Evaluating the impact of Choosing Wisely Canada recommendations on the overuse and inappropriate use of psychiatric medications among young people

by

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The following individuals certify that they have read, and recommend to the Faculty of Graduate and Postdoctoral Studies for acceptance, a thesis entitled:

Evaluating the impact of Choosing Wisely Canada recommendations on the overuse and inappropriate use of psychiatric medications among young people

Submitted by Talshyn Bolatova in partial fulfillment of the requirements for the degree of Master of Science in Population and Public Health

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Abstract

**Introduction:** The Choosing Wisely Canada (CWC) campaign aims to facilitate discussion between patients and providers about what procedures, tests, and treatments are unnecessary. The results of previous evaluations of the CWC recommendations on the use of unnecessary care from various specialties, however, are not consistent. This thesis aims to build upon the previous body of research by evaluating the impact of the CWC recommendations regarding the appropriate prescription of psychiatric medications for young people. Specifically, I assessed the impact of three specific recommendations on the drug utilization, time to treatment, and costs.

**Methods:** To evaluate the impact of the CWC recommendations on the use psychiatric medications among young people in British Columbia, I identified all patients with incident diagnoses and prescription fills for the recommendations under study: selective serotonin reuptake inhibitors (SSRIs) among adolescents (<=17) with major depressive disorder (MDD), psychostimulants among preschool aged children (<=5) with attention deficit and hyperactivity disorder (ADHD), and atypical antipsychotics (AAs) among ADHD patients comorbid with disruptive behaviour disorders (DBDs) (no age restriction). Using comprehensive administrative data from 2010 to 2017 and interrupted time series analyses, I assessed longitudinal trends in relevant outcomes for each recommendation, including the incidence of disease, prescription drug starting, and time to treatment initiation following a new diagnosis.

**Results:** For MDD, the CWC recommendations did not change the level or trend in monthly depression incidence, starting SSRIs, and the time to SSRI treatment. Similarly, following the
release of the recommendation for ADHD, the incidence of ADHD, number of stimulant starters, and time to treatment initiation did not change among preschool aged children. Finally, for antipsychotic use among ADHD/DBDs there was a significant trend increase in the number of starters who initiated treatment within 7 months, but these results were based on a very small sample size.

**Conclusion:** I did not find that the CWC campaign had a major impact on the inappropriate use of psychiatric medications in target populations. This is consistent with the existing literature that public campaigns alone are insufficient to change clinical practice in this area.
Lay Summary

Every year, Canadians spend billions of dollars on ineffective medical treatments that can harm patients. In response to this trend, CWC was created to educate medical practitioners and patients on practices that should be avoided in clinical practice. I studied whether three CWC recommendations, which warn against using certain psychiatric medications as first line treatment option for mental health conditions in children and adolescents, changed the prescribing of these medications by practitioners in British Columbia (BC). To do so, I identified three cohorts of people with the conditions cited in the recommendations: depression, ADHD, and ADHD with behavioral problems. Using these cohorts, I investigated longitudinal changes in drug use, starting, and time to treatment before and after the campaign started using interrupted time series analyses. Overall, I found that the launch of these recommendations was not associated with detectable decreases in the use of these medications by youth in BC.
Preface

The work in this thesis research was conducted and written by Talshyn Bolatova (TB) under the supervision of Dr. Michael Law. The development of research questions, study design, statistical analysis, and writing was conducted by TB under the supervision of Dr. Law. Committee members Dr. Nick Bansback and Dr. Tim Oberlander provided feedback to improve the methodology, statistical analysis, and reporting of the findings. None of the text of the dissertation is taken directly from previously published or collaborative articles.

The studies in this thesis were conducted as part of Dr. Law’s broader research program entitled *Improving Access to Medicines in Canada and Abroad* funded by the Canadian Institutes of Health Research (FDN-148412). This study was approved by The University of British Columbia Behavioural Research Ethics Board (certificate number: H16-02087).
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<td>Atypical Antipsychotics</td>
</tr>
<tr>
<td>ABIM</td>
<td>American Board of Internal Medicine</td>
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<tr>
<td>ADHD</td>
<td>Attention Deficit and Hyperactivity Disorder</td>
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<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical</td>
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<tr>
<td>BC</td>
<td>British Columbia</td>
</tr>
<tr>
<td>CACAP</td>
<td>Canadian Academy of Child and Adolescent Psychiatry</td>
</tr>
<tr>
<td>CADDRA</td>
<td>Canadian ADHD Resource Alliance</td>
</tr>
<tr>
<td>CD</td>
<td>Conduct disorder</td>
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<tr>
<td>CIHI</td>
<td>Canadian Institute of Health Information</td>
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<tr>
<td>CPA</td>
<td>Canadian Psychiatric Association</td>
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<tr>
<td>CW</td>
<td>Choosing Wisely</td>
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<tr>
<td>CWC</td>
<td>Choosing Wisely Canada</td>
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<tr>
<td>DAD</td>
<td>Discharge Abstract Database</td>
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<tr>
<td>DBDs</td>
<td>Disruptive Behavioural Disorders</td>
</tr>
<tr>
<td>DSM-5</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, 5th Edition</td>
</tr>
<tr>
<td>FGAs</td>
<td>First generation antipsychotics</td>
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<tr>
<td>ICD-10</td>
<td>International Classification of Diseases and Related Health Problems, 10th revision</td>
</tr>
<tr>
<td>ICD-9</td>
<td>International Classification of Diseases and Related Health Problems, 9th revision</td>
</tr>
<tr>
<td>IOM</td>
<td>Institute of Medicine</td>
</tr>
<tr>
<td>JAMA</td>
<td>The Journal of the American Medical Association</td>
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MDD  Major depressive disorder
MSP  Medical Services Plan
ODD  Oppositional defiant disorder
RCT  Randomized clinical trial
SGAs  Second generation antipsychotics
SSRIs  Selective Serotonin Reuptake Inhibitors
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Dedication

Жазылған жұмыс, Мама, бір өзіне арналады.
1 Introduction

1.1 Unnecessary Care

Unnecessary medical care refers to medical services, treatments, and tests that waste scarce financial resources without providing health benefits (1). Unnecessary medical care also has the potential to expose a patient to harm or provide minimal benefit at an unjustifiably high cost. The prevalence of unnecessary care is substantial and presents a high cost to health care systems. For instance, The Institute of Medicine (IOM) has estimated that 30% of medical care is unnecessary (2). Similarly, the Canadian Institute of Health Information (CIHI) and Choosing Wisely Canada (CWC) have estimated that up to 30% of all the medical interventions delivered in Canada are unnecessary (3).

The overuse of unnecessary medical care is ubiquitous across medical specializations and subdivisions. A growing body of evidence has shown the widespread prevalence of overuse of unnecessary medical care in adult and pediatric populations. For example, the Journal of the American Medical Association (JAMA) has published a series of studies demonstrating overuse across a range of adult patients (4–9). This series identified and summarized the most important original research articles on the overuse of medical care, categorized by overdiagnosis, overtreatment and questionable use of services, within different specialties. A similar series of articles on pediatric overuse have been published (10–12). Overall, this body of research has demonstrated that overdiagnosis, overtreatment, and overutilization are common for various childhood conditions as well.
There are a number of reasons why overuse occurs in healthcare, resulting in a low value care. In a study conducted by Lyu et. al, researchers surveyed physicians across the United States on the prevalence of unnecessary medical care, and the reasons for it within their respective practices (13). According to the survey, physicians believed that 20% of the all medical care was unnecessary. This included 22.0% of prescription drugs, 24.9% of tests, and 11.1% of procedures (13). This perspective on overuse was not restricted to the physicians. A survey conducted in 7 countries found that 10 - 20% of patients believed that they were provided unnecessary medical care (14). The top three reasons for overtreatment were fear of malpractice (85%), patient request (59%), and difficulty accessing prior medical records (38%) (13). In a recent Canadian study, the top three drivers of unnecessary medical care according to physicians were fear of litigation for refusing to provide health services, lack of time during patient visit, and pre-emptive ordering of tests due to uncertainty in the further treatment direction (15).

1.2 The Choosing Wisely Campaign

To tackle the issue of the overabundance of low value care, the American Board of Internal Medicine’s (ABIM) foundation initiated the Choosing Wisely (CW) campaign in 2012. Choosing Wisely aims to help clinicians and patients engage in conversation about unnecessary tests, treatments and procedures, thereby better enabling effective and evidence-based choices to increase the quality of health care (3). Since commencing, CW has expanded to 20 countries globally (including Italy, Australia, Switzerland, the Netherlands, England, Germany, Austria, Japan, New Zealand, Wales, Brazil, Israel, France, and Norway) and there are planned launches in several more countries (South Korea, Denmark, Singapore, Portugal, Poland, Spain, South Africa, and Saudi Arabia) (16).
As part of this expansion, the Choosing Wisely Canada (CWC) campaign was launched in 2014. This campaign assembles lists for different specialties that are specifically for the Canadian context. To start these lists, CWC had professionals from different specialties curate a list of common treatments and procedures within their specialty that are not supported by evidence and could consequently be exposing patients to harm. As of 2019, CWC listed 330 recommendations for 47 different clinical specialties (17). These recommendations range across clinical care, use of diagnostics, and drug treatments.

Since its launch, the CWC campaign has seen strong acceptance from physicians across Canada. A survey conducted in 2017 among the member physicians of the Canadian Medical Association found that 88.4% of all respondents were aware of the campaign, and 42.4% reported relying on recommendations in their practice (16). At the same time, however, a study conducted by Singer et.al demonstrated that 30% of primary care providers prescribe interventions counter to the CWC recommendations, with fee-for service physicians being more likely to prescribe antibiotics and salaried physicians being more likely to prescribe antipsychotics against the campaign recommendations (18). Other studies that have quantified the use of low value care according to the CWC metrics in Canada nationally and provincially have suggested the prevalence of unnecessary care varied between 20% and 40% (18–28). These numbers demonstrate that despite widespread awareness about the campaign, physicians are not universally following these recommendations.
1.3 Previous evaluations of the CW campaign

Previous evaluations of the CW campaign have shown mixed results. In general, when the campaign was evaluated alone, it has not shown any or limited reductions in the use of unnecessary care. In contrast, when the campaign was actively implemented, and was coupled with various quality improvement initiatives, it has resulted in a significant reduction in the utilization of low value care in some cases. The following section summarizes previous evaluations of the CW campaign recommendations within the North America at both the individual facility level and at the national or state/province level.

1.3.1 Evaluations within individual health care facilities

Some prior evaluations of particular CWC recommendations have found reductions in some types of low-value care in individual institutions that actively implemented them (16,29). For example, the Sunnybrook Health Sciences Centre in Toronto achieved a 37% reduction in their red blood cell transfusion rate in one year (30). Their active approach was multifaceted and utilized pre-printed reminders and prospective patient screening prior to administering blood transfusions. They also achieved a 50% reduction in unnecessary urinary catheter use through creating a standardized medical directive, and staff training (29,31). Similarly, St. Michael’s Hospital in Toronto achieved 27%, 23%, and 17% reductions in routine blood test per patient admitted in the department of general internal medicine, hematology/oncology, and cardiovascular/vascular surgery services, respectively (32). This was achieved by educating clinicians and revising order sets (32). Another facility, North York General hospital reduced the number of unnecessary emergency department laboratory testing and preoperative and postoperative assessments without negative outcomes in the long term (33). They achieved this
through engaging emergency department and lab staff at all levels and increasing awareness through education. Finally, implementation of the transfusion reduction initiative based on the CW recommendation, led to a substantial decrease in preoperative transfusions in gynecologic surgery in cancer center in Texas (34).

There have also been some evaluations of quality improvement initiatives based on CWC recommendations for prescription drug use. For example, an RCT conducted in Montreal found that 11% of patients reduced their dosage and 27% discontinued the use of benzodiazepines in a patient group that was given a CWC-informed decision aid tool at a pharmacy, compared to 5% discontinuation in a control group (35). Similarly, a team at Toronto Western Hospital achieved a 26% reduction in the inappropriate prescription of proton pump inhibitors via reassessment reminders embedded in their electronic medical record system (36).

