during the periods before and after the delisting with a two-tailed heteroskedastic Student's t-test.

Regression Analysis

Regression discontinuity models (RD) models were used for the statistical analysis. These models were used to identify possible discontinuities in the utilization of opioids at the point where the treatment (the delisting) was applied. As Bailey (2019) states, these models are good for "looking for jumps in data".

In our models each observation is associated with a sociodemographic category (or aggregation of such) and a time point. Utilization, measured by dose or number of prescriptions, was the outcome variable. Treatment was applied uniformly to every sociodemographic category (regardless of the magnitude they were affected by) when the policy came into effect on January 2017. For this reason, time, or more precisely the difference between the time period in an observation and the cut-off on January 2017, is the independent assignment variable. The treatment variable is binary (T=1 after the cut-off, T=0 before the cut-off), and its effect on utilization is the focus of our analysis. The effect of the assignment variable captures the background trends in utilization in time throughout the period of study, separating it from the desired effect of treatment itself on utilization. An interaction between treatment and the assignment variable can be used to isolate the effect of any possible change in trends after treatment started. Formula 2 represents the regression model for a single sociodemographic section:

$$Y_i = \beta_0 + \beta_1 T_i + \beta_2 (X_i - C) + \beta_3 (X_i - C) T_i + \epsilon_i \tag{2}$$

Where:

Y_i is the outcome variable (dose [in MMEs], number of prescriptions, or dose per prescription) of observation i

T_i is the treatment variable (1 after January 2017, 0 otherwise)

$X_i - C$ is the assignment variable - how much above or below the cut-off an observation is, where C is the cutoff, January 2017 and X_i is the time point of the observation

The RD models were modified for the analysis of multiple related sociodemographic categories in the same model (e.g., each one of the four age groups). The modified models pool together all the observations for each category and include the same terms for each category identified by a unique category-specific binary (dummy) variable. This type of pooling allowed for the compartmentalization of the discontinuity analysis for each category in a given sociodemographic variable within the same model. It also resulted in some shortcomings in the estimation of coefficient errors, which are addressed in the *Sensitivity Analysis* section of the results and in the supplementary materials. Pooling observations over multiple sociodemographic variables (e.g. both age groups and income levels) in the same model resulted in dummy variable trap errors. Formula 3 represents the pooled model used in this analysis:

$$Y_i = \sum_s \left\{ \beta_{s0} D_{si} + \beta_{s1} D_{si} T_i + \beta_{s2} D_{si}(X_i - C) + \beta_{s3} D_{si}(X_i - C) T_i \right\} + \epsilon_i \quad (3)$$

Where:

s is the subscript that refers to a sociodemographic category from a related group, such as each an income level (low, middle-high, etc.)

D_{si} is a dummy variable specific to each category; equals 1 if observation i is for the category s, 0 otherwise

Y_i is the outcome variable (dose [in MMEs], number of prescriptions, or dose per prescription) of observation i

T_i is the treatment variable (1 after January 2017, 0 otherwise)

$X_i - C$ is the assignment variable - how much above or below the cut-off an observation is, where C is the cut-off, January 2017

X_i is the time point of the observation

The time point of January 2017 (the month of policy implementation) is being excluded from the RD models to avoid *fuzzy* discontinuities. This decision is also informed by the reporting by Guan et al. (2018) of intermediate levels of dispensation of publicly funded fentanyl and hydromorphone in that precise month, with respect to the pre-implementation and post-implementation periods. During our descriptive statistical analysis, however, this month was considered in the pre-intervention period. The intercept terms were removed from the second model to be able to include terms for all the related categories within a sociodemographic category without running into the dummy variable trap.

RD models were selected for the analysis for two reasons: First, the data acquired is not structured at a patient-level or similar cross-sectional unit, but by a pharmacy-level aggregation of sales. This presented a challenge for the use of causal explanatory models at the individual level, but could work for identifying jumps in data between the periods before and after the policy implementation. Second, because the focus is on detecting significant changes only with the policy implementation, the complexity of panel data or other time series models was not necessary. The attempt is not at modeling the dynamics of opioids sales, but just to provide justification for the assumption of smoothness in the error term at the point of policy implementation.

The main assumption of RD models is that the error term is not discontinuous at the treatment threshold (Bailey, 2019). The exclusion of the month of January 2017 from the analysis, where transitional levels of opioid dispensation had been reported (Guan et al., 2018) can remove endogenous transitory effects. An example of this endogeneity could be that some proactive physicians might move their patients to a different analgesic product in anticipation of the implementation of the policy. Otherwise, the treatment is uniform across the sample, as the policy took effect for the entire province. The RD model assumptions are further supported by the reporting of no significant change in opioid dispensation between the date of the policy announcement and the month before it came into effect (Guan et al., 2018). Diagnostic tests have been proposed for RD models by Bailey (2019). However, in the case of this analysis a histogram of the assignment variable would not reveal any endogeneity, as exactly one observation per category, per time point is used in the model. No other explanatory independent variables are available to test any other variables that might jump at the treatment discontinuity.

Sensitivity Analysis

Comparison of Multi-category Pooled RD Models and Single-category Reference Models: A feature of the models including multiple sociodemographic categories (the pooled RD models) is that the category-specific binary variables (D_s in formula 3) and the covariates for the same part of the regression discontinuity, i.e., treatment variables (D_sT), trends ($D_s(X - C)$), and changes in trend ($D_s(X - C)T$), each have the same standard errors. This means, for instance that in the same pooled model, the estimates for D_s have the same standard error for all the values of s (e.g., for

all the age groups). The reason for this is that with the aggregation by time point, these regression discontinuity variables have the same distribution for all the categories. These pooled models were compared with independent single-category models similar to the ones used for the changes of overall utilization for reference (formula 2). Single-category independent models serve as a good standard for comparison, although they are impractical to cover all the sociodemographic variables and sources of funding included in this study. Arguably, the independent estimation of discontinuity for each category is also inadequate when a potential related discontinuity event is being estimated. The purpose of this comparison is to evaluate how much the statistical significance of the effect of the policy, in the pooled RD models, could be affected by the common standard errors.

Narrow Window Analysis: Bailey (2019) writes that analyzing a smaller window of observations just before and after the discontinuity "allow us to feel more confident that our results do not depend on sensitive polynomial models, but instead reflect the differences between treated and untreated observations near the cut-off". These narrow window models were performed in parallel to the full RD models (all available time points) including only the five closest observations to the cut-off before and after the delisting in the regression models.

Results

Descriptive Statistics and Naïve Estimates

Opioid product categories: One way of starting the analysis of the changes in utilization was to assess how much the market relied on the delisted products before and after the policy implementation. Table 2 shows that a dis-

proportionate amount of consumption of fentanyl was based on the delisted high-strength products. Thirteen out of forty-three fentanyl patch products were delisted (30.23%), but they counted for an average of 40.59% of the number of fentanyl patch prescriptions and 66% of all the dose consumption before the policy was implemented (across all sources of funding). Delisted hydromorphone and morphine products were less important in their categories. Only one oral meperidine product, however (Demerol^{TM} 50 mg) was available in the market and it was delisted. Some products seem to have been discontinued some time before the policy was implemented. Sales of one of the delisted products, the Cobalt Pharmaceuticals fentanyl 100 mcg transdermal patch, were not observed in this study.

Table 2: Product utilization by delisting status

Period	Status	Fentanyl	Hydromorphone	Morphine	Meperidine
Number of products					
Pre	Delisted	13 (30.23%)	3 (6.98%)	2 (6.9%)	1 (100%)
	Substitute	30 (69.77%)	40 (93.02%)	27 (93.1%)	0 (0%)
Post	Delisted	12 (31.58%)	3 (8.82%)	2 (7.41%)	1 (100%)
	Substitute	26 (68.42%)	31 (91.18%)	25 (92.59%)	0 (0%)
Avarage dose per month in MMEs					
Pre	Delisted	75,655,620 (66.04%)	4,920,856 (6.86%)	31,960,361 (20.55%)	612,808.9 (100%)
	Substitute	38,910,395 (33.96%)	66,783,701 (93.14%)	123,589,093 (79.45%)	0 (0%)
Post	Delisted	21,316,516 (29.56%)	1,090,945 (1.8%)	8,348,014 (5.98%)	505,405.5 (100%)
	Substitute	50,793,957 (70.44%)	59,682,977 (98.2%)	131,174,044 (94.02%)	0 (0%)
Average number of prescriptions per month					
Pre	Delisted	10,265.78 (40.05%)	597.3889 (1.17%)	5,492.278 (3.49%)	1,823.111 (100%)
	Substitute	15,364.17 (59.95%)	50,496.39 (98.83%)	151,984.9 (96.51%)	0 (0%)
Post	Delisted	3,031.182 (15.59%)	213.0909 (0.42%)	1,292.909 (0.78%)	1,439.545 (100%)
	Substitute	16,406 (84.41%)	50,084.64 (99.58%)	165,175.9 (99.22%)	0 (0%)

A closer look at the data revealed that three high-strength opioid products in the categories targeted by the policy were not delisted. All three of these

exempted products come from the same manufacturer and are brand products, while their generic versions were delisted. Table A1 presents more details about these products, and they are treated in more detail in the Appendix.

Utilization of opioid products across sociodemographic categories: Figures 1 through 4 show the average (per month) overall utilization, by dose and by number of prescriptions per month, of fentanyl, hydromorphone, morphine, and meperidine during the periods before (Pre) and after (Post) the delisting policy. The error bars represent the standard deviation of the monthly utilization around the mean. The p-values produced by comparing the Pre- and Post- delisting samples with Student's t-tests are shown above the two bars ($p<0.1$; $**p<0.05$; $***p<0.01$).

The overall figures show that the changes in utilization are statistically significant in most cases. Utilization of fentanyl and meperidine decreased in both dose and number of prescriptions with the delisting. The utilization of hydromorphone decreased in dose, but increased in the number of prescriptions, both with statistical significance. Meanwhile, the utilization of morphine decreased in dose, but did not change significantly in the number of prescriptions.

Figure 1: Mean overall utilization of fentanyl per month

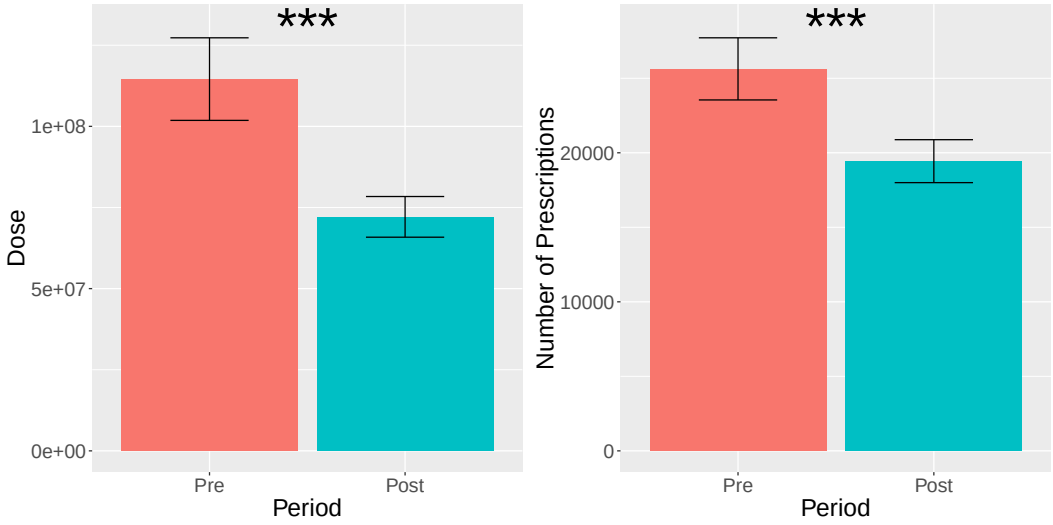


Figure 2: Mean overall utilization of hydromorphone per month

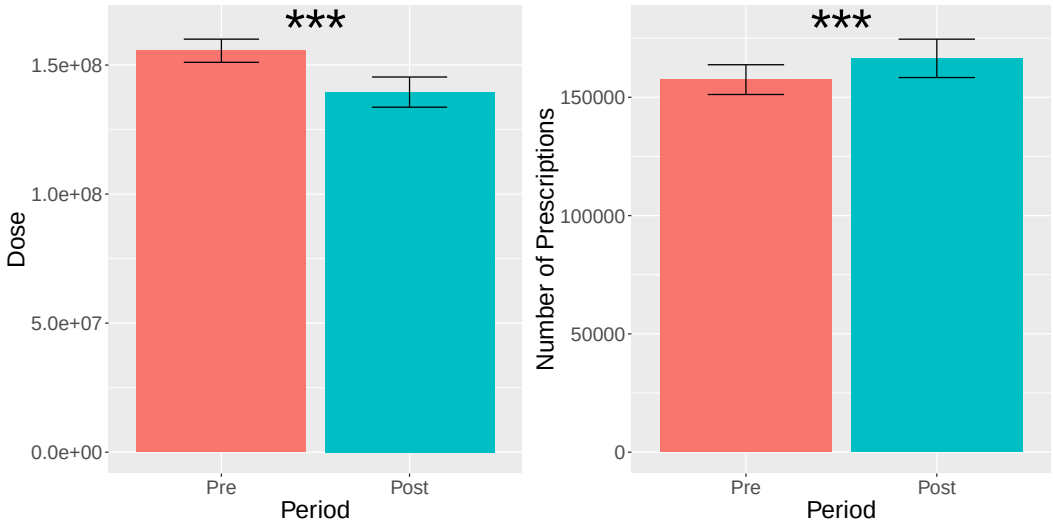


Figure 3: Mean overall utilization of morphine per month

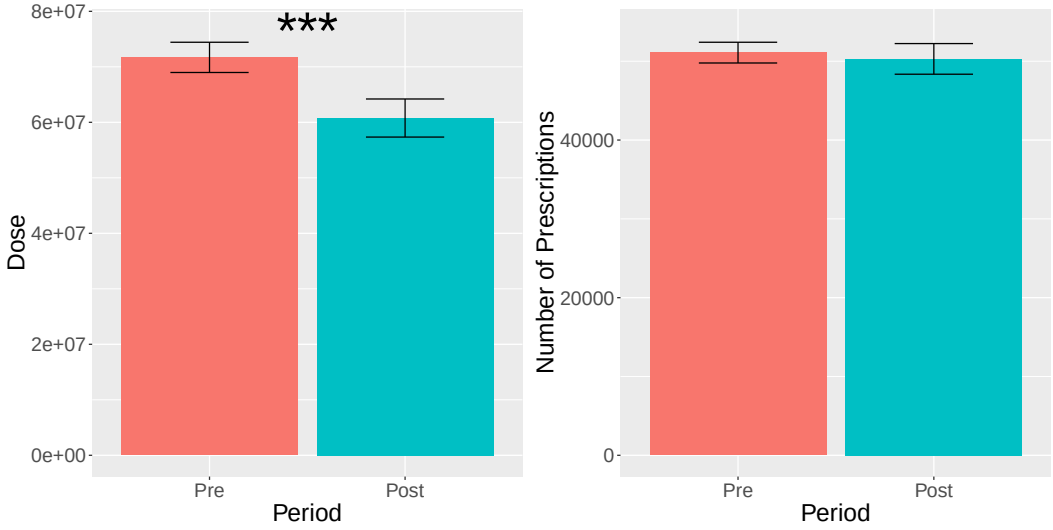
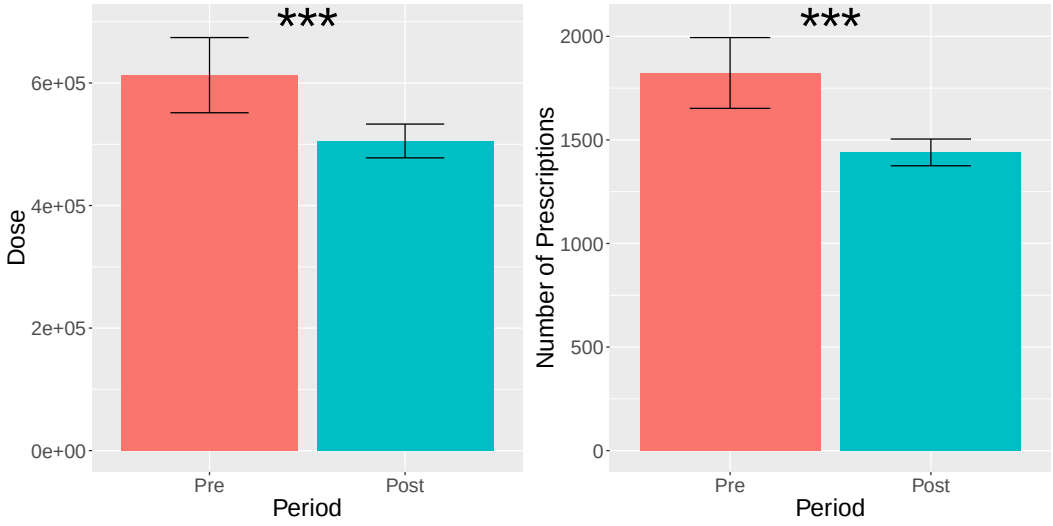


Figure 4: Mean overall utilization of meperidine per month



Figures 5 through 8 show the same analysis performed on the utilization of opioids by sociodemographic categories and sources of funding. They show that utilization of fentanyl and meperidine is higher among women than men, and that this feature did not change with the policy. These figures also show

that prescription of opioids to 'pediatric' and 'young adult' patients are very rare. By the differences in dose and numbers of prescriptions, 'adults' seem to consume stronger formulations of opioids than 'seniors'. Also, the utilization of fentanyl by 'adults' decreased considerably more after the policy than for 'seniors'.

Public insurance is by far the most common source of funding for these categories of opioids, except for meperidine. After the policy implementation, lower utilization was observed, but public funding for opioids did not decrease in importance compared to other sources of funding, except, again, for meperidine. Among income groups, the figures suggest a higher utilization among individuals in lower income levels, a feature that was unchanged by the policy. Throughout these graphs it is evident that overall utilization of opioids has decreased after the implementation of the policy for all sociodemographic categories and funding sources, except for meperidine purchased OOP.

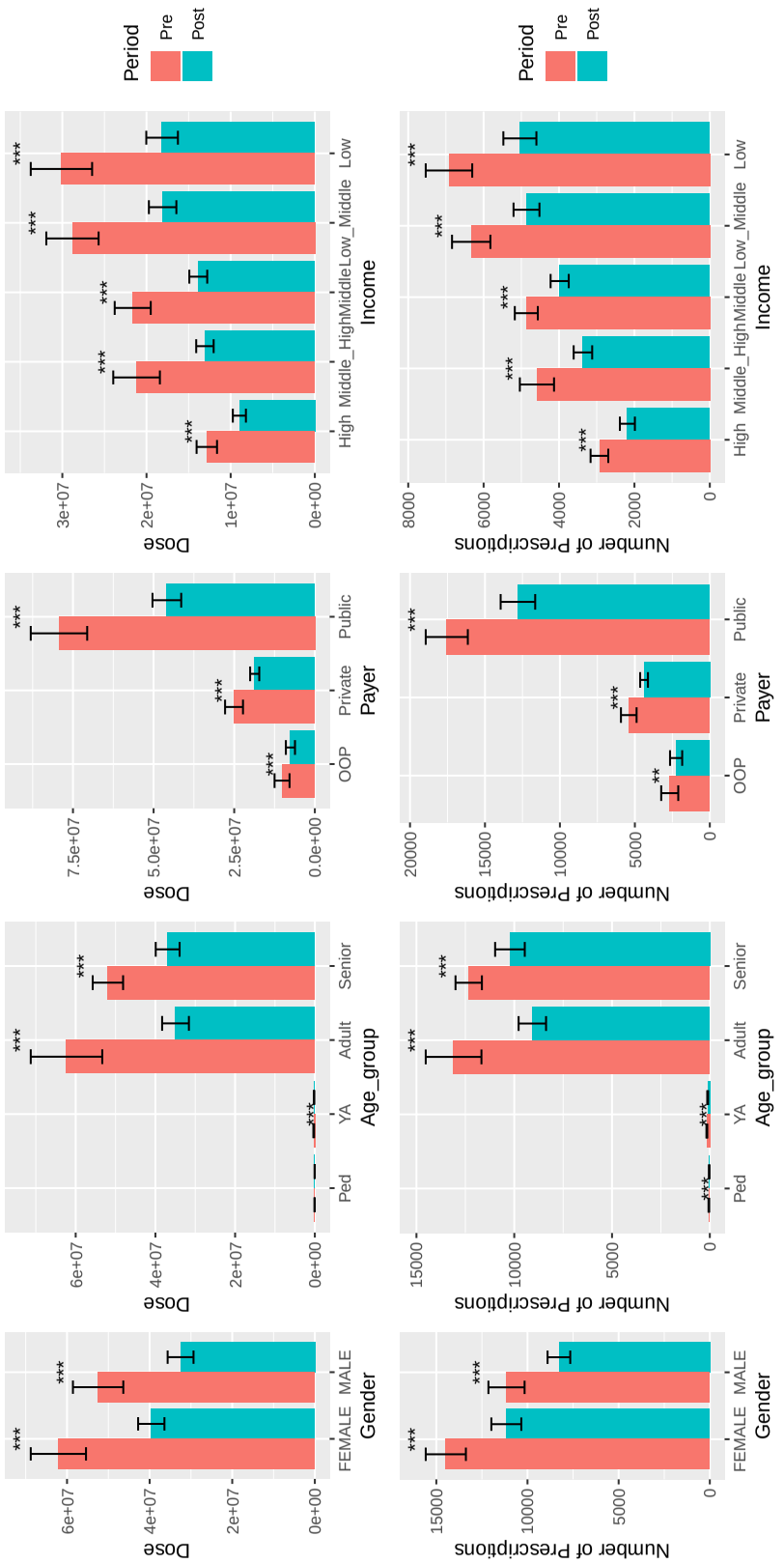


Figure 5: Mean utilization of fentanyl per Month, across sociodemographic categories and sources of funding

Figure 6: Mean utilization of hydromorphone per Month, across sociodemographic categories and sources of funding

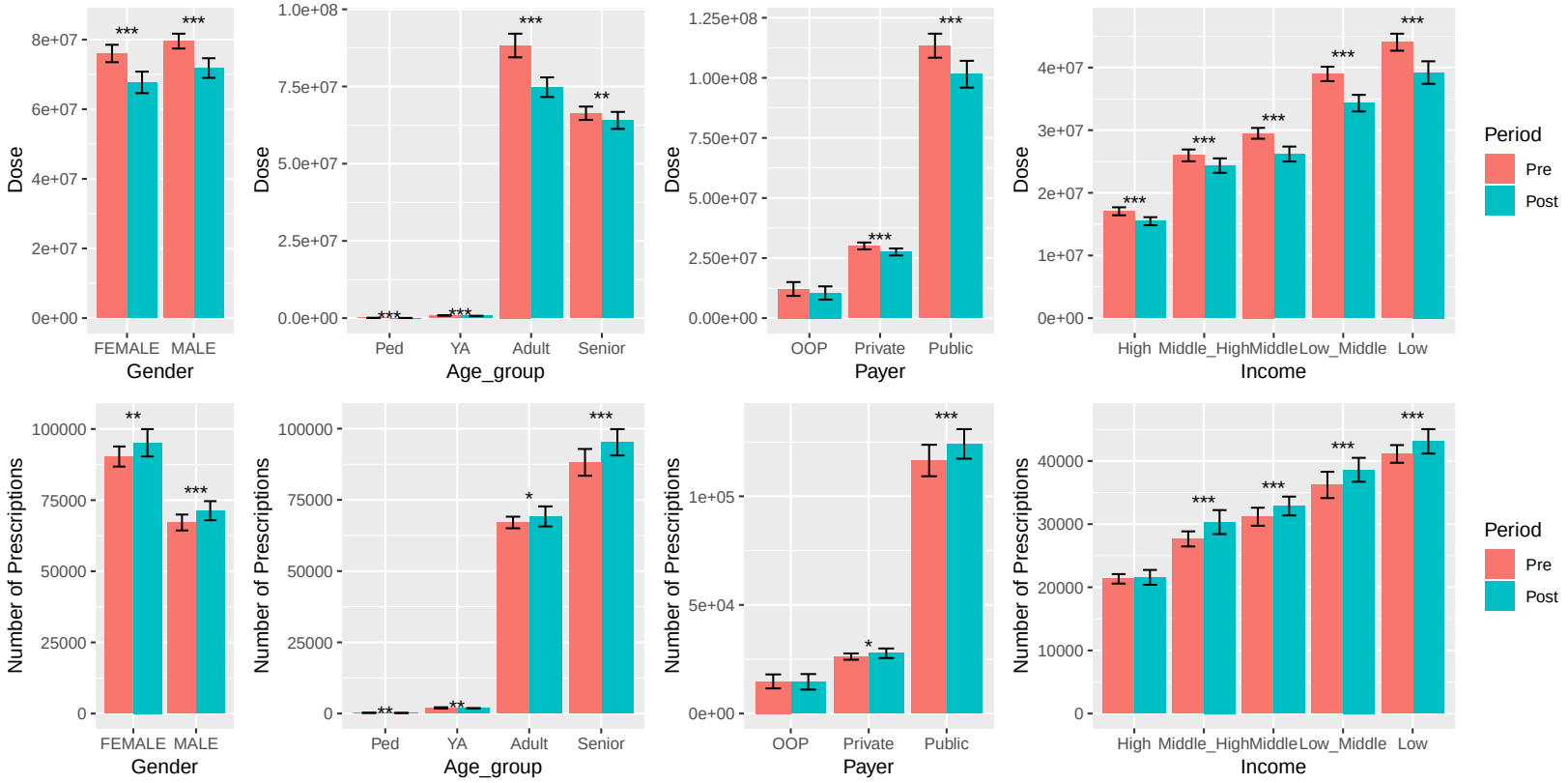


Figure 7: Mean utilization of morphine per Month, across sociodemographic categories and sources of funding

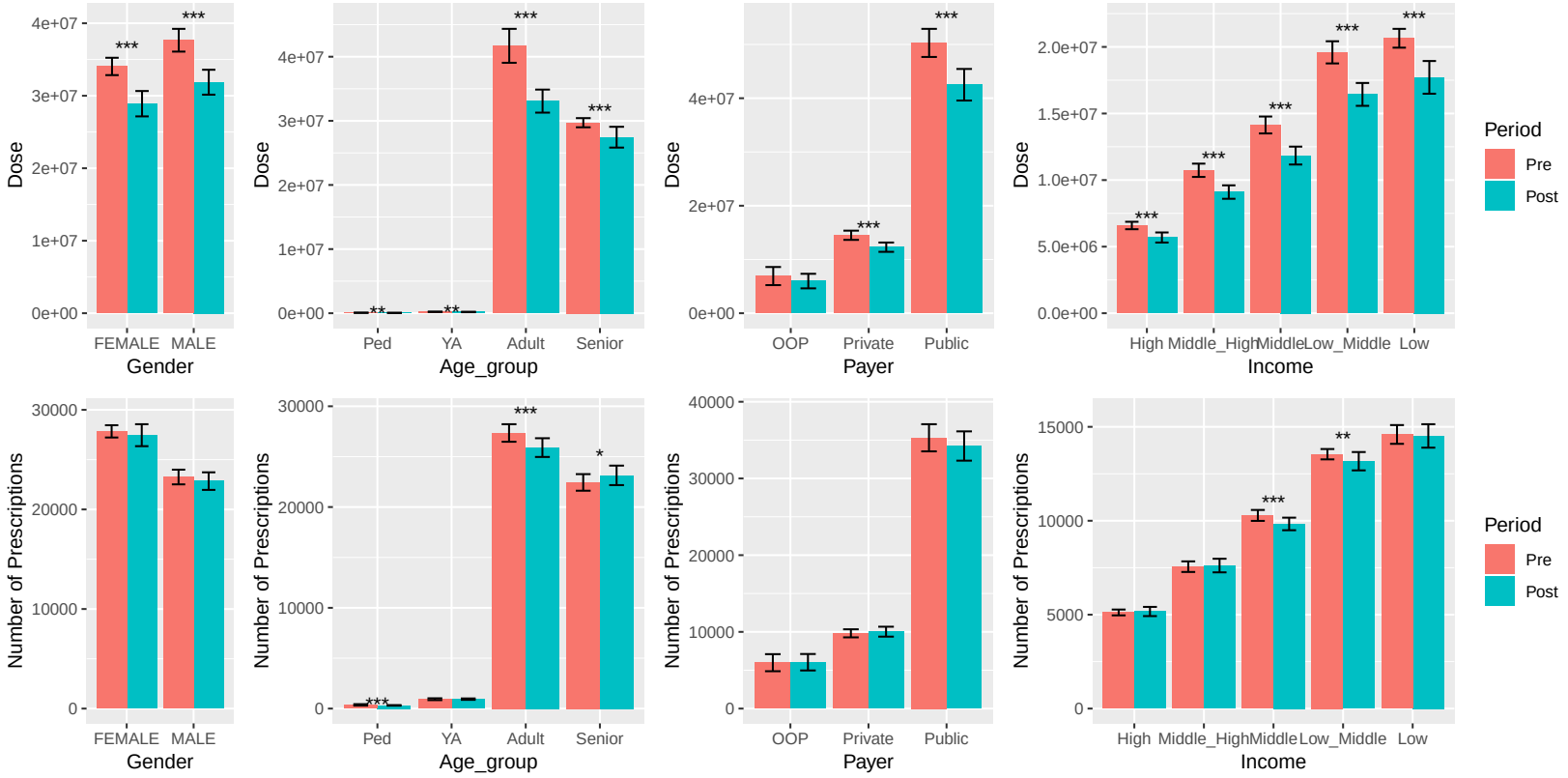
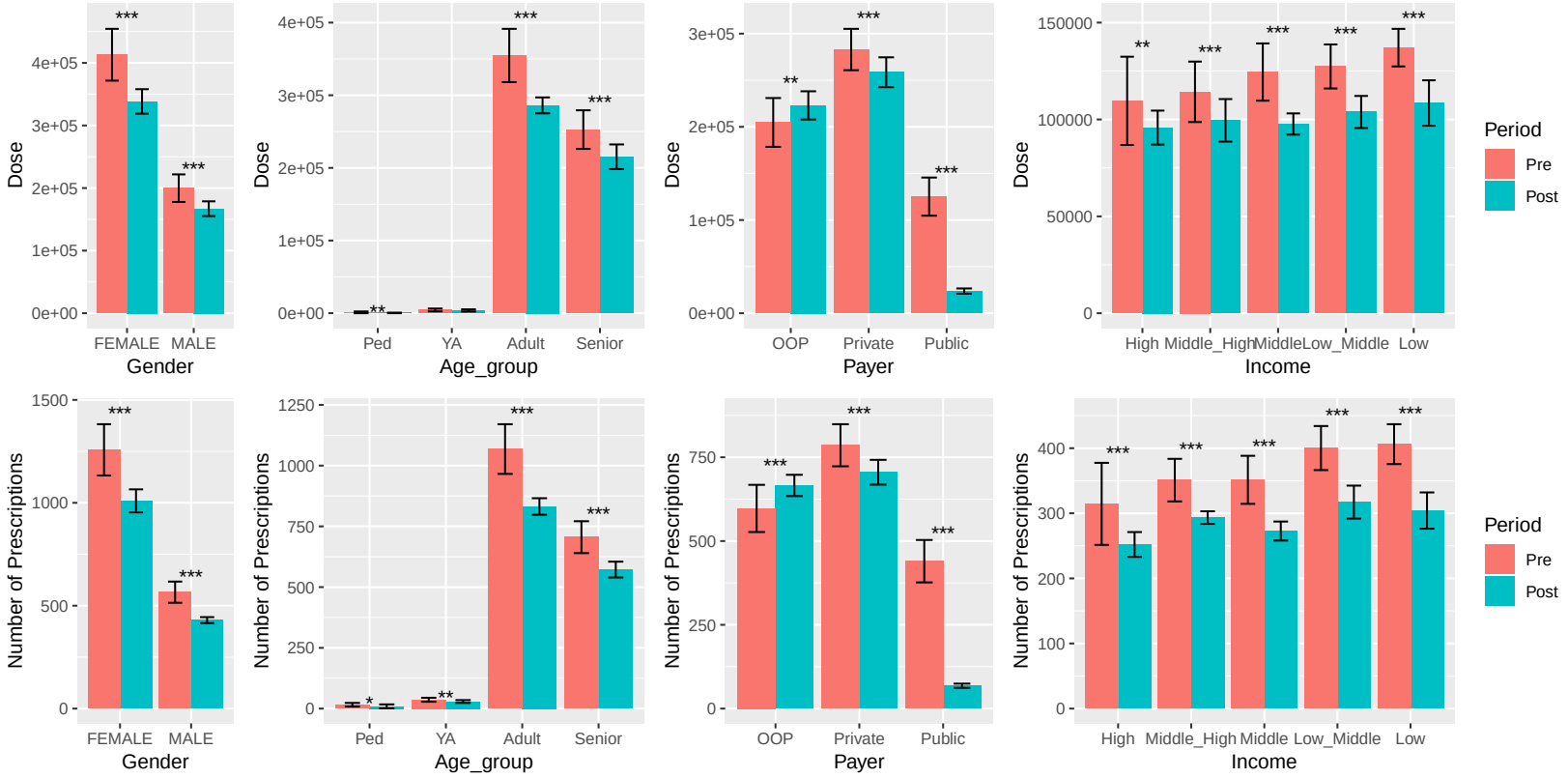


Figure 8: Mean utilization of meperidine per Month, across sociodemographic categories and sources of funding



Regression Analysis

Overall utilization: The first part of the research question of this study is concerned with the changes in overall utilization of opioids. Figures 9 through 12 follow the utilization of opioids through the study period. They also illustrate the application of the RD models on the data, showing the cut-off time point when the delisting happens, the overall (linear) trend in red before the delisting, and the trend after the delisting. Table 3 and Table 4 summarize the regression results by dose and by number of prescriptions, respectively. In these tables the *Delisting* rows show the estimate of the coefficient for the change at the time of the delisting (β_1 in formula 2). The *Overall trend* rows show the estimate of the coefficient for the effect of the overall trend (β_2 in formula 2). Similarly, the *Change in trend* estimates refer to the β_3 coefficients. Intercepts are unlabeled. The tables show that there was a statistically significant ($p<0.05$) decrease in the dose of fentanyl, hydromorphone, and morphine after the delisting, but that this was not the case for meperidine. Also, while fentanyl and morphine saw a trend of decrease in utilization throughout the study period, such trend was not significant for hydromorphone.

