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Off-Label Use of Second Generation Antipsychotics in Primary Care -An Exploratory Study

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Abstract

Over the past two decades, the use of antipsychotics has increased tremendously worldwide, and second-generation antipsychotics (SGAs) have been the main driver of this trend. The extensive use of SGAs for off-label purposes has raised concerns over their role in clinical practice. In particular, studies have revealed serious metabolic and cardiovascular effects, and evidence is lacking on SGAs' effectiveness. Despite the concerns, the extent and pattern of SGAs' off-label use is largely unknown within the context of the Canadian primary health care system. Using electronic medical record (EMR) data from 14 practices in southwestern Ontario, we investigated the number of patients who were prescribed SGAs in primary care for off-label uses between 2005 and 2015. Furthermore, we compared the history of diagnosis of the off-label population to this history of a reference population (non-SGA users) in the same setting.

The majority of patients who were prescribed SGAs lacked records of approved indications (72%), and the medications appeared to be prescribed much more frequently for off- than on-label uses in any given year in the study period. SGAs are reported to be prescribed off-label for a variety of conditions; in our data, SGA users in the off-label group were more likely to have a history of dementia, anxiety and depressive disorders, personality disorders, and substance abuse, which may have been the off-label indications for which the patients were prescribed SGAs in primary care.

Our findings indicate a need to promote evidence-based prescription of SGAs as well as the provision of further evidence on their use in off-label indications. Although off-label use has often preceded and outstripped supporting evidence, we encourage the regulatory agency, pharmaceutical industry, and science community to implement innovative policies and solutions to address the off-label prescribing practice

Keywords

Off-label use, second-generation antipsychotics, SGA, atypical antipsychotics, primary care, quetiapine, risperidone, olanzapine, aripiprazole, trend

Summary for Lay Audience

Second-generation antipsychotics (SGAs) are a group of medications that initially were tested for certain mental diseases (schizophrenia, bipolar disorders, etc.) and were officially assessed and received approval for market entry. Later, studies reported that these medications were used for conditions for which there is no standard treatment or for patients who did not respond well to standard medications. Such uses are called off-label as they are not officially assessed and approved in contrast to on-label uses (uses for approved conditions). Off-label use of existing medications may be a helpful option for certain patients but there are concerns that without enough experiments, there would not be enough information on how effective and safe these agents might be in off-label uses.

We studied patients who were prescribed SGAs in primary care between 2005 and 2015 in southwestern Ontario and compared the history of their diagnosis with the non-SGA users. The majority of patients in our data (72%) lacked records of approved indications and seemed to be off-label users. Health conditions like dementia, anxiety and depressive disorders, personality disorders, and substance abuse seemed to be the off-label uses of SGAs in our data.

Our findings show a need for further research in this area as well as further safe and effective medications for a variety of less-known psychiatric conditions.

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List of Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
AHRQ	Agency for Healthcare Research and Quality
APA	American Psychiatric Association
BC	British Columbia
CANMAT	Canadian Network for Mood and Anxiety Treatments
CPCSSN	Canadian Primary Care Sentinel Surveillance Network
DELPHI	Deliver Primary Health Care Information
FDA	Food and Drug Administration
FWER	Family-Wise Error Rate
GAD	General Anxiety Disorder
HRU	Health Care Resource Utilization
ICD 9 - CM	International Classification of Diseases, Ninth Revision, Clinical Modification.
IDD	Intellectual and Developmental Disabilities
IQR	Interquartile range
MDD	Major Depressive Disorder
NNH	Number Needed to Harm
NPS	National Physician Survey
ODB	Ontario Drug Benefit
OHIP	Ontario Health Insurance Program
PTSD	Post-Traumatic Stress Disorder
SGA	Second Generation Antipsychotic
TRD	Treatment-Resistant Depression
US	United States

Chapter 1

1 Introduction

Health Canada has the authority to approve medications for sale in Canada. As part of the approval process, Health Canada evaluates clinical trials for the candidate medication to assess the safety and effectiveness profile and decide on market authorization approval. Once the approval is issued, Health Canada specifies "the population for whom the drug can be prescribed, the indication(s) the drug can treat, and the dosage(s) that can be administered" and any use beyond these criteria is classified as "off-label" use (1). This includes medication prescribed for an indication or subpopulation (e.g. children or nursing women) not specified in the approval document. Prescribing a medication at a dose outside of approved dosing recommendations is also considered off-label use.