1.3.2 Evaluations at national and state/province level

At the national or state/province level, a handful of studies have examined the impact of the CW recommendations on the utilization of low value care. Most prominently, a study conducted by Rosenberg et.al was among the first to evaluate the utilization of low value care after the launch of the US CW campaign (37). The authors used administrative claims data to examine the utilization of low value care based on seven CW recommendations. The results of this study indicate that the usage of only two unnecessary procedures decreased by a small amount: imaging for headache and cardiac imaging, both declined by 1.5% and 1.1% respectively (37). Rates of use for the other five services did not decline.
While some studies have found modest reductions in the use of low value care following the release of the CWC recommendations (23,38), other studies show that CWC had little (39) to no effect on the prevalence of unnecessary care (20,25,40,41). In cases where the CW recommendations had an impact on the utilization of low value care, it was typically coupled with active quality improvement initiatives such as educational presentations, targeted outreach and report cards disseminated within health care facilities (34,38,42). For example, the CW recommendation advocating troponin-only testing for the diagnosis of myocardial infarction instead of other methods was associated with an increase in the prescription of high-value troponin-only testing in 26 hospitals in Chicago (42). These hospitals, however, were early adopters of the CW campaign, and had active quality improvement initiatives implemented regarding optimal testing prior to the recommendation being released (42). Similarly, a study conducted by Reyes et al. found that the CW campaign coupled with physician report card dissemination led to a modest reduction in the use of two out of five low value care metrics in 36 tertiary children’s hospitals in the US (38).

In contrast to studies examining the effect of CW in conjunction with more active interventions, studies that have evaluated the impact of the CWC recommendations alone have reported very modest or no effects. For example, an administrative database study from Ontario demonstrated that the CWC urology recommendations had no impact on the use of three types of low value care (41). Similarly, a study conducted by Lasser et.al showed that the campaign had no impact on the trends in the ordering of low value dual-energy X-ray absorptiometry scans (40). Similarly, Hong et al. found that 27 months after the launch of a CWC recommendation, the utilization rate of low-value back pain imaging decreased only by 4-5%(39). Finally, Kirkham et
al. demonstrated that the rate of preoperative laboratory tests prior to low risk surgeries
decreased only by less than 3% following a CWC recommendation (20).

In contrast to clinical services, there have been very few studies that have examined the impact
of CWC recommendations on the use of prescription drugs. A study conducted by Brett et.al
showed that after the launch of a CW recommendation both prevalent and incident use of
benzodiazepine prescription in older adults decreased in the US and Canada, and prevalent use
decreased in Australia (23). However, at that time benzodiazepine use had already been
decreasing in these countries, and it is unclear whether the modest decrease observed in this
study was a direct result of the CW campaign (23). Beyond this study, I am unaware of any
studies on the impact of CW recommendations on prescribing behaviour in a community setting.

1.4 Changing Physician Behaviour
Timely and appropriately prescribed medications are an essential part of many medical treatment
regimens. Almost two-thirds of all physician visits end in the prescribing of one or more
medications (43). However, when there is no alternative to a given medication, suboptimal
prescribing practices such as off-label drug use (prescribing approved medications to an
unapproved patient group) become more common (2,44,45). The reasons for inappropriate
physician prescribing include but are not limited to: lack of knowledge on new risk-benefit
findings of a given medication, excessive promotion of some medications by pharmaceutical
companies, a lack of effective therapeutic agents for many conditions, not understanding the
cost-effectiveness profile of medications, patient demand, overreliance on experience, fear of
malpractice, and the influence of other professionals and opinion leaders within the field (43).
Existing knowledge on changing physician behavior suggests that active interventions are effective in altering physician prescribing behavior. This includes educational interventions such as one-to-one academic detailing and small group detailing that have previously been shown to be effective in changing physician prescribing behavior (43). Audit and feedback have small to moderate effect on the improvement in professional practice, with the impact varying based on baseline performance, comprehensiveness of the design of the intervention, and the way it is delivered (46). In contrast, more passive measures have shown a mixed impact. For example, the impact of physician financial incentives on medication use and costs is low, and the impact on health outcomes is uncertain (47). Media campaigns with a simple message and widespread coverage have been shown to be effective in reducing inappropriate prescribing (48). Overall, multifaceted interventions that include strategies predisposing, enabling and reinforcing positive prescribing behavior are thought to be the most effective in achieving long term changes in physician prescribing behavior (43).

The evidence of mixed effectiveness of the CW recommendations is consistent with prior studies that have shown passive information dissemination interventions, such as distributing best practice guidelines, have little impact (43,49,50). However, it is unclear that CWC is simply a standard form of passive information dissemination as it has received widespread coverage and endorsement from various medical societies. The listed recommendations address the most commonly used low-value care outlined in best practice guidelines within different specialties. Compared to practice guidelines, the recommendations in CWC are written using simpler language and would be understandable to most patients. Given the prominence of CWC in
reaching physicians, it remains unclear whether this method might be more effective than past attempts at passive recommendations.

1.5 Choosing Wisely in Psychiatry

Within the broader CWC campaign, there are series of recommendations made specifically for psychiatrists. These recommendations were developed by The Canadian Psychiatric Association (CPA) working group, which includes representatives from CPA’s Professional Standards and Practice Committee, Research Committee, and Member-in-Training Section, the Canadian Academy of Geriatric Psychiatry (CAGP), the Canadian Academy of Child and Adolescent Psychiatry (CACAP) and the Canadian Mental Health Association representative with lived experience (2,17,51). To develop recommendations, CPA members and provincial associations such as Canadian Academy of Psychiatry and the Law (CAPL) and the Canadian Academy of Psychosomatic Medicine (CAPM) created a potential list of recommendations based on CPA membership survey and American Psychiatric Association’s (APA) recommendations for CW. Further, these potential recommendations were submitted to a working group, where they were reviewed and refined. To date, this group has developed 13 recommendations for CWC pertaining specifically to psychiatry. Notably, 11 of these recommendations specifically address prescribing behavior (2,17,51).

1.6 Prescribing in Pediatric Psychiatry

Mental illness is very common in Canada. Estimates suggest that 20% of Canadians experience a mental disorder during their lifetime, many of which onset during childhood, adolescence and young adulthood (52). At any given time, 12.6% of children and adolescents between ages four
to seventeen experience a mental health disorder (53). Alongside this high prevalence of mental disorders, over the last two decades the use of psychiatric medications has significantly increased in pediatric patients in Canada. The development and approval of new therapeutic agents, broadening of clinical indications for existing medications, and reduced stigmatization surrounding mental disorders have made psychiatric drugs more readily available to physicians and patients.

This increase has been widely documented in prior studies. For example, data from Saskatchewan showed a 3-fold increase in the use of antidepressants among youth aged 15-19 between 1989 and 2007 (54), while another administrative data study reported a 39 percent increase in the prescribing of selective serotonin reuptake inhibitors (SSRI) across Canada by pediatricians and a 44 percent increase by all specialists (55). Similarly, Morkem and colleagues demonstrated a 2.6-fold increase in the prescribing of ADHD medication in preschool-aged children and a 2.5-fold increase among school-aged children in Canadian primary care between 2005 and 2015 (56). Rosnley and colleagues reported a 3.8-fold increase in the prescription of antipsychotics overall, and an 18-fold increase in the prescription of second generation antipsychotics for youth under the age of 18 in British Columbia between 1996 to 2011 (57). Similar data form Manitoba showed a 3.9-fold increase in the use antipsychotics among children under the age 18 between 1999 and 2008 (58).

Despite these increasing trends in psychiatric use among Canadian children, it is known that overreliance on pharmacotherapy represents a significant strain on scarce healthcare resources and may cause harm to vulnerable pediatric patients. If prescribed inappropriately, psychiatric
medications can expose children and adolescents to a serious side effects. Physicians should be cautious when prescribing these medications and monitor patients closely during the course of treatment. For the most psychiatric conditions in children and adolescents, practice guidelines recommend prescribing psychiatric medications only if other initial psychosocial interventions such as cognitive behavioral therapy, parent training, and psychosocial therapy are unsuccessful.

The likelihood of inappropriate prescribing is also increased due to difficulties associated with the diagnosis of mental disorders among young children. Mental health disorders are complex, and oftentimes patients with one psychiatric condition are comorbid with another. This complexity can increase the probability of misdiagnosis and lead to increased rates in the off-label use of medications (2). For example, the national comorbidity survey in the United States found more than 60% of adolescent cases of major depressive disorder were comorbid with another mental health condition (59). Similarly, more than 50% cases ADHD patients are comorbid with a behavioral disorder such as oppositional defiant disorder or conduct disorder (60,61). Finally, among preschool aged children diagnosed with ADHD, nearly one-quarter had more than 2 additional psychiatric diagnoses (62).

Psychiatric conditions and mental disorders are diagnosed using the Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Mental and Behavioral Disorders (ICD) criteria. Unlike other medical fields, where objective measures such as diagnostic tests are more often standardized and interpreted similarly (e.g. white blood cell count, antibodies), the evaluation of psychiatric conditions using these criteria is subjective and largely based on individual specialist’ clinical opinions (2). In addition, diagnostic tools change
and evolve over time, making it difficult to apply the same diagnostic criteria across patient groups. Diagnosis and subsequent treatment of psychiatric conditions is further complicated by uncertainty in the diagnosis, since some younger children may not be able to adequately describe their internal mood state. In this context, the off-label prescribing of psychiatric medications remains high in children and adolescents in Canada.

There are three specific recommendations within CWC that focus on prescribing to children and adolescents. While the CWC guidelines attempt to outline some treatments that should be avoided as a first-line option with children, it is unknown whether these have been effective at changing the use of these medications. Therefore, the objective of this thesis was to examine the impact of the CWC drug-related recommendations on the use of psychiatric drugs among young people in British Columbia.

1.7 Research aims

The aims of this study were to evaluate the following CWC recommendations from psychiatry related to prescribing in the pediatric population (51):

- Don’t use SSRIs as the first-line intervention for mild to moderately depressed teens
- Don’t use psychostimulants as a first-line intervention in preschool children with ADHD
- Don’t use atypical antipsychotics as a first-line intervention for Attention Deficit Hyperactivity Disorder (ADHD) with disruptive behavior disorders
1.8 Methods (common for all three studies)

In order to estimate the impact of the CWC recommendations, I used administrative data and measured longitudinal changes in the number of drug starters, time to treatment initiation, costs and control outcome incidence using an interrupted time series study design.

1.8.1 Data sources

The study population and data were drawn from Population Data BC., a multi-university, data and education resource which contains information about 4.7 million British Columbia (BC) residents held within 23 linkable databases. I retrieved the information from the following databases between 2010 and 2017:

*MSP Consolidation File*

The Medical Services Plan (MSP) Consolidation File contain basic demographics and provincial health services registration data (63). From this database I obtained data on registration status with the provincial insurance Medical Services Plan, age, and sex.

*Discharge Abstract Database*

The Discharge Abstract Database (DAD) contains administrative, clinical, and demographic information on hospital discharges (inpatient acute, chronic, and rehabilitation) and day surgeries from acute care hospitals (64). The DAD includes diagnoses based on the ICD-10 system. From this dataset, I identified patients who registered with relevant ICD-10 codes at least once in the study period and combined these with outpatient data to establish prevalent disease cohorts.
Variables obtained from the DAD included hospitalization information including the admission date and reasons for admission.

*Medical Service Plan billings*

The Medical Service Plan (MSP) is the provincial insurance plan for medical services, which contains information about healthcare services provided by fee-for-service physicians to BC residents (65). Unlike the DAD, the MSP database uses ICD-9 for billing purposes. From this data I identified patients who had two or more claims with particular ICD-9 codes in the study period to establish disease cohorts. Variables from this database include service information date, ICD codes, and practitioner information (referring and prescribing clinician’s ID).

*PharmaNET*

PharmaNET is a province-wide network that links all B.C. pharmacies to a central data system (66). When a prescription is filled, pharmacists transmit the details of the prescription to PharmaNet. These details include patient demographic information, medication history, drug information, and claim information. From this database, I identified patients who filled prescriptions for psychiatric medications. Variables extracted from this database included practitioner information (specialty), drug information (dosage, strength), DIN/PIN (drug identification number), quantity dispensed, service date, and cost.

1.8.2 Study cohort

To study the impact of each CWC recommendation on the use of medications, I constructed cohorts of patients according to the following definitions:
1. 2 or more MSP claims with the relevant ICD-9 code at any time during the study period, and/or;

2. 1 or more hospital discharges with the relevant ICD-10 code in the DAD at any time during the study period, and;

3. At least 1-year of continuous registration within the MSP system prior to the first diagnosis date. The diagnosis date was defined as the earliest record of the relevant ICD-9 or ICD-10 code in either (MSP or DAD) of the datasets.