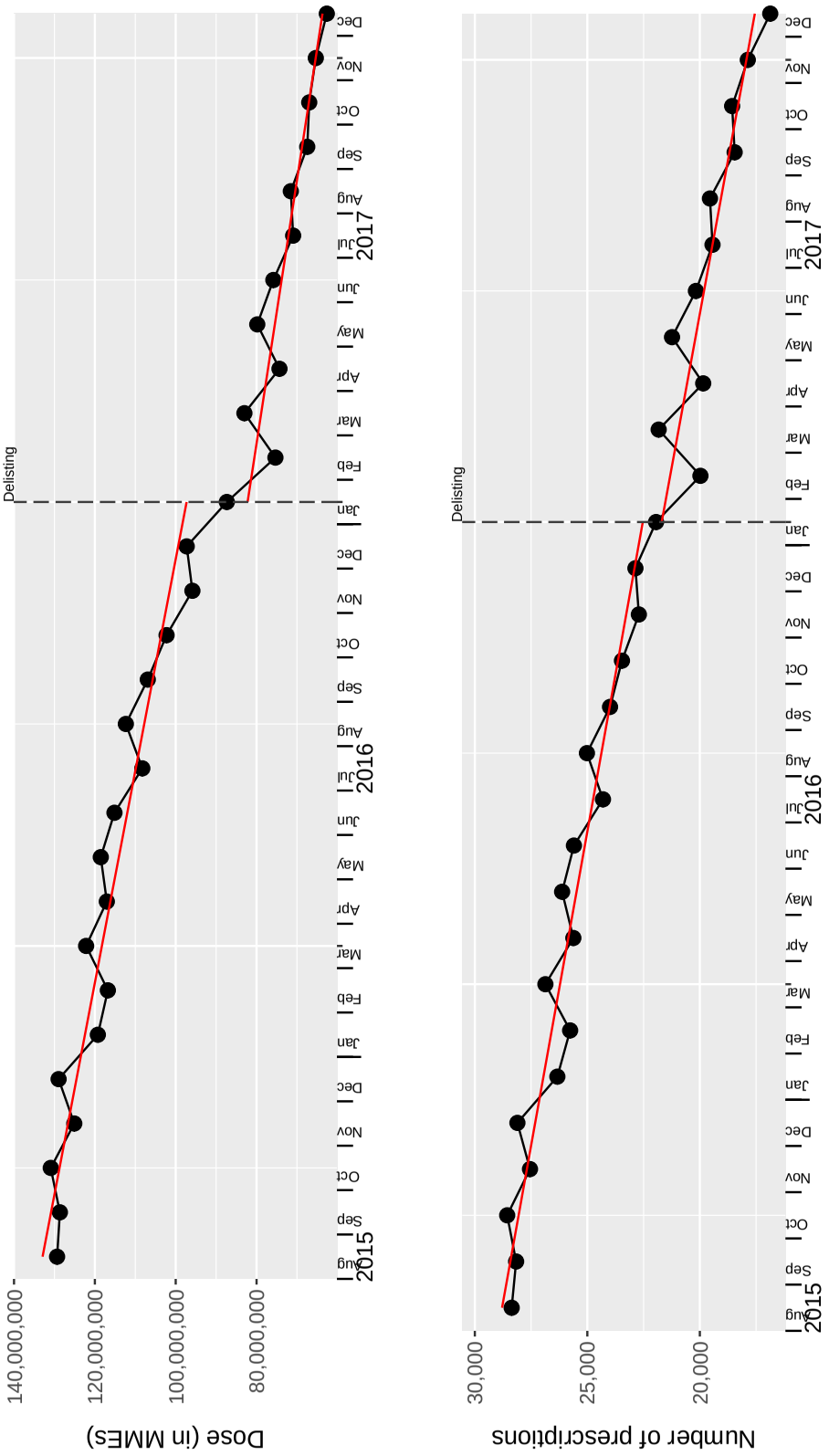
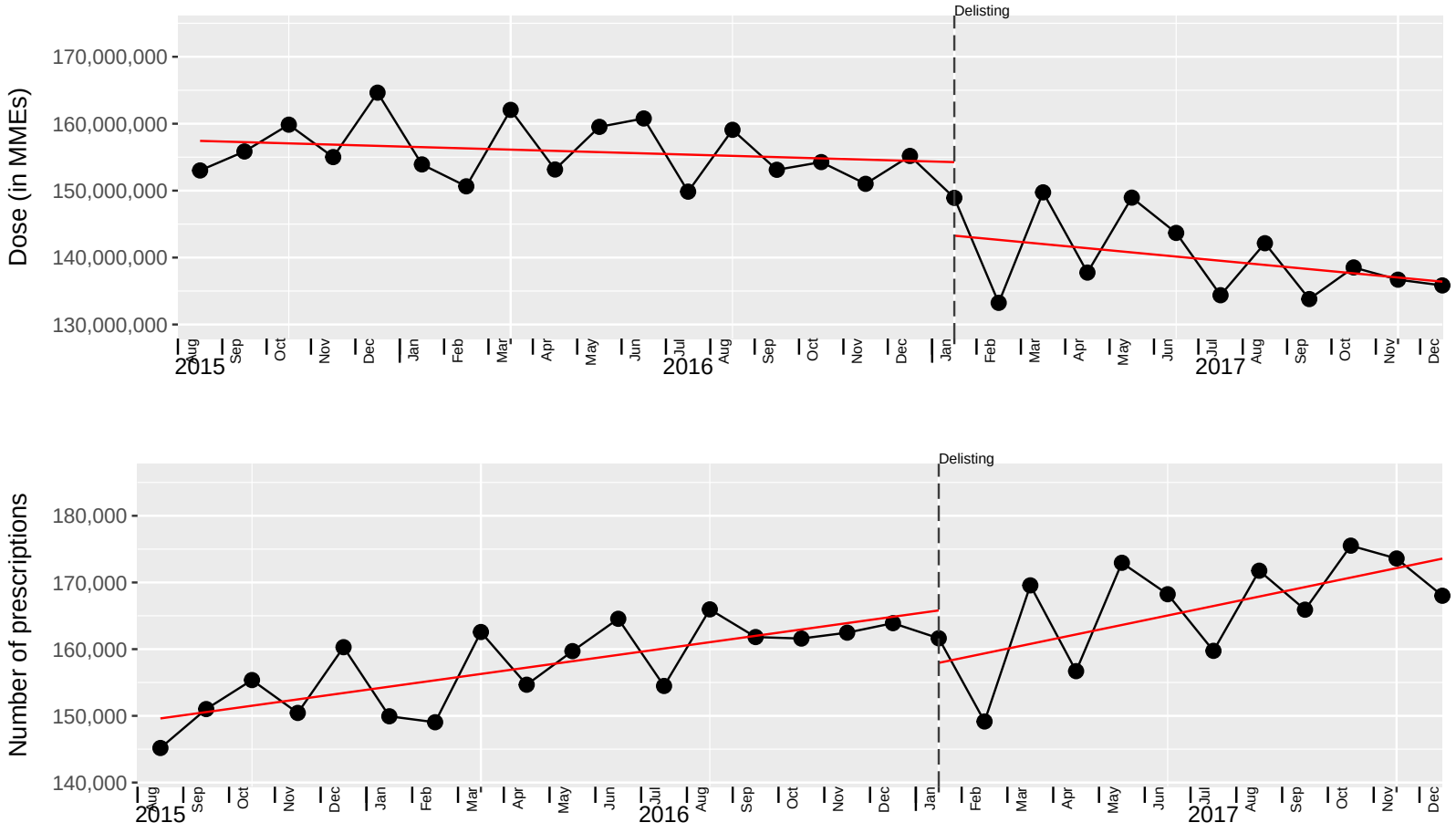


Figure 9: Overall utilization of fentanyl

Figure 10: Overall utilization of hydromorphone



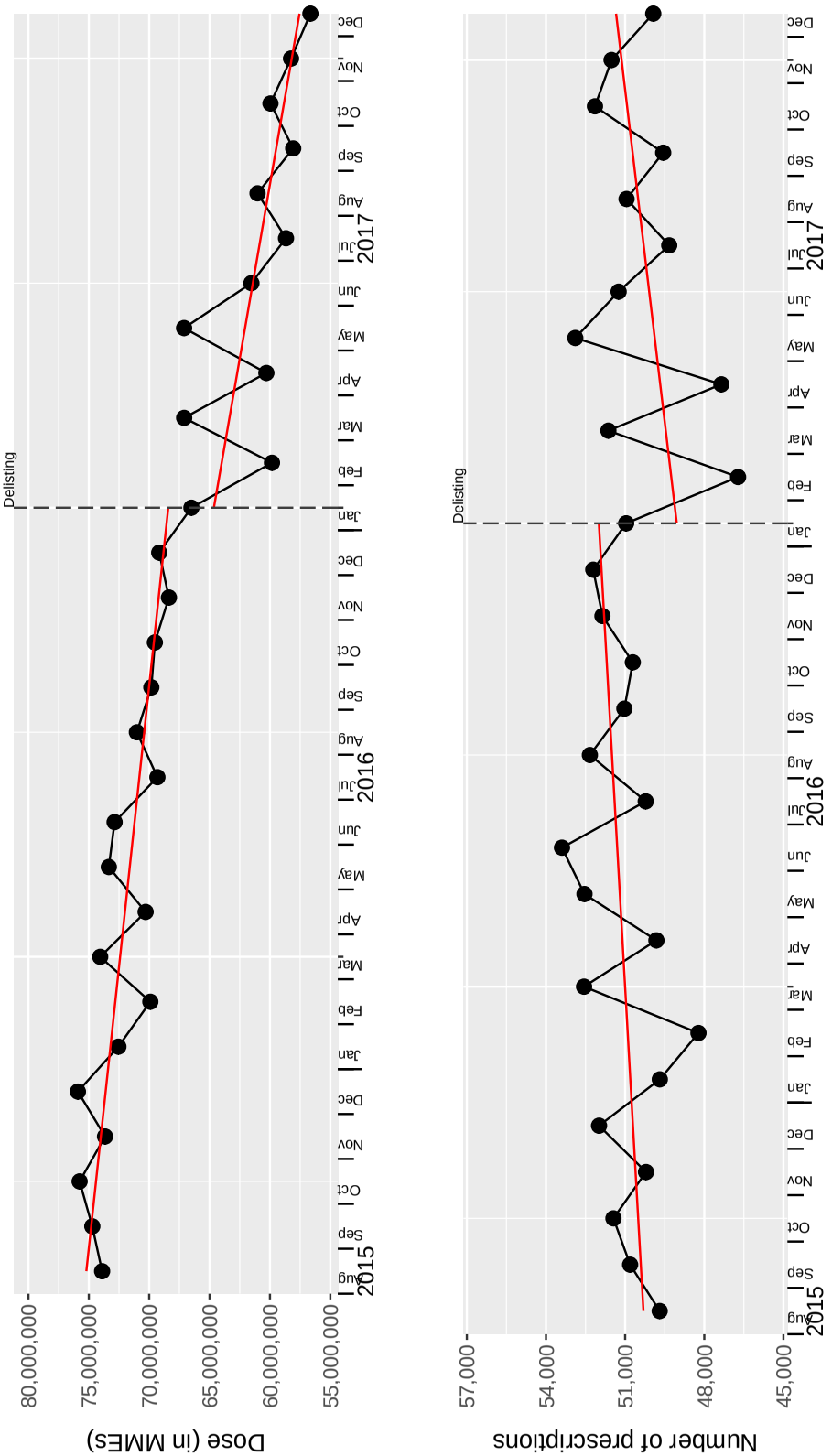


Figure 11: Overall utilization of morphine

Figure 12: Overall utilization of meperidine

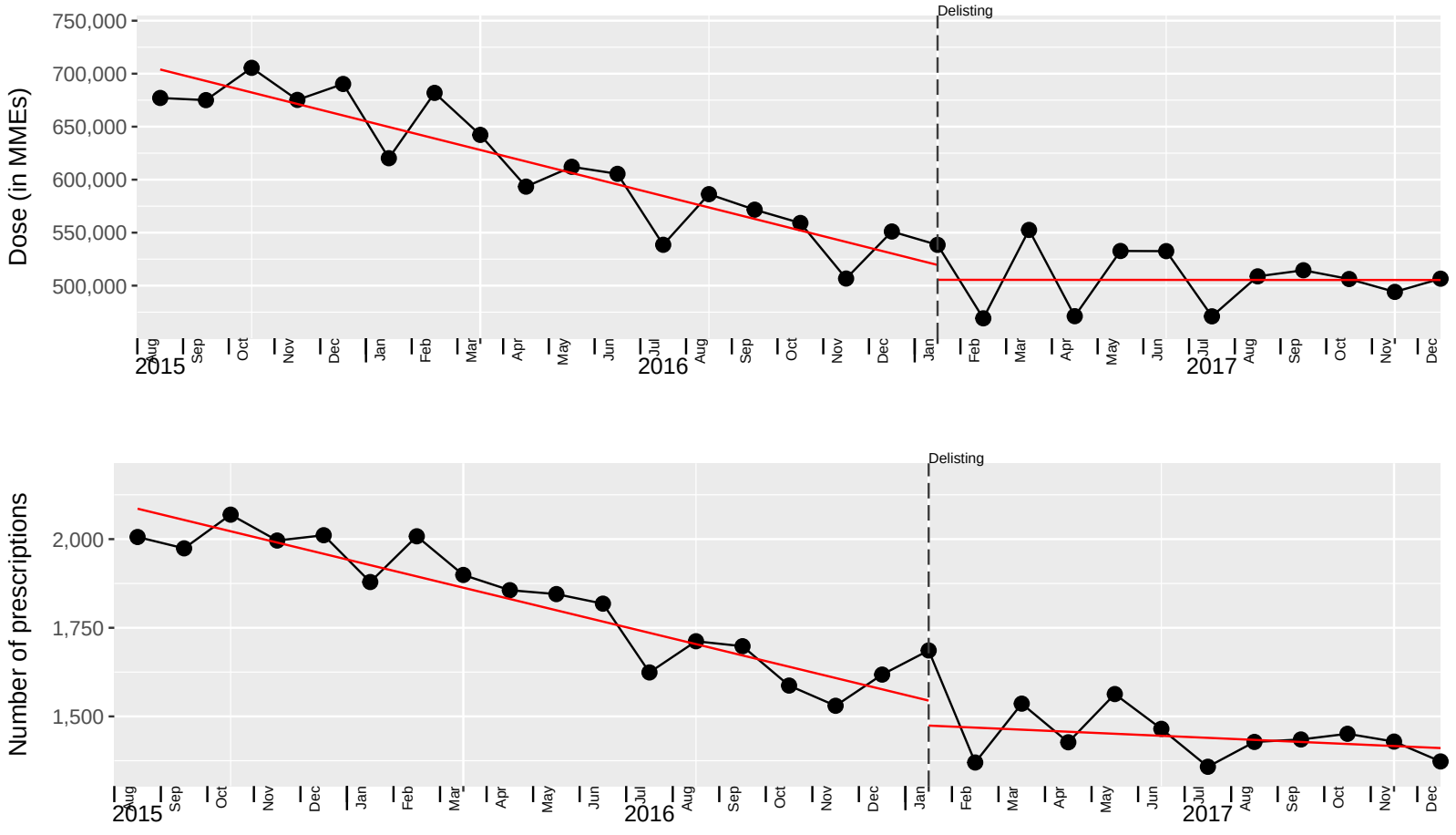


Table 3: Overall Utilization by Dose

	FENTANYL	HYDROMORPHONE	MORPHINE	MEPERIDINE
	(1)	(2)	(3)	(4)
Delisting	−15,082,524.000***	−10,989,115.000**	−3,776,635.000**	−14,029.800
	(2,689,062.000)	(4,046,273.000)	(1,716,701.000)	(22,340.490)
Overall trend	−2,096,109.000***	−186,683.800	−399,079.700***	−10,849.630***
	(161,974.600)	(243,725.700)	(103,404.800)	(1,345.671)
Change in trend	411,301.000	−438,006.700	−245,627.700	10,833.000***
	(351,491.900)	(528,895.400)	(224,393.000)	(2,920.165)
	97,301,843.000***	154,259,315.000***	68,418,802.000***	519,535.100***
	(1,659,745.000)	(2,497,445.000)	(1,059,584.000)	(13,789.020)
Observations	28	28	28	28
R^2	0.983	0.762	0.901	0.881
Adjusted R^2	0.981	0.732	0.889	0.866
Residual Std. Error (df = 24)	3,271,726.000	4,923,017.000	2,088,675.000	27,181.220
F Statistic (df = 3; 24)	469.215***	25.544***	72.889***	59.315***

Note: *p<0.1; **p<0.05; ***p<0.01

Table 4: Overall Utilization by Number of Prescriptions

	FENTANYL	HYDROMORPHONE	MORPHINE	MEPERIDINE
	(1)	(2)	(3)	(4)
Delisting	−839.852	−7,863.665*	−2,952.662**	−70.527
	(515.427)	(4,501.395)	(1,282.346)	(53.394)
Overall trend	−367.919***	952.713***	99.314	−31.836***
	(31.047)	(271.140)	(77.242)	(3.216)
Change in trend	−8.481	468.150	109.859	26.072***
	(67.372)	(588.385)	(167.618)	(6.979)
	22,535.430***	165,807.300***	51,995.350***	1,544.654***
	(318.132)	(2,778.356)	(791.491)	(32.956)
Observations	28	28	28	28
R^2	0.973	0.617	0.184	0.934
Adjusted R^2	0.970	0.570	0.082	0.926
Residual Std. Error (df = 24)	627.109	5,476.754	1,560.203	64.963
F Statistic (df = 3; 24)	292.578***	12.914***	1.801	113.855***
Note:				*p<0.1; **p<0.05; ***p<0.01

Changes in the number of prescriptions showed different patterns. Only morphine showed a significant decrease in prescriptions associated with the delisting. Unique among these results and unexpected was the upward trend in the number of prescriptions of hydromorphone. Also, meperidine started showing a trend of decreasing utilization, which levelled off after the delisting.

Utilization by sociodemographic category: The second part of the research question of this study is concerned with the changes in utilization after the implementation of the policy by sociodemographic category. The format of the regression results was modified for this section. Each output table shows the result of a multi-category RD model for a drug category and sociodemographic variable. However, the coefficients on the tables refer only to the effects of the change at the time of the delisting for that category (previously marked *Delisting* in Tables 3 and 4, and referring to the β_{s1} in formula 3). The estimate of coefficients for overall trends (β_{s2}) and changes in trends (β_{s3}) were included in the model for every category, but they were omitted from these output tables for reasons of space. Also, because the effects of the delisting are expected to be intrinsically linked with the source of funding, independent, but parallel models are included that break down each sociodemographic category by its interaction with a source of funding: public (x *Public*), private insurance (x *Private*), and OOP (x *Private*).

Tables 5 through 16 show the utilization of opioids by sociodemographic variable. For fentanyl, there was an unexpected decrease in the use of private insurance by adults, yet an increase in its use by seniors. Morphine and hydromorphone show mostly only a decrease in utilization by adults, driven largely by the impact in public funding. Use by gender tends to follow the same

trends. Both males and females saw a decrease in opioids utilization with the policy, changes strongly defined by the shift in publicly funded dispensations. This trend is somewhat less statistically significant with morphine. The use of opioids by income shows a decrease in the majority of the income categories. However, higher income levels tend to show less statistical significance, suggesting that they are less responsive to the delisting policy, even when the sources of funding are taken into account. Utilization by number of prescriptions usually changed in the same direction as the utilization by dose, but it shows statistical significance less often.

An exception to most of the trends above is observed with the utilization of meperidine. It is marked by a significant shift from publicly funded utilization to OOP funding. This has left its use by sociodemographic category statistically unchanged by the delisting if the sources of funding are not inspected in more detail.

Table 5: Fentanyl Utilization by gender

	MME	MME by payer	Rxs	Rxs by payer
	(1)	(2)	(3)	(4)
FEMALE	$-8,500,500.000^{***}$		-420.847	
	$(1,431,607.000)$		(268.473)	
x *Public*		$-8,679,117.000^{***}$		-655.922^{***}
		$(906,211.200)$		(220.435)
x *Private*		$-259,374.300$		51.863
		$(906,211.200)$		(220.435)
x *OOP*		$437,991.300$		183.212
		$(906,211.200)$		(220.435)
MALE	$-6,582,024.000^{***}$		-419.005	
	$(1,431,607.000)$		(268.473)	
x *Public*		$-7,188,441.000^{***}$		-555.924^{**}
		$(906,211.200)$		(220.435)
x *Private*		$-178,721.400$		-35.113
		$(906,211.200)$		(220.435)
x *OOP*		$785,138.200$		172.032
		$(906,211.200)$		(220.435)
Observations	56	168	56	168
R^2	0.999	0.998	0.999	0.997
Adjusted R^2	0.999	0.997	0.999	0.997
Residual Std. Error	1,741,807.000	1,102,568.000	326.646	268.199
F Statistic	$5,991.937^{***}$	$2,617.561^{***}$	$9,292.957^{***}$	$2,377.631^{***}$

Note: *p<0.1; **p<0.05; ***p<0.01

Table 6: Fentanyl Utilization by age group

	MME	MME by payer	Rxs	Rxs by payer
	(1)	(2)	(3)	(4)
ADULT	$-9,754,850.000^{***}$		-856.632^{***}	
	(1,021,049.000)		(198.227)	
x *Public*		$-7,386,712.000^{***}$		-743.659^{***}
		(699,169.800)		(174.825)
x *Private*		$-2,566,478.000^{***}$		-261.311
		(699,169.800)		(174.825)
x *OOP*		198,339.700		148.338
		(699,169.800)		(174.825)
PED	8,106.699		1.118	
	(1,021,049.000)		(198.227)	
x *Public*		4,810.466		2.372
		(699,169.800)		(174.825)
x *Private*		$-3,849.586$		-6.794
		(699,169.800)		(174.825)
x *OOP*		7,145.819		5.541
		(699,169.800)		(174.825)
SENIOR	$-5,269,083.000^{***}$		69.282	
	(1,021,049.000)		(198.227)	
x *Public*		$-8,441,449.000^{***}$		-443.363^{**}
		(699,169.800)		(174.825)
x *Private*		$2,111,646.000^{***}$		293.654^{*}
		(699,169.800)		(174.825)
x *OOP*		1,060,720.000		218.992
		(699,169.800)		(174.825)
YA	$-66,697.080$		-53.621	
	(1,021,049.000)		(198.227)	
x *Public*		$-44,207.840$		-27.196
		(699,169.800)		(174.825)
x *Private*		20,586.320		-8.799
		(699,169.800)		(174.825)
x *OOP*		$-43,075.560$		-17.627
		(699,169.800)		(174.825)
Observations	112	336	112	336
R^2	0.999	0.997	0.999	0.997
Adjusted R^2	0.999	0.997	0.999	0.996
Residual Std. Error	1,242,290.000	850,665.500	241.178	212.706
F Statistic	$5,859.949^{***}$	$2,236.459^{***}$	$8,263.404^{***}$	$1,890.922^{***}$

Note: *p<0.1; **p<0.05; ***p<0.01

Table 7: Fentanyl Utilization by income

	MME	MME by payer	Rxs	Rxs by payer
	(1)	(2)	(3)	(4)
HIGH	$-1,324,627.000^{**}$		-129.773	
	(625,877.500)		(118.834)	
x *Public*		$-1,375,718.000^{***}$		-146.061
		(391,414.900)		(92.028)
x *Private*		$-56,946.330$		3.153
		(391,414.900)		(92.028)
x *OOP*		108,037.400		13.134
		(391,414.900)		(92.028)
LOW	$-3,971,347.000^{***}$		-241.134^{**}	
	(625,877.500)		(118.834)	
x *Public*		$-4,408,311.000^{***}$		-422.547^{***}
		(391,414.900)		(92.028)
x *Private*		161,556.500		42.260
		(391,414.900)		(92.028)
x *OOP*		275,406.900		139.153
		(391,414.900)		(92.028)
LOW-MIDDLE	$-4,002,574.000^{***}$		-191.208	
	(625,877.500)		(118.834)	
x *Public*		$-4,047,137.000^{***}$		-262.657^{***}
		(391,414.900)		(92.028)
x *Private*		$-392,195.400$		-1.752
		(391,414.900)		(92.028)
x *OOP*		436,759.000		73.201
		(391,414.900)		(92.028)
MIDDLE	$-3,302,557.000^{***}$		-98.551	
	(625,877.500)		(118.834)	
x *Public*		$-3,362,162.000^{***}$		-187.562^{**}
		(391,414.900)		(92.028)
x *Private*		$-118,307.500$		7.053
		(391,414.900)		(92.028)
x *OOP*		177,912.600		81.958
		(391,414.900)		(92.028)
MIDDLE-HIGH	$-2,481,419.000^{***}$		-179.186	
	(625,877.500)		(118.834)	
x *Public*		$-2,674,229.000^{***}$		-193.020^{**}
		(391,414.900)		(92.028)
x *Private*		$-32,203.000$		-33.965
		(391,414.900)		(92.028)
x *OOP*		225,013.600		47.798
		(391,414.900)		(92.028)
Observations	140	420	140	420
R^2	0.999	0.998	0.999	0.997
Adjusted R^2	0.999	0.997	0.999	0.997
Residual Std. Error	761,492.200	476,226.400	144.583	111.969
F Statistic	$5,330.692^{***}$	$2,418.693^{***}$	$8,009.116^{***}$	$2,340.908^{***}$

Note: *p<0.1; **p<0.05; ***p<0.01

Table 8: Hydromorphone Utilization by gender

	MME	MME by payer	Rxs	Rxs by payer
	(1)	(2)	(3)	(4)
FEMALE	$-5,332,517.000^{**}$		$-4,673.186^{**}$	
	(2,042,145.000)		(2,298.763)	
x *Public*		$-4,543,895.000^{***}$		$-3,075.333^{*}$
		(1,508,609.000)		(1,765.804)
x *Private*		$-371,625.600$		-739.453
		(1,508,609.000)		(1,765.804)
x *OOP*		$-416,996.700$		-858.400
		(1,508,609.000)		(1,765.804)
MALE	$-5,656,597.000^{***}$		$-3,190.479$	
	(2,042,145.000)		(2,298.763)	
x *Public*		$-4,694,279.000^{***}$		$-1,727.707$
		(1,508,609.000)		(1,765.804)
x *Private*		$-541,068.100$		-742.306
		(1,508,609.000)		(1,765.804)
x *OOP*		$-421,250.400$		-720.467
		(1,508,609.000)		(1,765.804)
Observations	56	168	56	168
R^2	0.999	0.997	0.999	0.997
Adjusted R^2	0.999	0.997	0.999	0.996
Residual Std. Error	2,484,635.000	1,835,493.000	2,796.858	2,148.417
F Statistic	$6,357.913^{***}$	$2,228.550^{***}$	$5,921.060^{***}$	$1,969.972^{***}$

Note: *p<0.1; **p<0.05; ***p<0.01

Table 9: Hydromorphone Utilization by age group

	MME	MME by payer	Rxs	Rxs by payer
	(1)	(2)	(3)	(4)
ADULT	$-7,697,050.000^{***}$		$-3,806.354^{**}$	
	(1,534,962.000)		(1,680.334)	
x *Public*		$-5,752,259.000^{***}$		$-1,478.219$
		(1,196,489.000)		(1,522.016)
x *Private*		$-1,259,766.000$		$-1,302.029$
		(1,196,489.000)		(1,522.016)
x *OOP*		$-685,025.500$		$-1,026.106$
		(1,196,489.000)		(1,522.016)
PED	$-22,980.120$		-29.098	
	(1,534,962.000)		(1,680.334)	
x *Public*		4,052.732		7.628
		(1,196,489.000)		(1,522.016)
x *Private*		$-10,281.120$		-14.681
		(1,196,489.000)		(1,522.016)
x *OOP*		$-16,751.740$		-22.045
		(1,196,489.000)		(1,522.016)
SENIOR	$-2,972,325.000^{*}$		$-3,496.599^{**}$	
	(1,534,962.000)		(1,680.334)	
x *Public*		$-3,294,916.000^{***}$		$-3,032.344^{**}$
		(1,196,489.000)		(1,522.016)
x *Private*		399,327.500		-82.090
		(1,196,489.000)		(1,522.016)
x *OOP*		$-76,736.630$		-382.165
		(1,196,489.000)		(1,522.016)
YA	$-296,759.000$		-531.615	
	(1,534,962.000)		(1,680.334)	
x *Public*		$-195,051.300$		-300.105
		(1,196,489.000)		(1,522.016)
x *Private*		$-41,974.320$		-82.960
		(1,196,489.000)		(1,522.016)
x *OOP*		$-59,733.290$		-148.551
		(1,196,489.000)		(1,522.016)
Observations	112	336	112	336
R^2	0.999	0.997	0.999	0.996
Adjusted R^2	0.999	0.996	0.999	0.995
Residual Std. Error	1,867,556.000	1,455,743.000	2,044.428	1,851.806
F Statistic	$5,647.694^{***}$	$1,788.923^{***}$	$5,393.526^{***}$	$1,397.381^{***}$

Note: *p<0.1; **p<0.05; ***p<0.01

Table 10: Hydromorphone Utilization by income

	MME	MME by payer	Rxs	Rxs by payer
	(1)	(2)	(3)	(4)
HIGH	−827,409.900		−1,329.003	
	(892,969.300)		(980.772)	
x *Public*		−665,877.500		−806.547
		(638,686.100)		(720.662)
x *Private*		−62,516.950		−264.714
		(638,686.100)		(720.662)
x *OOP*		−99,015.410		−257.742
		(638,686.100)		(720.662)
LOW	−2,819,070.000***		−1,085.020	
	(892,969.300)		(980.772)	
x *Public*		−2,584,506.000***		−391.627
		(638,686.100)		(720.662)
x *Private*		−155,304.500		−307.779
		(638,686.100)		(720.662)
x *OOP*		−79,259.190		−385.614
		(638,686.100)		(720.662)
LOW-MIDDLE	−3,606,036.000***		−2,718.920***	
	(892,969.300)		(980.772)	
x *Public*		−3,101,506.000***		−2,026.907***
		(638,686.100)		(720.662)
x *Private*		−132,721.200		−259.802
		(638,686.100)		(720.662)
x *OOP*		−371,808.700		−432.211
		(638,686.100)		(720.662)
MIDDLE	−2,308,755.000**		−1,547.128	
	(892,969.300)		(980.772)	
x *Public*		−1,762,512.000***		−792.368
		(638,686.100)		(720.662)
x *Private*		−342,736.400		−419.735
		(638,686.100)		(720.662)
x *OOP*		−203,506.400		−335.025
		(638,686.100)		(720.662)
MIDDLE-HIGH	−1,427,843.000		−1,183.594	
	(892,969.300)		(980.772)	
x *Public*		−1,123,771.000*		−785.591
		(638,686.100)		(720.662)
x *Private*		−219,414.600		−229.729
		(638,686.100)		(720.662)
x *OOP*		−84,657.420		−168.274
		(638,686.100)		(720.662)
Observations	140	420	140	420
R^2	0.999	0.997	0.999	0.997
Adjusted R^2	0.999	0.997	0.999	0.996
Residual Std. Error	1,086,457.000	777,076.300	1,193.285	876.815
F Statistic	5,803.663***	2,219.272***	5,339.136***	1,964.546***

Note: *p<0.1; **p<0.05; ***p<0.01

Table 11: Morphine Utilization by gender

	MME	MME by payer	Rxs	Rxs by payer
	(1)	(2)	(3)	(4)
FEMALE	$-1,737,877.000^{*}$		$-1,448.953^{**}$	
	(886,125.500)		(655.599)	
x *Public*		$-1,114,163.000$		-900.638
		(738,114.400)		(553.836)
x *Private*		$-553,963.900$		-288.925
		(738,114.400)		(553.836)
x *OOP*		$-69,750.770$		-259.391
		(738,114.400)		(553.836)
MALE	$-2,038,757.000^{**}$		$-1,503.709^{**}$	
	(886,125.500)		(655.599)	
x *Public*		$-1,839,575.000^{**}$		$-1,366.913^{**}$
		(738,114.400)		(553.836)
x *Private*		$-351,971.700$		18.209
		(738,114.400)		(553.836)
x *OOP*		152,789.800		-155.005
		(738,114.400)		(553.836)
Observations	56	168	56	168
R^2	0.999	0.997	0.999	0.997
Adjusted R^2	0.999	0.996	0.999	0.996
Residual Std. Error	1,078,131.000	898,048.600	797.654	673.841
F Statistic	$6,948.128^{***}$	$1,805.984^{***}$	$7,153.495^{***}$	$1,747.255^{***}$

Note: *p<0.1; **p<0.05; ***p<0.01

Table 12: Morphine Utilization by age group

	MME	MME by payer	Rxs	Rxs by payer
	(1)	(2)	(3)	(4)
ADULT	$-3,365,206.000^{***}$		$-2,011.609^{***}$	
	(695, 124.900)		(465.689)	
x *Public*		$-2,356,996.000^{***}$		$-1,340.469^{***}$
		(597, 408.600)		(463.588)
x *Private*		−960, 612.200		−369.519
		(597, 408.600)		(463.588)
x *OOP*		−47, 597.140		−301.621
		(597, 408.600)		(463.588)
PED	−6, 160.618		−79.911	
	(695, 124.900)		(465.689)	
x *Public*		−1, 858.876		−22.847
		(597, 408.600)		(463.588)
x *Private*		−6, 152.938		−36.964
		(597, 408.600)		(463.588)
x *OOP*		1, 851.197		−20.100
		(597, 408.600)		(463.588)
SENIOR	−392, 303.700		−741.496	
	(695, 124.900)		(465.689)	
x *Public*		−563, 009.400		-837.130^{*}
		(597, 408.600)		(463.588)
x *Private*		58, 025.160		172.039
		(597, 408.600)		(463.588)
x *OOP*		112, 680.500		−76.406
		(597, 408.600)		(463.588)
YA	−12, 964.730		−119.646	
	(695, 124.900)		(465.689)	
x *Public*		−31, 873.600		−67.104
		(597, 408.600)		(463.588)
x *Private*		2, 804.400		−36.273
		(597, 408.600)		(463.588)
x *OOP*		16, 104.480		−16.269
		(597, 408.600)		(463.588)
Observations	112	336	112	336
R^2	0.999	0.996	0.999	0.995
Adjusted R^2	0.999	0.995	0.999	0.994
Residual Std. Error	845,744.100	726,854.800	566.594	564.038
F Statistic	$5,716.359^{***}$	$1,392.651^{***}$	$6,736.225^{***}$	$1,231.590^{***}$