While Health Canada has the authority to evaluate medications and specify approved uses (on-label use), it has no jurisdiction over how drugs are used in clinical practice. In other words, Health Canada has no legal authority over how physicians decide to prescribe medications for their patients. Off-label prescribing is legal in Canada and physicians are permitted to prescribe medications off-label if it is in the best interest of their patients. In fact, off-label prescribing is not an unapproved practice necessarily. Sometimes, not all indications that have been adequately studied are submitted to Health Canada for approval as Canada's market may be seen economically smaller compared to other markets or the medication may have moved to generic status, and the license holder has little incentive to spend its resources to officially get any further approvals for expanded indications. Moreover, for patients who are refractory to the approved treatments or those in conditions where no approved treatment is yet available, off-label prescribing of existing treatments might be a helpful option. However, the safety and effectiveness of this approach remains controversial (2–6), and a lack of evidence on benefits and harms of most off-label uses is a constant challenge. For example, quetiapine regular tablets, one of the most commonly prescribed antipsychotics, has been approved[1] for schizophrenia and bipolar disorders but is not formally evaluated by the proprietor for sleep disorders and consequently not approved for this indication. Clinical trials conducted by other researchers on this off-label indication since its market entry in 1997 are still limited, and none of them compared quetiapine with an active control (e.g. zopiclone). Yet this medication has been prescribed off-label for insomnia for the past two decades (7). If use of a medication is not evaluated for an indication and not supported by robust evidence, the efficacy could be more of a hope than an expectation. Safety and risk of adverse events would be a concern as well, especially when a medication is prescribed off-label for an unevaluated subgroup of the population (e.g. children or seniors).

Concerns regarding off-label use arise partly due to the fact that this phenomenon is remarkably common: in a study of prescribing patterns in the United States, Radley et al (2006) showed that 21% of medications commonly prescribed by outpatient physicians were for off-label indications

[1] Quetiapine extended-release (XR) tablet is approved for major depressive disorder as well as schizophrenia and bipolar disorders.

(8). However, this study likely underestimated the frequency of off-label prescribing, as the study only considered the indications for prescriptions, and off-label uses for unevaluated populations or dose ranges were not assessed. The prevalence of off-label use also varies in different therapeutic fields – for example, in Canada the prevalence of off-label use for unevaluated indications was reported to be 12.4% for gastrointestinal medications, 15.2% for ear, nose and throat medications, 66.6% for anticonvulsants, 44% for antipsychotics, and 33% for antidepressants (9).

Among psychiatric medications, second generation antipsychotics (SGAs) are of particular concern due to reports of increasing use, both for approved and off-label indications. Over the past two decades, use of antipsychotics has increased tremendously worldwide (10–12), and SGAs have been the main driver of this trend (12–20) (12). In Spain, a four-fold increase in antipsychotic use was observed between 1985 and 2000, and SGAs contributed the most to this increase (19). In the United States, 0.1% of the population used a SGA in 1996-1997, whereas in 2004-2005 this increased to 1.1%, which is more than seven-fold increase (21). In the United Kingdom, there was a nearly six-fold increase in total SGA prescriptions between 1996 and 2001 in primary care (22). These data are consistent with trends in Canada, where the number of annual antipsychotic prescriptions increased more than two-fold between 1993 and 2002, with more than 80% of prescriptions in 2002 for SGAs (18). Prescriptions for quetiapine in particular increased more than 300% between 2005 to 2012 across Canada (23).