Within these broader cohorts, I also created a sub-cohort of the patients who started a new medication. I based this on data from PharmaNET, where patients with no prescription fills for the medications in question for one year before the diagnosis date were identified. I defined patients who initiated treatment with the psychiatric medication after receiving no prescriptions in the previous year as starters (67).

I assumed that patients who experienced one year without any prescription fill for a given medication and any physician visit for a given mental disorder were treatment naïve. I based this assumption on the expectation that patients often visit their physician several times to get a diagnosis confirmed and to get both their initial prescription and refills. For example, the diagnosis of ADHD typically occurs over the course of several appointments (68). Similarly, the initial diagnosis of depression requires biweekly visits for at least 8 weeks (69). This assumption was further supported by empirical investigation of my data: the majority of patients who were diagnosed with a given mental disorder filled prescriptions multiple times a year after their initial diagnosis.
Further detailed information on cohort inclusion criteria for each recommendation’s target patient group are described within each chapter. Individuals who receive drug benefits through the Federal Government (such as First Nations, RCMP and veterans) were excluded from the study, as their drug data was not available. Patients who died during the study period, had missing data on key study variables, or who did not meet 1-year continuous registration with MSP prior to the diagnosis date were also excluded.

1.8.3 Study period

As shown below in figure 1, my study period ran between January 2010 and December 2017. All individuals who met the eligibility criteria between January 2010 and December 2017 were included in the analysis. This length of study period had enough data to establish pre-policy and post-policy trends. The intervention - release of the CWC psychiatry recommendations - was on June 2, 2015. My unit of analysis was months.
1.8.4 Outcomes (common for all three studies)

Incidence

Incidence was defined as the monthly average number of newly diagnosed cases. In my study, this included patients who had a diagnosis code of the condition under study while also maintaining no prior diagnosis in the preceding year. This outcome was obtained through merging patient data from the MSP and DAD databases. The earliest entry date of relevant ICD-9/ICD-10 code was flagged as the date of diagnosis. The incidence of disorders was used as a control outcome in my study. Since the recommendations target prescribing practices and not diagnosis, I hypothesized that trends in the incidence of these diagnoses would not be affected by the CWC recommendations.
Starting was defined as the monthly number of patients who were prescribed medication for the first time after their incident diagnosis. In my study, this outcome included people who initiated treatment with the psychiatric medications after receiving no prescriptions in the previous year (48). I hypothesized that after the campaign launch, the number of starters each month would decrease for the targeted prescribing behaviors. If the CWC campaign had an impact, fewer patients would be prescribed SSRIs, psychostimulants, and antipsychotics as a first line treatment for depression, ADHD, and ADHD comorbid with DBDs, respectively.

In order to avoid the inclusion of right-censored observations, I needed to cap my date range based on the date patients were first diagnosed to the date they actually filled their prescriptions. This run-in period needed to be long enough to allow patients to try non-medication options or other pharmacotherapies. From the preliminary analysis of my data, I first measured how long after diagnosis the majority of patients took to fill their prescriptions. Based on this information, the run-in period for each specific medication was defined and the appropriate number of months were removed from the end of the post-intervention period.

*Time to treatment*

Time to treatment was defined as the monthly average time interval in days between the diagnosing date and the first prescription fill date among starters. I hypothesized that if the campaign had an impact, the time between the diagnosing date and the first prescription fill date would increase. This hypothesis was based on the assumption that physicians and specialists who are informed about the campaign would follow the recommendation and would be more cautious prescribing psychiatric medications as a first line treatment. They would prescribe medication...
only after other non-medication treatment options failed and this would result in a longer time interval between the first diagnosing date and the first prescription fill date.

**Cost**

Drug costs were defined as the monthly average drug spending per person per month. This was calculated by dividing the total spending for medication for a given month by the number of patients who filled prescriptions in that month. Were CWC to have had an impact on prescribing rates I hypothesized that this impact would translate to potential savings to patients.

**1.8.5 Statistical analysis**

Bivariate statistics were conducted using two-sample t-tests. I analyzed the longitudinal effects of the CWC drug recommendations using Interrupted Time Series (ITS) Analysis. ITS is one of the strongest quasi-experimental designs which allows one to assess statistically the extent to which an intervention changes an outcome immediately after its implementation and over time, while controlling for other fixed factors (70). I analyzed the change in the use of prescription drugs for the period between January 2010 and December 2017. The intervention (i.e. the launch of the CWC psychiatry recommendations) occurred on June 2, 2015.

My general ITS model was the following (70):

\[ Yt = \beta_0 + \beta_1 \times Time + \beta_2 \times Level + \beta_3 \times Trend + \epsilon \]

Where the parameters represent the following estimates:

- \( \beta_0 \): is the baseline estimate of the outcome at time \( t=0 \)
\( \beta_1 \) – the coefficient for the baseline trend, which shows the monthly change in the mean estimate of the outcome before the intervention, June 2015

\( \beta_2 \) – estimate of the level change in the mean of the outcome immediately following the launch of the CWC recommendation

\( \beta_3 \) – estimate of the change in the trend after the launch of the CWC recommendation

\( \epsilon_t \) – an error term, that shows variability in outcome not explained by the model

The two parameters of interest were \( \beta_2 \) and \( \beta_3 \) that show change in the outcomes immediately (level change) and over time (trend change), respectively.

And the following variables were included in the model:

**Time** – a continuous variable indicating the time in months at time \( t \) beginning from the first month of observation (January 2010).

**Level** – an indicator variable that showed whether at time \( t \) CWC recommendation had been launched (intervention=1) or not (intervention=0). Intervention was equal to ‘0’ between January 2010 and May 2015 and is equal to ‘1’ starting June 2015 till the end of the study period in December 2017.
**Trend** – a continuous variable that represented the interaction between intervention and time variables and shows the time in the months after the CWC recommendation was launched. All months were marked 0 before May 2015, and starting from June 2015, all months were numbered sequentially with 1 in June 2015.

The CWC recommendations were implemented across the country and so there was no potential for a control group. Therefore, the effect of the intervention was compared to the counterfactual value, which is the estimate of the outcome if the intervention had not occurred. I also used trends of the incidence of each psychiatric condition as a control outcome. I expected that the incidence of the disorders under this study would not significantly change after the launch of the CWC recommendation.

**Modeling Approach**

As the ITS design uses data that is longitudinal in nature, the error terms of each observed outcome are potentially correlated, which would violate the assumptions of standard regression techniques. This is particularly a concern as psychiatric conditions may follow a cyclical and/or seasonal pattern. For example, the prevalence of major depressive episode has been shown to exhibit seasonal variation in Canada (71). Further, studies have shown that children who are younger relative to their classmates are more likely to receive medication treatment for ADHD and to be diagnosed with ADHD (72–74). As I had sufficient pre-policy observations to identify seasonality, I used appropriate modeling techniques to capture this impact. I used generalized least squares (GLS) models and checked for the presence of autocorrelation by visually
inspecting residual plots (ACF and PACF) and running the diagnostic Durbin Watson test. Any observed autocorrelation between observations was adjusted for in my models (70).
2 The impact of the CWC recommendation on the use of Selective Serotonin Reuptake Inhibitors among adolescents with depression

Recommendation 1: Do not use SSRIs as the first-line intervention for mild to moderately depressed teens

As outlined above, this first analytic chapter will assess the impact of the CWC recommendation regarding the use of SSRIs as a first-line intervention for mild to moderately depressed teens.

2.1 Introduction

2.1.1 Depression

Depression is an umbrella term for the group of symptoms related to a change in mood, thinking, and activity that has different causes. The ICD-10 and DSM classification systems distinguish mild, moderate, and severe depression based on the number and severity of the symptoms (75). Major depressive disorder (MDD) is a chronic condition that affects 4% to 8% of adolescents and has cumulative incidence of 20% by the age of 18 (76).

MDD mostly manifests during childhood with symptoms that include persistent low mood, feelings of sadness, lack of interest in previously pleasurable activities, sleep problems, decreased concentration, and low energy. Delayed treatment of depression might significantly impair social functioning, lead to poor academic performance, cause suicidal behavior, and increase the risk of substance abuse in the future. In Canada, the lifetime and past-year MDD prevalence are 11.4% and 4.7%, respectively, with the highest prevalence among adolescents.
In a recent epidemiologic study conducted using national surveys, the prevalence of major depressive episode among adolescents was stable between 2000 and 2014 in Canada (78).

2.1.2 MDD treatment approach

According to best practice guidelines, the first line treatment of depression for adolescent patients should include non-pharmacological treatment options (69,76). Guidelines for the treatment of depression in children aged 10 to 21 in primary care settings suggest that active support and monitoring should be the first step before initiating any evidence-based treatment in case of mild depression (69). The monitoring stage should last 6-8 weeks during which patients should visit the physician every two weeks. Specialty care guidelines suggest that education, support, and case management are sufficient in the management of mild or brief depression uncomplicated with other comorbidities (76). Following monitoring, if symptoms do not improve, evidence-based psychotherapy or antidepressant treatment may be prescribed (69,76).

2.1.3 Pharmacological treatment of MDD

The most common pharmacological treatment for MDD are Selective Serotonin Reuptake Inhibitors (SSRIs), a class of antidepressant drugs that increase the levels of serotonin in the brain and ease the symptoms of depression (79). Serotonin is a neurotransmitter that communicates the information within brain cells (79). SSRIs act by selectively blocking the reuptake (i.e. reabsorption) of serotonin and consequently increase the amount of serotonin available between the nerve cells in the brain (79). SSRIs have proven results in the treatment of depression in adults, however, results for children and adolescents are less consistent (80).
There are 6 classes of SSRIs available in Canada (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) that are approved for the treatment of depression in adults. In the United States, two SSRIs are specifically approved to treat depression in pediatric patients: fluoxetine to treat depression among children and adolescents (8-17 years of age), and escitalopram to treat depression among adolescents (12-17 years of age) (81). However, SSRIs have not been approved by Health Canada to treat depression in children and adolescents younger than 18 years of age and are frequently prescribed off-label on a case by case basis (5).

SSRIs are generally well tolerated in children and adolescents and have a long duration of action, with behavioral effects being observed only 2-3 weeks after the initiation of the treatment (79). The most common non-psychiatric side effects include headache, nausea, vomiting, abdominal pain, dry mouth, and discontinuation syndrome (82). Psychiatric side effects are grouped into spectrums: mania spectrum (mania, hypomania, elevated mood), depression spectrum (aggravation of depression, crying, irritability, anger, hypersensitivity), agitation spectrum (agitation, akathisia, restlessness, nervousness, hyperactivity), anxiety and panic symptoms, tremor and ‘feeling spacy’ altogether classified into activation syndrome (83). The most concerning, however, is the tendency of SSRIs to reinforce suicidal ideation, although the results of published studies have not been consistent (84,85).

2.1.4 Effectiveness of SSRI in youth

Evidence suggests that treatment with SSRI medications is less effective in children and adolescents up to the age of 17 years compared to adults (80,81,86). Systematic reviews and
meta-analyses have found that evidence on the effectiveness of SSRI compared with placebo in the treatment of depression in children and adolescents is not strong enough due to the methodological limitations of the studies and high placebo response rates (81,86). Only two SSRIs, fluoxetine and escitalopram, have been shown to have small impacts on the alleviation of depression symptoms in children and adolescents (81,87). The evidence from meta-analyses of RCTs show that up to 60% of MDD cases responded to placebo treatment (80,88).

2.1.5 Non-pharmacological treatment options

Depressive symptoms in youth appear to be responsive to psychological treatment alone, although the quality of evidence is low (76,89). A number of recent RCTs demonstrate the effectiveness of cognitive behavioral therapy (CBT) and interpersonal therapy in alleviating symptoms of mild to moderate depression in adolescents (90). The responsiveness of mild depression to CBT has been shown using functional and structural neuroimaging techniques (91). Such combined evidence leads to the CWC recommendation against using SSRIs as the first-line intervention for mild to moderately depressed teens.