Note: *p<0.1; **p<0.05; ***p<0.01

Table 13: Morphine Utilization by income

	MME	MME by payer	Rxs	Rxs by payer
	(1)	(2)	(3)	(4)
HIGH	−428,280.700		−134.246	
	(406,160.400)		(289.742)	
x *Public*		−207,164.800		−87.256
		(323,508.500)		(235.209)
x *Private*		−105,939.800		−12.592
		(323,508.500)		(235.209)
x *OOP*		−115,176.100		−34.399
		(323,508.500)		(235.209)
LOW	−694,096.600*		−665.938**	
	(406,160.400)		(289.742)	
x *Public*		−514,229.000		−398.455*
		(323,508.500)		(235.209)
x *Private*		−182,707.600		−67.013
		(323,508.500)		(235.209)
x *OOP*		2,840.035		−200.470
		(323,508.500)		(235.209)
LOW-MIDDLE	−917,788.300**		−709.663**	
	(406,160.400)		(289.742)	
x *Public*		−728,437.300**		−594.642**
		(323,508.500)		(235.209)
x *Private*		−223,407.900		−6.359
		(323,508.500)		(235.209)
x *OOP*		34,056.820		−108.662
		(323,508.500)		(235.209)
MIDDLE	−898,610.500**		−865.343***	
	(406,160.400)		(289.742)	
x *Public*		−772,390.700**		−772.313***
		(323,508.500)		(235.209)
x *Private*		−258,849.900		−40.875
		(323,508.500)		(235.209)
x *OOP*		132,630.100		−52.154
		(323,508.500)		(235.209)
MIDDLE-HIGH	−837,858.600**		−577.472**	
	(406,160.400)		(289.742)	
x *Public*		−731,516.300**		−414.885*
		(323,508.500)		(235.209)
x *Private*		−135,030.500		−143.876
		(323,508.500)		(235.209)
x *OOP*		28,688.180		−18.711
		(323,508.500)		(235.209)
Observations	140	420	140	420
R^2	0.999	0.997	0.999	0.997
Adjusted R^2	0.999	0.996	0.999	0.996
Residual Std. Error	494,166.900	393,606.100	352.523	286.174
F Statistic	5,998.111***	1,741.206***	6,508.916***	1,777.039***
Note:				*p<0.1; **p<0.05; ***p<0.01

Table 14: Meperidine Utilization by gender

	MME	MME by payer	Rxs	Rxs by payer
	(1)	(2)	(3)	(4)
FEMALE	$-2,473.463$		-10.330	
	$(12,898.800)$		(31.936)	
x *Public*		$-57,676.300^{***}$		-219.936^{***}
		$(6,738.820)$		(17.642)
x *Private*		$11,707.730^{*}$		43.978^{**}
		$(6,738.820)$		(17.642)
x *OOP*		$43,495.110^{***}$		165.628^{***}
		$(6,738.820)$		(17.642)
MALE	$-11,556.340$		-60.197^{*}	
	$(12,898.800)$		(31.936)	
x *Public*		$-18,405.720^{***}$		-87.563^{***}
		$(6,738.820)$		(17.642)
x *Private*		$-6,637.034$		-13.261
		$(6,738.820)$		(17.642)
x *OOP*		$13,486.420^{**}$		40.626^{**}
		$(6,738.820)$		(17.642)
Observations	56	168	56	168
R^2	0.998	0.995	0.998	0.996
Adjusted R^2	0.997	0.995	0.998	0.996
Residual Std. Error	15,693.710	8,198.983	38.855	21.465
F Statistic	$2,652.459^{***}$	$1,282.488^{***}$	$3,820.807^{***}$	$1,599.985^{***}$

Note: *p<0.1; **p<0.05; ***p<0.01

Table 15: Meperidine Utilization by age group

	MME	MME by payer	Rxs	Rxs by payer
	(1)	(2)	(3)	(4)
ADULT	$-15,965.930^{*}$		-57.116^{***}	
	(8,963.822)		(21.310)	
x *Public*		$-31,902.410^{***}$		-128.218^{***}
		(4,913.010)		(13.063)
x *Private*		$-5,262.240$		-15.288
		(4,913.010)		(13.063)
x *OOP*		$21,198.720^{***}$		86.390^{***}
		(4,913.010)		(13.063)
PED	241.279		4.189	
	(8,963.822)		(21.310)	
x *Private*		-16.571		1.809
		(4,913.010)		(13.063)
x *OOP*		257.850		2.380
		(4,913.010)		(13.063)
SENIOR	635.717		-20.959	
	(8,963.822)		(21.310)	
x *Public*		$-44,248.290^{***}$		-179.545^{***}
		(4,913.010)		(13.063)
x *Private*		$10,192.160^{**}$		45.766^{***}
		(4,913.010)		(13.063)
x *OOP*		$34,691.850^{***}$		112.820^{***}
		(4,913.010)		(13.063)
YA	1,059.132		3.359	
	(8,963.822)		(21.310)	
x *Public*		68.676		0.265
		(4,913.010)		(13.063)
x *Private*		157.348		-1.570
		(4,913.010)		(13.063)
x *OOP*		833.108		4.664
		(4,913.010)		(13.063)
Observations	112	308	112	308
R^2	0.998	0.995	0.998	0.996
Adjusted R^2	0.997	0.994	0.998	0.995
Residual Std. Error	10,906.100	5,977.558	25.927	15.894
F Statistic	$2,474.647^{***}$	$1,208.943^{***}$	$3,680.492^{***}$	$1,402.304^{***}$
Note:				*p<0.1; **p<0.05; ***p<0.01

Table 16: Meperidine Utilization by income

	MME	MME by payer	Rxs	Rxs by payer
	(1)	(2)	(3)	(4)
HIGH	5,703.237		13.767	
	(7,968.000)		(18.524)	
x *Public*		−7,985.388**		−30.359***
		(3,685.486)		(8.942)
x *Private*		3,496.550		7.349
		(3,685.486)		(8.942)
x *OOP*		10,192.080***		36.777***
		(3,685.486)		(8.942)
LOW	−13,731.000*		−39.884**	
	(7,968.000)		(18.524)	
x *Public*		−25,247.810***		−92.955***
		(3,685.486)		(8.942)
x *Private*		−5,600.447		0.172
		(3,685.486)		(8.942)
x *OOP*		17,117.260***		52.900***
		(3,685.486)		(8.942)
LOW-MIDDLE	−1,180.505		−9.057	
	(7,968.000)		(18.524)	
x *Public*		−18,535.000***		−81.992***
		(3,685.486)		(8.942)
x *Private*		5,483.276		24.391***
		(3,685.486)		(8.942)
x *OOP*		11,871.220***		48.545***
		(3,685.486)		(8.942)
MIDDLE	−1,653.725		−15.157	
	(7,968.000)		(18.524)	
x *Public*		−14,503.550***		−54.219***
		(3,685.486)		(8.942)
x *Private*		−971.748		−3.702
		(3,685.486)		(8.942)
x *OOP*		13,821.570***		42.764***
		(3,685.486)		(8.942)
MIDDLE-HIGH	−3,167.813		−20.196	
	(7,968.000)		(18.524)	
x *Public*		−9,810.280***		−47.973***
		(3,685.486)		(8.942)
x *Private*		2,663.066		2.508
		(3,685.486)		(8.942)
x *OOP*		3,979.402		25.268***
		(3,685.486)		(8.942)
Observations	140	420	140	420
R^2	0.994	0.990	0.996	0.993
Adjusted R^2	0.993	0.989	0.996	0.992
Residual Std. Error	9,694.501	4,484.055	22.537	10.879
F Statistic	999.188***	617.009***	1,593.443***	873.992***
Note:				*p<0.1; **p<0.05; ***p<0.01

Sensitivity Analysis

Comparison of Multi-category Pooled RD Models with Single-category Reference Models: Modified regression tables comparing the output of the multi-category (pooled) and reference model results are included in the supplementary materials. The regression output tables SM1 through SM12 have been modified to collate the treatment effect estimators of multiple single-category models under the same columns, labeled 'single'. Each result under these columns, however, corresponds to a separate independent single-category RD model. Because they do not apply for comparison, summary statistics have been omitted from these tables. Results are rounded to the closest integer. Tables SM1 through SM12 are equivalent to Tables 5 through 16.The pooled model renders the exact same coefficient estimators, even though the common standard error lies somewhere between the smallest and the largest of the standard errors reported by the reference (independent) models. Despite this, the statistical significance of the results differs meaningfully only in very few cases.

Narrow Window Discontinuity Analysis: In the supplementary materials, figures SM13 through SM26 show the results of a narrow window RD analysis, i.e., taking only the five observations closest to the cut-off before and after the policy. The narrow window models could not find any statistically significant effects on the overall utilization of the opioid categories, neither by dose, nor by number of prescriptions. In comparison, the full RD models found a significant effect in four out of eight cases. For the utilization by sociodemographic categories, the full RD and the narrow window models found a significant effect in a similar number of cases (111 and 107, respectively,

out of 351). The two types of models agreed on the evaluation of statistical significance in about 50% of the cases for the overall utilization and in about 65% for the utilization by sociodemographic category. It is possible that these differences are due to the standard errors of the estimators. Including more observations before and after the cut-off will more accurately describe the overall trends and changing trends, although they might also pickup endogenous effects present over a longer period. The narrow window models find much less statistical significance than the full models for overall utilization, while the narrow window models find somewhat more statistical significance for utilization by sociodemographic sectors. This further suggests that the disagreements are due to the variability of the estimators.

Discussion

The descriptive statistics in this study helped describe some general features of the utilization of opioids in Ontario. The gender breakdown of utilization varies from drug to drug, but suggests that men, with higher dose utilization and lower number of prescriptions, might use stronger formulations of these drugs. Notable too is the disproportionate use of meperidine among women. It also shows that lower income groups tend to have a greater utilization of opioids, and that this pattern did not seem to change with the policy. In fact, disability status could point out a common link between opioid prescription and lower income levels.

The naïve estimates showed statistical significance on changes in utilization more frequently than the RD did. This was an unexpected comparison, in part because the t-test does not account for the variation in the data due to trends and changes in trend, which would create larger standard errors

where strong trend behaviour is present. The naïve estimates also placed more statistical significance on the 'Ped' and 'YA' age group categories compared to the RD and pooled-RD models used in this study.

One of the differences between the naïve estimates and the RD analysis is that the former cannot account for ongoing trends in utilization and their change. Naïve estimates assume, instead, that the Pre- and Post-delisting samples are, each, normally distributed. Figures 9 through 12 show the importance of distinguishing between trend behaviour and the policy effect at the discontinuity. When comparing the naïve estimates and the RD results for overall utilization, we see some agreement in the decrease in utilization by dose of fentanyl and hydromorphone, for instance. The RD analysis, however, shows that the increase in hydromorphone prescriptions seen in the naïve estimates is due not to policy, but to an overall trend of increase across both periods. Also, while the naïve estimates failed to see a significant increase in morphine prescriptions (probably in part due to weak positive trends), the RD analysis shows a significant decrease due to the policy.

After the delisting of products from public formularies, a shift to private sources of funding would be expected. This too would be expected of products like opioids that can dramatically improve the quality of life of pain management patients and have a high potential for addiction. These are products that would be expected to have a low price elasticity of demand. Withdrawing the public subsidy for them could cause a shift of funding source to private insurance and OOP payments (effectively increasing the price faced by some consumers) and not change their overall utilization by much. This expected shift in funding could potentially defeat the purpose of the policy, which is to

reduce OUDs. Similarly, the shift in the use of fentanyl from higher to lower strength products (Guan et al., 2018) does not preclude the possibility of OUD. The results of this study show however, that the shift in funding sources was localized, for the most part, only to an increase in the use of private insurance for fentanyl for senior patients. The unexpected decrease in the use of private insurance for fentanyl prescriptions among adults could be due to changes in coverage policies in private insurance plans. Even then, a shift to private insurance is less financially harmful than paying for these drugs OOP. It is possible that some private insurers followed the public delisting and removed these high-strength opioids from their formularies, but no publicly available evidence of this was found.

As for the overall utilization of the four categories of products targeted by the policy, it decreased with the delisting, except for meperidine, suggesting that the policy achieved its intended purpose in a societal scale for three categories. An unexpected finding in this study was the overall increase in the trend of hydromorphone and morphine prescriptions. Fortunately, these increases in prescriptions go hand in hand with a decrease in overall dose, suggesting also a shift to lower strength (non-delisted) products, a lower dose per prescription, and a reduction in the potential of OUDs. Part of this trend could be explained by the use of hydromorphone for safe supply. As a harm-reduction measure, OUD patients can receive a safe, prescribed dose of hydromorphone pills, mostly for crushing and injecting. This explanation, although not a direct consequence of the delisting, suggests other policies to address opioid abuse are in effect.

Thanks to the analytical contributions of this study, it is possible to see the

effects of the policy on some of the categories most critically affected by the OUD epidemic. For instance, this study shows a significant decrease on the utilization of fentanyl by males, albeit a smaller reduction compared to females. This is accompanied by a non-significant decrease in the number of prescriptions in that category, suggesting that men are decreasing the strength of their fentanyl consumption with a relatively small impact on their access to fentanyl. This is potentially good news in the fight against opioids, as men accounted for 75% of the 2,913 opioid related deaths in Canada between 2016 and 2019, and fentanyl and fentanyl-analogues were involved in 78% of these deaths (Special Advisory Committee on the Epidemic of Opioid Overdoses, 2020).

The utilization of meperidine, however, raises some alarms. Habituation (dependence) and addiction to meperidine have been reported since the 1940s (Latta, Ginsberg, & Barkin, 2002). The continued prescription of this drug, despite its poor efficacy, its toxicity, and overall unsuitability for chronic pain management has been deemed problematic (Clubb, Loveday, & Ballantyne, 2013). Although meperidine counted for only about 0.71% of all the opioid prescriptions observed in this study, when the only product in this category (the 50 mg DemerolTM tablet) was delisted, its utilization showed a strong shift to OOP funding, suggesting an economic harm to patients who saw no substitute to their pain management medication. The decision to delist this drug was informed by the Pain Medication Formulary Review Subcommittee of the OPDP (2016b), which found this one to be a "very old drug [,] not indicated for chronic pain [and] associated with significant neurotoxicities". It also assessed that given other pain treatment alternatives for acute pain, "there is no therapeutic role for meperidine" (Dyer, 2016; Ontario Public Drug Pro-

grams, 2016b). Despite what seems to be clear clinical evidence, policymakers seem to have failed to communicate and convince prescribers of these alternatives.

Strengths and limitations

This study seeks to assess the change in utilization of the delisted categories of opioids at two levels, overall utilization and by sociodemographic category, after the implementation of the delisting policy. Its contributions reside in the inclusion of data for public and private sources of funding, as well as its inspection of changes by sociodemographic variables. The former is necessary to assess if the privately financed utilization of opioid drugs does not defeat the purpose of the policy or cause economic harm to patients. The latter contribution can help assess which groups are being most affected by the policy, whether the policy is not having a disproportionate effect on vulnerable groups (e.g. seniors or low-income individuals). The further breakdown of the policy effect by sociodemographic variables and by source of funding reveals more complexity in the dynamics of opioids utilization that can be lost by looking only at sociodemographic variables.

Some of the limitations of this study are related to the structure of the data and the data collection. First, the data records pharmaceutical sales, which are used as proxy for utilization. It does not cover the totality of points of sale of these opioid products, but it uses advanced methods to estimate the missing data from pharmacies out of the sample. The FSAs of these pharmacies are used as a proxy to map the income level of the patients filling their prescriptions. The income estimation makes use of national household

distribution data, even though it is applied to the province of Ontario. The median household income in Ontario, however, is one of the closest, among the provinces, to the national median ($74,287 to $70,336, respectively in 2015; Ontario Ministry of Finance, 2017).

Patient-level data would have been ideal to include more explanatory variables and provide a more complete causal relationship between the changes observed and the delisting policy. Because of the structure of the data, regression discontinuity analysis models were used to detect these changes. Despite this, the very high R^2 values reported in this study reveal that the variables included in the analysis, despite containing endogeneity, model well the observations in the data.

This policy came into effect around the same time as other policies that were part of the same strategy to combat OUD, such as a revision of prescription guidelines and increased access to naloxone and Suboxone^{TM} to treat addiction (OPDP, 2016a). It was also at the time of an increased awareness of the opioid overdose epidemic, among prescribers and the public in general. RD allows us to argue that we have captured a causal effect if there was no discontinuous change in the error term. Unless other policies were implemented at exactly the same time, then the effect of the other policy change should be estimated at the time when the other policy was implemented. The effects of other policies would be endogenously captured by the variables used in this analysis, such as the overall time trends. Another important factor not measured in this data is the illicit use of opioids (non-pharmaceutical or non-prescribed), which contributed more than 67% of the opioid-related deaths in Canada between January 2016 and September 2019 (Special Advisory Committee on the

Epidemic of Opioid Overdoses, 2020). Even though the policy only affects prescription opioids, it can also affect the illicit use.

The research presented in this thesis chapter can be complemented with an investigation of the policies undertaken by private insurers in response to the changes in public formulary and in collaboration with public policy. This could help explain in more detail the causes behind instances of shifts in funding from public to private insurance or OOP. Private formulary policy, however, is not as widely available as public formulary policy. It would also be necessary to investigate the changes in coverage made by multiple private insurers (at least the largest in the market) to get an idea of how their policies affected the utilization of opioids by source of funding.

The RD models presented in this chapter assume homoscedastic standard errors. The possible presence of heteroscedasticity would be difficult to detect given the small number of observations (for overall utilization or for each sociodemographic category) in the models (28 in total). If present, it would also be difficult to determine what form this heteroskedasticity takes. Preliminary work applying heteroscedasticity-consistent standard errors (HCSE) in this analysis, shows a small effect on the statistical significance of changes in the overall utilization of drugs. However, they show an apparent improvement over the homoskedastic pooled RD models in that they show different standard errors for each sociodemographic category in the same model. The pooled models with HCSE are closer to the single-category models used as references in the first sensitivity analysis section of the supplementary materials. Their main appeal appears to be that they produce different standard errors for each sociodemographic category while pooling the observations from

all the categories in the same model. As a consequence, categories with lower utilization (e.g. pediatric or young adult patients) no longer share the same standard errors as groups with higher utilization (e.g. adults or seniors). This means statistical inference tests are more responsive to the utilization levels of each group.

Another tentative research direction is the use of more novel inference approaches specially tailored to RD designs (as opposed to approaches based on ordinary least-squares models). One of these approaches is the local randomization framework (LRF) introduced by Cattaneo et al. (2017). The attractiveness of this model is that it does not require the assumption of a smooth error at the discontinuity as in conventional RD models like the ones used in this study. The LRF requires instead that treatment can be considered as-if randomly assigned near the cut-off. The applicability of the LRF assumptions on the data used in this study still needs to be tested.

Conclusions

North America has been facing a high rate of OUD since the 1990s (Fischer et al., 2019). One of the latest policies designed to curtail opioids abuse took place in January 2017, when the province of Ontario delisted high-strength pharmaceutical opioid products from its public formularies. The policy seems to be addressing key points in the OUD epidemic: Decreases in the overall utilization of fentanyl patches and oral forms of hydromorphone and morphine were observed, but this is not the case with meperidine. Utilization of these opioids also tends to follow a downward trend. It is possible that the increase in the number of hydromorphone prescriptions observed was caused by the utilization of this drug in harm reduction. Utilization of fentanyl was partic-

ularly responsive to the policy, showing statistically significant decreases in many sociodemographic categories. Most importantly in the fight against opioid addiction, fentanyl, which has been involved in more than three quarters of recent opioid-related deaths (Special Advisory Committee on the Epidemic of Opioid Overdoses, 2020), suggests a decrease in dose strength per prescription. The policy, however, does not seem very effective in curtailing the use of meperidine, an antiquated drug considered to have high potential for toxicity and limited clinical value in light of newer alternatives for pain management. Fortunately, meperidine prescriptions represent only 0.71% of all the opioid prescriptions observed in this study. It seems that many patients being treated with meperidine have actually started to pay OOP for this drug after the delisting. Another important finding was that the use of opioids by income shows a decrease in the majority of the income categories. However, higher income levels tend to show less statistical significance, suggesting less responsiveness to the delisting policy.

The delisting of OxyContin^{TM} (oxycodone) has been credited with the increase in use of fentanyl and other dangerous forms of high-strength opioids (Fischer et al., 2019, 2016), which corresponds with the new face of the opioid problem. This precedent points out that it is imperative that opioid policy foresee shifts in utilization and its effect on the public. The inclusion of multiple sources of funding and sociodemographic categories in this study helps shed light on the complexity of opioid utilization and the difficulty to address it with public policy. By assessing the effects of the 2017 delisting policy with this scope and focus, this study points out aspects where the policy shows some evidence of achieving its desired effect, cases where it did not, along with cases where it

might have provoked unintentional harm.

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Appendix

The 2017 delisting of high-strengths opioids form the ODB saw the removal of fentanyl patches of 75 micrograms per hour or more and hydromorphone pills of 24 milligrams or more. There were five products however, that should have been delisted by this logic yet were not. They are all brand products manufactured by the same company. The details about these products are shown in Table A1.

Because they remained as the only high-strength opioids under public subsidy, it was pertinent to assess whether they saw an increase in utilization that could potentially defeat the purpose of the policy. Figures A1, A2, and Table A2 show the overall utilization of these exempted products. The utilization of high-strength Duragesic^{TM} fentanyl patches changed in a similar way as other fentanyl patches, decreasing in dose, but not in number of prescriptions, as the policy intended. Jurnista^{TM} however, did not see a decrease in this change with the policy and its utilization (in dose or in number of prescriptions). It even saw a positive change in utilization trends with the policy. This is different from the changes in utilization observed for all oral hydromorphone products in Tables 3 and 4, which decreased significantly in dose, but not in number of prescriptions. Currently the Duragesic^{TM} products can be accessed in the public formulary through the Exceptional Access Program (EAP) (Government of Ontario, 2020), requiring an application and a case-by-case review (Government of Ontario, 2016). The sale of Jurnista^{TM} was discontinued on October 31, 2018 (Health Canada, 2019).

Table A1: High-strength Opioid Products that were Not Delisted

Molecule	Description	Strength	Form	Brand.Generic	DIN	Manufacturer
Fentanyl	Duragesic	100mcg	Patch	Brand	1937413	Janssen Pharma
Fentanyl	Duragesic	75mcg	Patch	Brand	1937405	Janssen Pharma
Fentanyl	Duragesic Mat	100mcg	Patch	Brand	2275856	Janssen Pharma
Fentanyl	Duragesic Mat	75mcg	Patch	Brand	2275848	Janssen Pharma
Hydromorphone	Jurnista	32mg	Oros Tab	Brand	2337290	Janssen Pharma

Figure A1: Overall Utilization of High-strength Duragesic

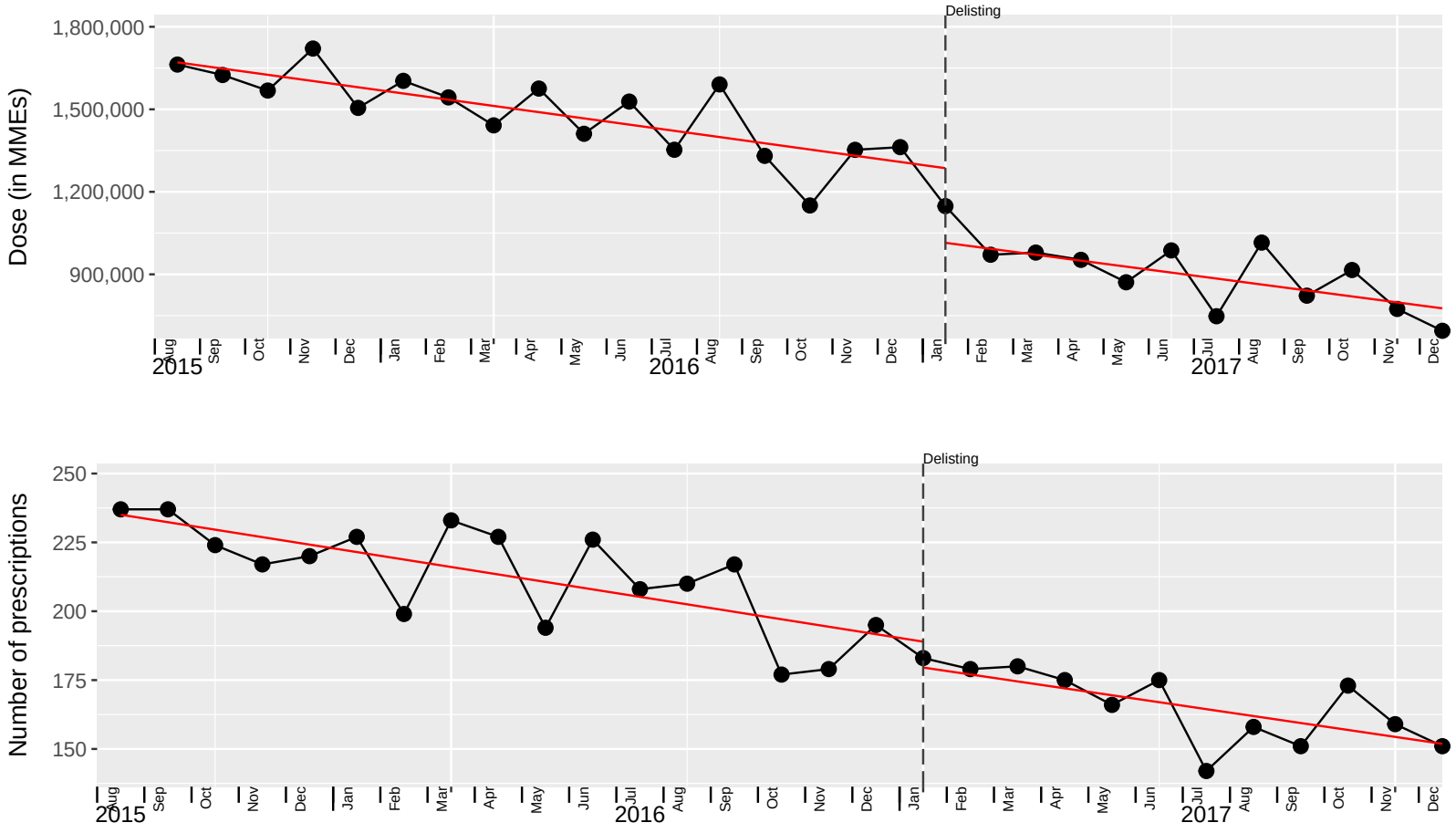


Figure A2: Overall Utilization of High-strength Jurnista

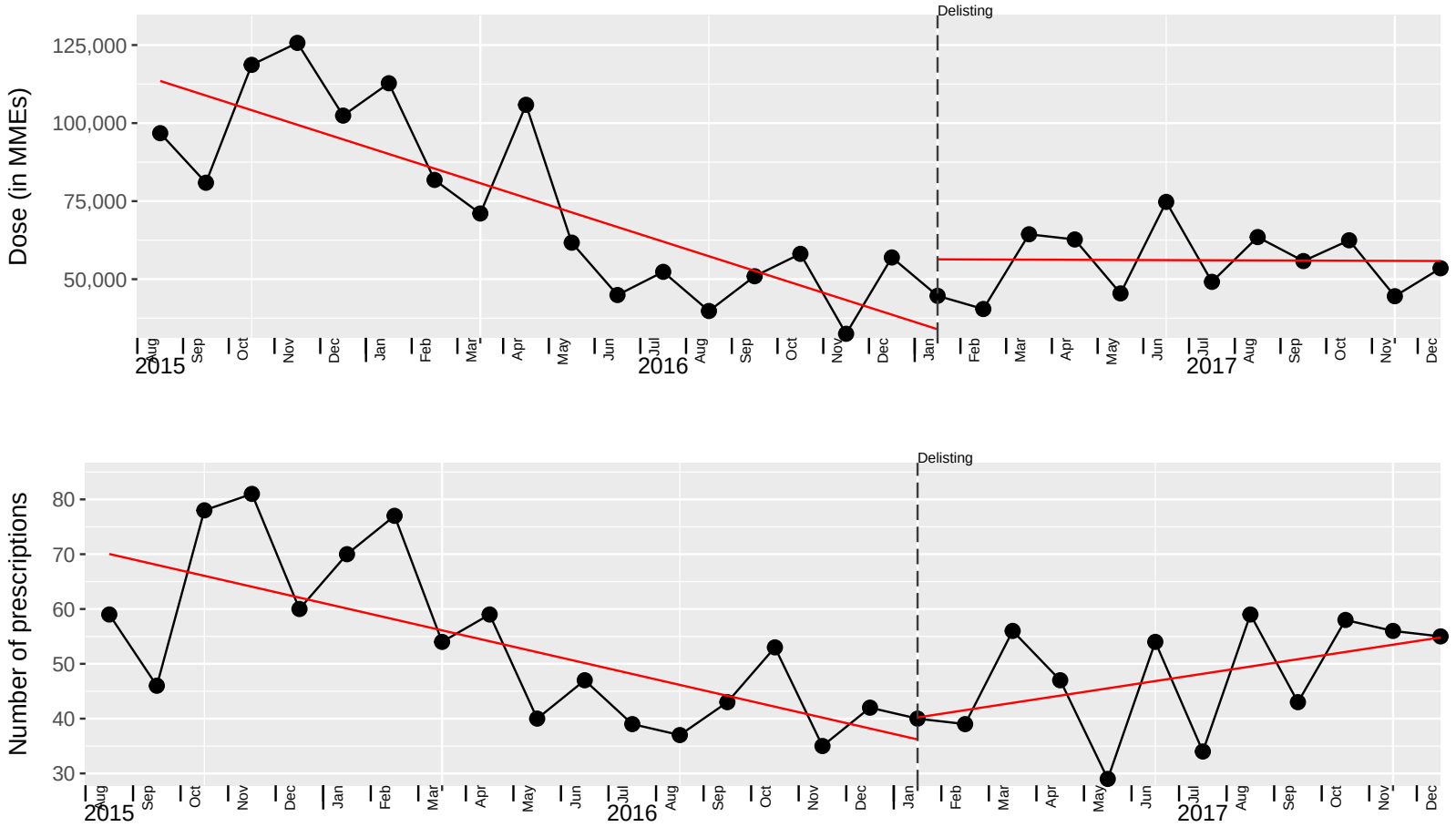


Table A2: Overall utilization of non-delisted high-strength opioids

	Duragesic MME	Duragesic Rxs	Jurnista MME	Jurnista Rxs
	(1)	(2)	(3)	(4)
Delisting	−271,281.800***	−9.392	22,394.880	4.012
	(76,023.610)	(10.168)	(13,162.420)	(9.056)
Overall trend	−22,633.240***	−2.711***	−4,678.588***	−1.990***
	(4,579.252)	(0.612)	(792.833)	(0.545)
Change in trend	971.053	0.193	4,629.716**	3.317***
	(9,937.178)	(1.329)	(1,720.483)	(1.184)
	1,285,939.000***	188.956***	33,962.350***	36.206***
	(46,923.370)	(6.276)	(8,124.122)	(5.589)
Observations	28	28	28	28
R^2	0.929	0.843	0.653	0.412
Adjusted R^2	0.921	0.823	0.610	0.339
Residual Std. Error (df = 24)	92,496.350	12.371	16,014.440	11.018
F Statistic (df = 3; 24)	105.381***	42.831***	15.082***	5.615***
Note:				*p<0.1; **p<0.05; ***p<0.01

Supplementary Materials

Sensitivity Analysis: Comparison of Multi-category Regression Discontinuity Models (Pooled) with Single-category Reference Models

Table SM1: Single-category model comparison of Fentanyl utilization by gender

	MME and MME Single		MME by payer and single		Rxs and Rxs single		Rxs by payer and single	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
FEMALE	$-8,500,500^{***}$	$-8,500,500^{***}$			-421	-421		
	$(1,431,607)$	$(1,708,527)$			(268)	(441)		
x *Public*			$-8,679,117^{***}$	$-8,679,117^{***}$			-656^{***}	-656
			$(906,211)$	$(1,492,154)$			(220)	(407)
x *Private*			$-259,374$	$-259,374$			52	52
			$(906,211)$	$(516,830)$			(220)	(125)
x *OOP*			$437,991$	$437,991$			183	183
			$(906,211)$	$(657,139)$			(220)	(173)
MALE	$-6,582,024^{***}$	$-6,582,024^{***}$			-419	-419		
	$(1,431,607)$	$(1,664,675)$			(268)	(289)		
x *Public*			$-7,188,441^{***}$	$-7,188,441^{***}$			-556^{**}	-556^{*}
			$(906,211)$	$(1,468,111)$			(220)	(287)
x *Private*			$-178,721$	$-178,721$			-35	-35
			$(906,211)$	$(394,916)$			(220)	(67)
x *OOP*			$785,138$	$785,138$			172	172
			$(906,211)$	$(486,459)$			(220)	(124)

Note: *p<0.1; **p<0.05; ***p<0.01

Table SM2: Single-category model comparison of Fentanyl utilization by age group

	MME and MME Single		MME by payer and single		Rxs and Rxs single		Rxs by payer and single	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
ADULT	$-9,754,850^{***}$	$-9,754,850^{***}$			-857^{***}	-857^{**}		
	(1,021,049)	(1,897,942)			(198)	(355)		
x *Public*			$-7,386,712^{***}$	$-7,386,712^{***}$			-744^{***}	-744^{**}
			(699,170)	(1,458,626)			(175)	(293)
x *Private*			$-2,566,478^{***}$	$-2,566,478^{***}$			-261	-261^{**}
			(699,170)	(585,196)			(175)	(99)
x *OOP*			198,340	198,340			148	148
			(699,170)	(501,051)			(175)	(130)
PED	8,107	8,107			1	1		
	(1,021,049)	(20,493)			(198)	(10)		
x *Public*			4,810	4,810			2	2^{*}
			(699,170)	(2,936)			(175)	(1)
x *Private*			$-3,850$	$-3,850$			-7	-7
			(699,170)	(6,935)			(175)	(6)
x *OOP*			7,146	7,146			6	6
			(699,170)	(13,152)			(175)	(5)
SENIOR	$-5,269,083^{***}$	$-5,269,083^{***}$			69	69		
	(1,021,049)	(1,517,080)			(198)	(389)		
x *Public*			$-8,441,449^{***}$	$-8,441,449^{***}$			-443^{**}	-443
			(699,170)	(1,627,491)			(175)	(422)
x *Private*			$2,111,646^{***}$	$2,111,646^{***}$			294^{*}	294^{*}
			(699,170)	(531,513)			(175)	(152)
x *OOP*			1,060,720	1,060,720			219	219
			(699,170)	(673,539)			(175)	(182)
YA	$-66,697$	$-66,697^{*}$			-54	-54^{***}		
	(1,021,049)	(36,399)			(198)	(15)		
x *Public*			$-44,208$	$-44,208^{**}$			-27	-27^{***}
			(699,170)	(16,571)			(175)	(5)
x *Private*			20,586	20,586			-9	-9
			(699,170)	(15,238)			(175)	(7)
x *OOP*			$-43,076$	$-43,076^{*}$			-18	-18^{**}
			(699,170)	(23,210)			(175)	(7)