Although the estimates from various studies differ based on the time period and the specific outcome defined, almost all studies confirm the increasing trend in the use of SGAs since their entry into the market. Given that the prevalence of psychotic disorders has been fairly constant over the last two decades (24), three main reasons are discussed to explain this increasing trend and the widespread use of SGAs:

1- First generation antipsychotics (FGA) were notorious for extrapyramidal related adverse events (such as tardive dyskinesia, Parkinsonism, akinesia, akathisia)(25), which made their use limited in clinical practice. SGAs were shown to have fewer extrapyramidal effects in trials and soon replaced first generation agents in treating psychotic disorders. They soon became first line treatments in psychotic disorders in clinical guidelines due to their relatively safer profile compared to FGAs (20). Their better tolerability has also led to a longer period of use (20).
2- On-label indications for SGAs were extended, and they received approval for treatment of bipolar disorder later – consequently, a larger portion of patient populations were prescribed SGAs (20).
3- Off-label prescribing of SGAs has significantly contributed to the increasing trends (11,14,26,27). In fact, some studies reported that SGAs are prescribed more frequently for off-label indications than approved indications (28,29).

The extensive off-label use of SGAs has raised concerns regarding the role of SGAs in clinical practice, especially when post-marketing[1] and other studies revealed significant metabolic,

[1] "Post-marketing surveillance (PMS) (also post market surveillance) is the practice of monitoring the safety of a pharmaceutical drug or medical device after it has been released on the market and is an important part of the science of pharmacovigilance." (30)

cardiovascular, and other side effects (31–35). If the effectiveness of SGAs have not been demonstrated for off-label uses, widespread use potentially puts a broader portion of the population at risk for adverse events like weight gain, diabetes mellitus, and sudden cardiac death (36) for little or no benefit. Therefore, evaluating the off-label use of SGAs and associated diagnoses in our health care system will be an important contribution to the existing literature and will be the focus of this study.

Using the data from 14 primary care practices in southwestern Ontario, we will add to the evidence in this field and improve our understanding of current situation in primary care, where many SGA prescriptions are generated (23) and yet are less investigated, especially for adult and senior populations. Using electronic medical record (EMR) data, we will explore the prevalence and factors associated with of off-label use of SGAs between 2005 and 2015. The following chapters report on previous works in this field, describe our methodology and results and discuss findings of the current study.

Chapter 2

2 Literature Review

This chapter presents the history and current definition of off-label use, the associated legal challenges, and the previous studies on the prevalence of off-label use, with a focus on off-label prescribing of SGAs in primary care.

2.1 Off-label Use – History and Current Definition

The term "off-label" originates from the medication labeling requirements of the United States (US) Food and Drug Administration (FDA). At early stages in 1938, safety was the only regulatory requirement for a new medication to be approved by the FDA. In 1962, effectiveness was added as another requirement for new medication approval (37). Manufacturers were required to provide evidence that a new medication candidate was shown to be safe and effective for a specific indication. The FDA then regulated the drug labeling with the intention to provide drug information to healthcare professionals and assist them in prescribing drugs appropriately. A summary of safety and effectiveness information became part of official FDA drug labels, and use of any FDA approved medication for an unapproved indication, population, dose or by a different dosage form was referred as off-label use (38).

Drug labels are updated and evolve over time in terms of adverse events, warnings, and contraindications, but updates occur less frequently for new indications (3). Beside the cost of new clinical trials, adding an additional indication for an already approved medication can be time consuming and costly to the proprietor. Additionally, revenues for the indication in the remaining patent protection period might not offset the cost, especially when prescribers are legally allowed to prescribe medications off-label and without the official approval requirements (3).

The FDA's regulatory approach and requirements were adopted later and followed by many governmental regulatory agencies across the world, including Health Canada, which has the authority to approve drugs and official drug labels for domestic sale in Canada. Yet medications do not necessarily receive the same exact approvals in every country. For example, olanzapine (Zyprexa) is approved for pediatric patients with schizophrenia or bipolar type I disorder by the US FDA, but it is not approved to be used in pediatric populations by Health Canada.