2.1.6 Diagnostic issues

Challenges associated with the diagnosis of depression in the adolescent population makes it difficult to accurately diagnose the condition, and thus might lead to inappropriate prescribing of antidepressants. To be diagnosed with MDD, an adolescent must present persistent symptoms of depression for at least two weeks (76,92). According to both the DSM-IV and ICD-10, the severity of depression is based on the number and severity of symptoms (table 1) (75,92,93). Based on the ICD-10 criteria, to be diagnosed with mild depression the adolescent needs to have
at least two out of three core symptoms (depressed mood, loss of interest, low energy) and an additional two symptoms from the remaining seven symptoms of depression (table 2) (75,93). The diagnosis of mild depression, according to DSM criteria requires at least one of the core symptoms in combination with an additional four symptoms from the remaining symptoms of depression (see table 2) (75,93). Moderate depression is characterized by the presence of a higher number of symptoms with more severe impairment in functioning (table 1) (75,93). Common signs and symptoms of depression in children and teenagers are similar to those of adults. However, the differences pertinent to social, physiological, psychological, and biological development stage make it challenging to draw a line between symptoms and healthy behaviour (76). Thus, false positive cases of depression identified through positive screening might lead to unnecessary antidepressant prescriptions and expose patients to the side effects of the drugs (94). Additionally, patients without depression who were told that they have a disorder, can experience the so called “nocebo effect” and start developing the symptoms (94).

Another issue in diagnosis of MDD may arise from the fact that depression is a heterogenous condition and can have various etiologies (root causes). To diagnose MDD, a specialist or primary care physician with special training must rule out the possibility of hypothyroidism, anemia, vitamin deficiencies, endocrinopathies, malignancies, chronic diseases, and others conditions which manifest with similar symptoms (95). Also, the symptoms of MDD are similar to the other mood disorders such as bipolar disorder, dysthymia, adjustment disorders with depressed mood, and disruptive behavioural disorders that also need to be excluded (76,92). When not specified, the term depression includes both “major depressive disorder” and
“dysthymia,” a chronic mood disturbance with the symptoms not severe or prolonged enough to meet the criteria for the full episode of depression (75,93).

<table>
<thead>
<tr>
<th>ICD–10 depressive episode</th>
<th>DSM–IV major depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Minimal above the minimum (5)</td>
</tr>
<tr>
<td>Moderate</td>
<td>Between mild and severe</td>
</tr>
<tr>
<td>Severe</td>
<td>Several symptoms in excess of 5</td>
</tr>
</tbody>
</table>

Table 2-1: Depression severity in ICD-10 and DSM-IV

<table>
<thead>
<tr>
<th>ICD–10</th>
<th>DSM–IV major/minor depressive disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressed mood(^*)</td>
<td>Depressed mood by self-report or observation made by others(^*)</td>
</tr>
<tr>
<td>Loss of interest(^*)</td>
<td>Loss of interest or pleasure(^*)</td>
</tr>
<tr>
<td>Reduction in energy(^*)</td>
<td>Fatigue/loss of energy</td>
</tr>
<tr>
<td>Loss of confidence or self-esteem</td>
<td>Worthlessness/excessive or inappropriate guilt</td>
</tr>
<tr>
<td>Unreasonable feelings of self-reproach or</td>
<td></td>
</tr>
<tr>
<td>inappropriate guilt</td>
<td></td>
</tr>
<tr>
<td>Recurrent thoughts of death or suicide</td>
<td>Recurrent thoughts of death, suicidal thoughts or actual suicide attempts</td>
</tr>
</tbody>
</table>
Diminished ability to think/concentrate or indecisiveness
Change in psychomotor activity with agitation or retardation
Sleep disturbance
Change in appetite with weight change

<table>
<thead>
<tr>
<th>ICD–10</th>
<th>DSM–IV major/minor depressive disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diminished ability to think/concentrate or</td>
<td>Diminished ability to think/concentrate or indecisiveness</td>
</tr>
<tr>
<td>indecisiveness</td>
<td></td>
</tr>
<tr>
<td>Change in psychomotor activity with agitation</td>
<td>Psychomotor agitation or retardation</td>
</tr>
<tr>
<td>or retardation</td>
<td></td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>Insomnia/hypersomnia</td>
</tr>
<tr>
<td>Change in appetite with weight change</td>
<td>Significant appetite and/or weight loss</td>
</tr>
</tbody>
</table>

*Core symptom

2.1.7 SSRI use trends among pediatric patients

Despite best practice guidelines, a growing body of evidence has shown an increasing trend in the use of antidepressants among pediatric patients both internationally and in Canada since the 1990s (54,55,96,97). For example, a study from the province of Saskatchewan reported a significant increase among those aged 10-14 and 15-19 in SSRI prescriptions between 1998 and 2007 (54). Similarly, a study by Lam et al. using Canadian administrative data showed that between 2005 and 2009 SSRI prescribing by pediatricians and all specialists increased by 39% and 44%, respectively (55). Longitudinal studies from Germany have also shown a marked increase in the prescribing of SSRIs in children and adolescents during the period of 2005 to 2012, and outpatient off-label prescribing of SSRIs between 2004 and 2011 (98)(99). Finally, in the United States, a black box warning put out by the FDA due to the reports of increased risk of suicidal ideation led to a temporal decrease in the use of SSRI antidepressants, but this was...
followed by a subsequent increase (96,100). How other guidelines and recommendations have impacted the use of SSRIs in adolescents remain largely unclear.

2.2 Methods

2.2.1 The CWC Recommendation

In light of the above evidence about the use of SSRIs, CWC created a recommendation that recommends against using SSRIs as a first line treatment option for mild to moderate depression in adolescents: *Do not use SSRIs as the first-line intervention for mild to moderately depressed teens (51).* This recommendation was first published on June 2\textsuperscript{nd}, 2015. However, since the launch of the recommendation, little is known about whether it affected physician prescribing of SSRIs. The aim of this study is to evaluate the impact of the CWC recommendation on the use of SSRIs in children up to the age of 17.

2.2.2 Data Sources and outcomes

Using the data sources outlined above in the first chapter, I studied the following outcomes in order to evaluate how the CWC recommendation affected drug use:

1. *Incidence of MDD* – I hypothesized that the campaign did not affect the incidence of MDD and the number of patients who were diagnosed with MDD before and after the recommendation would follow a similar trend.

2. *Starting* – I hypothesized that if the campaign had an impact, the number of starters would decrease following the release of the recommendation.
3 Time to treatment – I hypothesized that if the campaign had an impact, the average time to initiate treatment would increase.

4 Cost – I hypothesized that drug costs would gradually decrease over time.

2.2.3 Study cohort

To capture first onset of MDD, I used a definition similar to existing studies (101). All individuals who were diagnosed with depression with relevant ICD codes, were 17 years old or younger at the time of their diagnosis date, and who had at least 1-year continuous registration with MSP prior to the diagnosis date were eligible for this study. From the MSP payment information files, individuals registered with two or more ICD-9 codes of 296 (episodic mood disorder, 296.0 – 296.9) and 311 (depressive disorder, not elsewhere classified) between January 2010 and December 2017 were identified. From the DAD, patients registered with one or more ICD-10 codes of F32 (depressive episode) and F33 (recurrent depressive disorder) between January 2010 and December 2017 were identified. In the case of individuals appearing in both databases, I retrieved the earliest record and flagged it as the diagnosis date.

Starters

Patient information was further linked to the PharmaNet data, where all SSRI dispensations were identified based on ATC codes starting with N06AB (table 3). Linkage to the prescription data has previously shown to increase specificity of MDD diagnosis to 100% (102). From this merged
pharmacy and disease data, cost per patient was analyzed. As outlined above, patients who received an SSRI at any time in the study period after incident diagnosis, while maintaining no prescription during one year before diagnosing date were assembled as a sub-cohort. Starters were divided into those who initiated treatment within 1 month and 3 months. The cutoff of 1-month was used based on the preliminary data analysis which showed that the majority of the patients filled prescriptions within the 1st month; and 3-months was given based on the minimum duration of a monitoring period of at least 8 weeks. From this sub-cohort, I calculated the average monthly time to treatment among patients who initiated treatment within 1 month, and among patients who initiated treatment within 3 months.

<table>
<thead>
<tr>
<th>DRUG NAME</th>
<th>ATC CODE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CITALOPRAM</td>
<td>N06AB04</td>
</tr>
<tr>
<td>ESCITALOPRAM</td>
<td>N06AB10</td>
</tr>
<tr>
<td>FLUOXETINE</td>
<td>N06AB03</td>
</tr>
<tr>
<td>FLUVOXAMINE</td>
<td>N06AB08</td>
</tr>
<tr>
<td>PAROXETINE</td>
<td>N06AB05</td>
</tr>
<tr>
<td>SERTRALINE</td>
<td>N06AB06</td>
</tr>
</tbody>
</table>

Table 2-3: List of SSRIs included in this study
2.3 Results

Study cohort

There were 23,548 individuals under the age of 17 who were diagnosed with MDD for the first-time during my study period. The mean age of study cohort was 14.9 (SD = 2.2 years). Approximately two thirds (64.2 %) were female, and their mean age was 15.0 (SD = 1.9). The mean age of male patients was 14.6 (SD = 2.7). As shown in Table 2-4, 82.2% of the cohort had a primary diagnosis of depressive disorder (ICD-9 code 311) while 15.1% had primary diagnosis of episodic mood disorder (ICD-9 code 296).

<table>
<thead>
<tr>
<th>Primary diagnosis code</th>
<th>Database prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>296 (episodic mood disorder)</td>
<td>15.1%</td>
</tr>
<tr>
<td>311 (depressive disorder, not elsewhere classified)</td>
<td>82.2%</td>
</tr>
<tr>
<td>F32 (depressive episode)</td>
<td>2.5%</td>
</tr>
<tr>
<td>F33 (recurrent depressive disorder)</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

Table 2-4: Disorder diagnostic codes distribution

Incidence of MDD

Based on our statistical models, the monthly incidence of MDD in the population did not change significantly following the launch of the CWC recommendation. Before the recommendation, incidence was decreasing at a non-significant rate of -0.91 fewer new cases each month (95% confidence interval -3.33 to 1.51, p=0.46). Following the intervention, the level (estimate -2.02, 95% confidence interval-111.09 to 107.04, p=0.97) did not change in a statistically significant
fashion. While the estimate for the trend showed a decline of -6.82 per month, this result was also not statistically different from the null hypothesis (95% confidence interval-15.45 to 1.81, p=0.12).

![Incidence of MDD](image)

**Figure 2.1 Monthly average incidence of MDD among adolescents between 2010 and 2017**

**Starting**

I found that 40.2% of all diagnosed patients diagnosed with MDD were new SSRI starters. Before the launch of the campaign, the number of starters who filled a prescription within one month was increasing at a non-significant rate (+0.23, 95% confidence interval-0.34 to 0.79, p=0.43). After the launch of the recommendation, the level (-10.22, 95% confidence interval-
35.41 to 14.97, p=0.43) and trend (-0.70, 95 % confidence interval-2.81 to 1.41, p=52) of starters did not change significantly in comparison to existing trends (see Figure 2.2).

Figure 2.2 Monthly average number of starters who initiated SSRI treatment within 1 month
Similar to the starters who initiated treatment within one month, the number of starters who initiated treatment within three months following incident diagnosis was not affected by the release of the CWC recommendation. As shown in Figure 2.3, the number of starters who filled SSRI prescription within three months was stable before the launch of the campaign (+0.13, 95 % confidence interval-0.34 to 0.61, p=0.58). Following the release of the recommendation, I estimated a decrease in the level of -3.30 (95 % confidence interval-26.91 to 20.31, p=0.78) and
in the trend (-1.11, 95% confidence interval-3.27 to 1.06, p=0.32). These results, however, were not statistically different from the null hypothesis (P>0.05).

Figure 2.3 Monthly average number of starters who initiated SSRI treatment within 3 months

**Time to treatment**

As shown in the Figure 2.4, the CWC recommendation did not affect time to treatment. Before the campaign, the time to treatment of patients who filled prescription for SSRI within one month was slowly decreasing at a non-significant rate (-0.02, 95% confidence interval-0.04 to
Following the release of the recommendation, I estimated changes in the level (0.23, 95% confidence interval 1.46 to 1.91, p=0.79) and trend (-0.03, 95% confidence interval -0.15 to 0.09, p=0.61). Both changes, however, were very close to zero and not statistically significant (p>0.05).

**Figure 2.4 Monthly average time to treatment in days among people who initiated SSRI treatment within 1 month**

Similar to the average time to treatment of patients who filled SSRI prescription within one month, the time to treatment of patients who filled prescription within three months was not affected by the release of the recommendation (Figure 2.5). Before the campaign started, the average number of days between diagnosis and prescription fill among patients who filled SSRI
prescription within three months was decreasing (-0.08, 95 % confidence interval-0.12 to -0.04, p=0.00). Following the recommendation release, the trend (0.06, 95 % confidence interval-0.15 to 0.28, p=0.56) and level (-0.57, 95 % confidence interval-3.33 to 2.19, p=0.69) did not change significantly.