Note: *p<0.1; **p<0.05; ***p<0.01

Table SM3: Single-category model comparison of Fentanyl utilization by income

	MME and MME Single		MME by payer and single		Rxs and Rxs single		Rxs by payer and single	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
HIGH	$-1,324,627^{**}$	$-1,324,627^{**}$			-130	-130		
	(625,877)	(498,206)			(119)	(104)		
x *Public*			$-1,375,718^{***}$	$-1,375,718^{***}$			-146	-146^{*}
			(391,415)	(423,277)			(92)	(84)
x *Private*			$-56,946$	$-56,946$			3	3
			(391,415)	(169,773)			(92)	(30)
x *OOP*			108,037	108,037			13	13
			(391,415)	(156,525)			(92)	(30)
LOW	$-3,971,347^{***}$	$-3,971,347^{***}$			-241^{**}	-241		
	(625,877)	(1,000,678)			(119)	(191)		
x *Public*			$-4,408,311^{***}$	$-4,408,311^{***}$			-423^{***}	-423^{**}
			(391,415)	(806,370)			(92)	(185)
x *Private*			161,557	161,557			42	42
			(391,415)	(262,912)			(92)	(47)
x *OOP*			275,407	275,407			139	139^{*}
			(391,415)	(283,875)			(92)	(75)
LOW-MIDDLE	$-4,002,574^{***}$	$-4,002,574^{***}$			-191	-191		
	(625,877)	(839,275)			(119)	(171)		
x *Public*			$-4,047,137^{***}$	$-4,047,137^{***}$			-263^{***}	-263
			(391,415)	(700,823)			(92)	(162)
x *Private*			$-392,195$	$-392,195^{*}$			-2	-2
			(391,415)	(195,872)			(92)	(39)
x *OOP*			436,759	436,759			73	73
			(391,415)	(292,342)			(92)	(75)
MIDDLE	$-3,302,557^{***}$	$-3,302,557^{***}$			-99	-99		
	(625,877)	(627,967)			(119)	(148)		
x *Public*			$-3,362,162^{***}$	$-3,362,162^{***}$			-188^{**}	-188
			(391,415)	(658,835)			(92)	(153)
x *Private*			$-118,308$	$-118,308$			7	7
			(391,415)	(148,671)			(92)	(35)
x *OOP*			177,913	177,913			82	82
			(391,415)	(252,078)			(92)	(65)
MIDDLE-HIGH	$-2,481,419^{***}$	$-2,481,419^{***}$			-179	-179		
	(625,877)	(531,831)			(119)	(143)		
x *Public*			$-2,674,229^{***}$	$-2,674,229^{***}$			-193^{**}	-193
			(391,415)	(469,918)			(92)	(118)
x *Private*			$-32,203$	$-32,203$			-34	-34
			(391,415)	(205,915)			(92)	(51)
x *OOP*			225,014	225,014			48	48
			(391,415)	(252,624)			(92)	(60)

Note: *p<0.1; **p<0.05; ***p<0.01

Table SM4: Single-category model comparison of Hydromorphone utilization by gender

	MME and MME Single		MME by payer and single		Rxs and Rxs single		Rxs by payer and single	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
FEMALE	$-5,332,517^{**}$	$-5,332,517^{*}$			$-4,673^{**}$	$-4,673$		
	(2,042,145)	(2,821,364)			(2,299)	(3,456)		
x *Public*			$-4,543,895^{***}$	$-4,543,895$			$-3,075^{*}$	$-3,075$
			(1,508,609)	(2,772,125)			(1,766)	(3,377)
x *Private*			$-371,626$	$-371,626$			-739	-739
			(1,508,609)	(601,041)			(1,766)	(693)
x *OOP*			$-416,997$	$-416,997$			-858	-858
			(1,508,609)	(972,962)			(1,766)	(1,212)
MALE	$-5,656,597^{***}$	$-5,656,597^{**}$			$-3,190$	$-3,190$		
	(2,042,145)	(2,469,476)			(2,299)	(2,513)		
x *Public*			$-4,694,279^{***}$	$-4,694,279^{*}$			$-1,728$	$-1,728$
			(1,508,609)	(2,362,263)			(1,766)	(2,202)
x *Private*			$-541,068$	$-541,068$			-742	-742
			(1,508,609)	(549,519)			(1,766)	(512)
x *OOP*			$-421,250$	$-421,250$			-720	-720
			(1,508,609)	(828,910)			(1,766)	(877)

Note: *p<0.1; **p<0.05; ***p<0.01

Table SM5: Single-category model comparison of Hydromorphone utilization by age group

	MME and MME Single		MME by payer and single		Rxs and Rxs single		Rxs by payer and single	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
ADULT	$-7,697,050^{***}$	$-7,697,050^{**}$			$-3,806^{**}$	$-3,806$		
	(1,534,962)	(2,766,313)			(1,680)	(2,334)		
x *Public*			$-5,752,259^{***}$	$-5,752,259^{**}$			$-1,478$	$-1,478$
			(1,196,489)	(2,328,014)			(1,522)	(1,801)
x *Private*			$-1,259,766$	$-1,259,766^{*}$			$-1,302$	$-1,302^{**}$
			(1,196,489)	(672,366)			(1,522)	(550)
x *OOP*			$-685,025$	$-685,025$			$-1,026$	$-1,026^{*}$
			(1,196,489)	(773,546)			(1,522)	(592)
PED	$-22,980$	$-22,980^{*}$			-29	-29		
	(1,534,962)	(12,840)			(1,680)	(28)		
x *Public*			4,053	4,053			8	8
			(1,196,489)	(4,350)			(1,522)	(6)
x *Private*			$-10,281$	$-10,281^{**}$			-15	-15
			(1,196,489)	(4,562)			(1,522)	(16)
x *OOP*			$-16,752$	$-16,752^{*}$			-22	-22
			(1,196,489)	(8,905)			(1,522)	(13)
SENIOR	$-2,972,325^{*}$	$-2,972,325$			$-3,497^{**}$	$-3,497$		
	(1,534,962)	(2,575,667)			(1,680)	(3,671)		
x *Public*			$-3,294,916^{***}$	$-3,294,916$			$-3,032^{**}$	$-3,032$
			(1,196,489)	(2,977,128)			(1,522)	(4,037)
x *Private*			399,327	399,327			-82	-82
			(1,196,489)	(803,814)			(1,522)	(1,141)
x *OOP*			$-76,737$	$-76,737$			-382	-382
			(1,196,489)	(1,067,421)			(1,522)	(1,509)
YA	$-296,759$	$-296,759^{***}$			-532	-532^{***}		
	(1,534,962)	(66,015)			(1,680)	(141)		
x *Public*			$-195,051$	$-195,051^{***}$			-300	-300^{**}
			(1,196,489)	(24,825)			(1,522)	(109)
x *Private*			$-41,974$	$-41,974$			-83	-83^{*}
			(1,196,489)	(24,640)			(1,522)	(45)
x *OOP*			$-59,733$	$-59,733^{*}$			-149	-149^{***}
			(1,196,489)	(34,765)			(1,522)	(41)

Note: *p<0.1; **p<0.05; ***p<0.01

Table SM6: Single-category model comparison of Hydromorphone utilization by income

	MME and MME Single		MME by payer and single		Rxs and Rxs single		Rxs by payer and single	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
HIGH	−827,410	−827,410			−1,329	−1,329		
	(892,969)	(607,936)			(981)	(856)		
x *Public*			−665,878	−665,878			−807	−807
			(638,686)	(580,126)			(721)	(843)
x *Private*			−62,517	−62,517			−265	−265
			(638,686)	(176,395)			(721)	(204)
x *OOP*			−99,015	−99,015			−258	−258
			(638,686)	(204,656)			(721)	(246)
LOW	−2,819,070***	−2,819,070*			−1,085	−1,085		
	(892,969)	(1,510,544)			(981)	(1,571)		
x *Public*			−2,584,506***	−2,584,506*			−392	−392
			(638,686)	(1,454,103)			(721)	(1,402)
x *Private*			−155,305	−155,305			−308	−308
			(638,686)	(316,775)			(721)	(313)
x *OOP*			−79,259	−79,259			−386	−386
			(638,686)	(457,537)			(721)	(529)
LOW-MIDDLE	−3,606,036***	−3,606,036***			−2,719***	−2,719*		
	(892,969)	(1,138,757)			(981)	(1,371)		
x *Public*			−3,101,506***	−3,101,506**			−2,027***	−2,027
			(638,686)	(1,199,608)			(721)	(1,378)
x *Private*			−132,721	−132,721			−260	−260
			(638,686)	(224,267)			(721)	(230)
x *OOP*			−371,809	−371,809			−432	−432
			(638,686)	(454,915)			(721)	(470)
MIDDLE	−2,308,755**	−2,308,755**			−1,547	−1,547		
	(892,969)	(1,025,423)			(981)	(1,148)		
x *Public*			−1,762,512***	−1,762,512*			−792	−792
			(638,686)	(964,969)			(721)	(1,060)
x *Private*			−342,736	−342,736			−420	−420
			(638,686)	(232,327)			(721)	(255)
x *OOP*			−203,506	−203,506			−335	−335
			(638,686)	(337,841)			(721)	(421)
MIDDLE-HIGH	−1,427,843	−1,427,843			−1,184	−1,184		
	(892,969)	(1,120,453)			(981)	(1,222)		
x *Public*			−1,123,771*	−1,123,771			−786	−786
			(638,686)	(999,217)			(721)	(1,049)
x *Private*			−219,415	−219,415			−230	−230
			(638,686)	(242,950)			(721)	(250)
x *OOP*			−84,657	−84,657			−168	−168
			(638,686)	(371,857)			(721)	(431)

Note: *p<0.1; **p<0.05; ***p<0.01

Table SM7: Single-category model comparison of Morphine utilization by gender

	MME and MME Single		MME by payer and single		Rxs and Rxs single		Rxs by payer and single	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
FEMALE	$-1,737,877^{*}$	$-1,737,877$			$-1,449^{**}$	$-1,449$		
	(886,126)	(1,294,812)			(656)	(881)		
x *Public*			$-1,114,163$	$-1,114,163$			-901	-901
			(738,114)	(1,211,253)			(554)	(812)
x *Private*			$-553,964$	$-553,964^{*}$			-289	-289
			(738,114)	(299,615)			(554)	(239)
x *OOP*			$-69,751$	$-69,751$			-259	-259
			(738,114)	(489,758)			(554)	(403)
MALE	$-2,038,757^{**}$	$-2,038,757$			$-1,504^{**}$	$-1,504^{*}$		
	(886,126)	(1,212,083)			(656)	(771)		
x *Public*			$-1,839,575^{**}$	$-1,839,575$			$-1,367^{**}$	$-1,367^{**}$
			(738,114)	(1,101,250)			(554)	(629)
x *Private*			$-351,972$	$-351,972$			18	18
			(738,114)	(263,893)			(554)	(233)
x *OOP*			152,790	152,790			-155	-155
			(738,114)	(495,101)			(554)	(312)

Note: *p<0.1; **p<0.05; ***p<0.01

Table SM8: Single-category model comparison of Morphine utilization by age group

	MME and MME Single		MME by payer and single		Rxs and Rxs single		Rxs by payer and single	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
ADULT	$-3,365,206^{***}$	$-3,365,206^{**}$			$-2,012^{***}$	$-2,012^{**}$		
	(695,125)	(1,266,277)			(466)	(803)		
x *Public*			$-2,356,996^{***}$	$-2,356,996^{**}$			$-1,340^{***}$	$-1,340^{**}$
			(597,409)	(930,844)			(464)	(526)
x *Private*			$-960,612$	$-960,612^{***}$			-370	-370
			(597,409)	(314,745)			(464)	(224)
x *OOP*			$-47,597$	$-47,597$			-302	-302
			(597,409)	(432,516)			(464)	(231)
PED	$-6,161$	$-6,161$			-80	-80^{*}		
	(695,125)	(19,451)			(466)	(40)		
x *Public*			$-1,859$	$-1,859$			-23	-23^{***}
			(597,409)	(1,648)			(464)	(6)
x *Private*			$-6,153$	$-6,153$			-37	-37^{*}
			(597,409)	(7,692)			(464)	(21)
x *OOP*			1,851	1,851			-20	-20
			(597,409)	(11,584)			(464)	(18)
SENIOR	$-392,304$	$-392,304$			-741	-741		
	(695,125)	(1,261,768)			(466)	(799)		
x *Public*			$-563,009$	$-563,009$			-837^{*}	-837
			(597,409)	(1,461,160)			(464)	(1,007)
x *Private*			58,025	58,025			172	172
			(597,409)	(383,549)			(464)	(353)
x *OOP*			112,681	112,681			-76	-76
			(597,409)	(591,509)			(464)	(484)
YA	$-12,965$	$-12,965$			-120	-120		
	(695,125)	(35,954)			(466)	(76)		
x *Public*			$-31,874$	$-31,874^{***}$			-67	-67^{***}
			(597,409)	(6,425)			(464)	(24)
x *Private*			2,804	2,804			-36	-36
			(597,409)	(12,574)			(464)	(33)
x *OOP*			16,104	16,104			-16	-16
			(597,409)	(22,859)			(464)	(35)

Note: *p<0.1; **p<0.05; ***p<0.01

Table SM9: Single-category model comparison of Morphine utilization by income

	MME and MME Single		MME by payer and single		Rxs and Rxs single		Rxs by payer and single	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
HIGH	−428,281	−428,281			−134	−134		
	(406,160)	(298,720)			(290)	(180)		
x *Public*			−207,165	−207,165			−87	−87
			(323,509)	(202,988)			(235)	(129)
x *Private*			−105,940	−105,940			−13	−13
			(323,509)	(103,720)			(235)	(81)
x *OOP*			−115,176	−115,176			−34	−34
			(323,509)	(104,618)			(235)	(68)
LOW	−694,097*	−694,097			−666**	−666		
	(406,160)	(913,041)			(290)	(560)		
x *Public*			−514,229	−514,229			−398*	−398
			(323,509)	(808,684)			(235)	(477)
x *Private*			−182,708	−182,708			−67	−67
			(323,509)	(182,290)			(235)	(119)
x *OOP*			2,840	2,840			−200	−200
			(323,509)	(289,948)			(235)	(187)
LOW-MIDDLE	−917,788**	−917,788*			−710**	−710*		
	(406,160)	(504,750)			(290)	(397)		
x *Public*			−728,437**	−728,437			−595**	−595
			(323,509)	(527,461)			(235)	(367)
x *Private*			−223,408	−223,408			−6	−6
			(323,509)	(137,804)			(235)	(118)
x *OOP*			34,057	34,057			−109	−109
			(323,509)	(255,443)			(235)	(196)
MIDDLE	−898,610**	−898,610			−865***	−865***		
	(406,160)	(543,021)			(290)	(273)		
x *Public*			−772,391**	−772,391			−772***	−772***
			(323,509)	(523,285)			(235)	(269)
x *Private*			−258,850	−258,850***			−41	−41
			(323,509)	(90,682)			(235)	(81)
x *OOP*			132,630	132,630			−52	−52
			(323,509)	(220,992)			(235)	(151)
MIDDLE-HIGH	−837,859**	−837,859**			−577**	−577*		
	(406,160)	(387,505)			(290)	(284)		
x *Public*			−731,516**	−731,516**			−415*	−415
			(323,509)	(344,041)			(235)	(247)
x *Private*			−135,030	−135,030			−144	−144
			(323,509)	(100,334)			(235)	(87)
x *OOP*			28,688	28,688			−19	−19
			(323,509)	(142,800)			(235)	(120)

Note: *p<0.1; **p<0.05; ***p<0.01

Table SM10: Single-category model comparison of Meperidine utilization by gender

	MME and MME Single		MME by payer and single		Rxs and Rxs single		Rxs by payer and single	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
FEMALE	$-2,473$	$-2,473$			-10	-10		
	(12,899)	(19,404)			(32)	(49)		
x *Public*			$-57,676^{***}$	$-57,676^{***}$			-220^{***}	-220^{***}
			(6,739)	(4,675)			(18)	(17)
x *Private*			$11,708^{*}$	11,708			44^{**}	44
			(6,739)	(12,550)			(18)	(29)
x *OOP*			$43,495^{***}$	$43,495^{***}$			166^{***}	166^{***}
			(6,739)	(8,388)			(18)	(22)
MALE	$-11,556$	$-11,556$			-60^{*}	-60^{***}		
	(12,899)	(9,410)			(32)	(19)		
x *Public*			$-18,406^{***}$	$-18,406^{***}$			-88^{***}	-88^{***}
			(6,739)	(3,113)			(18)	(8)
x *Private*			$-6,637$	$-6,637$			-13	-13
			(6,739)	(4,802)			(18)	(8)
x *OOP*			$13,486^{**}$	$13,486^{**}$			41^{**}	41^{***}
			(6,739)	(5,653)			(18)	(10)

Note: *p<0.1; **p<0.05; ***p<0.01

Table SM11: Single-category model comparison of Meperidine utilization by age group

	MME and MME Single		MME by payer and single		Rxs and Rxs single		Rxs by payer and single	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
ADULT	$-15,966^{*}$	$-15,966$			-57^{***}	-57		
	(8,964)	(11,450)			(21)	(35)		
x *Public*			$-31,902^{***}$	$-31,902^{***}$			-128^{***}	-128^{***}
			(4,913)	(2,043)			(13)	(5)
x *Private*			$-5,262$	$-5,262$			-15	-15
			(4,913)	(6,970)			(13)	(22)
x *OOP*			$21,199^{***}$	$21,199^{***}$			86^{***}	86^{***}
			(4,913)	(6,653)			(13)	(16)
PED	241	241			4	4		
	(8,964)	(338)			(21)	(7)		
x *Private*			-17	-17			2	2
			(4,913)	(120)			(13)	(4)
x *OOP*			258	258			2	2
			(4,913)	(233)			(13)	(3)
SENIOR	636	636			-21	-21		
	(8,964)	(17,326)			(21)	(30)		
x *Public*			$-44,248^{***}$	$-44,248^{***}$			-180^{***}	-180^{***}
			(4,913)	(6,121)			(13)	(20)
x *Private*			$10,192^{**}$	10,192			46^{***}	46^{***}
			(4,913)	(10,037)			(13)	(14)
x *OOP*			$34,692^{***}$	$34,692^{***}$			113^{***}	113^{***}
			(4,913)	(7,242)			(13)	(16)
YA	1,059	1,059			3	3		
	(8,964)	(1,016)			(21)	(4)		
x *Public*			69	69			0	0
			(4,913)	(117)			(13)	(2)
x *Private*			157	157			-2	-2
			(4,913)	(513)			(13)	(3)
x *OOP*			833	833			5	5^{**}
			(4,913)	(577)			(13)	(2)

Note: *p<0.1; **p<0.05; ***p<0.01

Table SM12: Single-category model comparison of Meperidine utilization by income

	MME and MME Single		MME by payer and single		Rxs and Rxs single		Rxs by payer and single	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
HIGH	5,703	5,703			14	14		
	(7,968)	(6,975)			(19)	(13)		
x *Public*			−7,985**	−7,985***			−30***	−30***
			(3,685)	(1,303)			(9)	(4)
x *Private*			3,497	3,497			7	7
			(3,685)	(5,192)			(9)	(10)
x *OOP*			10,192***	10,192**			37***	37***
			(3,685)	(3,657)			(9)	(7)
LOW	−13,731*	−13,731			−40**	−40*		
	(7,968)	(9,582)			(19)	(23)		
x *Public*			−25,248***	−25,248***			−93***	−93***
			(3,685)	(1,754)			(9)	(6)
x *Private*			−5,600	−5,600			0	0
			(3,685)	(4,757)			(9)	(11)
x *OOP*			17,117***	17,117***			53***	53***
			(3,685)	(5,114)			(9)	(13)
LOW-MIDDLE	−1,181	−1,181			−9	−9		
	(7,968)	(4,984)			(19)	(17)		
x *Public*			−18,535***	−18,535***			−82***	−82***
			(3,685)	(2,030)			(9)	(7)
x *Private*			5,483	5,483*			24***	24***
			(3,685)	(3,009)			(9)	(8)
x *OOP*			11,871***	11,871***			49***	49***
			(3,685)	(3,235)			(9)	(12)
MIDDLE	−1,654	−1,654			−15	−15		
	(7,968)	(5,960)			(19)	(17)		
x *Public*			−14,504***	−14,504***			−54***	−54***
			(3,685)	(1,630)			(9)	(7)
x *Private*			−972	−972			−4	−4
			(3,685)	(3,910)			(9)	(9)
x *OOP*			13,822***	13,822***			43***	43***
			(3,685)	(3,111)			(9)	(8)
MIDDLE-HIGH	−3,168	−3,168			−20	−20		
	(7,968)	(11,172)			(19)	(15)		
x *Public*			−9,810***	−9,810***			−48***	−48***
			(3,685)	(1,219)			(9)	(4)
x *Private*			2,663	2,663			3	3
			(3,685)	(5,907)			(9)	(9)
x *OOP*			3,979	3,979			25***	25***
			(3,685)	(5,241)			(9)	(6)

Note: *p<0.1; **p<0.05; ***p<0.01

Sensitivity Analysis: Narrow window - Overall Utilization

Table SM13: Narrow window - Overall Utilization by Dose

	FENTANYL	HYDROMORPHONE	MORPHINE	MEPERIDINE
	(1)	(2)	(3)	(4)
Delisting	−12,270,782.000*	−14,920,673.000	−5,882,334.000	−34,785.000
	(5,057,651.000)	(8,325,998.000)	(4,410,082.000)	(49,363.510)
Overall trend	−4,115,894.000***	−990,033.000	−515,482.500	−13,543.000
	(1,078,295.000)	(1,775,109.000)	(940,232.700)	(10,524.330)
Change in trend	3,901,145.000**	3,000,877.000	856,519.000	24,234.000
	(1,524,939.000)	(2,510,383.000)	(1,329,690.000)	(14,883.660)
	90,584,143.000***	151,562,237.000***	68,035,264.000***	514,351.000***
	(3,576,299.000)	(5,887,370.000)	(3,118,399.000)	(34,905.270)
Observations	10	10	10	10
R^2	0.962	0.680	0.667	0.536
Adjusted R^2	0.943	0.520	0.501	0.304
Residual Std. Error (df = 6)	3,409,867.000	5,613,387.000	2,973,277.000	33,280.870
F Statistic (df = 3; 6)	50.611***	4.250*	4.012*	2.309

Note: *p<0.1; **p<0.05; ***p<0.01

Table SM14: Narrow window - Overall Utilization by Number of Prescriptions

	FENTANYL	HYDROMORPHONE	MORPHINE	MEPERIDINE
	(1)	(2)	(3)	(4)
Delisting	−1,259.500	−11,247.400	−4,926.300	−115.100
	(1,123.061)	(9,374.112)	(2,825.497)	(106.284)
Overall trend	−559.300*	−347.200	57.600	−35.600
	(239.437)	(1,998.567)	(602.398)	(22.660)
Change in trend	539.900	4,501.600	973.500	57.300
	(338.616)	(2,826.401)	(851.920)	(32.046)
	21,930.500***	162,105.800***	51,802.000***	1,522.200***
	(794.124)	(6,628.498)	(1,997.928)	(75.154)
Observations	10	10	10	10
R^2	0.881	0.420	0.446	0.719
Adjusted R^2	0.822	0.131	0.170	0.579
Residual Std. Error (df = 6)	757.168	6,320.025	1,904.950	71.657
F Statistic (df = 3; 6)	14.865***	1.451	1.613	5.119**
Note:				*p<0.1; **p<0.05; ***p<0.01

Sensitivity Analysis: Narrow window - Utilization by Sociodemographic Category

Table SM15: Narrow window - Fentanyl Utilization by gender

	MME	MME by payer	Rxs	Rxs by payer
	(1)	(2)	(3)	(4)
FEMALE	$-7,714,749.000^{**}$		-689.900	
	$(2,572,083.000)$		(581.946)	
x *Public*		$-10,064,976.000^{***}$		$-1,350.100^{***}$
		$(1,420,249.000)$		(356.777)
x *Private*		$268,564.300$		129.400
		$(1,420,249.000)$		(356.777)
x *OOP*		$2,081,663.000$		530.800
		$(1,420,249.000)$		(356.777)
MALE	$-4,556,033.000$		-569.600	
	$(2,572,083.000)$		(581.946)	
x *Public*		$-7,266,871.000^{***}$		$-1,026.200^{***}$
		$(1,420,249.000)$		(356.777)
x *Private*		$254,376.700$		27.100
		$(1,420,249.000)$		(356.777)
x *OOP*		$2,456,461.000^{*}$		429.500
		$(1,420,249.000)$		(356.777)
Observations	20	60	20	60
R^2	0.999	0.998	0.999	0.998
Adjusted R^2	0.999	0.997	0.999	0.997
Residual Std. Error	1,734,098.000	957,532.000	392.348	240.539
F Statistic	$1,745.905^{***}$	987.422^{***}	$2,033.773^{***}$	930.730^{***}

Note: *p<0.1; **p<0.05; ***p<0.01

Table SM16: Narrow window - Fentanyl Utilization by age group

	MME	MME by payer	Rxs	Rxs by payer
	(1)	(2)	(3)	(4)
ADULT	$-7,238,742.000^{***}$		$-1,153.300^{***}$	
	(1,883,850.000)		(406.302)	
x *Public*		$-6,456,620.000^{***}$		$-1,102.400^{***}$
		(1,064,145.000)		(263.595)
x *Private*		$-2,407,060.000^{**}$		−397.100
		(1,064,145.000)		(263.595)
x *OOP*		1,624,938.000		346.200
		(1,064,145.000)		(263.595)
PED	6,385.680		−5.100	
	(1,883,850.000)		(406.302)	
x *Public*		2,160.000		0.800
		(1,064,145.000)		(263.595)
x *Private*		−7,984.080		−11.000
		(1,064,145.000)		(263.595)
x *OOP*		12,209.760		5.100
		(1,064,145.000)		(263.595)
SENIOR	$-4,961,095.000^{**}$		−72.000	
	(1,883,850.000)		(406.302)	
x *Public*		$-10,826,032.000^{***}$		$-1,261.200^{***}$
		(1,064,145.000)		(263.595)
x *Private*		$2,942,147.000^{***}$		561.600^{**}
		(1,064,145.000)		(263.595)
x *OOP*		$2,922,790.000^{***}$		627.600^{**}
		(1,064,145.000)		(263.595)
YA	−77,330.880		−29.100	
	(1,883,850.000)		(406.302)	
x *Public*		−51,354.000		−13.500
		(1,064,145.000)		(263.595)
x *Private*		−4,161.600		3.000
		(1,064,145.000)		(263.595)
x *OOP*		−21,815.280		−18.600
		(1,064,145.000)		(263.595)
Observations	40	120	40	120
R^2	0.999	0.998	0.999	0.998
Adjusted R^2	0.998	0.997	0.999	0.997
Residual Std. Error	1,270,092.000	717,446.300	273.929	177.716
F Statistic	$1,609.682^{***}$	897.942^{***}	$2,020.764^{***}$	855.867^{***}

Note: *p<0.1; **p<0.05; ***p<0.01

Table SM17: Narrow window - Fentanyl Utilization by income

	MME	MME by payer	Rxs	Rxs by payer
	(1)	(2)	(3)	(4)
HIGH	−1,431,726.000		−163.500	
	(1,133,031.000)		(240.046)	
x *Public*		−1,986,692.000***		−274.900*
		(637,976.600)		(150.162)
x *Private*		90,040.320		20.800
		(637,976.600)		(150.162)
x *OOP*		464,925.600		90.600
		(637,976.600)		(150.162)
LOW	−3,102,707.000**		−305.300	
	(1,133,031.000)		(240.046)	
x *Public*		−4,902,780.000***		−657.300***
		(637,976.600)		(150.162)
x *Private*		469,615.000		61.600
		(637,976.600)		(150.162)
x *OOP*		1,330,458.000**		290.400*
		(637,976.600)		(150.162)
LOW-MIDDLE	−2,942,068.000**		−380.800	
	(1,133,031.000)		(240.046)	
x *Public*		−3,862,623.000***		−597.400***
		(637,976.600)		(150.162)
x *Private*		−106,041.600		21.400
		(637,976.600)		(150.162)
x *OOP*		1,026,597.000		195.200
		(637,976.600)		(150.162)
MIDDLE	−3,065,489.000**		−258.500	
	(1,133,031.000)		(240.046)	
x *Public*		−3,735,169.000***		−531.600***
		(637,976.600)		(150.162)
x *Private*		−199,991.500		34.400
		(637,976.600)		(150.162)
x *OOP*		869,672.200		238.700
		(637,976.600)		(150.162)
MIDDLE-HIGH	−1,728,793.000		−151.400	
	(1,133,031.000)		(240.046)	
x *Public*		−2,844,583.000***		−315.100**
		(637,976.600)		(150.162)
x *Private*		269,318.900		18.300
		(637,976.600)		(150.162)
x *OOP*		846,470.900		145.400
		(637,976.600)		(150.162)
Observations	50	150	50	150
R^2	0.999	0.998	0.999	0.998
Adjusted R^2	0.998	0.997	0.999	0.997
Residual Std. Error	763,889.600	430,123.800	161.839	101.239
F Statistic	1,520.094***	838.646***	2,012.680***	897.993***

Note: *p<0.1; **p<0.05; ***p<0.01

Table SM18: Narrow window - Hydromorphone Utilization by gender

	MME	MME by payer	Rxs	Rxs by payer
	(1)	(2)	(3)	(4)
FEMALE	−7,460,320.000		−6,646.400	
	(4,199,310.000)		(4,764.319)	
x *Public*		−10,015,016.000***		−9,742.300***
		(2,352,319.000)		(2,542.759)
x *Private*		666,102.400		721.800
		(2,352,319.000)		(2,542.759)
x *OOP*		1,888,594.000		2,374.100
		(2,352,319.000)		(2,542.759)
MALE	−7,460,354.000		−4,601.000	
	(4,199,310.000)		(4,764.319)	
x *Public*		−8,648,657.000***		−6,112.100**
		(2,352,319.000)		(2,542.759)
x *Private*		−326,213.000		−63.000
		(2,352,319.000)		(2,542.759)
x *OOP*		1,514,517.000		1,574.100
		(2,352,319.000)		(2,542.759)
Observations	20	60	20	60
R^2	0.999	0.999	0.999	0.999
Adjusted R^2	0.999	0.998	0.998	0.998
Residual Std. Error	2,831,174.000	1,585,933.000	3,212.104	1,714.328
F Statistic	1,726.656***	1,052.043***	1,648.076***	1,142.633***

Note: *p<0.1; **p<0.05; ***p<0.01

Table SM19: Narrow window - Hydromorphone Utilization by age group

	MME	MME by payer	Rxs	Rxs by payer
	(1)	(2)	(3)	(4)
ADULT	−10,633,611.000***		−6,398.100*	
	(2,962,405.000)		(3,387.307)	
x *Public*		−9,369,822.000***		−4,826.800**
		(1,748,769.000)		(1,980.501)
x *Private*		−2,074,607.000		−1,986.000
		(1,748,769.000)		(1,980.501)
x *OOP*		810,817.000		414.700
		(1,748,769.000)		(1,980.501)
PED	−5,860.600		17.100	
	(2,962,405.000)		(3,387.307)	
x *Public*		−2,301.200		2.300
		(1,748,769.000)		(1,980.501)
x *Private*		−3,205.000		12.900
		(1,748,769.000)		(1,980.501)
x *OOP*		−354.400		1.900
		(1,748,769.000)		(1,980.501)
SENIOR	−4,024,549.000		−4,655.500	
	(2,962,405.000)		(3,387.307)	
x *Public*		−9,119,126.000***		−10,847.600***
		(1,748,769.000)		(1,980.501)
x *Private*		2,469,199.000		2,673.600
		(1,748,769.000)		(1,980.501)
x *OOP*		2,625,378.000		3,518.500*
		(1,748,769.000)		(1,980.501)
YA	−256,652.400		−210.900	
	(2,962,405.000)		(3,387.307)	
x *Public*		−172,424.200		−182.300
		(1,748,769.000)		(1,980.501)
x *Private*		−51,497.800		−41.700
		(1,748,769.000)		(1,980.501)
x *OOP*		−32,730.400		13.100
		(1,748,769.000)		(1,980.501)
Observations	40	120	40	120
R^2	0.999	0.998	0.999	0.999
Adjusted R^2	0.999	0.997	0.998	0.998
Residual Std. Error	1,997,253.000	1,179,020.000	2,283.722	1,335.254
F Statistic	1,734.117***	960.465***	1,593.421***	999.745***

Note: *p<0.1; **p<0.05; ***p<0.01

Table SM20: Narrow window - Hydromorphone Utilization by income

	MME	MME by payer	Rxs	Rxs by payer
	(1)	(2)	(3)	(4)
HIGH	−1,481,424.000		−1,763.600	
	(1,757,795.000)		(1,998.920)	
x *Public*		−1,751,779.000*		−2,325.700**
		(977,486.700)		(1,044.589)
x *Private*		97,873.200		104.700
		(977,486.700)		(1,044.589)
x *OOP*		172,481.200		457.400
		(977,486.700)		(1,044.589)
LOW	−3,689,018.000**		−2,060.300	
	(1,757,795.000)		(1,998.920)	
x *Public*		−4,771,171.000***		−3,304.400***
		(977,486.700)		(1,044.589)
x *Private*		−30,144.000		190.500
		(977,486.700)		(1,044.589)
x *OOP*		1,112,296.000		1,053.600
		(977,486.700)		(1,044.589)
LOW-MIDDLE	−4,361,086.000**		−4,415.700**	
	(1,757,795.000)		(1,998.920)	
x *Public*		−5,463,106.000***		−5,299.200***
		(977,486.700)		(1,044.589)
x *Private*		297,531.400		133.400
		(977,486.700)		(1,044.589)
x *OOP*		804,488.200		750.100
		(977,486.700)		(1,044.589)
MIDDLE	−3,118,878.000*		−1,634.600	
	(1,757,795.000)		(1,998.920)	
x *Public*		−3,634,905.000***		−2,512.000**
		(977,486.700)		(1,044.589)
x *Private*		4,974.600		175.000
		(977,486.700)		(1,044.589)
x *OOP*		511,052.600		702.400
		(977,486.700)		(1,044.589)
MIDDLE-HIGH	−2,270,267.000		−1,373.200	
	(1,757,795.000)		(1,998.920)	
x *Public*		−3,042,713.000***		−2,413.100**
		(977,486.700)		(1,044.589)
x *Private*		−30,345.800		55.200
		(977,486.700)		(1,044.589)
x *OOP*		802,792.200		984.700
		(977,486.700)		(1,044.589)
Observations	50	150	50	150
R^2	0.999	0.999	0.999	0.999
Adjusted R^2	0.999	0.998	0.998	0.998
Residual Std. Error	1,185,105.000	659,021.400	1,347.671	704.262
F Statistic	1,722.255***	1,087.468***	1,540.005***	1,127.055***