**Figure 2.5 Monthly average time to treatment in days among people who initiated SSRI treatment within 3 months**

**Monthly costs**

Monthly cost per patient was the only outcome that had a small but significant change following the release of the CWC recommendation. Before the intervention, the monthly total spending on SSRIs per patient was decreasing at a rate of - $0.26 per month (95 % confidence interval -0.31
to -0.22, p=0.00), as shown in Figure 2.6. There was a statistically non-significant decrease of -$0.71 in level (95% confidence interval -2.64 to 1.21, p=0.47), and statistically significant increase of $0.20 in the trend (95% confidence interval 0.1 to 0.3, p=0.00) of drug spending per person per month.

![Monthly Costs of SSRI per Patient](image)

**Figure 2.6** Monthly average costs per medication among people who were prescribed SSRIs
2.4 Discussion

Canada has seen substantial increases in the prescribing of SSRIs to teens for MDD. I found that the CWC recommendation pertaining to the appropriate use of SSRI as a first line treatment in mild to moderately depressed teens did not have an impact on the use of SSRIs in this population. After the launch of the recommendation, the trend and level in starting, time to treatment, and incidence of MDD did not change in a statistically significant manner. This suggests that prescribing physicians were not influenced by the CWC recommendation, with both the number of drug starters and time to medication treatment initiation continuing pre-existing trends.

These results are in line with the previous body of evidence, which suggests that passive information dissemination is not sufficient to alter a physician prescribing behaviour, despite the prominence of CWC. In order to reduce prescribing of SSRIs among mild to moderately depressed adolescents, healthcare facilities and clinics should consider adopting more evidence-based strategies in conjunction with CWC. Another potential explanatory factor for the lack of impact of CWC on the prescription of SSRIs might be a lack of availability of mental health facilities that would provide adequate non-medication treatment options. It has been previously suggested that the lack of access to CBT services might cause physicians to overly rely on prescribe antidepressant treatment (103).

Beside reflecting the inefficiency of the campaign, the observed constant rate of the number of starters of SSRI treatment might also be attributable to the fact that trained physicians were already strictly following guidelines and were not prescribing SSRIs to a patient who shows up
with depression diagnosis for the first time. They might be prescribing non-medication treatment options as first line treatment for mild to moderate cases in this age group. My findings are similar to the study conducted using primary care data from the Canadian Primary Care Sentinel Surveillance Network (CPCSSN), which found that among people between 16-24, the increase in the incidence of antidepressant treatment between 2006 to 2012 was small and statistically non-significant (104).

With respect to the duration of time until antidepressant initiation, I am not aware of other studies that have evaluated the change in this duration. However, one prior study reported the impact of timing of antidepressant treatment initiation among adolescents on healthcare utilization and costs (105). In this study, they found that adolescents who were early initiators (within one month following diagnosis) of antidepressant treatment had lower medical and total healthcare costs compared to the late initiators (after one month following diagnosis) during a 12-months follow up period. In this study, however, their 6-month baseline period was shorter than in my study, which might result in the accumulation of more severe cases of depression among early initiators. This assumption was supported in the study, where early initiators had generally worse health. Unlike this study, I targeted adolescents who were diagnosed with depression for the first time in a longer baseline period of 1 year.

As noted in the introduction, previous studies have shown that warnings by regulators can substantially decrease the prescribing and dosage of SSRIs (48,106). When suicidal ideation was a concern, the FDA required pharmaceutical companies to put warning message called black box warning in the labeling of prescription SSRIss. The decline during this warning period was
temporary, and prescribing pattern of SSRI gradually increased, which was shown in the studies that examined long term trends in SSRI use (48,100). These results suggest that if policy makers act in concert with CWC recommendations, it may have the potential to reduce unnecessary prescribing of SSRIs.

Limitations

In a single series ITS study, co-interventions can be a threat to validity. In this case, at approximately the time of the CWC recommendation release, Israeli researchers published a systematic review reporting an increased prevalence of activation syndrome in children and adolescents taking SSRIs compared to the adult population (83). This research may have caused physicians to prescribe fewer SSRIs to pediatric populations, leading to an overestimation of the impact of the CWC recommendation. Another limitation is the fact that pharmacy data only shows dispensations of medications, and it is unable to measure primary prescribing or consumption of SSRIs. Also, access to detailed diagnosis information was lacking. For a given patient record, administrative databases provide only an F32 record, while mild depression is coded as F32.0, moderate F32.1, and severe F32.2. Thus, only a portion of my cohort will consist of severe cases of depression. I mitigated the impact of these by using a conservative case definition of major depressive disorder and not including other codes for similar disorders that might also require SSRI treatment. Another limitation is that the one-year prior continuous registration within the provincial system might not be enough to capture incident cases of MDD. Due to the age sensitivity of the cohort, I did not require longer surveillance time before MDD was diagnosed. There is a possibility that the captured date might not reflect the true first-time diagnosing date of the patient, and consequently treatment might not be first line. However, one
would not expect this potential bias to change over time. Finally, I was not able to measure the use of mental health services for depression, such as psychotherapy, or CBT as such mental health services are not included in my databases.
3 The impact of the CWC recommendation on the use of Psychostimulants in preschool children with ADHD

Recommendation 2: Don’t use psychostimulants as a first-line intervention in preschool children with ADHD

The second analytic chapter will assess the impact of the CWC recommendation regarding the use of psychostimulants as a first-line intervention for ADHD in preschool aged children.

3.1 Introduction

3.1.1 ADHD

ADHD is the most prevalent neurodevelopmental disorder in a pediatric population characterized by the persistent symptoms of hyperactivity, impulsivity, and inattentiveness. According to a systematic review conducted by Polanczyk and colleagues, the worldwide pooled lifetime prevalence of ADHD is as high as 5.3%. (107,108). The prevalence of ADHD in preschool aged children varied between 1% to 6% depending on the study (109–112). In the US, the prevalence of ADHD among the community sample of four years old preschoolers was between 2.0% to 5.7% (111). The national prevalence of parent-reported ADHD in the US among two to five-year-old children was 2.1% (112). Similarly, in the Norwegian sample of four-year-olds, the prevalence was 1.9% (109).

In Canada, several administrative linkage studies have examined trends in the incidence and prevalence of ADHD (113–115). These studies reported that the rates among preschool age
children were stable over time and were lower than that of a general population (114,115). A cross-sectional administrative data linkage study from Ontario conducted by Hauck et al. estimated that ADHD prevalence in young people between one and 24 years was 5.4% (113). A study conducted by Vasiliadis et al. reported that the prevalence and incidence of ADHD in young people between one and 24 years of age increased between the fiscal period of 1999-2000 and 2011-2012 in four provinces. When stratified by age, both incidence and prevalence were stable in preschool aged children between one and four years of age, varying from 1.8 to 5.0 per 1000 cases (114). Similarly, a study conducted by Brault et al. reported that the prevalence of ADHD medication intake and diagnosis of ADHD in preschoolers were stable between 1994 and 2007 at less than 1% (115).

3.1.2 Treatment approach for ADHD

The clinical practice guidelines published by the American Academy of Pediatrics (AAP) recommend prescription of parental and/or teacher-administered behaviour therapy as the first-line treatment for preschool age children diagnosed with ADHD (116). This recommendation is in line with the practice parameter published by American Academy of Child and Adolescent Psychiatry (AACAP), which recommends medication treatment with methylphenidate only if the first-line behavioural treatment does not significantly improve the child’s condition, and there is moderate-to-severe continuing impairment in functioning (117). Non-pharmacological behavioural treatment should be administered for at least eight weeks (117). Prior to initiating the medication treatment, physicians should assess the severity of the symptoms, and prescribe medication only if the criteria for moderate to severe impairment is met.
3.1.3 Pharmacological treatment of ADHD

Psychostimulants are commonly used to treat ADHD in children and adults. They act through affecting dopamine levels and thereby reduce the symptoms of ADHD. In the US, the FDA approved pharmacologic treatment with stimulant medication as a first line treatment option for ADHD in children and adolescents older than six years of age. Similarly, in Canada, stimulants are not approved to treat ADHD in preschool aged children younger than six years. The most common adverse effects of stimulant medications include reduced appetite, sleep disturbances, headaches, and stomachache (116). Compared to school aged children, preschool aged children experience more severe side effects (118) and are more likely to discontinue the treatment as a result (119,120).

3.1.4 Effectiveness of stimulants in preschool age children

Evidence shows that the effectiveness of stimulants in preschoolers is limited, and the effect size is smaller compared to school-age children. This was shown in a Preschool ADHD Treatment Study (PATS), a multicenter, randomized placebo-controlled trial funded by the National Institute of Mental Health (120,121). In this study, the stimulant methylphenidate was administered in 2.5, 5.0, and 7.5mg doses three times per day and significantly reduced ADHD symptoms compared to the placebo in preschool aged children, although the effect size was smaller than for school-age children (119). Continuation of this study also showed that the effect of stimulant treatment on the social functioning of preschool aged children with ADHD was less evident than in elementary school aged children (120). Based on these results, the CWC in collaboration with the Canadian Academy of Child and Adolescent Psychiatry (CACAP) and the
Canadian Psychiatric Association (CPA) recommended against using stimulants as a first line treatment option for preschool children diagnosed with ADHD.

### 3.1.5 Non-pharmacological treatment options

Non-pharmacological treatment options have shown to be effective in improving ADHD symptoms in preschool aged children. As a result, practice guidelines recommend behavioural interventions as first-line treatment for preschool aged children diagnosed with ADHD (116,117). Psychosocial interventions such as parental education have been demonstrated to significantly reduce parent reported ADHD symptoms and improve parent well-being (122–124). Parent behavioural training based on child rewarding has also been shown to be more effective in improving symptoms of ADHD in preschool children at high risk of ADHD (125). If the CWC guidelines were successful at increasing the use of these alternatives, I would expect the use of prescriptions to decrease in this group, and for the time lag between diagnosis and pharmacological treatment to increase.

However, the evidence from North American studies shows that physicians do not strictly adhere to the practice guideline recommendations pertinent to the prescription of non-medication psychotherapy as a first line treatment option for ADHD among preschool aged children. In the US, insured children aged between two to five received first-line psychological treatment only 50% of the time, while almost 75% received a stimulant prescription as a first-line treatment (126). A recent study conducted by Chung et al. showed that out of 339 board certified child and adolescent psychiatrists, only 7.4% reported following specialist guidelines on preschool ADHD treatment initiation and medication selection, and only 31.6% confirmed that they never
prescribe medication as a first line treatment (127). Given that more than half of the parents of treatment naive at-risk ADHD preschool children were against medication (128), the CWC campaign that promotes patient-physician conversation might significantly reduce medication use in this patient group.

3.1.6 Diagnostic issues

The diagnostic criteria for ADHD according to the Canadian ADHD Resource Alliance (CADDRA) is based on a holistic approach, which includes meeting symptom criteria on the DSM rating scales, having a developmental history consistent with the disorder, experiencing functional impairment due to symptoms and not having other conditions that can potentially cause ADHD symptoms. According to the clinical practice guidelines published by AAP, drug treatment for preschool aged children should be reserved only for moderate to severe cases (116). The criteria for moderate to severe cases include prolonged symptoms (at least nine months) that did not respond to initial behaviour treatment and that are manifested in both home and other child care settings (116).

Difficulties associated with diagnosing of ADHD in preschool age children and subsequent potential overdiagnosis may lead to the overreliance on the stimulants as the first line of treatment. The diagnosis of psychiatric conditions in children, and especially in young children, is complicated by the fact that it is difficult to draw a line between variation in normal behaviour and the true symptomatic behaviour of ADHD (129). Many children occupy the so-called “zone of diagnostic ambiguity”, where different specialist and non-specialist observers might disagree on whether a child has actual ADHD symptoms impairing functioning or behaves within the
boundaries of normal behaviour (130). A study conducted by Bruchmuller showed that physicians who did not adhere to diagnostic criteria tended to over diagnose ADHD, oftentimes among boys who display prototypical behaviour (131).

It has also been argued that DSM-based criteria for the identification of ADHD might not be appropriate for preschool age children due to its focus mainly on the frequency of symptoms and not focusing on the developmental features of the young child (132). There are only two DSM-IV-based tools, Conners Comprehensive Behaviour Rating Scales, and the ADHD Rating Scale IV that have been validated in the preschool age group. However, these tools are not free and are not endorsed by Canadian practice guidelines (68).

Further, most preschool children that exhibit ADHD symptoms in their behaviour do not demonstrate the pathology in the future. For example, a study conducted by Smidts reported that one-third of all ADHD behaviours listed in the DSM-IV-based Preschool Behaviour Questionnaire were present in more than 40% of preschool age children attending preschool in the Netherlands (133). Another study found that almost half of the preschoolers diagnosed with ADHD will not continue having the symptoms later in life (134).

The diagnosis of ADHD in preschool age children can be complicated by the difficulty of gathering information on key symptoms from multiple sources. To diagnose ADHD, information on the presence of the symptoms of ADHD must be obtained from multiple sources in separate settings. Young children who do not attend daycare or other preschool programs are not likely to have a qualified observer other than their parents. If they attend daycare programs, however,
observer staff in these facilities might not have an adequate qualification to assess the child for ADHD compared to certified teachers in schools (116).

3.1.7 Stimulant use trends in preschool aged children

Despite the stable rates of diagnosis and prevalence, the number of studies from Canada and the US indicates increasing trends in the use of stimulants by preschool age children (56,115,135–137). Some studies have reported the opposite, however (138). For example, some work that examined national trends of psychotropic medications use among two to five year old children in the US showed that diagnosis of psychotropic conditions increased, with stimulants being the most commonly prescribed medication between 1994 and 2009 (138). A study conducted by Fontanella et al. demonstrated that the prevalence of stimulant prescriptions in preschoolers increased from 0.5% in 2002 to 0.8% in 2008 (137).

In Canada, Brault et al. reported that the prevalence and diagnosis of ADHD among Canadian preschool children were relatively stable at a low rate (115). However, researchers have also found that the off-label prescription of ADHD medication was most common among the preschool age group (115). In a population-based study using Canadian Primary Care Sentinel Surveillance Network (CPCSSN), Morkem and colleagues showed a 5% increase in the prescription of ADHD medications among preschoolers between 2010 and 2015 (56). Given that patients with ADHD have previously been reported to utilize more healthcare services and in general, have a higher burden of comorbid conditions compared to patients without ADHD, any reduction in unnecessary stimulant prescription use would be beneficial (113). It is in this context that the CWC recommendation was released. Since the launch of the CWC
recommendation, little is known about whether it affected physician prescribing of stimulants to preschool children as a first line treatment option for ADHD.

3.2 Methods

3.2.1 The CWC recommendation

The aim of this study is to evaluate the impact of the CWC recommendation pertinent to the use of stimulants as a first line treatment option of ADHD among preschool age children in British Columbia: *Don’t use psychostimulants as a first-line intervention in preschool children with ADHD*. For the purpose of this research, preschool age was defined as less than or equal to 5 years of age with no minimum cutoff since the DSM-5 does not specify the minimum age when symptoms start appearing. I evaluated how the CWC affected the following outcomes:

3.2.2 Data sources and outcomes

In order to assess the impact of the recommendation, I used data sources outlined above and evaluated how the CWC recommendation affected the following outcomes:

1. Incidence of ADHD – I hypothesized that the campaign did not alter the incidence of ADHD among preschoolers.

2. Starting – I hypothesized that if the campaign had an impact, the number of starters would decrease following the release of the recommendation.
Time to treatment – I hypothesized that if the campaign had an impact, there would be an increase in average time to initiate treatment following diagnosis.

Cost – I hypothesized that medication costs would gradually decrease over time.

3.2.3 Study cohort

All individuals who were: five years old or younger at their first service use date, were diagnosed with the relevant ICD codes, and who had at least one-year continuous registration with MSP prior to the diagnosis date were eligible for this study. To capture incident cases of ADHD, the case definition protocol described previously in studies conducted by Vasiliadis et al. and Lindemann et al. were modified to require at least one year of continuous registration prior to the diagnosis date without diagnosis of ADHD (101,127). To be diagnosed with ADHD, a patient must have had two or more claims in the MSP database with ICD-9 code 314 (hyperkinetic syndrome of childhood), or one claim in the DAD database with the equivalent ICD-10 code F.90 (attention-deficit hyperactivity disorders). When patients appeared several times in either one or both in both databases, the earliest date was retrieved and flagged as their diagnosis date.

From this merged disease cohort, the outcomes incidence of ADHD was analyzed. My age limit was in line with the recommendation of Canadian Association of Pharmacists, that do not recommend prescribing ADHD medications to children who are younger than five years old (140). I did not restrict my cohort to a minimum age in order to capture all the patients with
ADHD who subsequently filled stimulant prescriptions, since it has been previously suggested that the symptoms of ADHD can manifest as early as two years of age (110).

Starting

Patient information was further linked to PharmaNet data, and patients who filled a stimulant prescription after having no prescription fills during the previous year were assembled into a sub-cohort. The list of stimulants and their corresponding ATC codes are listed below in table 3.1. Based on the preliminary data analysis, and the duration of non-medication therapy, starters were divided into those who filled prescriptions within three months and within one year of the date of diagnosis. Based on this cohort, the time to treatment between diagnosis and prescription fill date of starters was analyzed.

<table>
<thead>
<tr>
<th>Drug generic name</th>
<th>Drug brand name</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate</td>
<td>Ritalin®</td>
<td>N06BA04</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>Biphentin®</td>
<td>N06BA04</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>Concerta®</td>
<td>N06BA04</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>Foquest®</td>
<td>N06BA04</td>
</tr>
<tr>
<td>Amphetamine salt</td>
<td>Vyvanse®</td>
<td>N06BA01</td>
</tr>
<tr>
<td>Amphetamine salt</td>
<td>Adderall XR®</td>
<td>N06BA01</td>
</tr>
<tr>
<td>Amphetamine salt</td>
<td>Dexedrine®</td>
<td>N06BA01</td>
</tr>
</tbody>
</table>

Table 3-1: List of psychostimulants included in this study
3.3 Results

Study cohort

There were 3386 patients diagnosed with ADHD for the first-time with a mean age of 4.29 (SD = 0.89) during the study period. The majority of patients, 80%, were male patients with a mean age of 4.30 years (SD = 0.88). The mean age of female patients was 4.24 (SD = 0.94).

Monthly incidence of ADHD

The incidence of ADHD among preschool aged children was not affected by the release of CWC recommendation, as shown in Figure 3.1. The coefficients for the time (-0.6, 95% confidence interval -0.55 to 0.43, p=0.81), level (-0.84, 95% confidence interval -24.08 to 22.39, p=0.94) and trend (-0.37, 95% confidence interval -2.45 to 1.7, p=0.72) in the model were not significant, indicating that the CWC recommendation did not have a statistically significant impact on the diagnosis of the condition.
Based on my statistical models, the number of preschool aged starters who initiated stimulant treatment within three months was not affected by the campaign. Before the recommendation release, the number of stimulant starters was increasing at a non-significant rate (+0.02, 95% confidence interval -0.08 to 0.13, p=0.67). Following the release of the recommendation, there were non-significant changes in trend (0.15, 95% confidence interval -0.32 to 0.64, p=0.52) and level (-2.66, 95% confidence interval -8.58 to 3.26, p=0.38), as shown in Figure 3.2.

Figure 3.1 Monthly average incidence of ADHD among preschool aged children between 2010 and 2017

Starting

42.8% of patients diagnosed with ADHD initiated stimulant treatment during study period.
Similar to the starters who initiated stimulant treatment within three months, the number of starters who filled a stimulant prescription within one year after diagnosis date was not affected by the release of the CWC recommendation. As shown in Figure 3.3, the number of starters who filled a prescription for a stimulant within one year was increasing at a non-significant rate (0.05, 95% confidence interval -0.1 to 0.22, \( p=0.49 \)) prior to the CWC recommendation. Following the intervention, there were non-significant changes in the level (1.62, 95% confidence interval -9.62 to 12.87, \( p=0.77 \)) and trend (-0.66, 95% confidence interval -2.38 to 1.07, \( p=0.45 \)) of this outcome.
Figure 3.3 Monthly average number of starters who initiated stimulant treatment within 1 year following diagnosis date

**Time to treatment**

The CWC recommendation did not significantly change the level or trend of average time to treatment among patients who filled a prescription within three months, as shown in Figure 3.4. Before the recommendation, the average number of days was slowly increasing (+0.09, 95% confidence interval -0.11 to 0.3, p=0.38). Following the intervention, there were decrease in trend (-0.77, 95% confidence interval -1.98 to 0.44, p=0.21) and level (11.84, 95% confidence interval -3.41 to 27.09, p=0.13), however, both changes were not statistically significant.
Similarly, the CWC recommendation did not significantly impact the level or trend of the time to treatment of patients who initiated stimulant treatment within one year following the diagnosis date. As shown in Figure 3.5, prior to the intervention time to treatment was increasing at a low rate (0.10, 95% confidence interval -0.65 to 0.85, p=0.79). Following the intervention, both trend (7.97, 95% confidence interval -1.21 to 17.16, p=0.09) and level (-28.17, 95% confidence interval -89.28 to 32.93, p=0.37) did not change in a statistically significant manner.

Figure 3.4 Monthly average time to treatment in days among people who initiated stimulant treatment within 3 months following diagnosis date
Figure 3.5 Monthly average time to treatment in days among people who initiated stimulant treatment within 1 year following diagnosis date

**Monthly costs**

The release of the CWC recommendation was associated with a statistically significant reduction in the cost per medication per patient. Before the intervention, the monthly total spending on stimulants (both public and private) per patient was increasing at a rate +$0.69 per month (95% confidence interval 0.62 to 0.77, p=0.00) as shown in Figure 3.6. While the level did not change significantly (-$0.25, 95% confidence interval -3.8 to 3.3, p=0.88) immediately after the intervention, there was a statistically significant decrease in the trend (-$0.47, 95% confidence
interval -0.67 to -0.28, p=0.00) of drug spending per person per month following the intervention.

![Costs of stimulant per Patient](image)

**Figure 3.6** Monthly average costs per medication among people who were prescribed stimulants
3.4 Discussion

The current study used seven years of administrative data from British Columbia’s public health care system to assess the impact of the CWC recommendation on the use of prescription stimulants among preschool age children under five years who were diagnosed with ADHD. I found that the CWC recommendation did not appear to decrease the use of psychostimulants among these patients. Observed results are in line with the previous body of evidence that passive information dissemination unless coupled with active quality improvement initiatives is not sufficient to change physician prescribing behaviour.

The incidence of ADHD diagnosis in preschool aged children was stable in my study. This might indicate that the CWC campaign did not appear to affect diagnosing practices. A constant rate throughout the study period might also indicate that the diagnosing of ADHD had already reached its saturation by the time of the study period. In 2011, the American Academy of Pediatrics released a new guideline that contributed to the standardization of diagnosis and treatment of ADHD in preschool aged children (141). A previous administrative database study conducted by Vasidalis et al. reported that the diagnosed incidence of ADHD amongst preschool aged children increased in three out of four provinces studied between 1999-2000 and 2012 (114). Other administrative database studies from Canada showed that the prevalence of ADHD in preschool aged children was constant and ran at a low rate (115).

The number of stimulant treatment starters was stable throughout the study period and was not influenced by the CWC recommendation. My findings are similar to the study conducted by Brault et al., which demonstrated that the prevalence of preschoolers with ADHD prescribed
medication was stable at a low rate between 1994 and 2007 (115). My findings differed from a recent study conducted using the Canadian Primary Care Sentinel Surveillance Network (CPCSSN). In this study, the authors reported a 2.6-fold increase in the prevalence of ADHD medication prescriptions among very young children between 2005 and 2015 (56). The stable trends observed amongst starters in my study could be due to physicians already strictly following guidelines and prescribing parent behavioural treatment as a first treatment option to preschoolers. This assumption, however, is not supported by a recent cross-sectional study conducted in the USA, which asked child and adolescent psychiatrists whether they follow guidelines when it comes to preschool aged children. Out of 339 board specified child and adolescent psychiatrists, only 7.4% reported following specialist guidelines on preschool ADHD treatment initiation and medication selection, with a mere 31.6% confirming that they never prescribe medication as a first line treatment to this age group (127).

The time to initiation of the stimulant treatment did not change over time in my study. While there is no study that analyzed time to the initiation of stimulant treatment following the diagnosis of ADHD in very young children, several studies examined the relationship between the age of onset of the stimulant treatment on the long-term substance use outcomes. A large national multi-cohort sample in the U.S. showed that the early onset of ADHD medication treatment during preschool/early elementary age alongside a long duration of treatment is associated with lower risk of substance use during adolescent ages (142).