Note: *p<0.1; **p<0.05; ***p<0.01

Table SM21: Narrow window - Morphine Utilization by gender

	MME	MME by payer	Rxs	Rxs by payer
	(1)	(2)	(3)	(4)
FEMALE	−2,820,411.000		−2,417.000	
	(2,227,860.000)		(1,426.298)	
x *Public*		−3,184,361.000**		−3,003.000***
		(1,230,264.000)		(731.370)
x *Private*		−485,469.000		−63.500
		(1,230,264.000)		(731.370)
x *OOP*		849,419.000		649.500
		(1,230,264.000)		(731.370)
MALE	−3,061,923.000		−2,509.300	
	(2,227,860.000)		(1,426.298)	
x *Public*		−3,979,546.000***		−2,952.100***
		(1,230,264.000)		(731.370)
x *Private*		−295,133.500		−56.800
		(1,230,264.000)		(731.370)
x *OOP*		1,212,756.000		499.600
		(1,230,264.000)		(731.370)
Observations	20	60	20	60
R^2	0.999	0.998	0.999	0.999
Adjusted R^2	0.998	0.997	0.999	0.998
Residual Std. Error	1,502,023.000	829,444.100	961.610	493.089
F Statistic	1,226.550***	720.871***	1,757.833***	1,156.446***

Note: *p<0.1; **p<0.05; ***p<0.01

Table SM22: Narrow window - Morphine Utilization by age group

	MME	MME by payer	Rxs	Rxs by payer
	(1)	(2)	(3)	(4)
ADULT	$-4,739,803.000^{***}$		$-3,570.300^{***}$	
	(1,589,611.000)		(971.623)	
x *Public*		$-3,674,930.000^{***}$		$-2,681.400^{***}$
		(951,666.900)		(588.082)
x *Private*		$-1,567,456.000$		-922.500
		(951,666.900)		(588.082)
x *OOP*		502,583.000		33.600
		(951,666.900)		(588.082)
PED	$-65,640.500$		-171.200	
	(1,589,611.000)		(971.623)	
x *Public*		$-6,777.500$		-34.700
		(951,666.900)		(588.082)
x *Private*		$-28,969.000$		-91.600
		(951,666.900)		(588.082)
x *OOP*		$-29,894.000$		-44.900
		(951,666.900)		(588.082)
SENIOR	$-1,074,907.000$		$-1,169.900$	
	(1,589,611.000)		(971.623)	
x *Public*		$-3,428,492.000^{***}$		$-3,208.700^{***}$
		(951,666.900)		(588.082)
x *Private*		803,484.000		908.800
		(951,666.900)		(588.082)
x *OOP*		1,550,101.000		$1,130.000^{*}$
		(951,666.900)		(588.082)
YA	$-1,984.000$		-14.900	
	(1,589,611.000)		(971.623)	
x *Public*		$-53,707.500$		-30.300
		(951,666.900)		(588.082)
x *Private*		12,338.500		-15.000
		(951,666.900)		(588.082)
x *OOP*		39,385.000		30.400
		(951,666.900)		(588.082)
Observations	40	120	40	120
R^2	0.999	0.998	0.999	0.998
Adjusted R^2	0.998	0.996	0.999	0.997
Residual Std. Error	1,071,715.000	641,613.700	655.068	396.485
F Statistic	$1,211.443^{***}$	607.339^{***}	$1,796.025^{***}$	887.171^{***}

Note: *p<0.1; **p<0.05; ***p<0.01

Table SM23: Narrow window - Morphine Utilization by income

	MME	MME by payer	Rxs	Rxs by payer
	(1)	(2)	(3)	(4)
HIGH	−763,315.000		−529.200	
	(1,009,100.000)		(621.344)	
x *Public*		−637,258.000		−533.700
		(552,107.500)		(324.358)
x *Private*		−204,894.000		−76.800
		(552,107.500)		(324.358)
x *OOP*		78,837.000		81.300
		(552,107.500)		(324.358)
LOW	−1,154,309.000		−1,276.700**	
	(1,009,100.000)		(621.344)	
x *Public*		−1,622,894.000***		−1,421.800***
		(552,107.500)		(324.358)
x *Private*		−173,597.000		−88.300
		(552,107.500)		(324.358)
x *OOP*		642,182.000		233.400
		(552,107.500)		(324.358)
LOW-MIDDLE	−1,428,758.000		−1,389.700**	
	(1,009,100.000)		(621.344)	
x *Public*		−1,879,385.000***		−1,678.100***
		(552,107.500)		(324.358)
x *Private*		−175,493.500		−6.500
		(552,107.500)		(324.358)
x *OOP*		626,120.500		294.900
		(552,107.500)		(324.358)
MIDDLE	−1,649,523.000		−956.600	
	(1,009,100.000)		(621.344)	
x *Public*		−1,817,699.000***		−1,372.500***
		(552,107.500)		(324.358)
x *Private*		−264,346.000		80.100
		(552,107.500)		(324.358)
x *OOP*		432,521.500		335.800
		(552,107.500)		(324.358)
MIDDLE-HIGH	−886,429.000		−774.100	
	(1,009,100.000)		(621.344)	
x *Public*		−1,206,671.000**		−949.000***
		(552,107.500)		(324.358)
x *Private*		37,728.000		−28.800
		(552,107.500)		(324.358)
x *OOP*		282,514.000		203.700
		(552,107.500)		(324.358)
Observations	50	150	50	150
R^2	0.999	0.998	0.999	0.999
Adjusted R^2	0.998	0.996	0.998	0.998
Residual Std. Error	680,334.800	372,230.800	418.910	218.682
F Statistic	1,086.468***	664.556***	1,650.232***	1,082.490***

Note: *p<0.1; **p<0.05; ***p<0.01

Table SM24: Narrow window - Meperidine Utilization by gender

	MME	MME by payer	Rxs	Rxs by payer
	(1)	(2)	(3)	(4)
FEMALE	−15,926.000		−32.500	
	(28,025.590)		(60.988)	
x *Public*		−60,784.500***		−237.900***
		(12,517.450)		(28.405)
x *Private*		−6,827.000		15.500
		(12,517.450)		(28.405)
x *OOP*		51,685.500***		189.900***
		(12,517.450)		(28.405)
MALE	−18,859.000		−82.600	
	(28,025.590)		(60.988)	
x *Public*		−28,280.500**		−106.400***
		(12,517.450)		(28.405)
x *Private*		−4,202.500		−9.100
		(12,517.450)		(28.405)
x *OOP*		13,624.000		32.900
		(12,517.450)		(28.405)
Observations	20	60	20	60
R^2	0.997	0.996	0.999	0.998
Adjusted R^2	0.996	0.994	0.998	0.996
Residual Std. Error	18,894.850	8,439.260	41.118	19.150
F Statistic	564.779***	397.088***	1,032.495***	647.470***

Note: *p<0.1; **p<0.05; ***p<0.01

Table SM25: Narrow window - Meperidine Utilization by age group

	MME	MME by payer	Rxs	Rxs by payer
	(1)	(2)	(3)	(4)
ADULT	−20,343.500		−89.600*	
	(19,808.960)		(43.486)	
x *Public*		−29,290.000***		−122.300***
		(8,760.615)		(20.621)
x *Private*		−18,491.500**		−50.300**
		(8,760.615)		(20.621)
x *OOP*		27,438.000***		83.000***
		(8,760.615)		(20.621)
PED	569.000		8.400	
	(19,808.960)		(43.486)	
x *Private*		233.000		3.900
		(8,760.615)		(20.621)
x *OOP*		336.000		4.500
		(8,760.615)		(20.621)
SENIOR	−17,093.500		−38.500	
	(19,808.960)		(43.486)	
x *Public*		−59,618.000***		−217.500***
		(8,760.615)		(20.621)
x *Private*		6,356.000		50.300**
		(8,760.615)		(20.621)
x *OOP*		36,168.500***		128.700***
		(8,760.615)		(20.621)
YA	2,083.000		4.600	
	(19,808.960)		(43.486)	
x *Public*		−157.000		−4.500
		(8,760.615)		(20.621)
x *Private*		873.000		2.500
		(8,760.615)		(20.621)
x *OOP*		1,367.000		6.600
		(8,760.615)		(20.621)
Observations	40	110	40	110
R^2	0.997	0.996	0.998	0.997
Adjusted R^2	0.995	0.994	0.997	0.996
Residual Std. Error	13,355.200	5,906.405	29.319	13.903
F Statistic	504.042***	397.539***	869.209***	582.161***
Note:				*p<0.1; **p<0.05; ***p<0.01

Table SM26: Narrow window - Meperidine Utilization by income

	MME	MME by payer	Rxs	Rxs by payer
	(1)	(2)	(3)	(4)
HIGH	−9,997.000		−6.400	
	(15,023.680)		(30.852)	
x *Public*		−10,451.500		−33.500**
		(6,701.135)		(15.180)
x *Private*		−9,349.000		−11.500
		(6,701.135)		(15.180)
x *OOP*		9,803.500		38.600**
		(6,701.135)		(15.180)
LOW	−28,065.000*		−70.500**	
	(15,023.680)		(30.852)	
x *Public*		−27,466.500***		−100.600***
		(6,701.135)		(15.180)
x *Private*		−14,159.000**		−11.000
		(6,701.135)		(15.180)
x *OOP*		13,560.500**		41.100***
		(6,701.135)		(15.180)
LOW-MIDDLE	5,705.500		9.800	
	(15,023.680)		(30.852)	
x *Public*		−23,417.500***		−89.100***
		(6,701.135)		(15.180)
x *Private*		9,194.500		30.900**
		(6,701.135)		(15.180)
x *OOP*		19,928.500***		68.000***
		(6,701.135)		(15.180)
MIDDLE	1,006.000		−37.900	
	(15,023.680)		(30.852)	
x *Public*		−15,596.000**		−69.500***
		(6,701.135)		(15.180)
x *Private*		2,002.000		−4.600
		(6,701.135)		(15.180)
x *OOP*		14,600.000**		36.200**
		(6,701.135)		(15.180)
MIDDLE-HIGH	−3,434.500		−10.100	
	(15,023.680)		(30.852)	
x *Public*		−12,133.500*		−51.600***
		(6,701.135)		(15.180)
x *Private*		1,282.000		2.600
		(6,701.135)		(15.180)
x *OOP*		7,417.000		38.900**
		(6,701.135)		(15.180)
Observations	50	150	50	150
R^2	0.995	0.992	0.997	0.995
Adjusted R^2	0.991	0.987	0.996	0.992
Residual Std. Error	10,128.970	4,517.904	20.800	10.234
F Statistic	281.021***	197.180***	565.994***	316.211***

Note: *p<0.1; **p<0.05; ***p<0.01

Chapter Four: Increase in Access to Oral-delivery Chemotherapy Drugs for Cancer with OHIP Plus

Abstract

On January first, 2018, Ontario implemented OHIP plus, a policy that expanded public funding for more than 4,400 pharmaceutical products to every permanent resident and citizen less than 25 years of age in the province. This included coverage for some oral antineoplastic (anticancer) drugs. Patients often prefer these drugs to intravenous drugs because of their ease of use, and reduced need for hospital visits. In many cases oral agents represent the current standard of care for specific cancer types. Many of them are, however, very expensive with monthly costs exceeding $10,000. Those without coverage are expected to cover the full cost from their own pockets. On April first, 2019, the province changed OHIP plus to cover people under the age of 25 only if they are not covered by private prescription drug insurance, to cut seemingly unnecessary public spending. This chapter answers the question: 'which oral antineoplastic drugs saw an increase in utilization because of OHIP plus?'. The analysis here makes use of pharmacy sales data and regression discontinuity models to achieve three objectives: 1) screen for those oral antineoplastic drugs that were affected by the policy, 2) look for statistical significance in the changes in utilization among those drugs, and 3) analyze how the utilization changed after OHIP plus was redesigned. The results show that twelve drugs in this category fell under the scope of the policy, being both prescribed to patients in the targeted demographics and actively covered by public subsidies. Of these, eight showed statistically significant changes in utilization with the

start of OHIP plus, and four were affected by the redesign of the policy (which we refer to here as 'OHIP minus'). This chapter also provides some clinical and economic context to discuss what these changes in utilization can tell us about access to these prescription drugs, where OHIP plus succeeded and where it failed to fulfill its objectives, and whether OHIP minus hurt these objectives.

Introduction

It is estimated that one in two Canadians will develop cancer in their lifetime, and one in four will die from it. In 2020, on average, 617 Canadians will be diagnosed with and 228 will die from cancer every day. Cancer has also become the single most common cause of death, accounting for 30% of all deaths in Canada (Canadian Cancer Society, 2020a; Canadian Cancer Statistics Advisory Committee, 2019). Ontario is among the provinces with the highest age-standardized incidence rates (ASIR) of cancer in Canada, with roughly 546.9 per 100,000 per year (Canadian Cancer Statistics Advisory Committee, 2019).

Childhood cancers (0-14 years of age) and cancers in young adults (15-29), are the clinical age categories roughly covered in this chapter. They account for about 1 and 0.5 percent of all cancer cases in Canada, respectively (Canadian Cancer Society, 2020a), yet in 2016 cancer was the number one disease-related cause of death in the first age group (Canadian Cancer Statistics Advisory Committee, 2019). Despite their small share of all cancer cases, cancer in these age groups requires special considerations. For one reason the distribution of cancer types is different at these ages than later in life: leukemia, central nervous system cancer, and lymphoma are the most common childhood cancers; and thyroid, testicular, Hodgkin and non-Hodgkin lymphomas,

and melanomas, for young adults. These give way to breast, prostate, lung, and colorectal cancer among the most common at later stages in life, when incidence of cancer in general is higher. Also, with a much higher survival rate than cancer at later stages in life (Canadian Cancer Statistics Advisory Committee, 2019) and with more years of life after treatment, there is more of an emphasis on quality of life for younger cancer patients.

It became easier for Ontario patients under 25 years of age and their families to pay for prescription medications when the province decided to make public funding for more than 4,400 drugs available to this category of patients. The only eligibility requirements were having an active prescription and a provincial health card. Oral anticancer medications (OAMs) were included in this policy, which was named OHIP plus (OHIP+) and was implemented in January 2018 (Ontario Public Drug Programs, 2017). Prior to this, the drugs included in the province's largest public formulary, the Ontario Drug Benefit (ODB), were only publicly financed for seniors (65 and over), households and individuals eligible for social assistance programs (Trillium Drug Program, Ontario Works, Ontario Disability Support Program), individuals in long-term care facilities, or receiving home and community care services (Government of Ontario, 2020). OHIP plus was redesigned later (a policy change we henceforth label as 'OHIP minus') to cover only people under 25 who were not covered by private insurance plans (those with access to the ODB through other programs would still be covered). These changes took effect on April 2019 (Ontario Ministry of Health and Long-Term Care, 2019). The motivation behind OHIP minus was to cut unnecessary public spending. During the first stage of OHIP plus, giving public drug coverage to people with private insurance effectively trans-

ferred the bulk of the cost to the public payer (financed by tax-payer dollars) with little additional economic benefit to the patients, their families, and the public.

This chapter analyzes the changes in utilization of OAMs due to OHIP plus. Most of the drugs analyzed in this chapter are targeted OAMs. Although there is no standardized differentiation between cytotoxic and targeted anticancer medications, Winkler et al. (2014) present a set of criteria after a literature review. According to them, a cytotoxic agent indiscriminately kills both healthy and tumour cells, acting by "disrupting the DNA structure or mitotic function" of cells, but without a mechanism that selects between tumour and non-tumour cells. On the other hand, targeted anticancer drugs "do not meet this definition as these do not directly interact with DNA or DNA-maintenance processes, and act on targets that suggest a preferential or selective action on cancer cells as compared to healthy cells" (Winkler et al., 2014). From these definitions, the importance of targeted agents becomes clear. It is indeed the case that targeted OAMs have had a rapid expansion since the first one, imatinib, was approved by the FDA in 2001, and they have been constituting a substantial part of recently approved drugs and those in development (Smieliauskas, Chien, Shen, Geynisman, & Shih, 2014).

The rationale for focusing on oral cancer drugs is that Medicare, throughout Canada, does not cover this category. Because IV drugs need to be administered in a health care centre, these are provided at no cost to the patient (if the drug is included in public formularies) (Canadian Cancer Society, 2020b). This is not the case for any oral chemotherapy drugs, however (Government of Canada, 2018), as they are not dispensed in health care centres and their

purchase depends on provincial formularies and their eligibility criteria, which before OHIP plus in Ontario, used to focus on seniors and households on social assistance. Private insurers have drug formularies that tend to imitate the provincial ones, but this is not strictly the case. The age cut-off of 25 in OHIP plus is important because children are covered by their parents' private insurance plans only until the age of 18, 21 (depending on the plan), or 25 if the child is a university or college student.

On multiple occasions, patients' preference for oral antineoplastic drugs (over IV) has been documented. Eek et al. (2016) report that patients preferred oral drugs over IV treatment on 84.6% of the 13 selected articles, on varied cancer care scenarios. In a seminal Canadian study, 92% of 103 palliative cancer patients preferred oral chemotherapy to IV, 10 preferred IV, and one had no preference (Liu, Franssen, Fitch, & Warner, 1997). The reasons commonly given for this preference are the convenience and cost-savings from not having to go to a health care centre to receive treatment, the ability to receive the treatment at home, the perception of efficacy, and previous experiences with IV, such as pain and the difficulty of opening IV lines (Eek et al., 2016; Liu et al., 1997). For some types of cancer, OAMs have become the standard of treatment.

Some of the issues with these oral drugs have been the possibility of non-adherence to self-administered medication, side effects, and misconceptions regarding their convenience (Eek et al., 2016; Smieliauskas et al., 2014). Another significant concern is the cost of treatment associated with these drugs. Many of them are priced at thousands or even tens of thousands of dollars a month, making long-term treatment a considerable financial burden for pa-

tients and health-care systems. Controversy followed when governments made the decision to pay for some of these drugs, such as when the UK decided to cover imatinib, Australia covered vemurafenib, and Canada covered sorafenib (Smieliauskas et al., 2014).

This chapter answers the question of which OAMs saw an increase in utilization because of OHIP plus. The study makes use of pharmacy sales data to achieve the following objectives: 1) Screen for those drugs that were affected by the policy in their utilization, 2) look for statistical significance in the changes in utilization among those drugs, and 3) analyze how utilization changed after OHIP minus. This chapter also provides some clinical and economic context to discuss what these changes in utilization can tell us about access to these prescription drugs, where OHIP plus succeeded and failed to fulfill its objectives, and whether OHIP minus defeated the purpose of the original policy.

Throughout this chapter these targeted oral antineoplastic drugs are referred to as 'drugs', 'cancer drugs', or 'OAMs'. Also, the term 'drug' refers to all pharmaceutical products with the same (main) active ingredient or molecule, regardless of strength, manufacturer, or DIN of the product.

Methodology

Data

Time points: Monthly data for prescription OAM drug sales in Ontario was acquired from IQVIA (https://www.iqvia.com/). The period included in this analysis spans from August 2015 to July 2019. In our analysis, drug sales data is used as a proxy for utilization.

Coverage: The data set recorded point-of-sale (pharmacy) data of prescrip-

tions purchases made in retail pharmacies across Ontario participating in IQVIA's data acquisition network. In Ontario, the coverage is for 42.5% of all the pharmacies in the province, but it includes most of the largest stores, accounting for a considerably greater percentage of all the prescriptions in the province. The data does not include dispensations made in health care centres. Data from pharmacies out of the network was estimated by IQVIA using geospatial projections, based on store size, number of stores, and distance (IQVIA, personal communication, April 14, 2020); see the *Dependent variables* section below for more details.

Population: The analysis in this study makes use of data only from patients under 25, the population directly affected by OHIP plus.

Payer type: The sale of OAMs according to the primary source of payment, public or private funding, was analyzed. The term 'private' funding includes sales when the primary source of funding was either private insurance or out-of-pocket (OOP) payments. The latter category was also observed separately due to its implications on financial access. The combined sales from all sources of funding ('total') are also analyzed.

Unit of observation: The unit of observation in this study is the aggregation of prescription sales by drug, month, and payer type. This organization is derived from the structure of the IQVIA data set acquired. The unit of observation was initially specific to each individual pharmaceutical product (as defined by a single DIN), but these observations were aggregated by drug type (active molecule). Sociodemographic data about the type of patient filling the prescription and data for individual products was aggregated due to the small number of prescriptions of cancer drugs among patients under 25.

Dependent variables: The number of prescriptions sold at each time point was used as the dependent variables. For each pharmacy not participating in IQVIA's data acquisition network, the number of prescriptions was projected using geospatial statistics based on data reported by the closest two to ten participating pharmacies. The reported data was factored by the geographical distance to the non-participating pharmacy and weighted for differences in store size between them (IQVIA, 2018). A potential source of error introduced was that the projected number of prescriptions for non-participating pharmacies was rounded down to the closest integer, unlike other available sales data on drug quantity (IQVIA, personal communication, November 9, 2018). To reduce this error, any observations showing a non-zero drug quantity, but a zero number of prescriptions had the number of prescriptions rounded up to one. This is consistent with the data analysis performed in chapter three, an analysis of opioid utilization.

Descriptive Analysis and Naïve Estimates

Drug Selection: To start screening for those drugs whose utilization changed due to OHIP plus, a descriptive selection was performed for those drugs that would be affected by the policy. Only antineoplastic drugs of oral administration are included in this analysis. These forms include tablets, capsules and their variations observed in the data set: film coating tablets, gel capsules, and tablets for oral suspension. This data set includes mostly targeted oral drugs, although for some drugs, their classification as targeted or cytotoxic agents can be inconsistent (Winkler et al., 2014). Only drugs that were observed to be both prescribed to patients under 25 AND to be paid for with public funding were selected. Two drugs (alectinib and regorafenib) began to fulfill

these criteria only after OHIP minus had come into effect, meaning that the effect of the initial policy could not be observed in them.

Naïve Estimates: Naïve estimates of the changes in overall utilization (all funding sources) were prepared. These naïve estimates compare the utilization per month during the three periods of this policy: First, before OHIP plus; second, after the start of OHIP plus but before the start of OHIP minus; and third, after the start of OHIP minus. Then monthly utilization during the first and second periods were compared with a two-tailed heteroskedastic Student's t-test. The same comparison was made for the second and third periods.

Regression Analysis

As with the previous chapter, regression discontinuity (RD) models were used for the statistical analysis. As Bailey (2019) states, RD models are good for "looking for jumps in data". These models were used to identify possible discontinuities in the utilization of OAMs at the point where the treatments (the start of OHIP plus and of OHIP minus) were applied. This part of the analysis was divided into two phases to isolate the effect of each policy: the first one is focused on the changes before and after the start of OHIP plus and includes the time points between August 2015 (earliest available) and March 2019 (before the start of OHIP minus), with the start of OHIP plus on January 2018 as the cut-off when treatment start. The second phase focuses on OHIP minus and includes the time points between January 2018 (start of OHIP plus) and July 2019 (latest available), with the start of OHIP minus on April 2019 as the cut-off time when treatment is applied.

Utilization measured by number of prescriptions was the outcome variable.

Each treatment was applied uniformly to the entire population and to all applicable drugs on January 2018 (start of OHIP plus) and April 2019 (start of OHIP minus). For this reason, time, or more precisely the difference between the time point in an observation and the cut-off points in each phase of the analysis is the independent assignment variable. The treatment variable is binary. The effect of the assignment variable captures the background trends in utilization in time throughout the period of study, separating it from the desired effect of treatment itself on utilization. An interaction between treatment and the assignment variable can be used to isolate the effect of any possible change in trends after treatment started. Formula 1 represents the regression model:

$$Y_i = \beta_0 + \beta_1 T_i + \beta_2 (X_i - C) + \beta_3 (X_i - C) T_i + \epsilon_i \tag{1}$$

Where:

Y_i is the outcome variable (number of prescriptions) of observation i

T_i is the treatment variable: 0 before January 2018, 1 otherwise for the analysis of the start of OHIP plus; and 0 prior to April 2019, 1 otherwise for the analysis of OHIP minus

$X_i - C$ is the assignment variable - how much above or below the cut-off an observation is, where

C is the cut-off date for each part of the analysis and ...

X_i is the time point of the observation

The drugs that were affected by the policy (prescribed to patients under 25 AND with public funding) were analyzed for statistically significant changes in utilization with OHIP plus in the first phase of the regression analysis. The effect of the treatment variable (β_1 in formula 1) is the focus of this analysis. The changes in trend (β_3) after the policy are also reported. The drugs were then analyzed for changes in the number of prescriptions after OHIP minus in the second phase of the analysis. Effects due to OHIP minus were expected only on those drugs significantly affected by OHIP plus. The second phase results for these drugs are included in the main body of this chapter. The results for drugs that were not significantly affected by OHIP plus are included in the appendix section. The effects of other policies that could have possibly been put in place during the same period of observation would be endogenously captured by the variables used in this analysis, such as the overall time trends (β_2).

RD models were selected as the statistical models for two reasons. First, the data acquired is not structured at a patient-level or similar cross-sectional unit, but by a pharmacy-level aggregation of sales, which presented a challenge for the use of causal explanatory models at the individual level, but could work for identifying jumps in data between the periods before and after the policy implementation. Second, because the focus is on detecting significant changes only with the policy implementation, the complexity of panel data or other time series models was not necessary. The attempt is not at modeling the dynamics of OAM sales, but to provide justification for the assumption of smoothness in the error term at the point of policy implementation.

The main assumption of RD models is that the error term is not discontinuous

at the treatment threshold. Diagnostic tests have been proposed for RD models (Bailey, 2019). However, in the case of this analysis, a histogram of the assignment variable would not reveal any endogeneity, as exactly one observation per category per time point is used in the model. No other explanatory independent variables are available to test any other variables that might jump at the treatment discontinuity. If this assumption holds, RD allows us to argue that the effect of the treatment variable (β_1) captures a causal effect of the policy. Additional assumptions would need to be fulfilled before attributing a causal effect to the policy for the changes in trend (β_3).

Sensitivity Analysis

Narrow Window Analysis: As with the previous chapter, these narrow window models were performed in parallel to the full RD models (all available time points) including only the five closest observations to the cut-off before and after the delisting in the regression models for the OHIP plus analysis. For the OHIP minus analysis, only the four closest observations before and after the cut-off were included because only four observations after the cut-off were available.

Results

Descriptive Analysis and Naïve Estimates

Drug Selection: The data set started with 29 (N = 29) OAM drugs. Only drugs that were observed to be both prescribed to patients under the age of 25 AND to be paid for with public funding were considered drugs that were affected by the policy. This reduced the number of drugs to twelve (N = 12). Of interesting notice were drugs that started being prescribed with the above

criteria only some time after OHIP minus had taken place, meaning that the effect of the initial policy could not be observed in them (N = 2). Figure 1 summarizes the drug selection at the descriptive and the statistical stages.

Figure 1: Process of drug selection

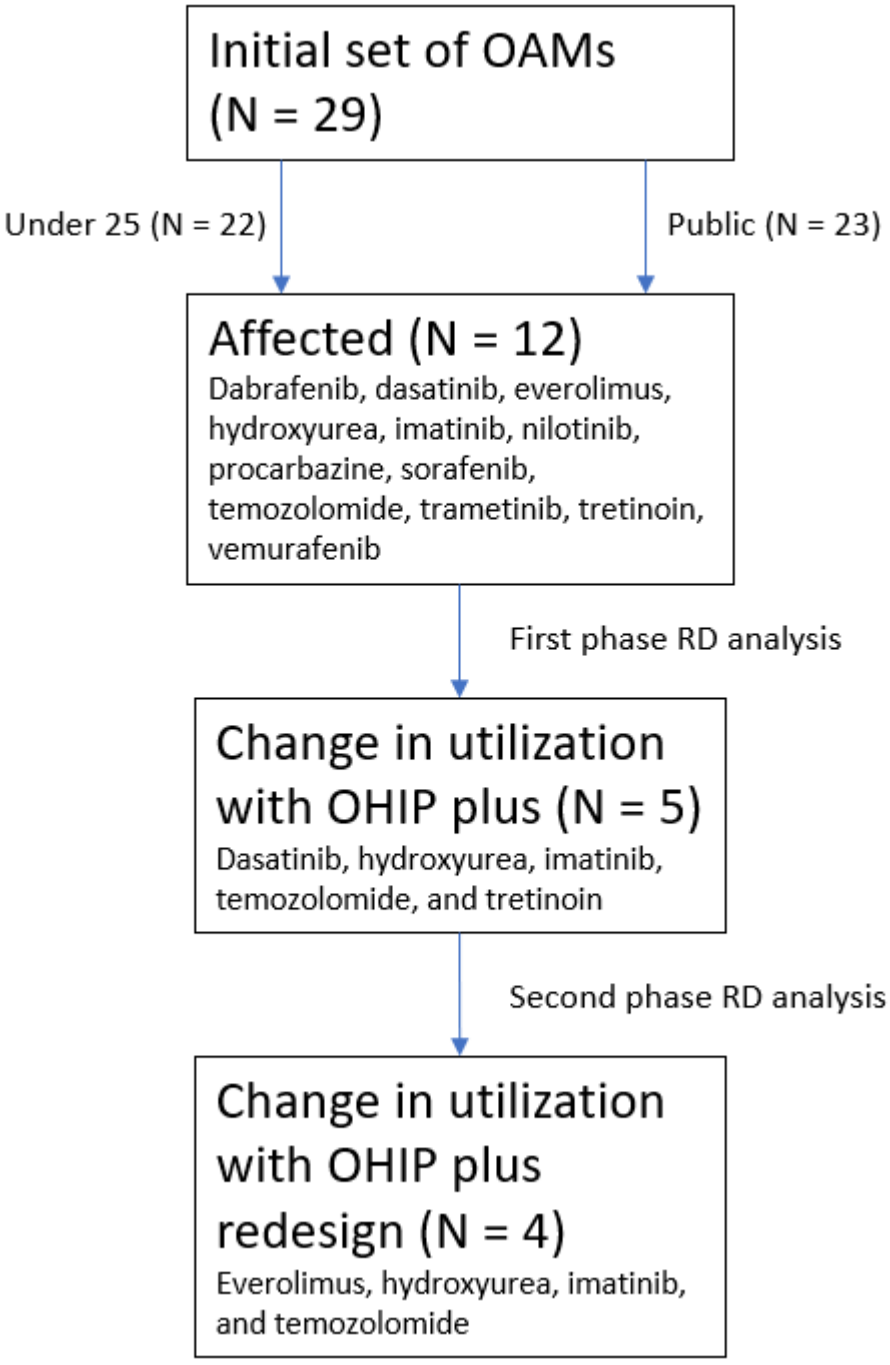


Table 1 presents in detail the initial list of drugs and some information about their commercial availability, such as whether generic versions of the drug are available and in what strengths (in milligrams). The table also summarizes the initial selection of drugs affected by the policy, namely if the drug was prescribed to any patients under 25 (*Under 25*), and if it was paid for at any time with public funding (*Public*). When both these criteria applied to the same observations the drug was considered affected by OHIP plus (*Affected* column). Those products that saw a later uptake in prescriptions are pointed out under the *Later* column. Finally, the table also presents brief clinical information about each drug, the classification (cytotoxic or targeted) the year of FDA approval, and the therapeutic class (type of cancer it is prescribed for) as reported by Sun et al. (2017) for drugs approved before 2015.

Table 1: Cancer Drugs of Oral Administration

Drug	Generic	Strength	Under 25	Public	Affected	Later	Classification	Approval year	Therapeutic class
Abiraterone Acetate	No	250, 500	Yes	Yes	No	No	Targeted	2011	Prostate cancer
Alectinib	No	150	No	No	No	Yes			
Cobimetinib	No	20	No	Yes	No	No			
Dabrafenib	No	50, 75	Yes	Yes	Yes	No	Targeted	2013	Melanoma
Dasatinib	No	20, 50, 70, 80, 100, 140	Yes	Yes	Yes	No	Targeted	2006	Leukemia
Everolimus	No	2, 2.5, 5, 7.5, 10	Yes	Yes	Yes	No	Targeted	2009	Breast cancer; Brain cancer; Kidney cancer; Pancreatic cancer
Hydroxyurea	Yes	500	Yes	Yes	Yes	No	Targeted	2010	Melanoma; Leukemia; Ovarian cancer; Head and neck cancer
Idelalisib	No	100, 150	Yes	Yes	No	No	Targeted	2014	Leukemia; Lymphoma
Imatinib	Yes	100, 400	Yes	Yes	Yes	No	Targeted	2001	Leukemia; Stomach cancer
Ixazomib	No	2.3, 3, 4	No	Yes	No	No			
Lapatinib	No	250	Yes	Yes	No	No	Targeted	2007	Breast cancer

(continued)

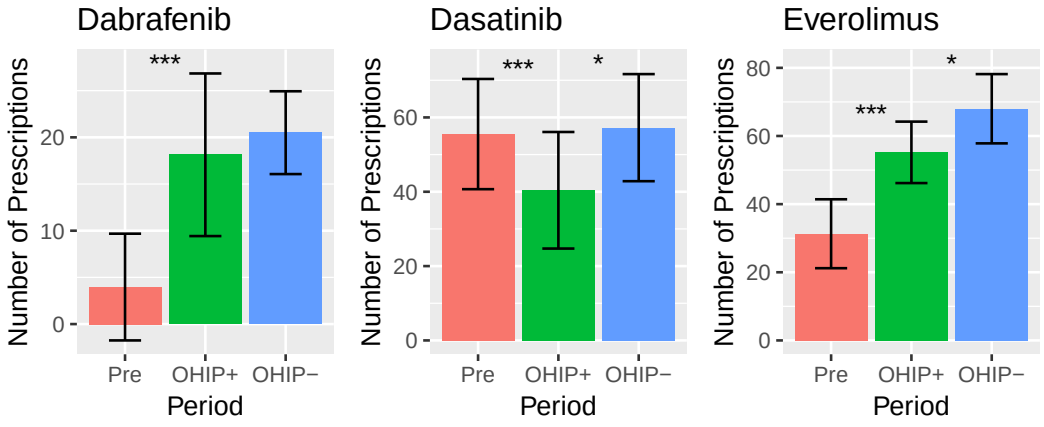
Drug	Generic	Strength	Under 25	Public	Affected	Later	Classification	Approval year	Therapeutic class
Mitotane	No	500	Yes	No	No	No	Cytotoxic	1970	Adrenal cortical carcinoma
Nilotinib	No	150, 200	Yes	Yes	Yes	No	Targeted	2007	Leukemia
Olaparib	No	50, 100, 150	Yes	Yes	No	No	Targeted	2014	Ovarian cancer
Palbociclib	No	75, 100, 125	Yes	Yes	No	No			
Pomalidomide	No	1, 2, 3, 4	No	Yes	No	No	Targeted	2013	Multiple myeloma
Procarbazine	No	50	Yes	Yes	Yes	No	Cytotoxic	1969	Lymphoma
Regorafenib	No	40	Yes	Yes	No	Yes	Targeted	2012	Colorectal cancer; Stomach cancer
Ribociclib	No	200	No	No	No	No			
Ruxolitinib	No	5, 10, 15, 20	Yes	Yes	No	No	Targeted	2011	Myelofibrosis
Sorafenib	No	200	Yes	Yes	Yes	No	Targeted	2005	Liver cancer; Kidney cancer; Thyroid cancer
Sunitinib	No	12.5, 25, 50	Yes	Yes	No	No	Targeted	2006	Stomach cancer; Kidney cancer; Pancreatic cancer
Temozolomide	Yes	5, 20, 100, 140, 180, 250	Yes	Yes	Yes	No	Cytotoxic	1999	Brain cancer
Trametinib	No	0.5, 2	Yes	Yes	Yes	No	Targeted	2013	Melanoma

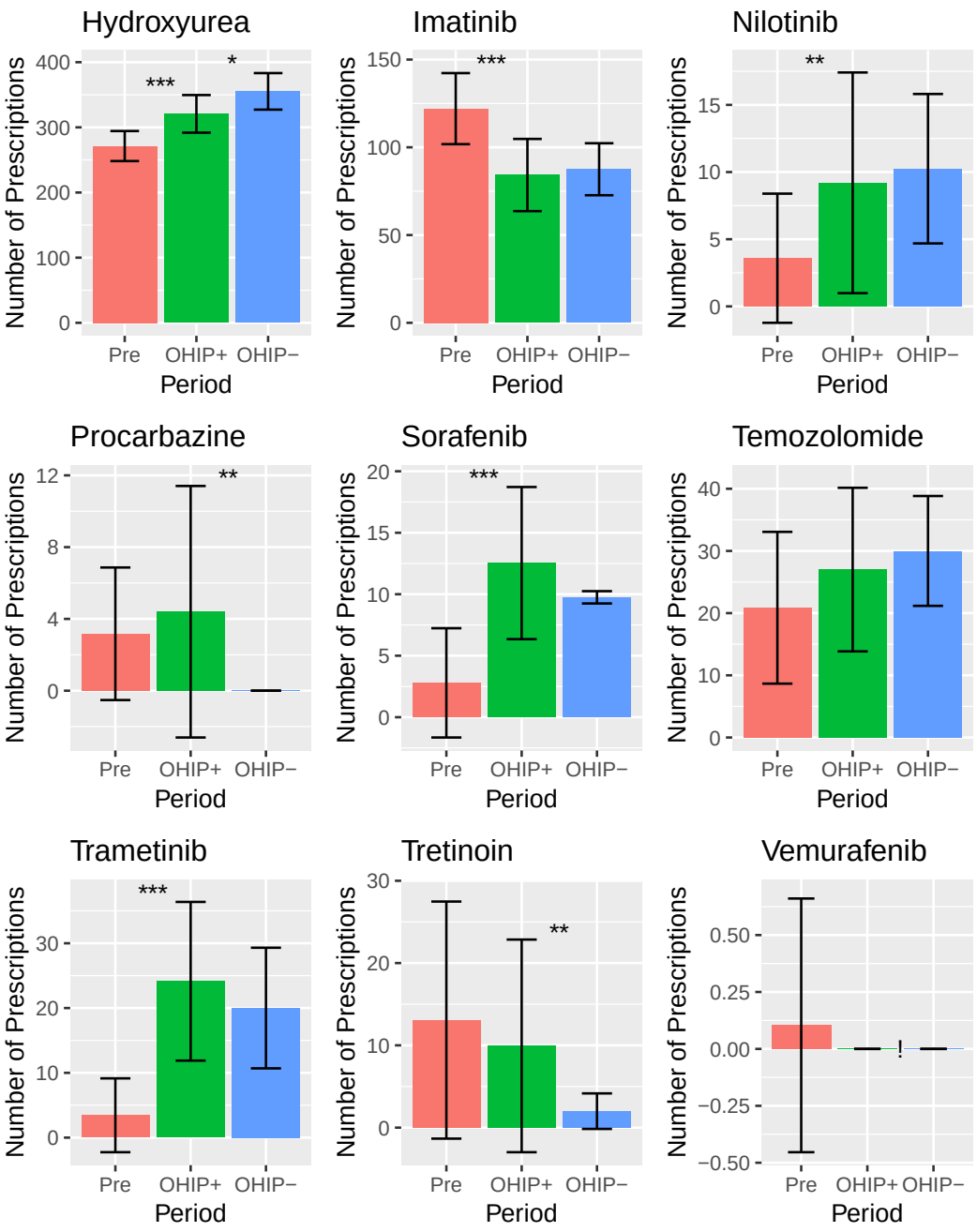
(continued)

Drug	Generic	Strength	Under 25	Public	Affected	Later	Classification	Approval year	Therapeutic class
Tretinoin	No	10	Yes	Yes	Yes	No			
Vemurafenib	No	240	Yes	Yes	Yes	No	Targeted	2011	Melanoma
Venetoclax	No	10, 50, 100	Yes	No	No	No			
Vismodegib	No	150	No	No	No	No	Targeted	2012	Basal cell carcinoma
Vorinostat	No	100	No	No	No	No	Targeted	2006	Lymphoma

Naïve Estimates: Figure 2 shows the average (per month) overall utilization, by dose and by number of prescriptions, of the twelve OAMs prescribed to patients under 25 with at least some public funding. It includes these figures for the three policy periods: before OHIP plus (labeled 'Pre'); the period after the start of OHIP plus but before the start of OHIP minus ('OHIP+'); and after the start of OHIP minus ('OHIP-'). The error bars in the figure represent the standard deviations in each period. The statistical significance of the changes between periods (between 'Pre' and 'OHIP+' and between 'OHIP+' and 'OHIP-'), as determined by Student t-tests, is represented with stars ($p<0.1$; $**p<0.05$; $***p<0.01$). No prescriptions of procarbazine were made after OHIP minus. Vemurafenib was only prescribed in one month ('Pre' period). An exclamation mark (!) denotes the lack of data to evaluate changes in utilization of this drug.

Figure 2: Mean Utilization of OAMs per Month in Each Policy Period




Hydroxyurea
Imatinib
Nilotinib
Procarbazine
Sorafenib
Temozolomide
Trametinib
Tretinoin
Vemurafenib
Number of Prescriptions
Period
Pre
OHIP+
OHIP−
***
**
*
!

Changes in Utilization Because of OHIP Plus

The twelve drugs that were considered affected by the policy were analyzed with RD models to find changes in utilization. Figures 2 through 13 follow the utilization of these drugs for the first phase of the statistical analysis. They also illustrate the application of the RD models on the data, showing the cut-off time point when the policy started, the overall (linear) trend of publicly funded prescriptions before the OHIP plus, and the change in trend after the policy took place. The number of privately funded prescriptions is also included for reference.

Tables 2 through 13 summarize the regression results for the first stage of the statistical analysis. In these tables the *OHIP plus* rows show the estimates of the coefficient for the change at the time of the beginning of the policy (β_1 in formula 1). The *Overall trend* rows show the estimates of the coefficient for the effect of the overall trend (β_2 in formula 1). Similarly, the *Change in trend* estimations refer to the β_3 coefficients. Constants (β_0) are included, too.

Figure 3: Utilization of dabrafenib with OHIP plus

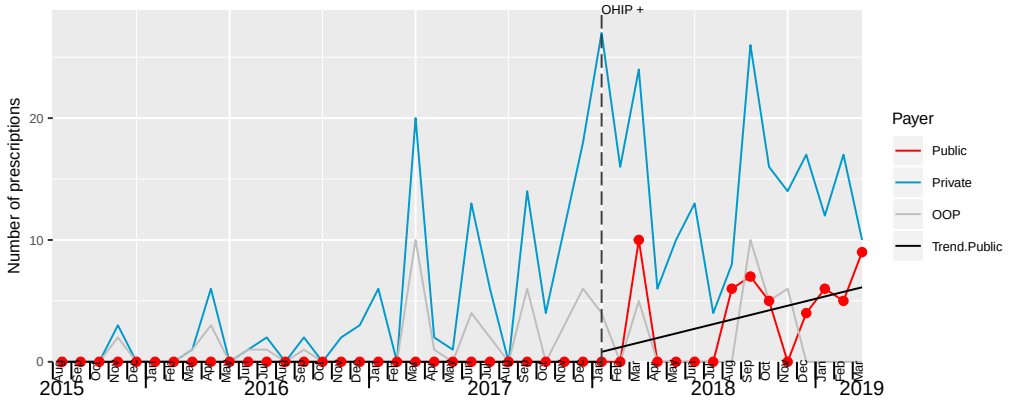


Table 2: Utilization of dabrafenib in number of prescriptions with OHIP plus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP plus	0.817	0.002	−0.812	7.743*
	(1.195)	(0.051)	(1.628)	(3.996)
Overall trend	−0.000	−0.000	0.118**	0.400***
	(0.043)	(0.002)	(0.058)	(0.143)
Change in trend	0.379***	0.023***	−0.172	−0.339
	(0.122)	(0.005)	(0.167)	(0.410)
Constant	0.000	−0.000	3.187***	9.966***
	(0.732)	(0.031)	(0.997)	(2.449)
Observations	44	44	44	44
R^2	0.518	0.595	0.106	0.583
Adjusted R^2	0.482	0.565	0.039	0.552
Residual Std. Error (df = 40)	1.921	0.082	2.617	6.424
F Statistic (df = 3; 40)	14.357***	19.595***	1.586	18.659***
Note:				*p<0.1; **p<0.05; ***p<0.01

Figure 4: Utilization of dasatinib with OHIP plus

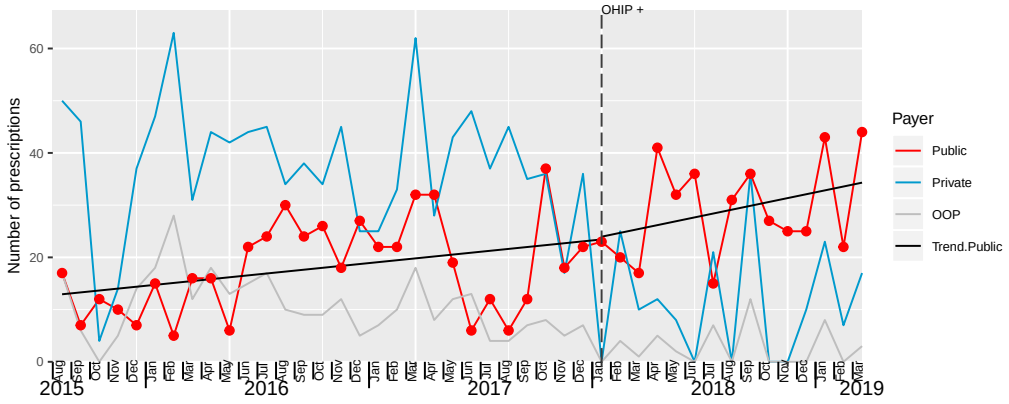


Table 3: Utilization of dasatinib in number of prescriptions with OHIP plus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP plus	0.527	0.376***	−4.704	−26.349***
	(5.397)	(0.111)	(3.193)	(9.411)
Overall trend	0.362*	0.002	−0.233**	0.305
	(0.193)	(0.004)	(0.114)	(0.336)
Change in trend	0.377	−0.001	0.272	0.645
	(0.553)	(0.011)	(0.327)	(0.964)
Constant	23.431***	0.372***	7.229***	60.099***
	(3.307)	(0.068)	(1.956)	(5.767)
Observations	44	44	44	44
R^2	0.353	0.585	0.410	0.228
Adjusted R^2	0.305	0.554	0.366	0.170
Residual Std. Error (df = 40)	8.676	0.179	5.132	15.128
F Statistic (df = 3; 40)	7.284***	18.780***	9.257***	3.934**
Note:				*p<0.1; **p<0.05; ***p<0.01

Figure 5: Utilization of everolimus with OHIP plus

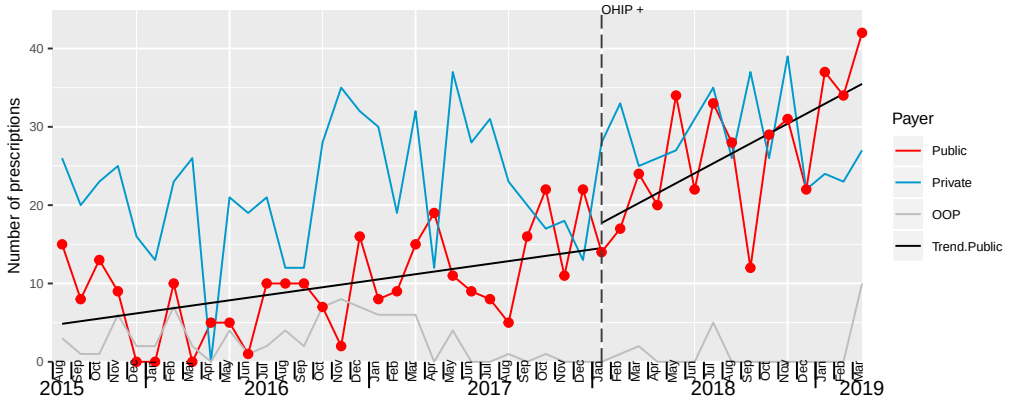


Table 4: Utilization of everolimus in number of prescriptions with OHIP plus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP plus	3.205	−0.027	−1.875	9.805*
	(3.736)	(0.114)	(1.675)	(5.638)
Overall trend	0.333**	0.006	−0.067	0.447**
	(0.133)	(0.004)	(0.060)	(0.201)
Change in trend	0.934**	0.008	0.242	0.606
	(0.383)	(0.012)	(0.172)	(0.578)
Constant	14.520***	0.402***	1.850*	38.020***
	(2.290)	(0.070)	(1.026)	(3.455)
Observations	44	44	44	44
R^2	0.712	0.230	0.135	0.659
Adjusted R^2	0.690	0.172	0.070	0.634
Residual Std. Error (df = 40)	6.006	0.182	2.693	9.063
F Statistic (df = 3; 40)	32.903***	3.983**	2.075	25.806***
Note:				*p<0.1; **p<0.05; ***p<0.01

Figure 6: Utilization of hydroxyurea with OHIP plus

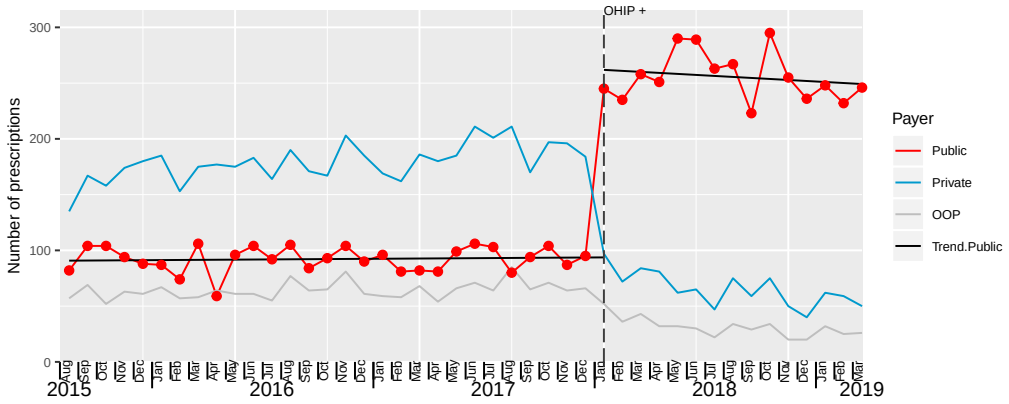


Table 5: Utilization of hydroxyurea in number of prescriptions with OHIP plus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP plus	168.169***	0.438***	−28.660***	52.910***
	(9.902)	(0.019)	(4.319)	(13.835)
Overall trend	0.100	−0.001*	0.321**	1.333**
	(0.353)	(0.001)	(0.154)	(0.494)
Change in trend	−1.008	0.007***	−1.650***	−4.686***
	(1.015)	(0.002)	(0.443)	(1.418)
Constant	93.714***	0.321***	69.094***	291.298***
	(6.068)	(0.011)	(2.647)	(8.478)
Observations	44	44	44	44
R^2	0.963	0.983	0.857	0.610
Adjusted R^2	0.960	0.982	0.846	0.580
Residual Std. Error (df = 40)	15.918	0.030	6.942	22.241
F Statistic (df = 3; 40)	347.258***	769.046***	79.971***	20.825***
Note:				*p<0.1; **p<0.05; ***p<0.01

Figure 7: Utilization of imatinib with OHIP plus

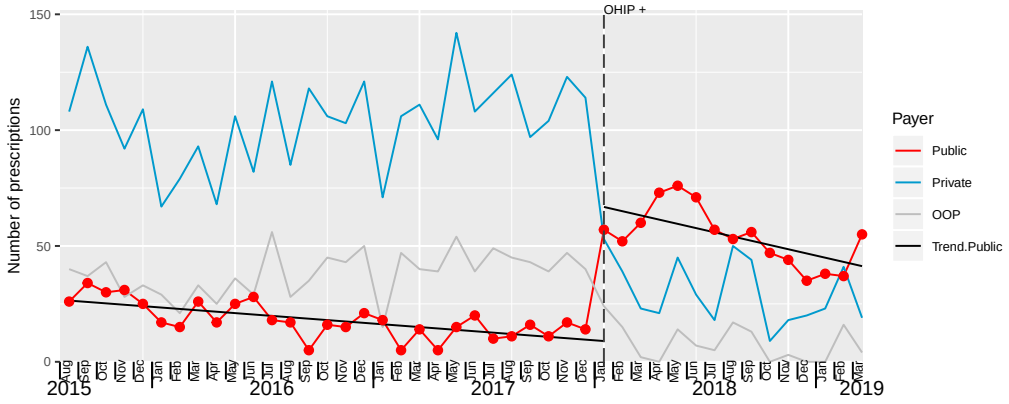


Table 6: Utilization of imatinib in number of prescriptions with OHIP plus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP plus	57.879***	0.570***	−32.600***	−17.119
	(4.646)	(0.046)	(5.300)	(12.012)
Overall trend	−0.602***	−0.005***	0.465**	0.012
	(0.166)	(0.002)	(0.189)	(0.429)
Change in trend	−1.223**	0.006	−1.118**	−2.998**
	(0.476)	(0.005)	(0.543)	(1.231)
Constant	8.963***	0.076**	45.175***	122.219***
	(2.847)	(0.028)	(3.248)	(7.361)
Observations	44	44	44	44
R^2	0.867	0.921	0.767	0.527
Adjusted R^2	0.857	0.915	0.750	0.492
Residual Std. Error (df = 40)	7.469	0.074	8.519	19.309
F Statistic (df = 3; 40)	86.813***	155.093***	43.992***	14.885***
Note:				*p<0.1; **p<0.05; ***p<0.01

Figure 8: Utilization of nilotinib with OHIP plus

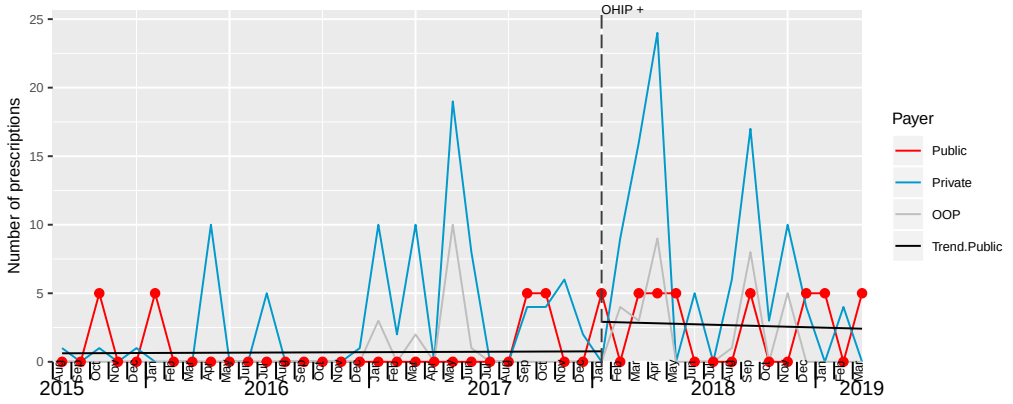


Table 7: Utilization of nilotinib in number of prescriptions with OHIP plus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP plus	2.153	0.226	2.032	6.701*
	(1.316)	(0.211)	(1.482)	(3.721)
Overall trend	0.005	−0.003	0.048	0.189
	(0.047)	(0.008)	(0.053)	(0.133)
Change in trend	−0.041	0.012	−0.233	−0.750*
	(0.135)	(0.022)	(0.152)	(0.381)
Constant	0.764	0.056	1.268	6.424***
	(0.807)	(0.130)	(0.908)	(2.280)
Observations	44	44	44	44
R^2	0.179	0.121	0.134	0.248
Adjusted R^2	0.117	0.055	0.069	0.192
Residual Std. Error (df = 40)	2.116	0.340	2.382	5.981
F Statistic (df = 3; 40)	2.906**	1.832	2.059	4.401***
Note:				*p<0.1; **p<0.05; ***p<0.01

Figure 9: Utilization of procarbazine with OHIP plus

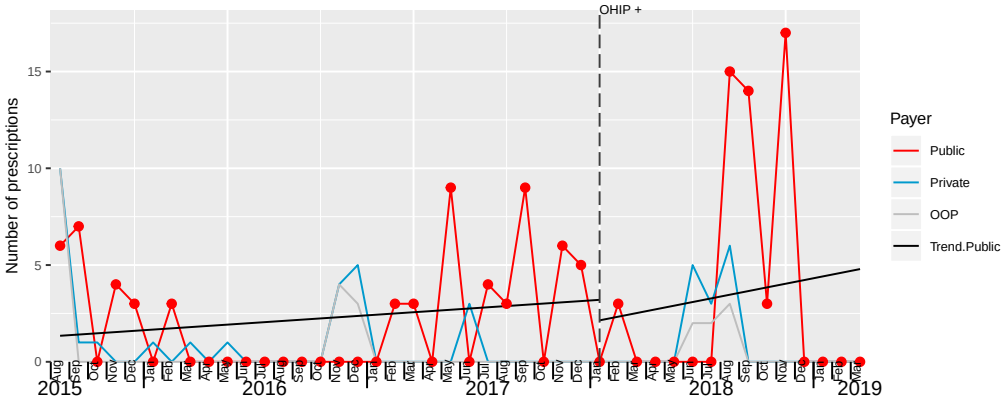


Table 8: Utilization of procarbazine in number of prescriptions with OHIP plus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP plus	−1.060	−0.310	0.991	0.361
	(2.727)	(0.301)	(1.079)	(3.208)
Overall trend	0.064	0.013	−0.064	−0.009
	(0.097)	(0.011)	(0.038)	(0.114)
Change in trend	0.125	−0.013	0.043	0.152
	(0.279)	(0.031)	(0.111)	(0.329)
Constant	3.202*	0.625***	−0.374	3.039
	(1.671)	(0.185)	(0.661)	(1.966)
Observations	44	44	44	44
R^2	0.041	0.049	0.067	0.019
Adjusted R^2	−0.030	−0.022	−0.003	−0.054
Residual Std. Error (df = 40)	4.384	0.485	1.734	5.157
F Statistic (df = 3; 40)	0.576	0.688	0.953	0.260
Note:				*p<0.1; **p<0.05; ***p<0.01

Figure 10: Utilization of sorafenib with OHIP plus

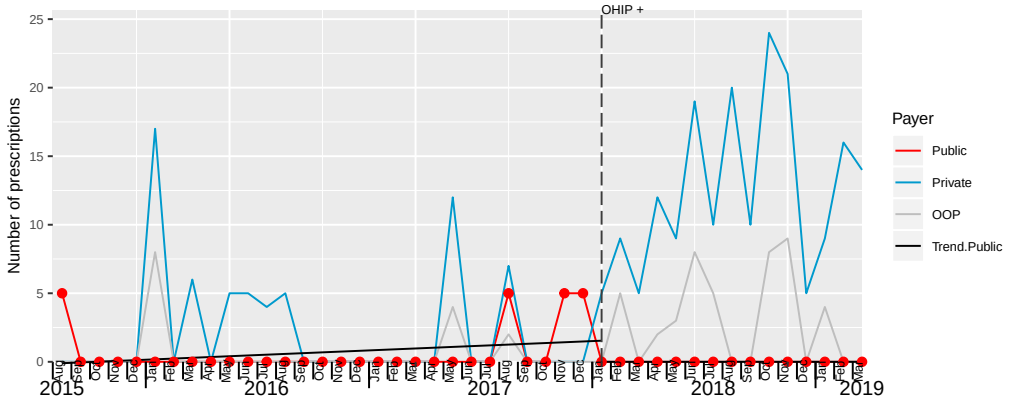


Table 9: Utilization of sorafenib in number of prescriptions with OHIP plus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP plus	−1.539*	−0.245	2.753*	6.114*
	(0.878)	(0.159)	(1.510)	(3.134)
Overall trend	0.057*	0.008	−0.012	0.003
	(0.031)	(0.006)	(0.054)	(0.112)
Change in trend	−0.057	−0.008	−0.006	0.507
	(0.090)	(0.016)	(0.155)	(0.321)
Constant	1.539***	0.245**	0.305	2.845
	(0.538)	(0.098)	(0.926)	(1.921)
Observations	44	44	44	44
R^2	0.123	0.097	0.202	0.499
Adjusted R^2	0.058	0.029	0.142	0.461
Residual Std. Error (df = 40)	1.411	0.256	2.428	5.038
F Statistic (df = 3; 40)	1.877	1.434	3.378**	13.275***
Note:				*p<0.1; **p<0.05; ***p<0.01

Figure 11: Utilization of temozolomide with OHIP plus

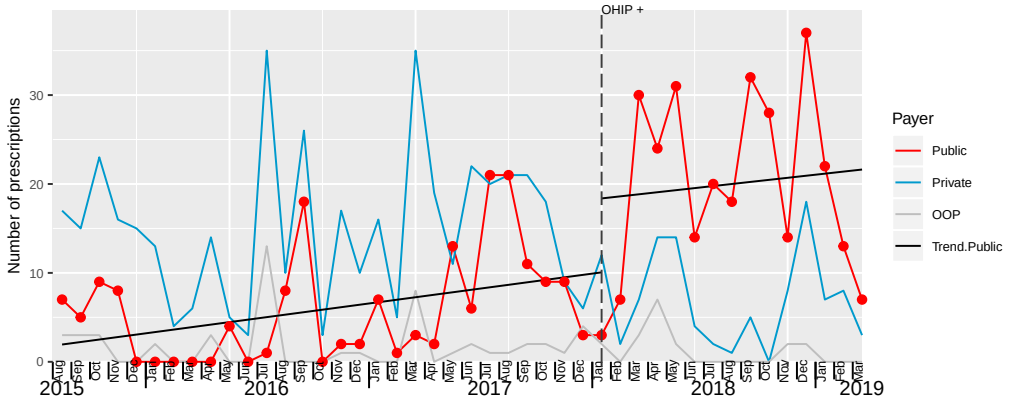


Table 10: Utilization of temozolomide in number of prescriptions with OHIP plus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP plus	8.316*	0.294**	0.607	−0.216
	(4.812)	(0.111)	(1.589)	(7.812)
Overall trend	0.280	0.009**	0.004	0.372
	(0.172)	(0.004)	(0.057)	(0.279)
Change in trend	−0.048	0.0002	−0.179	−0.261
	(0.493)	(0.011)	(0.163)	(0.801)
Constant	10.059***	0.371***	1.818*	26.441***
	(2.949)	(0.068)	(0.974)	(4.787)
Observations	44	44	44	44
R^2	0.473	0.680	0.043	0.094
Adjusted R^2	0.434	0.656	−0.029	0.026
Residual Std. Error (df = 40)	7.735	0.179	2.555	12.557
F Statistic (df = 3; 40)	11.978***	28.283***	0.597	1.388
Note:				*p<0.1; **p<0.05; ***p<0.01

Figure 12: Utilization of trametinib with OHIP plus

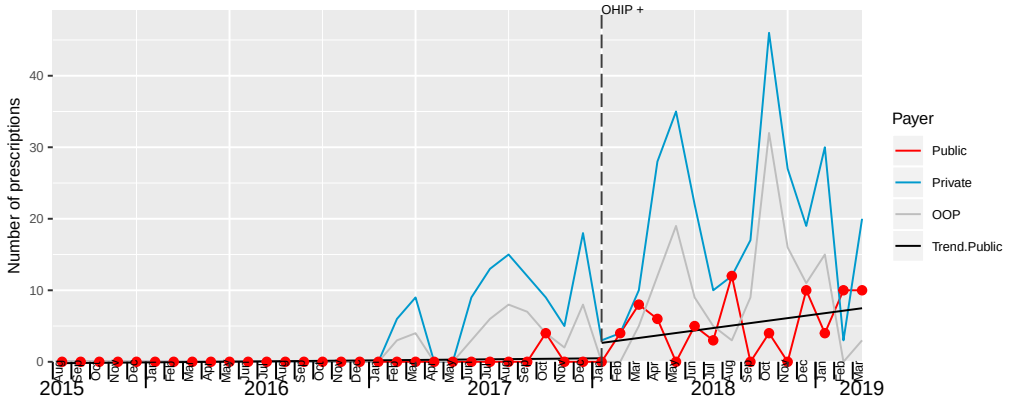


Table 11: Utilization of trametinib in number of prescriptions with OHIP plus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP plus	2.149	0.144	1.668	5.575
	(1.464)	(0.089)	(3.303)	(4.583)
Overall trend	0.024	0.002	0.223*	0.499***
	(0.052)	(0.003)	(0.118)	(0.164)
Change in trend	0.323**	0.007	0.163	0.590
	(0.150)	(0.009)	(0.338)	(0.470)
Constant	0.493	0.038	4.899**	10.933***
	(0.897)	(0.054)	(2.024)	(2.809)
Observations	44	44	44	44
R^2	0.554	0.413	0.393	0.700
Adjusted R^2	0.520	0.369	0.348	0.678
Residual Std. Error (df = 40)	2.354	0.143	5.309	7.367
F Statistic (df = 3; 40)	16.537***	9.399***	8.648***	31.122***
Note:				*p<0.1; **p<0.05; ***p<0.01

Figure 13: Utilization of tretinoin with OHIP plus

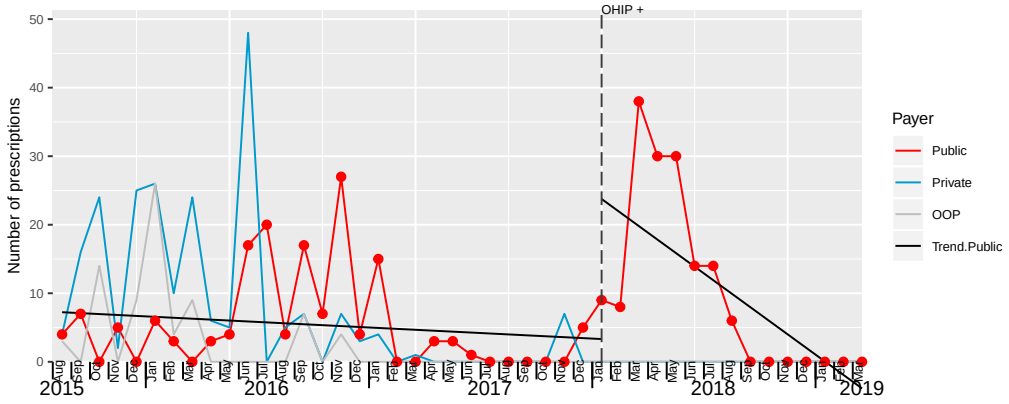


Table 12: Utilization of tretinoin in number of prescriptions with OHIP plus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP plus	20.438***	0.757***	2.049	23.465***
	(5.012)	(0.227)	(2.654)	(7.350)
Overall trend	−0.135	0.003	−0.311***	−0.852***
	(0.179)	(0.008)	(0.095)	(0.262)
Change in trend	−1.840***	−0.103***	0.311	−1.123
	(0.514)	(0.023)	(0.272)	(0.753)
Constant	3.320	0.476***	−2.049	0.293
	(3.071)	(0.139)	(1.626)	(4.504)
Observations	44	44	44	44
R^2	0.340	0.357	0.267	0.323
Adjusted R^2	0.290	0.309	0.212	0.272
Residual Std. Error (df = 40)	8.057	0.364	4.266	11.815
F Statistic (df = 3; 40)	6.868***	7.401***	4.847***	6.356***
Note:				*p<0.1; **p<0.05; ***p<0.01

Figure 14: Utilization of vemurafenib with OHIP plus

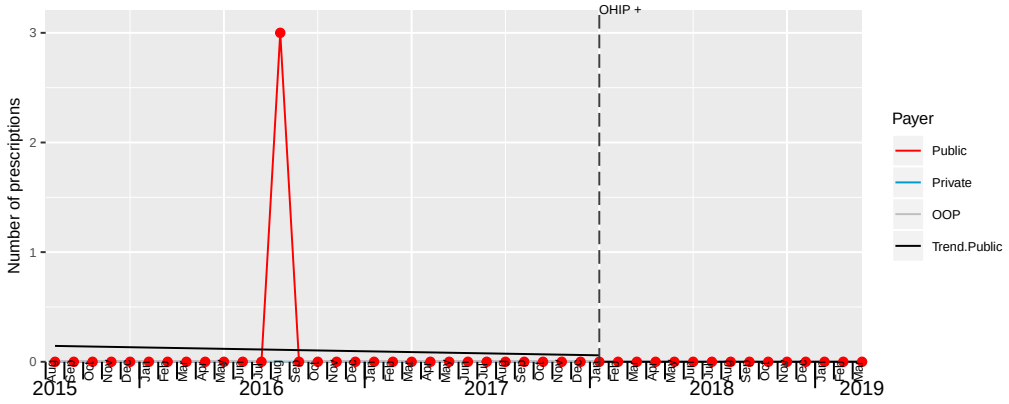


Table 13: Utilization of vemurafenib in number of prescriptions with OHIP plus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP plus	−0.059	−0.020	0.000	−0.059
	(0.290)	(0.097)	(0.000)	(0.290)
Overall trend	−0.003	−0.001	0.000	−0.003
	(0.010)	(0.003)	(0.000)	(0.010)
Change in trend	0.003	0.001	0.000	0.003
	(0.030)	(0.010)	(0.000)	(0.030)
Constant	0.059	0.020	0.000	0.059
	(0.177)	(0.059)	(0.000)	(0.177)
Observations	44	44	44	44
R^2	0.014	0.014		0.014
Adjusted R^2	−0.060	−0.060		−0.060
Residual Std. Error (df = 40)	0.466	0.155	0.000	0.466
F Statistic (df = 3; 40)	0.190	0.190		0.190
Note:				*p<0.1; **p<0.05; ***p<0.01

Statistically significant changes due to the policy were not observed for seven of the twelve drugs considered affected by the policy: dabrafenib, everolimus, nilotinib, procarbazine, sorafenib, trametinib, and vemurafenib. This was probably, in part, due to a low number of prescriptions showing up only sporadically, in some cases. Some of these drugs did presented significant overall trends or changes in trends, but the outcome of interest in this screening was a statistically significant change in utilization at the discontinuity (β_1).