**Limitations**
My study has some limitations worth noting. First, due to the small sample size and missing data on prescribing specialist information, I was not able to examine outcomes stratified by clinician specialties. For example, a study conducted by Morkem et al. demonstrated a sharp increase in the prescription of stimulants to preschool age children by primary care physicians between 2012-2015 (56). Secondly, pharmacy data reports only dispensation date, and cannot capture actual medication consumption by patients. Thirdly, administrative databases might have variation in diagnosis due to the use of different disease classification tools. Namely, practitioners use ICD-9 and ICD-10 codes for billing purposes, while most of the questionnaires are built on DSM-IV and DSM-5 systems. The diagnosis of ADHD is classified as a hyperkinetic disorder in ICD-10, which has shown to be more restrictive compared to DSM systems. The study that compared the comparative validity of the recent versions of ICD-10 and DSM-5 showed that the two classification systems are different in their criteria of pervasiveness and identification of comorbidities with the hyperkinetic disorder being less prevalent than ADHD (143). Lastly, due to the run-in period for drug starters, I had shorter post intervention observation time for the outcomes of starters and time to treatment. A longer post intervention observation period would lead to more precise and longer-term estimates of the effect of the campaign.
Impact of the CWC recommendation on the use of Atypical Antipsychotics for ADHD comorbid with Disruptive Behavioural Disorders

Recommendation 3: Don’t use atypical antipsychotics as a first-line intervention for Attention Deficit Hyperactivity Disorder (ADHD) with disruptive behaviour disorders (DBDs).

The third analytic chapter of this thesis research will assess the impact of the CWC recommendation regarding the use of atypical antipsychotics as a first-line intervention for ADHD comorbid with disruptive behavioural disorders.

4.1 Introduction

4.1.1 ADHD with Disruptive Behavioural Disorders

ADHD is the most common neurodevelopmental disorder in children, with a worldwide prevalence of 5.3% (107)(108). In more than 60% of all ADHD cases, patients have comorbid disruptive behaviour disorders (DBDs) such as oppositional defiant disorder (ODD) and/or conduct disorders (CD). These behaviour disorders are a group of related behavioural disorders with common symptoms of uncooperative, antisocial, and defiant behaviour. The most common types of DBDs are ODD, CD, and unspecified DBDs. According to the ICD-10 system, ODD occurs in younger children who exhibit defiant, disobedient, and hostile behaviour towards authority figures, which are manifested by anger, arguing, loss of temper, and other negativistic actions that last for at least six months (144). CD is associated with more extreme symptoms
than ODD and include violations of socially appropriate rules lasting at least one year (144). These symptoms include lying, theft, and harming other people or animals. Both children with ODD disorder and CD have a hostile attitude towards authority figures. Oftentimes ODD diagnosed during childhood develops into more aggressive CD in adolescents and adults.

4.1.2 Treatment approach of ADHD comorbid with DBDs

Practice guidelines recommend psychosocial treatment options as a first line treatment for ADHD comorbid with disruptive behavioural disorder (145). If treatment with psychosocial therapy is not sufficient, the use of psychostimulants is recommended to treat the core symptoms of ADHD (145). A systematic review conducted by Pringsheim found that stimulants have a moderate to large effect on the alleviation of symptoms of disruptive and aggressive behaviour among children with ADHD comorbid with ODD and CD (60). Guidelines recommend trying several stimulants before switching to another drug class since children might respond to some types of stimulants better than others (145). Following stimulant medication, if treatment was not successful, non-stimulant ADHD medications such as guanfacine, atomoxetine, and clonidine have shown effectiveness in the management of aggressive behaviour (145). Due to the serious side effects of atypical antipsychotics (AAs), their prescription should be reserved only for severe cases, and when previous methods did not show sufficient benefit (117).

4.1.3 Atypical Antipsychotics

AAs, also known as second generation antipsychotics, are a class of drugs that are used to relieve symptoms of psychosis. They were developed to replace the first-generation antipsychotics and have a superior risk-benefit profile. AAs act through affecting dopamine and serotonin levels and
have milder extrapyramidal side effects compared to their predecessor first generation antipsychotics, the latter of which acts through dopaminergic pathways only. AAs start working within hours, with the full therapeutic effect being achieved after 4-6 weeks from the beginning of the treatment.

There are only two AA medications that have been approved for use among pediatric populations in Canada. One of them is olanzapine, which was approved by Health Canada to treat schizophrenia and bipolar disorder in adolescents between 13 to 17 years (146). Another AA, aripiprazole, has been approved for use in the pediatric population starting between 15 to 17 for the treatment of schizophrenia, and between 13 to 17 for the treatment of bipolar disorder (146). Atypical antipsychotics provide only symptomatic relief, temporarily relieving the symptoms of psychosis without curing the cause of the disease. Before prescribing antipsychotic treatment, clinicians should perform an extensive assessment of the individual patient and carefully consider drug related side effects.

4.1.4 Effectiveness of Atypical Antipsychotics in ADHD with DBD

The systematic review conducted by Pringsheim et al. cited above also reviewed the safety and effectiveness of second-generation antipsychotics in the management of disruptive behavioural disorders, namely CD, ODD, and aggressive behaviour in children (147). According to this review, only risperidone was shown to have moderate quality evidence of a moderate to large effect on disruptive and aggressive behaviour in children with subaverage IQ and ODD, not specified DBD or CD, both with or without ADHD. For children with an average IQ, the authors indicated high-quality evidence of the moderate effect of risperidone on the alleviation of
disruptive and aggressive behaviour in patients with ODD or CD, with or without ADHD. The effectiveness of other antipsychotics in the management of DBD is weak or non-existent (147). Similarly, another systematic review conducted by Lyu et al. reported that only risperidone was associated with improved behaviour in children and youths with disruptive behaviour disorders, although the treatment was associated with significant weight gain (148).

Despite having less severe side effects compared to the first-generation antipsychotics, AAs also have potentially serious side effects. Evidence from RCTs has shown that treatment with AAs is associated with adverse metabolic and neurological effects in children that include weight-gain, diabetes mellitus, and abnormal cholesterol and liver ferment levels (92). These side effects are also present within the general population who are taking AAs (150). AA intake has also been linked with a significantly increased rate of hypertension and abdominal obesity among Canadians aged three to seventy nine years (151).

4.1.5 Atypical Antipsychotic use trends

A growing number of pharmacoepidemiologic studies from Canada and the US have found increased use of AAs by young people in both provincial and national studies (57,58,113,152). For example, a population-based study conducted by Rosnley et al. showed that the prescription of AAs increased 18-fold in British Columbia between 1996 and 2011 (57). The highest increase was observed among males. Similarly, another study conducted by Alessi-Severini reported extensive off-label use of AAs, and a 3-fold prevalence increase among female youth and a 4-fold increase among male youth between 1999 and 2008 in Manitoba (58). A similar increase in
the use of AAs among all age groups and patient categories was observed in a study conducted using Nova Scotian administrative data (153).

When the BC study was stratified by the reason for AA initiation, a diagnosis of ADHD comprised 20% of users and DBDs combined constituted 40% of all prescriptions in children aged between 0 to 5. In children between six to twelve years old, the most common diagnosis for antipsychotic initiation was the diagnosis of ADHD (57). Another analysis found that as many as 11% of all ADHD patients filled prescriptions for antipsychotics in Ontario (113). Finally, a study conducted in the US found that approximately 66% of all pediatric prescriptions for AAs were prescribed off-label, with ADHD being the most common reason for prescription (154).

4.2 Methods

4.2.1 The CWC recommendation

Given the increasing trend in the use of AAs, CWC created a recommendation against using them as a first line treatment option for ADHD comorbid with DBDs: Don’t use atypical antipsychotics as a first-line intervention for Attention Deficit Hyperactivity Disorder (ADHD) with disruptive behavior disorders. Since the launch of the recommendations, little is known about whether it affected physician prescribing and use by patients. Therefore, I studied the impact of this CWC recommendation in British Columbia.

4.2.2 Data sources and outcomes

Using the data sources outlined in the first methods section, I studied how the CWC recommendation affected the following outcomes:
1 Incidence of ADHD comorbid with DBDs – I hypothesized that the campaign did not alter the incidence of ADHD comorbid with DBDs among BC residents.

2 Starters – I hypothesized that if the campaign had an impact, the number of starters would decrease following the release of the recommendation.

3 Time to treatment – I hypothesized that if the campaign had an impact, it would lead to a decrease in average time to initiate antipsychotic treatment.

4 Cost – I hypothesized that AA costs would gradually decrease over time if the CWC recommendation had an impact on prescribing.

4.2.3 Study cohort

I studied all individuals who were diagnosed with ADHD and had comorbid DBD, who had a 1-year continuous registration with the MSP database prior to the diagnosis date, and who filled prescription for antipsychotics during the study period. To identify these individuals, three databases were merged together: MSP, DAD, and PharmaNET. Eligible individuals needed to have at least two inpatient or one outpatient diagnosis codes of ADHD comorbid with DBDs during the study period. From the MSP payment information file, I identified all individuals with two or more claims with the ICD 9 diagnosis code 314 and from the DAD database I identified all individuals with a claim with the ICD-10 diagnosis code F90. In the case of multiple records, the first date was kept as the diagnosis date for my study. Further, the study cohort was restricted
to the individuals who had comorbid codes for DBDs (ICD-9: 312 or 313, ICD-10: F91). Monthly incidence of ADHD comorbid with DBD, and costs per person per medication were analyzed from merged patient data.

*Starters*

I also created a sub-cohort of individuals who started therapy during the study period. Patients who were dispensed AAs (ATC codes listed in table 4.1), for the first time after a year without such a prescription were identified. From this cohort, the outcomes of starting and time-to treatment were analyzed. Based on preliminary data analysis, and the duration of non-medication therapy, starters were divided into those who filled a prescription within seven months (3rd quartile of patients filled within seven months) and one year after the date of diagnosis. For the starters who filled prescriptions within seven months and twelve months, I truncated the respective number of months studied post intervention to allow people to have enough time to fill prescription during the relevant timeframe (and thus avoid right censoring).

<table>
<thead>
<tr>
<th>Second Generation Antipsychotic name</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>N05AX12</td>
</tr>
<tr>
<td>Clozapine</td>
<td>N05AH02</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>N05AH03</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>N05AX13</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>N05AH04</td>
</tr>
<tr>
<td>Risperidone</td>
<td>N05AX08</td>
</tr>
</tbody>
</table>
### Table 4-1: List of Atypical Antipsychotics included in this study

<table>
<thead>
<tr>
<th>Ziprasidone</th>
<th>N05AE04</th>
</tr>
</thead>
</table>

#### 4.3 Results

**Study cohort**

There were 733 individuals diagnosed with ADHD comorbid with other DBDs during my study period. The mean age of these patients was 13.07 (SD = 6.57) at their time of diagnosis. As expected, the majority of patients were male (73.4%) and had a mean age of 12.8 (SD = 6.09). The mean age of female patients was slightly higher at 13.8 (SD=7.73).