Five drugs (N = 5) that had statistically significant changes in utilization because of OHIP plus were identified: dasatinib, hydroxyurea, imatinib, temozolomide, and tretinoin. All five of these drugs showed a shift towards public funding (an increase in the proportion of funding coming from the public payer). Hydroxyurea, imatinib, and tretinoin saw an increase in the number of publicly funded prescriptions. Only hydroxyurea saw an increase in the total number of prescriptions (all sources of funding combined), while dasatinib saw a decrease in this same number.

We can also observe changes in utilization trends, although these cannot causally be attributed to the policy given the current RD models, unless additional assumptions are met. We see that four drugs showed a positive trend in total utilization: Dabrafenib and trametinib started showing positive changes in their trends of publicly funded utilization after the start of OHIP plus. Everolimus has a continuous trend of uptake with public funding, made even sharper with the policy. Hydroxyurea presents a positive total trend, but the trend is diminished after OHIP plus. Hydroxyurea also shows a sharp shift from private to public funding, along with an increase in total utilization right at the time the policy starts.

On the other hand, two drugs show a downward trend of utilization, probably a sign of the process of being phased out: Imatinib looks like a drug in decreasing demand for public funding, as it shows a negative overall trend in publicly funded utilization, made sharper after the policy. There is a substantial increase in publicly funded utilization due to the policy along with a decrease in private funding, but a trend of decreasing prescriptions resumes soon after. Similarly, tretinoin showed a negative trend throughout the study until it showed nearly zero prescriptions, then enjoyed a brief and sharp increase due to OHIP plus, but the downward trend resumes fast until the drug seems to disappear from the market.

Changes in Utilization Because of OHIP Minus

The analysis was repeated for these twelve drugs for the second phase of the statistical analysis. This time, the focus was on the changes in utilization before and after the start of OHIP minus. Figures 14 through 21 and Tables 14 through 21 illustrate this analysis in much the same way as it was done for the initial phase. Generally, it was more difficult to detect statistical significance in changes in trends after the start of OHIP minus due to the availability of only four time periods in the data. However, some observations were significant.

Figure 15: Utilization of dabrafenib with OHIP minus

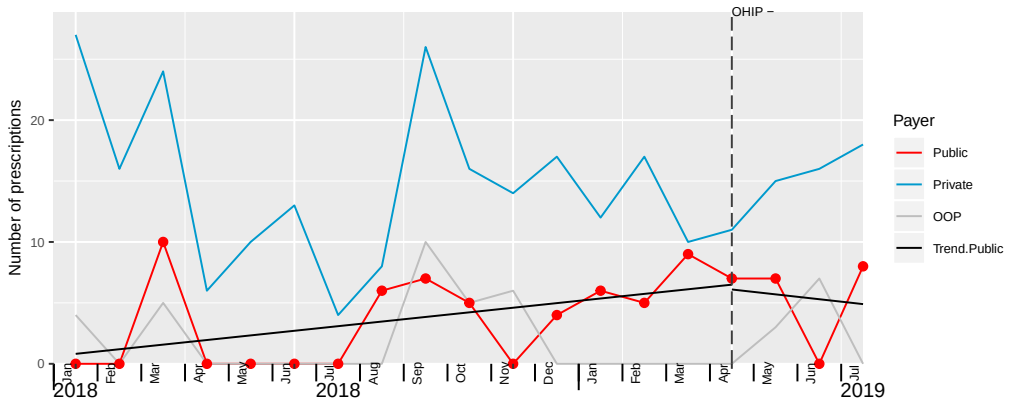


Table 14: Utilization of dabrafenib in number of prescriptions with OHIP minus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP minus	−0.395	−0.003	0.329	−0.819
	(3.530)	(0.151)	(3.392)	(8.557)
Overall trend	0.379*	0.023**	−0.054	0.061
	(0.211)	(0.009)	(0.203)	(0.513)
Change in trend	−0.779	−0.079	0.454	1.739
	(1.596)	(0.068)	(1.534)	(3.870)
Constant	6.495***	0.341***	1.571	18.619***
	(1.923)	(0.082)	(1.847)	(4.660)
Observations	19	19	19	19
R^2	0.223	0.352	0.014	0.031
Adjusted R^2	0.068	0.223	−0.184	−0.163
Residual Std. Error (df = 15)	3.538	0.151	3.400	8.577
F Statistic (df = 3; 15)	1.437	2.718*	0.069	0.158
Note:				*p<0.1; **p<0.05; ***p<0.01

Figure 16: Utilization of dasatinib with OHIP minus

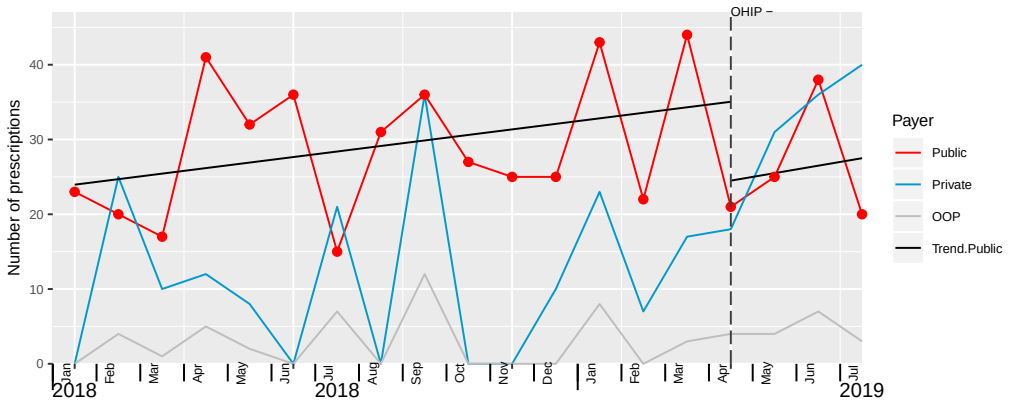


Table 15: Utilization of dasatinib in number of prescriptions with OHIP minus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP minus	−10.548	−0.234	1.386	−2.900
	(9.164)	(0.202)	(3.670)	(15.207)
Overall trend	0.739	0.002	0.039	0.950
	(0.549)	(0.012)	(0.220)	(0.911)
Change in trend	0.261	−0.057	−0.039	7.150
	(4.145)	(0.091)	(1.660)	(6.878)
Constant	35.048***	0.775***	3.114	48.000***
	(4.991)	(0.110)	(1.999)	(8.283)
Observations	19	19	19	19
R^2	0.130	0.331	0.045	0.298
Adjusted R^2	−0.044	0.197	−0.146	0.157
Residual Std. Error (df = 15)	9.186	0.203	3.678	15.244
F Statistic (df = 3; 15)	0.747	2.476	0.235	2.119
Note:				*p<0.1; **p<0.05; ***p<0.01

Figure 17: Utilization of everolimus with OHIP minus

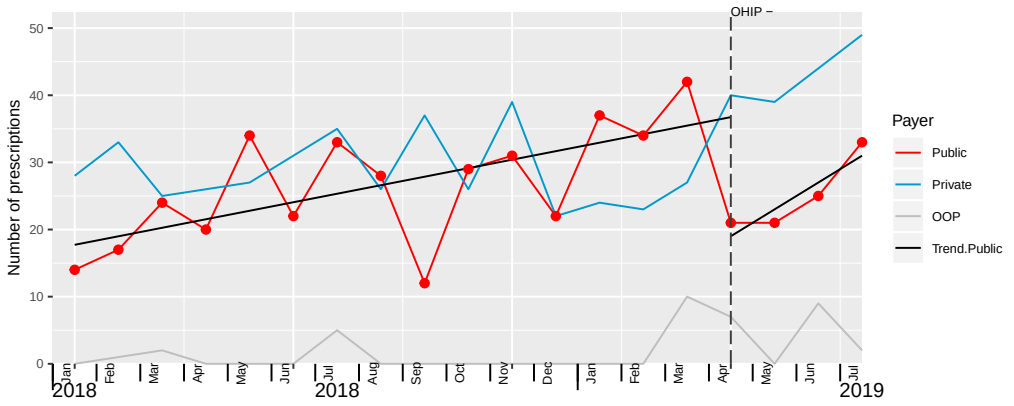


Table 16: Utilization of everolimus in number of prescriptions with OHIP minus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP minus	−17.743**	−0.250***	2.800	−6.429
	(6.544)	(0.083)	(3.165)	(7.634)
Overall trend	1.268***	0.014**	0.175	1.054**
	(0.392)	(0.005)	(0.190)	(0.457)
Change in trend	2.732	0.005	−0.775	6.146*
	(2.960)	(0.038)	(1.432)	(3.453)
Constant	36.743***	0.586***	2.600	63.629***
	(3.564)	(0.045)	(1.724)	(4.158)
Observations	19	19	19	19
R^2	0.455	0.476	0.229	0.553
Adjusted R^2	0.346	0.371	0.074	0.464
Residual Std. Error (df = 15)	6.560	0.083	3.173	7.652
F Statistic (df = 3; 15)	4.169**	4.544**	1.482	6.190***
Note:				*p<0.1; **p<0.05; ***p<0.01

Figure 18: Utilization of hydroxyurea with OHIP minus

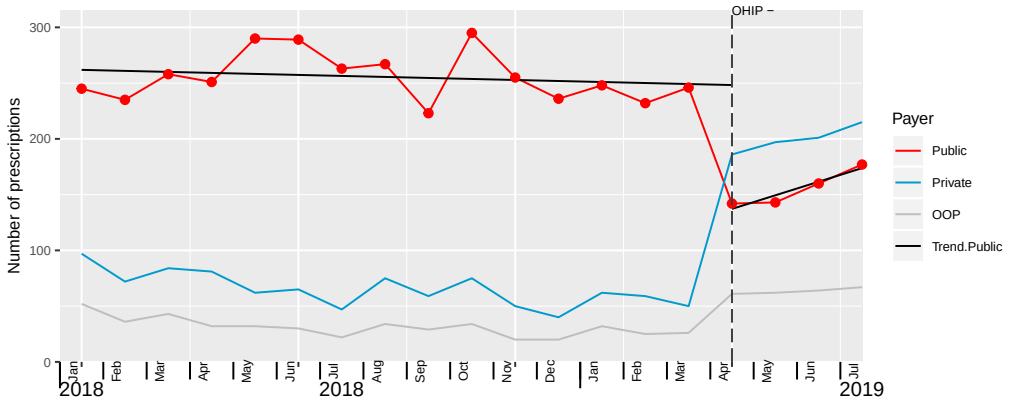


Table 17: Utilization of hydroxyurea in number of prescriptions with OHIP minus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP minus	−111.076***	−0.417***	39.995***	29.395
	(20.926)	(0.029)	(5.910)	(23.888)
Overall trend	−0.907	0.006***	−1.329***	−3.354**
	(1.254)	(0.002)	(0.354)	(1.431)
Change in trend	13.107	0.002	3.329	24.654**
	(9.464)	(0.013)	(2.673)	(10.804)
Constant	248.276***	0.842***	20.505***	293.905***
	(11.398)	(0.016)	(3.219)	(13.011)
Observations	19	19	19	19
R^2	0.832	0.971	0.879	0.516
Adjusted R^2	0.798	0.965	0.855	0.420
Residual Std. Error (df = 15)	20.976	0.029	5.925	23.945
F Statistic (df = 3; 15)	24.677***	166.254***	36.300***	5.337**

Note: *p<0.1; **p<0.05; ***p<0.01

Figure 19: Utilization of imatinib with OHIP minus

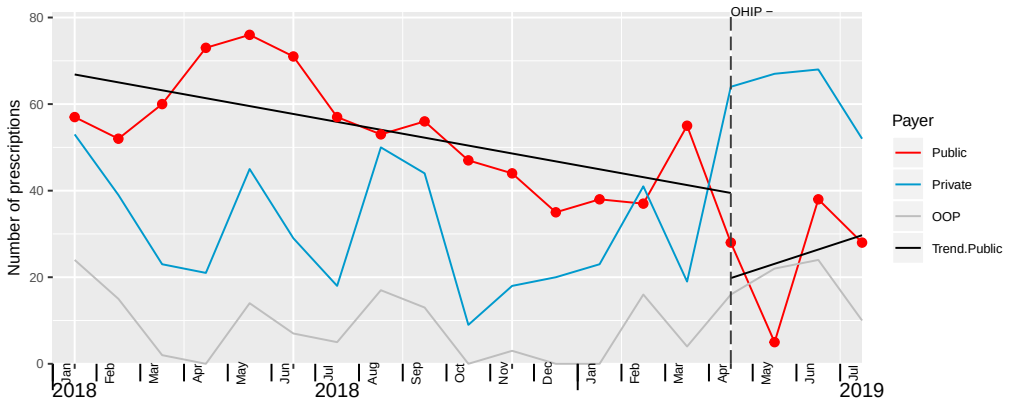


Table 18: Utilization of imatinib in number of prescriptions with OHIP minus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP minus	−19.667*	−0.453***	17.629**	27.486
	(11.087)	(0.119)	(7.473)	(16.463)
Overall trend	−1.825**	0.001	−0.654	−2.986***
	(0.664)	(0.007)	(0.448)	(0.986)
Change in trend	5.125	0.042	−0.946	2.786
	(5.014)	(0.054)	(3.380)	(7.446)
Constant	39.467***	0.659***	2.771	60.314***
	(6.039)	(0.065)	(4.070)	(8.967)
Observations	19	19	19	19
R^2	0.666	0.687	0.347	0.383
Adjusted R^2	0.600	0.625	0.217	0.259
Residual Std. Error (df = 15)	11.114	0.119	7.490	16.503
F Statistic (df = 3; 15)	9.989***	10.999***	2.663*	3.097*
Note:				*p<0.1; **p<0.05; ***p<0.01

Figure 20: Utilization of temozolomide with OHIP minus

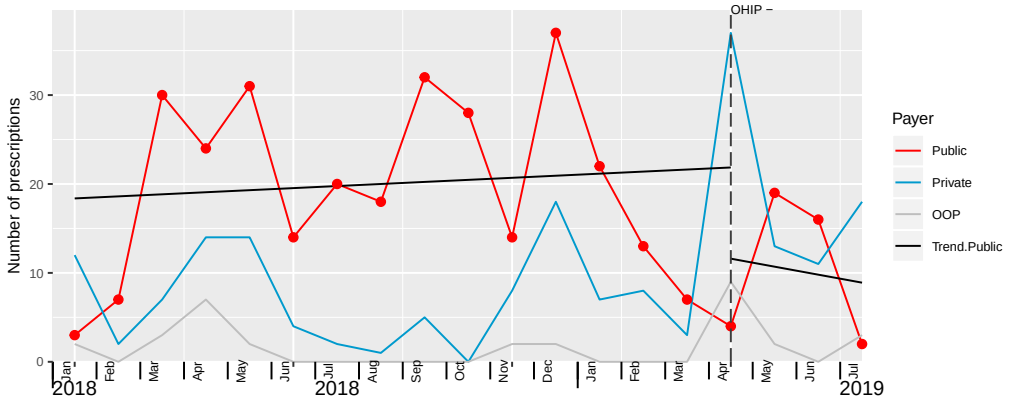


Table 19: Utilization of temozolomide in number of prescriptions with OHIP minus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP minus	−10.257	−0.465*	6.700***	12.314
	(10.582)	(0.218)	(2.137)	(12.675)
Overall trend	0.232	0.010	−0.175	0.111
	(0.634)	(0.013)	(0.128)	(0.759)
Change in trend	−1.132	−0.009	−1.825*	−6.911
	(4.786)	(0.099)	(0.966)	(5.732)
Constant	21.857***	0.810***	−0.200	27.886***
	(5.763)	(0.119)	(1.164)	(6.904)
Observations	19	19	19	19
R^2	0.159	0.410	0.397	0.098
Adjusted R^2	−0.009	0.292	0.276	−0.082
Residual Std. Error (df = 15)	10.607	0.219	2.142	12.705
F Statistic (df = 3; 15)	0.946	3.473**	3.290**	0.543
Note:				*p<0.1; **p<0.05; ***p<0.01

Figure 21: Utilization of trametinib with OHIP minus

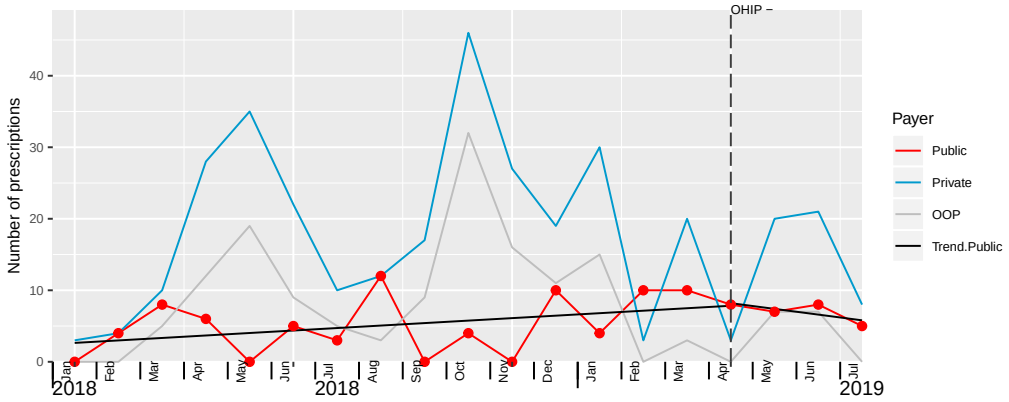


Table 20: Utilization of trametinib in number of prescriptions with OHIP minus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP minus	0.362	0.245	−8.852	−14.048
	(3.734)	(0.234)	(8.466)	(11.589)
Overall trend	0.346	0.009	0.386	1.089
	(0.224)	(0.014)	(0.507)	(0.694)
Change in trend	−1.146	−0.110	−0.386	−0.289
	(1.689)	(0.106)	(3.829)	(5.241)
Constant	7.838***	0.318**	12.352**	32.848***
	(2.034)	(0.127)	(4.611)	(6.312)
Observations	19	19	19	19
R^2	0.188	0.164	0.120	0.161
Adjusted R^2	0.025	−0.003	−0.057	−0.006
Residual Std. Error (df = 15)	3.743	0.234	8.486	11.617
F Statistic (df = 3; 15)	1.157	0.983	0.679	0.962
Note:				*p<0.1; **p<0.05; ***p<0.01

Figure 22: Utilization of tretinoin with OHIP minus

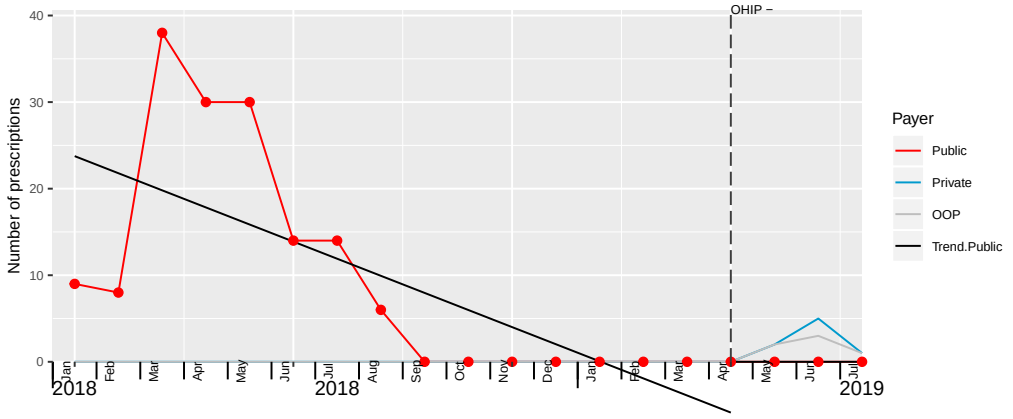


Table 21: Utilization of tretinoin in number of prescriptions with OHIP minus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP minus	5.867	0.267	0.900	6.967
	(9.088)	(0.249)	(0.528)	(9.132)
Overall trend	−1.975***	−0.100***	−0.000	−1.975***
	(0.544)	(0.015)	(0.032)	(0.547)
Change in trend	1.975	0.100	0.400	2.575
	(4.110)	(0.113)	(0.239)	(4.130)
Constant	−5.867	−0.267*	0.000	−5.867
	(4.950)	(0.136)	(0.288)	(4.974)
Observations	19	19	19	19
R^2	0.530	0.798	0.653	0.507
Adjusted R^2	0.436	0.758	0.584	0.408
Residual Std. Error (df = 15)	9.110	0.249	0.529	9.154
F Statistic (df = 3; 15)	5.639***	19.812***	9.411***	5.142**
Note:				*p<0.1; **p<0.05; ***p<0.01

The inevitable shifts away from public to private funding due to OHIP minus were statistically significant for everolimus, hydroxyurea, and imatinib. Increases in OOP payments for hydroxyurea, imatinib, and temozolomide can also be attributed to this policy.

The analysis of trends shows that everolimus continued having positive utilization trends, in public funding (despite the negative effect of OHIP minus) and in total utilization throughout this second phase of the analysis. Dasatinib and trametinib did not show any significant trends or effects due to the policy. Also, tretinoin nearly disappeared from the market during this phase. This second phase of the analysis. Statistically significant changes in trends were not detected, in part due to the availability of only four time points after the start of OHIP minus. The only exception was hydroxyurea, that despite having an overall negative trend in utilization, saw a positive change after the policy. This could suggest that hydroxyurea could be substituted by other drugs when they are covered by the public payer. Hydroxyurea could be preferred over those substitutes for price reasons.

Sensitivity Analysis

Narrow Window Analysis: In the supplementary materials, figures SM1 through SM20 show the results of a narrow window RD analysis. These analyses took only the five observations closest to the cut-off before and after OHIP plus and four observations (before and after) OHIP minus. The full RD models found statistical significance in 21 (out of 89) cases, while the narrow window models found significance in only 13 (out of 78) cases. For some drugs there were long periods of time without any prescriptions (e.g. sorafenib and vemu-

rafenib after the start of OHIP-), and some narrow window regressions could not be performed due to the absence of prescriptions. The models agreed on their evaluation of statistical significance on 62 of the 78 cases where both were applicable (79%). Many of these drugs were only sporadically prescribed to the demographic group of interest, and prescription counts are typically low for most drugs. A narrow window approach can be used to focus the RD model on the discontinuity, where it is more important, rather than on long periods before and after the discontinuity (Bailey, 2019). In this case, however, because of the sporadic prescriptions and low counts, including as many time points as possible (as in the full RD models) might be a more accurate way to evaluate the policy.

Discussion

Before interpreting the statistical results, it would be useful to make a few sensible assumptions. We can assume that the overall number of active chemotherapy treatments is stable (if not slightly increasing) during the duration of this analysis, and that this might be the case for all the major types of cancer for people under 25. This way, changes in utilization of a drug are not due to clinical changes in diagnoses, but to the policy and ongoing trends of preferences (clinical and economic) between patients and prescribers. If the number of cancer cases for each type of cancer is stable, shifts at the beginning of the policy can be assumed to be results of drug substitutions.

An important factor to keep in mind is that cancer drug prescriptions are organized by line of treatment. For instance, first line drugs for a type of cancer are prescribed first to a patient, and if the treatment is ineffective, the patient is moved to a second line drug, and later to a third line drug,

and so on. This organization is in place because of clinical and economic preferences. Safer and cheaper drugs are typically first-line drugs and they tend to get the largest number of patients in active treatment at any given point. Pharmaceutical advancements, new clinical evidence, and changes in guidelines, can cause drugs to be moved from one therapy line to another. For instance, newer and better drugs can come to the market and replace older drugs. Evidence can re-evaluate the safety or effectiveness of some drugs compared to others.

Changes in policy, such as OHIP plus and OHIP minus, can also elicit not only a change in funding source, but also a substitution in prescription drugs. For instance, an older drug might be commonly prescribed to patients with a particular cancer type even though a newer, safer, or more effective drug is available, but this new drug is prohibitively expensive and its coverage in private plans may be limited. With OHIP plus the alternative drug can become more financially accessible and the decision is made to substitute the old drug with the newer one. There is also the potential for diagnosed patients that were treated with IV drugs to switch to oral chemotherapy drugs due to the policy, or for patients that were unable to afford a treatment that required one of these OAMs to begin treatment.

Although it was never explicitly stated, we can assume that the main goal of OHIP plus was to increase financial access to patients under 25 to the drugs in the provincial formulary. We can further ascertain that the most desired effect of this policy was to allow previously uncovered individuals who needed prescription, but could not afford them, to now have access to these treatments. This would be evident by an increase in the total utilization of

a drug (ignoring possible drug substitutions). A second most desirable effect would be to reduce the out-of-pocket costs people under 25 and their families currently pay for their medications. Even when a significant overall increase in utilization of these drugs is not detected, but a greater share of the funding is public, this could count as decreased financial barriers to access. This is particularly beneficial for drugs as expensive as OAMs.

Throughout this section, increases and decreases in prescriptions due to the policies are interpreted as positive and negative (respectively) statistically significant changes at the time of the start of OHIP plus and OHIP minus (β_1 in formula 1).

Start of OHIP Plus

From the analysis in this study, it would be difficult to assess if the first desired effect is being realized. Total utilization increased significantly only for hydroxyurea, but substitution between drugs could belie an overall increase in financial access. By this metric, higher shares of public funding were achieved for five drugs: dasatinib, hydroxyurea, imatinib, temozolomide, and tretinoin. It is important to remember, though, that with drugs like tretinoin, the increase in public funding quickly subsided due to the overall trend of phasing out of the drug. Another meaningful sign of the benefits of this policy would be evidence of the reduction in the number of prescriptions paid OOP. By this criterion, reductions in OOP funding were brought about by the start of OHIP plus for hydroxyurea and imatinib only.

Start of OHIP Minus

A potentially wasteful side of OHIP plus was the coverage of drugs for patients who already had coverage through private insurance. We can assume that the motivation behind OHIP minus was to reduce provincial health care spending by ceasing the coverage of these cases. The public benefits from extending public subsidy to these individuals were small compared to the cost to the province, as it meant, for the most part, transferring the burden to pay from private insurers to the province (and tax-payer dollars). For most of these individuals and their households, public subsidy meant no longer having to pay for prescription drug co-payments, as the province assumed, in most cases, the total cost of the prescription drugs and pharmacy fees [2] (Government of Ontario, 2017).

A more minute analysis would be necessary to assess the benefit of OHIP minus. This policy was, arguably, unlikely to cause most households and individuals with private insurance to discontinue private coverage and stop paying premiums. Most people in Canada obtain private prescription drug insurance through their employers, not to mention that in most cases, household members over 25 and under 65 would still require private insurance to pay for drugs. It is also possible private insurers did not cover some of the most expensive drugs in the list during the duration of the study.

Shifts from public back to private funding with OHIP minus were inevitable. They were, arguably, even desired, as long as they are not accompanied by decreases in the total number of prescriptions (decrease in overall access) or

[2]OHIP plus beneficiaries pay neither co-payments, nor premiums, nor dispensing fees "up to the lowest cost alternative price listed on the ODB formulary" (Government of Ontario, 2017) (OTIP, n.d.).

increases in the cases of OOP funding. The shift to private sources of funding (negative changes in the share of public funding) was significant for everolimus, hydroxyurea, imatinib, and arguably for temozolomide ($p < 0.1$).

The transition from unnecessary public funding back to private insurance might not have been as smooth as expected, as OOP spending went up for three of the most common drugs in this study. Everolimus did not see an increase in OOP funding after the shift to private funding. Unfortunately, hydroxyurea, imitinib, and temozolomide did. These changes, however, tended to be high only around the time the changes in OHIP plus took place. Due to the availability of only four time points from the start of OHIP minus, changes in prescription trends were difficult to identify. However, an unexpected find here was a positive change in the trend of total utilization of hydroxyurea after the changes to OHIP plus. This further supports the notion that alternatives to hydroxyurea are preferred when they are affordable (as with the start of OHIP plus), but when the affordability of substitutes decreased (as with the start of OHIP minus), there was a shift back to hydroxyurea, even when this drug was simultaneously affected by the changes.

Contributions and limitations

To the best of the knowledge of the author, there are no published studies with empirical evaluations of the effects of OHIP plus (on cancer drugs or any drugs), let alone the redesign of this policy. The work in this chapter can become the first study of this kind. The focus on pediatric and young-adult cancer is also of strategic importance. Even though there are a small number of diagnoses in this category, costs of treatment can be remarkably high, and

the decision to publicly fund drugs for these conditions, especially drugs like the OAMs in this study are controversial. High prices are attached to the high benefits from saving lives at an early age.

This study also reveals some trends in the utilization of drugs that were in place before OHIP plus and OHIP minus, but that interacted with the policies. For instance, it becomes apparent that everolimus is a drug gaining popularity, while imatinib and tretinoin are losing ground or in the process of being phased out of the market. Other drugs like hydroxyurea, while popular, might be a second choice to many patients and their physicians when other alternatives are more affordable. The analysis of these trends can inform future formulary policy (e.g., what drugs could be delisted without causing too much public harm) and can also be of commercial value.

Just as in chapter three, some of the limitations of this study are related to the structure of the data and the data collection. First, the data records pharmaceutical sales, which are used as proxy for utilization. It does not cover the totality of points of sale of these antineoplastic products, but it uses advanced methods to estimate the missing data from pharmacies out of the sample. Patient-level data would have been ideal to include more explanatory variables and provide a more complete causal relationship between the changes observed and the delisting policy. Because of the structure of the data, regression discontinuity analysis models were used to detect these changes.

Another important factor not captured in this data are the switching of prescriptions to and from IV chemotherapy drugs (which were not captured in the data) or decisions to start or stop treatment. Given the reports in the literature of preference for oral drugs over IV, this might account for some of

the upward trends in utilization. The inclusion of these factors could paint a clearer picture of the implications of OHIP plus for access to cancer drugs.

The data set and the analysis in this study are limited in their ability to describe the utilization of drugs in cancer treatment. For instance, hydroxyurea is used not only for cancer, but also for sickle cell anemia, HIV infection, psoriasis, and other conditions (Madaan et al., 2012). The analysis of the data can describe the changes in utilization happening due to the policy but cannot discern how much of this change was due to the utilization of the drug for cancer treatment or the other conditions.

The low incidence of cancer for patients under 25, let alone the prescription of OAMs for their treatment, resulted in overall low prescription counts, compared to other drugs and patient categories. The coverage in data acquisition (42.5% of all retail pharmacies in Ontario and no dispensations in health care centres) is, most likely, too limited to measure nuanced impacts on the use and financing of relatively low-volume, specialized drug treatments. With these low numbers, the use of geospatial projections to make up for uncaptured data might introduce considerable amounts of error. The low prescription numbers throughout this study also made the finding of statistical significance more difficult. Finally, the availability of only four time points from the time of the start of OHIP minus presented a similar challenge. This analysis could be complemented with a more thorough cross-reference of utilization numbers with therapeutic uses and costs of treatment. They could help explain, for instance, if the substitution of some drugs by others could have caused the trends and shifts observed in the data.

As in the previous chapter, the RD models presented in this study assume ho-

moscedastic standard errors. The possible presence of heteroscedasticity would be difficult to detect given the small number of observations in the models. If present, it would also be difficult to determine what form this heteroskedasticity takes. Preliminary work applying heteroscedasticity-consistent standard errors (HCSE) in this analysis, suggests only a small effect on the statistical significance of changes in the utilization in standard RD models, unlike for the pooled RD models in the previous chapter. Another tentative research direction is the use of more novel inference approaches specially tailored to RD designs (as opposed to approaches based on ordinary least-squares models). One of these approaches is the local randomization framework (LRF) introduced by Cattaneo et al. (2017). The attractiveness of this model is that it does not require the assumption of a smooth error at the discontinuity as in conventional RD models like the ones used in this study. The LRF requires instead that treatment can be considered as-if randomly assigned near the cut-off. The applicability of the LRF assumptions on the data used in this study still needs to be tested.

Conclusions

This chapter is possibly the first empirical evaluation of the effects of OHIP plus and its redesign. Its focus is on the effects of the policies on the utilization of OAMs among cancer patients under 25 years of age. Five drugs in the OAM category were significantly affected by the policy, and this study examined these changes and their meaning in the context of the objectives of the policy. Overall trends in the utilization of these drugs were also examined.

The policy was successful in significantly increasing public funding to several drugs. It is unclear, however, if OHIP plus allowed uncovered patients who

could not afford their chemotherapy drugs to start treatment. There seems to have been substitutions between these drugs, as not all of them simply increased in publicly funded utilization. This type of results underscore the complexity of the changes in the demand for drugs, when policies affect the price patients pay for them.

Cancer is the most common cause of death in Canada and many other developed nations. Even though pediatric and young adults represent a small fraction of all the cancer cases, they constitute an important patient population for the personal and social benefits of treating these patients. OHIP plus is likely to have had an effect on relieving the financial stress on many families that take care of young cancer patients. This is particularly the case for some of expensive drugs that were the focus of this chapter. Correcting the possibly wasteful policy of giving public drug funding for people with private insurance might have had the undesired effect of increasing OOP spending on these drugs in the short term, but a longer evaluation period would be needed to examine longer trends.