**Monthly incidence**

Incidence of ADHD comorbid with DBDs was significantly affected by the campaign. As shown in Figure 4.1, the monthly incidence of ADHD cases comorbid with the DBD was stable before the launch of the CWC recommendation (0.04 cases, 95% confidence interval -0.01 to 0.11, p=0.13). There was a statistically significant change in the level (+3.49, 95% confidence interval 0.53 to 6.46, p=0.02) and decrease in trend (-0.24 cases per month, 95% confidence interval -0.45 to -0.03, p=0.03) of the monthly average number of incident cases of ADHD comorbid with DBDs following the release of recommendation.
Figure 4.1 Monthly average incidence of ADHD comorbid with DBDs between 2010 and 2017

**Time to treatment**

Average time to treatment of starters who filled an AAP prescription within seven months following diagnosis date was not affected by the campaign. As shown in figure 4.2, before the launch of the CWC campaign, time to initiate antipsychotic treatment within seven months was stable over time (+0.05 days, 95% confidence interval -0.85 to 0.95, p=0.91). Following the campaign, I found no significant change in either the trend (-1.30, 95% confidence interval -7.35 to 4.75, p=0.67) or the level (25.40, 95% confidence interval -35.37 to 86.18, p=0.41).
Unlike to time treatment within seven months, time to treatment among starters who initiated AAP treatment within a year was significantly affected by the campaign. The time to treatment with antipsychotic was increasing before the campaign (0.55, 95% confidence interval -0.07 to 1.17, p=0.08), as shown in figure 4.3. Following the launch of the CWC recommendation, the level increased by 126.90 days (95% confidence interval 57.31 to 196.5, p=0.00), while the trend decreased by -21.2 days (95% confidence interval -32.37 to -10.08, p=0.00). However, it is likely that these results were driven by two larger outlier values immediately following the launch of the CWC recommendation.
**Figure 4.3** Monthly average time to treatment in days among people who initiated atypical antipsychotic treatment within 1 year following diagnosis date

**Monthly costs**

As shown in figure 4.4, cost of antipsychotics per patient per month was decreasing (-0.14, 95% confidence interval -0.26 to -0.03, p=0.01) before the CWC campaign. Following the CWC recommendation, there was an increase in the level (2.28, 95% confidence interval -3.96 to +8.53, p= 0.47) and a decrease in trend (-0.03, confidence interval -0.38 to +0.32, p= 0.87). These changes, however, were not statistically significant. Following the intervention, costs per patient per month continued to decrease.
15.4% of patients diagnosed with ADHD comorbid with DBD initiated antipsychotic treatment during the study period. Starters who filled an AAP prescription within seven months were affected by the campaign. As shown in figure 4.5, prior to the CWC guideline, the number of starters who initiated antipsychotic treatment was increasing at a non-significant rate (+0.01, 95% confidence interval -0.01 to 0.03, p=0.24). Following the intervention, the level did not change significantly (-0.87, 95% confidence interval -2.24 to 0.5, p=0.21), while there was a small increase in trend (+0.14, 95% confidence interval 0.01 to 0.28, p=0.04).
In contrast to the above results, the number of starters who filled AA prescriptions within one year did not change in a statistically significant manner. As shown in figure 4.6, the number of starters who initiated antipsychotic treatment within one year was increasing non-significantly (+0.01, 95% confidence interval -0.01 to 0.03, p=0.15) prior to the CWC recommendation. Following the launch of the recommendation, there was a decrease in level (-0.44, 95% confidence interval -2.05 to 1.16, p=0.59) and increase in trend (0.05, 95% confidence interval -0.19 to 0.29, p=0.67). The observed changes, however, were not statistically significant.
Figure 4.6 Monthly average number of starters who initiated atypical antipsychotic treatment within 1 year following diagnosis date
4.4 Discussion

The CWC recommendation did not appear to impact the use of antipsychotic medication in people diagnosed with ADHD comorbid with DBDs. However, due to small sample size and a limited number of observations per time point, these results might not be reliable. As a result, the risk of committing a type II error may have been high. I observed a significant increase in trend in the number of starters who initiated treatment within seven months, and a significant increase in level and decrease in trend in time to treatment of patients who initiated treatment within one year. The incidence of the diagnosis of ADHD comorbid with DBDs decreased following the release of the recommendation. I believe these results are mostly the consequence of sample size limitations, which I will return to below in the limitations section.

My findings that the use of AAs is increasing is consistent with previous literature from British Columbia (57), Manitoba (58), Ontario (113), Alberta (155), and across Canada (152). My results are also similar to a study conducted by Wang et al., where scientists evaluated the impact of large federal and state settlements on the off-label use of olanzapine. Following legal prosecution against the pharmaceutical company Eli Lilly for off-label marketing of their drug, the incidence of off-label prescribing for olanzapine did not decrease significantly (156). The observed increase in use and lack of impact of the CWC recommendation is concerning. In addition to increasing healthcare system costs, off label prescribing of AAPs poses significant risks to health.
Limitations

This study has a number of limitations worth noting. I had a small sample size and the limited number of observations per time point, which led to a lack of stability in my data. For example, for my analysis of starting there were several months with no cases. Another limitation arises from having few post-intervention observations that might not be sufficient enough to estimate the true effect of the campaign. The use of ICD codes for the diagnosis of ADHD comorbid with DBDs that were not previously validated might be another limitation of this study. To mitigate this, and improve internal validity, I used conservative definitions of ADHD and DBDs, and did not include codes for other mood disorders that might also result in antipsychotic prescriptions. Finally, I used pharmacy data, which captures antipsychotic dispensations only and does not show the true consumption of medications by patients.
Conclusions

4.5 Main findings

To my knowledge, this is the first longitudinal evaluation of CWC recommendations pertinent to the use of psychiatric medications among young people with mental disorders. Overall, the results are not consistent with a major impact on the rate of use for these medications. First, the CWC recommendations against the use of psychotropic medications as a first-line treatment option among young people did not appear to influence the use of medications by target populations. Second, for the recommendations regarding the use of SSRIs and stimulants, I did not observe a statistically significant decrease in trends. Finally, for the third recommendation regarding the first line use of antipsychotic medication, I actually observed increased utilization. However, a small sample size likely means the reliability of this result is low. Overall, despite these recommendations having a strong evidence base, being widely disseminated, and being endorsed by professional societies, they do not appear to have had a major impact on physician prescribing behaviour on their own.

The CWC campaign alone, as might be expected from the previous body of evidence, was unable to result in a significant reduction in unnecessary prescribing in pediatric psychiatry. My findings are consistent with the previous body of research evaluating the impact of the CWC campaign in Canada and the CW campaign in the US, which found a moderate to no impact of the campaign when the recommendations were not coupled with active quality improvement initiatives. My results are also consistent with several studies across a range of clinical areas that also found a limited impact of guideline release alone (41)(19,20) (40).
4.6 Potential reasons for campaign ineffectiveness

There are a number of potential reasons why the CWC campaign did not have a substantial impact on physician prescribing behaviour. Likely the most significant reason is that the campaign was not coupled with any reinforcing actions. The body of evidence shows that passive information dissemination is an inefficient form of intervention to change physician prescribing behaviour (43,157). The research evidence is very clear that continuing medical education and multifaceted interventions are effective in changing physician behaviour and implementing clinical practice guidelines into general practice(49,50). Particularly for changing physician prescribing behaviour multifaceted interventions which predispose, enable, and reinforce positive prescribing behaviour are required to promote change (43).

The psychological biases present in de-implementation strategies might be another reason for the lack of impact from this aspect of the CWC campaign. Previous studies have indicated that psychological biases such as confirmation bias and loss aversion exist in de-implementation initiatives that are not present in campaigns focused on implementation alone (158,159). Confirmation bias within medical practice happens when physicians prefer practices that confirm their existing beliefs, while loss aversion bias happens when physicians prescribe more to avoid potential loss (159). While it has also been shown that physicians’ personal motivation and lack of cost-benefit considerations hamper the abandonment of low value care (158).

Another reason might be inadequate access to mental health facilities, and subsequently to non-pharmacologic treatment options. It has been suggested that young children and adolescents do
not have adequate access to non-pharmacologic treatment options in Canada (137). For example, a study by Kowalewski reported that only 31% of mental health agencies met the benchmark of waiting time for mental health service access according to the Canadian Psychiatric Association’s regulations in 2010 (160). Consequently, physicians might prescribe medication treatment against the best practice guidelines or the CWC recommendation in an effort to get their patients more immediate interventions.

Parental demand for a “quick fix” might be another reason why off-label use of psychiatric medications still remains high, despite the CWC recommendations. Non-medication treatments, such as parent education, CBT, and interpersonal therapies often require significant time and/or sufficient supplemental insurance coverage. The provincial health insurance plan does not cover psychosocial interventions in BC and coverage by private extended health insurance plans varies substantially. This creates barriers for low income Canadians, who are less likely to pay out of pocket to utilize non-physician psychotherapy, compared to higher income individuals (161). As a result, parents might see pharmacologic treatment options as an affordable, and time saving option.

Finally, the lack of focus on the campaign in British Columbia might be another possible explanation of why I did not observe any impact. To date, eight provinces and two territories have formally endorsed and launched provincial campaigns, which are supported by local institutions and healthcare leaders. As a part of local campaigns, each jurisdiction reviews and identifies healthcare services that are being overused or inappropriately used and implements active strategies such as patient education, physician education (including continued integration
into medical education and practice), audit and feedback to combat overuse. The provinces and territories of Alberta, Newfoundland and Labrador, New Brunswick, Ontario, and the Yukon specifically target psychiatric medication overuse in their local campaigns, which my results would suggest is a likely precursor to them having any impact.

4.7 **Strengths and limitations**

The main strength of my studies derives from my use of a strong research method and population-based data in a large Canadian province. Further, the fact that I analyzed the use of medications among patients who were diagnosed with the underlying condition for the first time is an additional strength. My strict inclusion criteria were used to increase internal validity, and to select treatment-naïve patients with an incident diagnosis.

Although interrupted time series is a particularly strong quasi-experimental study design, there were limitations to my study. There was no randomization of health practitioners to the policy; the campaign was implemented nationwide and therefore I do not have a conventional control group. Due to a small sample size for some outcomes I could not assess the specialization type or years of practice for prescribing clinicians and was therefore unable to assess if the guidelines were effective in psychiatrists specifically. I was also unable to assess the impact of physician age: there is a high probability that recently practicing physicians are likely to evaluate patients more thoroughly, and therefore to wait longer before prescribing medications. This is important, as previous studies have demonstrated that older physicians with more years of practice were more likely to prescribe radiographs for low-risk LBP patients, which is considered low value care in the CWC recommendations (162). Finally, in terms of external validity, my sample may
not be representative of the pediatric psychotropic use of the overall Canadian population or populations in BC for which I did not have access to data, including First Nations populations covered by the Federal government drug plan.

4.8 Recommendations for further research

In order to present a more comprehensive evaluation of CWC’s campaign impact, further research is warranted. In terms of expanding on the studies in this thesis, there are several avenues for more investigation. First, although my study adds value to the larger body of evidence surrounding the impact of the CWC campaign on suboptimal psychiatric medication usage, evaluation of recommendations from other specialties is needed. A greater breadth of research would enable conclusions to be drawn on the effectiveness of the overall CWC campaign, which comprises over 200 recommendations, only 3 of which were examined in this study. More studies would add to the developing policy story of the need for more comprehensive interventions than just passive dissemination.

From a methods standpoint, there are also improvements that could be made in future work. Stratifying further research according to physician type is recommended as it will help us better understand differences in practice, highlight those most at risk of administering low value prescriptions, and assess whether different specialties respond differently to intervention. I also recommend that future work examine long-term trends in the impacts of these interventions. My study had a restricted number of observations post intervention, which might have reduced my ability to detect an impact. Further research with a broader time range post intervention would provide more precise estimates of the campaign’s effectiveness (or lack thereof).
4.9 Policy implications

The primary policy implication of my study derives from the ineffectiveness of the CWC campaign in reducing inappropriate prescribing of psychiatric medications in pediatric psychiatry across all three recommendations I studied. Therefore, CWC should utilize a more comprehensive and broader approach than simple passive information dissemination in order to change physician prescribing behaviour and reduce unnecessary care. In its current state within British Columbia, CWC has not shown an impact on the outcomes I studied.

To date, only one CWC recommendation has been shown to be successful in reducing Canadian prescribing: a study of low value prescription of benzodiazepines among older adults at the provincewide level (23). Brett and his colleagues showed in their study that the rate of benzodiazepine use among older adults moderately decreased. However, the steepest decrease was shown in the years of 2011 and 2012, when the province implemented concentrated programs to combat benzodiazepine use in these age groups. The decrease in benzodiazepine use is mostly attributable to these programs, not to the release of CWC recommendations, which was two years later in 2014. This evidence, combined with the results of my study, suggests that CWC recommendations alone may not be powerful enough to reduce unnecessary prescriptions.

Healthcare facilities in British Columbia should follow the examples of individual hospitals within Canada that achieved significant reduction in the use of low value care through implementing various quality improvement initiatives in conjunction with CWC. These facilities implemented multifaceted and active strategies that included but were not limited to engaging
staff at all levels, creating reminders and directives and integrating the campaign in continuous medical education (30–33,35,36). Some provinces also demonstrated reductions through creating local subdivisions of nationwide CWC and highly targeted campaigns such as ‘Antibiotic wisely’ (16). The common thing between all effective factions was their ability to execute at a highly centralized, consistent and coordinated level.

Therefore, to achieve a significant reduction in the inappropriate utilization of low value psychiatric prescription medications, BC’s healthcare facilities and the Provincial Ministry of Health should implement and evaluate multifaceted quality-centered improvement initiatives that are governed by strong healthcare champions.
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