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Appendix

Figure A1: Utilization of nilotinib with OHIP minus

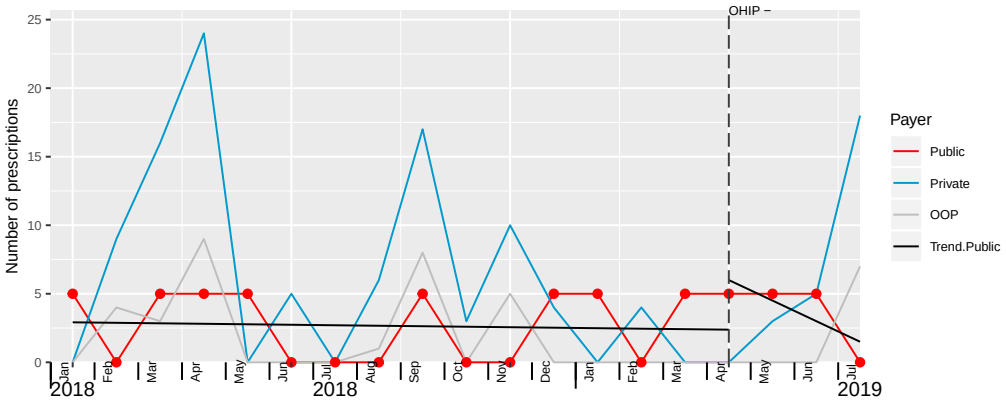

Table A1: Utilization of nilotinib in number of prescriptions with OHIP minus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP minus	3.619	0.580	−1.914	−0.614
	(2.582)	(0.419)	(3.059)	(7.576)
Overall trend	−0.036	0.009	−0.186	−0.561
	(0.155)	(0.025)	(0.183)	(0.454)
Change in trend	−1.464	−0.322	2.286	4.661
	(1.168)	(0.190)	(1.384)	(3.426)
Constant	2.381	0.420*	0.514	4.714
	(1.406)	(0.228)	(1.666)	(4.126)
Observations	19	19	19	19
R^2	0.132	0.190	0.184	0.169
Adjusted R^2	−0.041	0.028	0.021	0.002
Residual Std. Error (df = 15)	2.588	0.420	3.066	7.594
F Statistic (df = 3; 15)	0.762	1.170	1.131	1.015
Note:				*p<0.1; **p<0.05; ***p<0.01

Figure A2: Utilization of procarbazine with OHIP minus

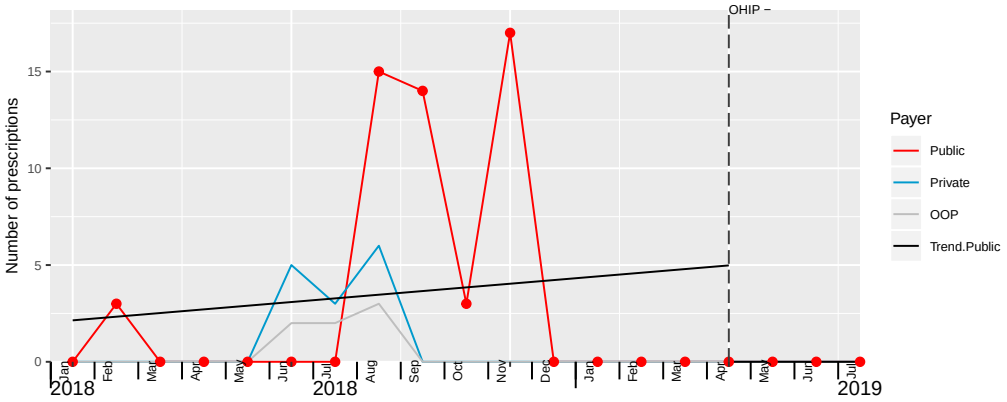

Table A2: Utilization of procarbazine in number of prescriptions with OHIP minus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP minus	−4.981	−0.314	−0.295	−5.543
	(5.973)	(0.448)	(0.950)	(6.726)
Overall trend	0.189	−0.000	−0.021	0.143
	(0.358)	(0.027)	(0.057)	(0.403)
Change in trend	−0.189	−0.000	0.021	−0.143
	(2.701)	(0.203)	(0.430)	(3.042)
Constant	4.981	0.314	0.295	5.543
	(3.253)	(0.244)	(0.517)	(3.664)
Observations	19	19	19	19
R^2	0.082	0.093	0.057	0.089
Adjusted R^2	−0.102	−0.088	−0.132	−0.093
Residual Std. Error (df = 15)	5.987	0.449	0.952	6.742
F Statistic (df = 3; 15)	0.446	0.515	0.300	0.490
Note:				*p<0.1; **p<0.05; ***p<0.01

Figure A3: Utilization of sorafenib with OHIP minus

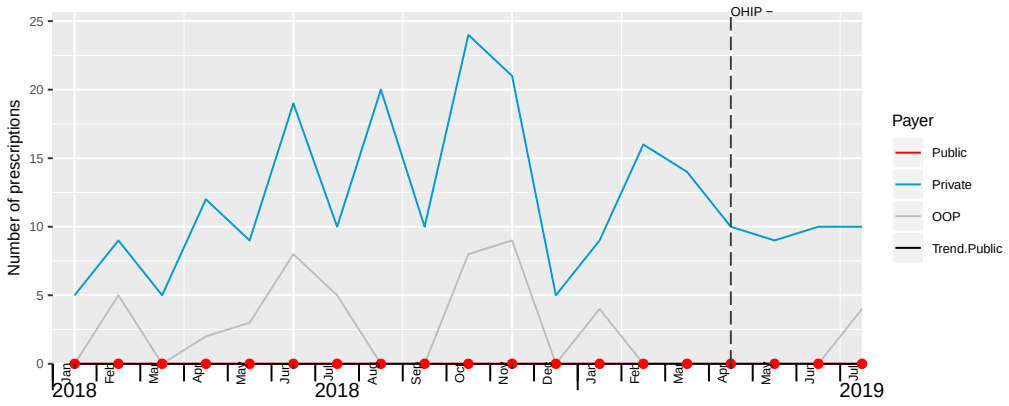

Table A3: Utilization of sorafenib in number of prescriptions with OHIP minus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP minus	0.000	0.000	−3.590	−7.019
	(0.000)	(0.000)	(3.295)	(5.545)
Overall trend	0.000	0.000	−0.018	0.511
	(0.000)	(0.000)	(0.197)	(0.332)
Change in trend	0.000	0.000	1.218	−0.411
	(0.000)	(0.000)	(1.490)	(2.508)
Constant	0.000	0.000	2.790	16.619***
	(0.000)	(0.000)	(1.795)	(3.020)
Observations	19	19	19	19
R^2			0.104	0.174
Adjusted R^2			−0.075	0.009
Residual Std. Error (df = 15)	0.000	0.000	3.303	5.558
F Statistic (df = 3; 15)			0.583	1.053
Note:				*p<0.1; **p<0.05; ***p<0.01

Figure A4: Utilization of vemurafenib with OHIP minus

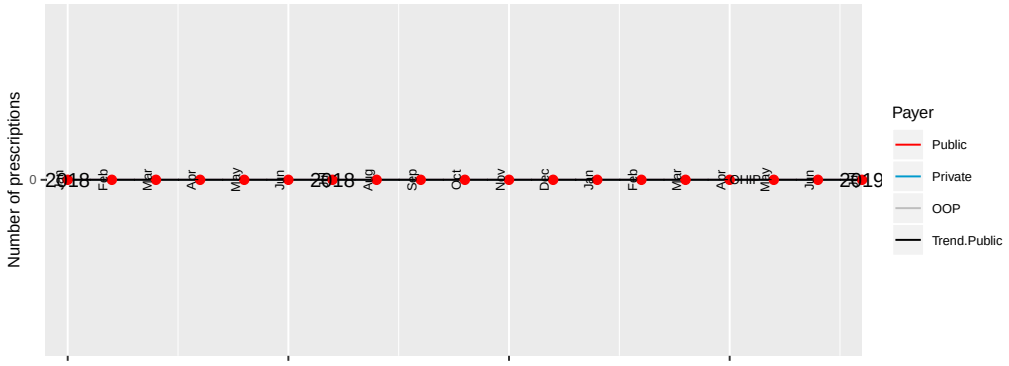

Table A4: Utilization of vemurafenib in number of prescriptions with OHIP minus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP minus	0.000	0.000	0.000	0.000
	(0.000)	(0.000)	(0.000)	(0.000)
Overall trend	0.000	0.000	0.000	0.000
	(0.000)	(0.000)	(0.000)	(0.000)
Change in trend	0.000	0.000	0.000	0.000
	(0.000)	(0.000)	(0.000)	(0.000)
Constant	0.000	0.000	0.000	0.000
	(0.000)	(0.000)	(0.000)	(0.000)
Observations	19	19	19	19
Residual Std. Error (df = 15)	0.000	0.000	0.000	0.000
Note:				*p<0.1; **p<0.05; ***p<0.01

Supplementary Materials

Sensitivity Analysis: Narrow window - Changes in Utilization Because of OHIP Plus

Table SM1: Narrow Window - Utilization of dabrafenib in number of prescriptions with OHIP plus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP plus	2.000	0.059	−2.300	8.100
	(4.761)	(0.140)	(3.622)	(11.415)
Overall trend	−0.000	0.000	0.900	3.300
	(1.155)	(0.034)	(0.878)	(2.769)
Change in trend	0.000	0.000	−1.700	−7.700*
	(1.633)	(0.048)	(1.242)	(3.915)
Constant	−0.000	−0.000	5.700*	19.300*
	(3.830)	(0.113)	(2.913)	(9.182)
Observations	10	10	10	10
R^2	0.111	0.111	0.281	0.528
Adjusted R^2	−0.333	−0.333	−0.078	0.292
Residual Std. Error (df = 6)	3.651	0.107	2.778	8.755
F Statistic (df = 3; 6)	0.250	0.250	0.782	2.236
Note:				*p<0.1; **p<0.05; ***p<0.01

Table SM2: Narrow Window - Utilization of dasatinib in number of prescriptions with OHIP plus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP plus	−11.600	0.154	−6.000*	−24.200
	(13.473)	(0.252)	(2.602)	(18.708)
Overall trend	3.800	0.078	0.400	0.200
	(3.268)	(0.061)	(0.631)	(4.537)
Change in trend	0.100	−0.085	0.100	4.000
	(4.621)	(0.087)	(0.893)	(6.417)
Constant	30.400**	0.589**	7.400**	53.400**
	(10.838)	(0.203)	(2.093)	(15.048)
Observations	10	10	10	10
R^2	0.408	0.647	0.627	0.379
Adjusted R^2	0.111	0.471	0.441	0.069
Residual Std. Error (df = 6)	10.334	0.194	1.996	14.348
F Statistic (df = 3; 6)	1.376	3.672*	3.364*	1.222

Note: *p<0.1; **p<0.05; ***p<0.01

Table SM3: Narrow Window - Utilization of everolimus in number of prescriptions with OHIP plus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP plus	−10.700	−0.367**	1.000	7.300
	(7.271)	(0.132)	(1.051)	(6.938)
Overall trend	2.900	0.083**	−0.200	0.700
	(1.764)	(0.032)	(0.255)	(1.683)
Change in trend	1.400	−0.029	0.100	2.700
	(2.494)	(0.045)	(0.361)	(2.380)
Constant	23.900***	0.689***	−0.200	35.500***
	(5.849)	(0.106)	(0.846)	(5.581)
Observations	10	10	10	10
R^2	0.669	0.619	0.133	0.820
Adjusted R^2	0.504	0.429	−0.300	0.731
Residual Std. Error (df = 6)	5.577	0.101	0.806	5.321
F Statistic (df = 3; 6)	4.050*	3.252	0.308	9.142**

Note: *p<0.1; **p<0.05; ***p<0.01

Table SM4: Narrow Window - Utilization of hydroxyurea in number of prescriptions with OHIP plus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP plus	135.700***	0.372***	−10.700	43.900*
	(15.936)	(0.040)	(8.401)	(22.192)
Overall trend	2.300	0.008	−3.900	−0.500
	(3.865)	(0.010)	(2.038)	(5.382)
Change in trend	8.300	0.012	−0.500	5.000
	(5.466)	(0.014)	(2.882)	(7.612)
Constant	98.900***	0.350***	58.500***	282.100***
	(12.819)	(0.032)	(6.758)	(17.851)
Observations	10	10	10	10
R^2	0.987	0.989	0.918	0.797
Adjusted R^2	0.981	0.983	0.877	0.695
Residual Std. Error (df = 6)	12.222	0.030	6.443	17.021
F Statistic (df = 3; 6)	152.299***	175.025***	22.315***	7.836**
Note:				*p<0.1; **p<0.05; ***p<0.01

Table SM5: Narrow Window - Utilization of imatinib in number of prescriptions with OHIP plus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP plus	35.900***	0.438***	−23.000*	−35.300
	(5.608)	(0.091)	(9.443)	(20.186)
Overall trend	0.700	0.004	−0.600	1.300
	(1.360)	(0.022)	(2.290)	(4.896)
Change in trend	5.200**	0.039	−2.900	1.200
	(1.924)	(0.031)	(3.239)	(6.924)
Constant	15.900**	0.121	41.000***	130.100***
	(4.511)	(0.073)	(7.596)	(16.238)
Observations	10	10	10	10
R^2	0.983	0.962	0.894	0.559
Adjusted R^2	0.975	0.942	0.841	0.338
Residual Std. Error (df = 6)	4.301	0.070	7.242	15.482
F Statistic (df = 3; 6)	118.074***	50.139***	16.868***	2.533

Note: *p<0.1; **p<0.05; ***p<0.01

Table SM6: Narrow Window - Utilization of nilotinib in number of prescriptions with OHIP plus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP plus	2.500	0.392	2.200	4.300
	(3.571)	(0.598)	(3.849)	(11.753)
Overall trend	−0.500	−0.056	−0.000	0.100
	(0.866)	(0.145)	(0.934)	(2.850)
Change in trend	1.000	0.073	0.500	1.900
	(1.225)	(0.205)	(1.320)	(4.031)
Constant	0.500	0.056	−0.000	5.500
	(2.872)	(0.481)	(3.097)	(9.454)
Observations	10	10	10	10
R^2	0.250	0.138	0.350	0.316
Adjusted R^2	−0.125	−0.292	0.024	−0.026
Residual Std. Error (df = 6)	2.739	0.458	2.952	9.014
F Statistic (df = 3; 6)	0.667	0.322	1.075	0.923

Note: *p<0.1; **p<0.05; ***p<0.01

Table SM7: Narrow Window - Utilization of procarbazine in number of prescriptions with OHIP plus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP plus	−3.700	−0.400	0.000	−3.700
	(3.816)	(0.652)	(0.000)	(3.816)
Overall trend	0.100	0.000	0.000	0.100
	(0.926)	(0.158)	(0.000)	(0.926)
Change in trend	−0.400	−0.100	0.000	−0.400
	(1.309)	(0.224)	(0.000)	(1.309)
Constant	4.900	0.800	0.000	4.900
	(3.070)	(0.524)	(0.000)	(3.070)
Observations	10	10	10	10
R^2	0.444	0.400		0.444
Adjusted R^2	0.166	0.100		0.166
Residual Std. Error (df = 6)	2.927	0.500	0.000	2.927
F Statistic (df = 3; 6)	1.595	1.333		1.595
Note:				*p<0.1; **p<0.05; ***p<0.01

Table SM8: Narrow Window - Utilization of sorafenib in number of prescriptions with OHIP plus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP plus	−4.500	−1.133**	2.200	4.100
	(2.791)	(0.390)	(2.302)	(5.658)
Overall trend	0.500	0.217*	−0.400	−0.900
	(0.677)	(0.095)	(0.558)	(1.372)
Change in trend	−0.500	−0.217	0.700	2.000
	(0.957)	(0.134)	(0.790)	(1.941)
Constant	4.500*	1.133**	−0.800	1.700
	(2.245)	(0.314)	(1.852)	(4.552)
Observations	10	10	10	10
R^2	0.476	0.663	0.322	0.318
Adjusted R^2	0.214	0.494	−0.016	−0.024
Residual Std. Error (df = 6)	2.141	0.299	1.765	4.340
F Statistic (df = 3; 6)	1.818	3.930*	0.952	0.931
Note:				*p<0.1; **p<0.05; ***p<0.01

Table SM9: Narrow Window - Utilization of temozolomide in number of prescriptions with OHIP plus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP plus	5.200	0.107	−2.100	9.400
	(7.218)	(0.239)	(2.683)	(7.712)
Overall trend	−3.800*	−0.018	0.500	−8.000***
	(1.751)	(0.058)	(0.651)	(1.870)
Change in trend	11.100***	0.101	0.200	16.900***
	(2.476)	(0.082)	(0.920)	(2.645)
Constant	−0.800	0.349	3.500	1.600
	(5.806)	(0.193)	(2.158)	(6.203)
Observations	10	10	10	10
R^2	0.823	0.488	0.262	0.874
Adjusted R^2	0.734	0.232	−0.108	0.811
Residual Std. Error (df = 6)	5.536	0.184	2.058	5.915
F Statistic (df = 3; 6)	9.284**	1.908	0.709	13.889***
Note:				*p<0.1; **p<0.05; ***p<0.01

Table SM10: Narrow Window - Utilization of trametinib in number of prescriptions with OHIP plus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP plus	2.400	0.227	−7.100*	−10.700
	(4.245)	(0.288)	(3.653)	(6.305)
Overall trend	0.000	0.000	−0.500	−0.100
	(1.030)	(0.070)	(0.886)	(1.529)
Change in trend	0.200	−0.032	5.500***	9.100***
	(1.456)	(0.099)	(1.253)	(2.163)
Constant	0.800	0.062	4.300	12.300*
	(3.415)	(0.232)	(2.939)	(5.072)
Observations	10	10	10	10
R^2	0.239	0.207	0.845	0.869
Adjusted R^2	−0.141	−0.189	0.768	0.804
Residual Std. Error (df = 6)	3.256	0.221	2.802	4.836
F Statistic (df = 3; 6)	0.629	0.523	10.930***	13.294***

Note: *p<0.1; **p<0.05; ***p<0.01

Table SM11: Narrow Window - Utilization of tretinoin in number of prescriptions with OHIP plus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP plus	6.200	0.200	0.000	2.700
	(9.878)	(0.337)	(0.000)	(9.968)
Overall trend	1.000	0.200**	0.000	1.700
	(2.396)	(0.082)	(0.000)	(2.418)
Change in trend	5.400	−0.200	0.000	4.700
	(3.388)	(0.115)	(0.000)	(3.419)
Constant	4.000	0.800**	0.000	7.500
	(7.946)	(0.271)	(0.000)	(8.018)
Observations	10	10	10	10
R^2	0.826	0.833		0.810
Adjusted R^2	0.738	0.750		0.716
Residual Std. Error (df = 6)	7.576	0.258	0.000	7.645
F Statistic (df = 3; 6)	9.463**	10.000***		8.551**
Note:				*p<0.1; **p<0.05; ***p<0.01

Table SM12: Narrow Window - Utilization of vemurafenib in number of prescriptions with OHIP plus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP plus	0.000	0.000	0.000	0.000
	(0.000)	(0.000)	(0.000)	(0.000)
Overall trend	0.000	0.000	0.000	0.000
	(0.000)	(0.000)	(0.000)	(0.000)
Change in trend	0.000	0.000	0.000	0.000
	(0.000)	(0.000)	(0.000)	(0.000)
Constant	0.000	0.000	0.000	0.000
	(0.000)	(0.000)	(0.000)	(0.000)
Observations	10	10	10	10
Residual Std. Error (df = 6)	0.000	0.000	0.000	0.000
Note:				*p<0.1; **p<0.05; ***p<0.01

Sensitivity Analysis: Narrow window - Changes in Utilization Because of OHIP Minus

Table SM13: Narrow Window - Utilization of dabrafenib in number of prescriptions with OHIP minus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP minus	−3.400	−0.154	1.900	−1.700
	(4.942)	(0.228)	(4.208)	(5.379)
Overall trend	1.400	0.074	0.000	−0.200
	(1.490)	(0.069)	(1.269)	(1.622)
Change in trend	−1.800	−0.131	0.400	2.000
	(2.107)	(0.097)	(1.794)	(2.293)
Constant	9.500*	0.492*	0.000	19.500**
	(4.080)	(0.188)	(3.475)	(4.441)
Observations	8	8	8	8
R^2	0.200	0.341	0.292	0.243
Adjusted R^2	−0.400	−0.154	−0.238	−0.324
Residual Std. Error (df = 4)	3.332	0.154	2.837	3.626
F Statistic (df = 3; 4)	0.333	0.689	0.551	0.428
Note:				*p<0.1; **p<0.05; ***p<0.01

Table SM14: Narrow Window - Utilization of dasatinib in number of prescriptions with OHIP minus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP minus	−18.000	−0.203*	1.500	−12.900
	(17.253)	(0.092)	(5.332)	(26.046)
Overall trend	3.600	0.013	0.100	4.100
	(5.202)	(0.028)	(1.608)	(7.853)
Change in trend	−2.600	−0.068	−0.100	4.000
	(7.357)	(0.039)	(2.274)	(11.106)
Constant	42.500**	0.743***	3.000	58.000*
	(14.246)	(0.076)	(4.403)	(21.506)
Observations	8	8	8	8
R^2	0.252	0.904	0.107	0.325
Adjusted R^2	−0.309	0.832	−0.563	−0.182
Residual Std. Error (df = 4)	11.632	0.062	3.595	17.560
F Statistic (df = 3; 4)	0.449	12.581**	0.159	0.641
Note:				*p<0.1; **p<0.05; ***p<0.01

Table SM15: Narrow Window - Utilization of everolimus in number of prescriptions with OHIP minus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP minus	−29.000***	−0.320***	−4.600	−18.300*
	(6.218)	(0.044)	(6.683)	(8.308)
Overall trend	5.700**	0.032*	3.000	7.100**
	(1.875)	(0.013)	(2.015)	(2.505)
Change in trend	−1.700	−0.013	−3.600	0.100
	(2.651)	(0.019)	(2.850)	(3.543)
Constant	48.000***	0.657***	10.000	75.500***
	(5.134)	(0.036)	(5.518)	(6.860)
Observations	8	8	8	8
R^2	0.849	0.965	0.403	0.852
Adjusted R^2	0.736	0.939	−0.045	0.741
Residual Std. Error (df = 4)	4.192	0.030	4.506	5.601
F Statistic (df = 3; 4)	7.503**	37.105***	0.900	7.664**

Note: *p<0.1; **p<0.05; ***p<0.01

Table SM16: Narrow Window - Utilization of hydroxyurea in number of prescriptions with OHIP minus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP minus	−106.800***	−0.377***	32.000***	19.800
	(11.632)	(0.035)	(6.102)	(18.120)
Overall trend	1.400	−0.007	1.100	4.100
	(3.507)	(0.011)	(1.840)	(5.464)
Change in trend	10.800*	0.015	0.900	17.200*
	(4.960)	(0.015)	(2.602)	(7.727)
Constant	244.000***	0.802***	28.500***	303.500***
	(9.605)	(0.029)	(5.039)	(14.962)
Observations	8	8	8	8
R^2	0.984	0.993	0.977	0.944
Adjusted R^2	0.972	0.987	0.960	0.902
Residual Std. Error (df = 4)	7.842	0.024	4.114	12.217
F Statistic (df = 3; 4)	82.407***	177.570***	56.645***	22.424***

Note: *p<0.1; **p<0.05; ***p<0.01

Table SM17: Narrow Window - Utilization of imatinib in number of prescriptions with OHIP minus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP minus	−36.200	−0.456*	8.400	2.300
	(18.392)	(0.212)	(11.489)	(20.106)
Overall trend	5.900	0.017	2.800	7.400
	(5.545)	(0.064)	(3.464)	(6.062)
Change in trend	−2.600	0.025	−4.400	−7.600
	(7.842)	(0.090)	(4.899)	(8.573)
Constant	56.000**	0.662**	12.000	85.500***
	(15.186)	(0.175)	(9.487)	(16.602)
Observations	8	8	8	8
R^2	0.557	0.756	0.619	0.603
Adjusted R^2	0.225	0.573	0.333	0.305
Residual Std. Error (df = 4)	12.400	0.143	7.746	13.555
F Statistic (df = 3; 4)	1.676	4.137	2.167	2.022

Note: *p<0.1; **p<0.05; ***p<0.01

Table SM18: Narrow Window - Utilization of temozolomide in number of prescriptions with OHIP minus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP minus	16.600	−0.328	7.500	47.200***
	(11.330)	(0.374)	(3.796)	(6.679)
Overall trend	−9.900**	−0.006	−0.600	−14.300***
	(3.416)	(0.113)	(1.145)	(2.014)
Change in trend	9.000	0.006	−1.400	7.500*
	(4.831)	(0.159)	(1.619)	(2.848)
Constant	−5.000	0.673*	−1.000	−7.000
	(9.355)	(0.309)	(3.134)	(5.515)
Observations	8	8	8	8
R^2	0.743	0.479	0.603	0.939
Adjusted R^2	0.550	0.088	0.305	0.894
Residual Std. Error (df = 4)	7.639	0.252	2.559	4.503
F Statistic (df = 3; 4)	3.854	1.224	2.025	20.662***

Note: *p<0.1; **p<0.05; ***p<0.01

Table SM19: Narrow Window - Utilization of trametinib in number of prescriptions with OHIP minus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP minus	−1.800	0.018	6.000	−3.200
	(3.924)	(0.403)	(8.046)	(16.543)
Overall trend	0.600	0.062	−3.900	−1.800
	(1.183)	(0.121)	(2.426)	(4.988)
Change in trend	−1.400	−0.163	3.900	2.600
	(1.673)	(0.172)	(3.431)	(7.054)
Constant	10.000**	0.546	−2.500	22.000
	(3.240)	(0.333)	(6.644)	(13.660)
Observations	8	8	8	8
R^2	0.253	0.194	0.470	0.173
Adjusted R^2	−0.307	−0.410	0.072	−0.448
Residual Std. Error (df = 4)	2.646	0.272	5.424	11.153
F Statistic (df = 3; 4)	0.452	0.321	1.180	0.278
Note:				*p<0.1; **p<0.05; ***p<0.01

Table SM20: Narrow Window - Utilization of tretinoin in number of prescriptions with OHIP minus

	Public	Public share	OOP	Total
	(1)	(2)	(3)	(4)
OHIP minus	0.000	0.000	0.900	1.100
	(0.000)	(0.000)	(1.520)	(2.590)
Overall trend	0.000	0.000	0.000	0.000
	(0.000)	(0.000)	(0.458)	(0.781)
Change in trend	0.000	0.000	0.400	0.600
	(0.000)	(0.000)	(0.648)	(1.105)
Constant	0.000	0.000	0.000	0.000
	(0.000)	(0.000)	(1.255)	(2.139)
Observations	8	8	8	8
R^2			0.558	0.445
Adjusted R^2			0.226	0.030
Residual Std. Error (df = 4)	0.000	0.000	1.025	1.746
F Statistic (df = 3; 4)			1.683	1.071
Note:				*p<0.1; **p<0.05; ***p<0.01

Chapter Five: Conclusions

The present chapter outlines how the preceding studies formed a coherent and substantial body of work, summarises their contributions, limitations, and policy implications, and suggests some directions for future research.

The ethics study developed ethical definitions for accessible pricing of pharmaceuticals. In the process, it provided the economic and business context in which this accessibility of drugs must take place. These definitions and the context were applied later in the two empirical case studies. First, the implications of the changes in utilization observed on access to pharmaceuticals were discussed, making use of the definition of access as utilization according to need (Aday & Andersen, 1974; Hurley, 2010) and of barriers to access (Gulliford et al., 2002). Second, the interactions between the three funding sources (public, private insurance, and OOP) were introduced in the stakeholder model of the ethics study. Third, the ethics chapter included examples of public policy that can improve price-access to prescription drugs. The subject of the opioids study is a delisting policy that sought to decrease access to harmful drugs. The subject of the cancer study is a policy intended to increase access to life-saving drugs by expanding the eligibility criteria for public formularies.

Contributions and Policy Implications

The ethics study brings together a social and a business perspective on the ethics of pharmaceutical pricing into a novel framework that draws from health economic evaluation. The stakeholder model is also a novel theoretical model outlining the interplay between the main parties involved in making pharmaceuticals accessible to patients. The findings from this study were applied into

the relational model of 'enlightened risk sharing', which is treated in more detail in the published journal version of this work (Balderrama, Schwartz, & Longo, 2020).

The opioids study expands from the previously published Canadian study by Guan et al. (2017) to include opioid sales paid for mainly with private insurance and OOP. It also registers sociodemographic information about the patients filling the prescriptions, namely the gender, age group, and income group. The RD model was modified to create the pooled RD model for the purpose of this study. The drugs were categorized differently in the opioids study by delisted and substitute status, compared to the organization by strength, by Guan et al. (2017). This organization led to the finding of the three high-strength opioid products that were exempted from the delisting, and whose utilization is analyzed in the appendix of the opioids study. Another omission by Guan et al. (2017) was the dispensation of meperidine, which showed some of the most problematic findings from the policy in our study.

The findings about shifts in funding sources can help elaborate on the success of the policy. For instance, the policy seems to have worked better for adults (25-59 years of age) than for seniors (60 and over) on curbing the use of high-strength opioids, especially when economic harm is considered. Adult fentanyl users seem to have shifted to lower-strength products, while seniors started making more use of private insurance and even OOP payments to continue their use of high-strength fentanyl. Although this suggests the policy was not very effective with seniors and might even be causing economic harm to them, it had a positive effect when it is kept in mind that adults constitute the majority of the opioid-related deaths and emergency medical services. Seniors, however,

count for a disproportionately high share of opioid-related hospitalizations (Special Advisory Committee on the Epidemic of Opioid Overdoses, 2020).

The findings for hydromorphone were positive in terms of the effectiveness of the delisting and other opioid polices. The overall trend of increase in the utilization of hydromorphone seems to be relegated to lower-strength formulations, possibly linked to its use for safe supply. Adults even reduced their use of private insurance to pay for the delisted high-strength versions, and the use of substitutes (low-strength versions, except for Jansen's 32 mg Jurnista^{TM}) increased for both seniors and adults through public subsidy.

A few counterproductive effects of the policy were discovered in this analysis. Although meperidine counted for only about 0.71 % of all the opioid prescriptions observed in this study and its overall utilization of meperidine decreased with the delisting, the use of OOP payments for this drug went up for both genders, for adults and seniors, and for most income levels, with private insurance reducing this economic burden for only a few sociodemographic categories. This happened despite the vast evidence of the unsuitability of meperidine for chronic pain management (Dyer, 2016; Ontario Public Drug Programs, 2016).

Somewhat troubling was also the exemption of Jansen's high-strength Duragesic^{TM} and Jurnista^{TM} products from the delisting, which gave this line of products an advantaged position over competitors and a way for patients to circumvent the policy and continue to get high-strength opioids. The former did not show an increase in utilization, but the latter showed an increase in its utilization trend after the policy's implementation. Currently the Duragesic^{TM} products can be accessed in the public formulary through the Exceptional Access Program (EAP) (Government of Ontario, 2020b).

The sale of Jurnista^{TM} was discontinued on October 31, 2018 (Health Canada, 2019).

The cancer study is, to the best of our knowledge, the first empirical paper about OHIP plus and 'OHIP minus'. Its focus on the utilization of OAMs, many of them novel and expensive, on patients under 25 is of strategic importance for the health care system, due to the high-cost/high-benefit dynamic of treating cancer on this sociodemographic category.

Given the inclusiveness and the comprehensiveness of OHIP plus (before OHIP minus came into effect), in theory it would have been expected that private insurance and OOP payments would no longer be used to pay for these expensive drugs. Both sources of funding, however, were still observed for drugs that were prescribed regularly. This points out some of the shortcomings of the policy on its diffusion (public knowledge) or administrative burden (e.g., the paperwork required to use the public system), that might compel patients to keep using private funding.

The findings of the study support the success of OHIP plus in increasing the share of public funding for many of the oral-delivery cancer drugs in the study, especially those that were prescribed regularly enough that statistically significant results could be observed. Of particular importance was the decrease of OOP payments for these drugs.

The complementarity of OHIP plus and OHIP minus is an important point of discussion. Many papers have evaluated the effects of delisting policies in general, fewer papers looked at policies that expanded public formulary benefits, but OHIP plus and OHIP minus present a very uncommon case of a

drug benefit expansion coupled with a partial retraction of the original policy. The cancer study in this thesis could possibly be the first one to examine this type of interacting policies. The study provides some criteria to evaluate both policies in the context of accessibility to drugs and barriers to access. OHIP minus had the purpose of stopping unnecessary public subsidy for individuals who were already covered by private drug insurance. The study found that four drugs saw a significant shift back to private insurance funding, but three of these drugs also saw an increase in OOP payment, suggesting that the switch from public funding back to private insurance funding was not as smooth as originally thought, at least for the short term.

Limitations and future research directions

Some of the limitations in the studies of this thesis came from the structure of the IQVIA data set and the process of data acquisition. Patient level data would have been ideal to include more explanatory variables and better model the factors that influence the changes in drug utilization. The pooled RD models developed in the opioids study are useful for looking at changes in various sociodemographic and pharmaceutical categories. They have the technical shortcoming, however, of giving the same standard error for similar RD coefficients in each category. The supplementary materials in the opioids study show the estimates of the standard errors in which each category is an isolated regression model. An interesting venue of research would be to modify the pooled-models to adjust the error estimation according to the representation in the data of each category (e.g., applying statistical weights), without requiring each category to be isolated from the rest and fitting multiple categories in the same model.

With the logistical and statistical resources developed for this study it is also possible to study changes in the utilization of antidepressants, anti-cholesterol drugs, antiemetics, and analgesics. For Ontario, the effects of OHIP plus and OHIP minus can be explored, particularly for antidepressants. Antidepressants are widely used by the younger demographics targeted by OHIP plus, but are more dependent on private funding. This means that extending public subsidy for this drug could have had a compelling effect on their utilization. Other delisting policies in Ontario or other provinces could also be the subject of future research. It is also possible to perform differences-in-differences analyses comparing changes in utilization before and after a policy, between two provinces, one where the policy was implemented and one where it was not. This would require, however, finding pairs of provinces with similar sociodemographic characteristics and similar public formulary policies.

Conclusions

This thesis presents a theoretical introduction to the accessibility of pharmaceuticals and financial barriers to access. These concepts are applied in two empirical case studies of public policy that sought to change the access to pharmaceuticals through modifications in the public formulary and the price patients pay for drugs. The studies in this thesis include novel theoretical frameworks, and relational models to explain the implications of pharmaceutical prices on patient access to pharmaceuticals. The empirical studies present novel regression analysis methods. Their findings focus on the effects of public policy within specific sociodemographic categories and specific drug groups.

This thesis illustrates how complex predicting demand for pharmaceuticals can be. Public policy can act through public formularies to obstruct access

to harmful drugs, such as high-strength opioids, or to facilitate access to vital drugs, such as anti-cancer medications. There are many factors that complicate the fulfillment of the objectives of the policy, such as the existence of private sources of funding, substitution effects between drugs, new trends in preferences (as is the case with novel OAMs) and entrenched utilization behaviours that are difficult to change (as seems to be the case with meperidine). At times, the policy itself is flawed, as what happened with the exemption of specific high-strength opioid products or with the clauses of OHIP plus that were considered unnecessary and retracted with OHIP minus. While it might be impossible to predict all the effects these policies might have, the approach taken in this thesis, i.e., observing the effects in multiple sociodemographic categories, for multiple drugs, and at different stages of the policy, can help us understand the different factors at play. That can inform the design of future policy aimed at improving access to necessary drugs, decreasing access to harmful drugs, reducing wasteful spending, and causing the least economic harm, particularly for the most vulnerable populations.

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