2.2 Legal Issues

In both the US and Canada, the FDA and Health Canada, respectively, have the authority to evaluate drugs and specify approved uses (on-label use), but they have no jurisdiction over how medications are used in clinical practice. In other words, they have no legal authority over how physicians decide to prescribe medications for their patients. Physicians are permitted to prescribe medications off-label, but if a legal claim arises (e.g. following an adverse effect), they must justify their action on available scientific evidence and show that it was in the best interest of their patients, otherwise the prescriber might be accused of medical negligence (38).

Off-label use of available treatments was historically accepted because it gives clinicians the

flexibility to help patients who are not responsive to approved treatments or those who have a condition where no approved treatment is yet available (36). The logic of using medications off-label in these situations relies on one of the following two major assumptions:

- The *common pharmacologic class effect* assumption assumes that drugs in the same class share similar common effects. According to this assumption, if, for example, one SGA is approved for irritability with autistic disorder in pediatric populations, other SGAs with similar chemical structure and pharmacologic properties would be expected to have a comparable efficacy and safety profile in pediatric populations.
- The *common pathophysiologic pathway assumption* assumes that conditions with mutual physiologic mechanisms and pathways could be treated with common treating agents: for example, metformin, an oral antidiabetic agent, is used in infertility treatment and to induce ovulation in women with polycystic ovary syndrome (PCOS) through its action on insulin level and controlling insulin effects on ovarian androgen biosynthesis (39).

These assumptions are not always valid, and hence direct promoting of off-label use by pharmaceutical companies is illegal and prohibited in US and Canada. However, as Stafford argues (3), there are areas of this prohibition policy that are not completely defined or enforced. For instance, the pharmaceutical industry may take advantage of promotional activities such as continuing medical education, and may provide physicians with a journal article regarding an off-label use. Although this is considered a form of education, it could be potentially biased and partial as trials may have been selected from industry sponsored and placebo controlled trials of limited quality (3). The Zyprexa (Olanzapine) settlement is an example of off-label promotion: in 2009 Eli Lilly agreed to pay US $1.4 billion in settlement for off-label promotion of Zyprexa for agitation, depression, and sleep problems, which was the highest corporate fine in history at the time (40). Zyprexa was only approved for schizophrenia and bipolar disorders at the time this occurred.

2.3 Challenges in Assessing Off-label Prescribing

The way that off-label use is defined and measured affects prevalence estimates; not all studies use a universal definition of off-label use, and researchers may limit their definition and measurement to off-label use for either unapproved indication, dose, or age category rather than considering all three aspects. The majority of the literature that we found on off-label use is based on retrospective studies in primary and secondary care practice that assess off-label use of medications for unapproved indications, with relatively fewer studies on other types of off-label use or in other settings. The accurate capture of diagnoses associated with the prescribed medication is the single major limitation in measuring off-label use in many retrospective studies. The following section provides estimates and gives an overall understanding of how common off-label use is in practice.

2.4 Prevalence of Off-label Prescribing

Off-label prescribing is a widespread and common practice. Radley et al. (2006) showed that 21% of medications commonly prescribed by outpatient physicians were for off-label indications in the US (8), but did not assess off-label uses associated with unevaluated populations or dose

range. A study by Lat et al. (2011) assessed both indication and dose range in adult patients in 37 critical care units in the US and reported that 36.2% of medications were for off-label uses (41). In another study, Loder et al., (2004) studied prescriptions for adults in a headache specialty practice and reported that 47% of prescriptions were for off-label indications or doses (42).

The prevalence of off-label use varies depending on several factors. For one, off-label use is more common in some fields than others. Medications used in psychiatry and neuropsychiatry tend to be used more frequently off-label than gastrointestinal medications (9). Off-label use also varies in different populations: medications are not usually pre-tested in nursing or pregnant women, and the majority of medication use is off-label in these populations. Children, seniors, and women also have a higher rate of off-label use compared to the adult male population. The time since medication approval also affects off-label use, as older medications are usually perceived as having a better-known safety and efficacy profile and are therefore used off-label more frequently. Prescribers' characteristics may also have a role in off-label prescribing, with male and older physicians being more likely to prescribe medications off-label compared to female and younger physicians (43–45).

For off-label prescribing to children, a study by Shah et al (2007) showed that 78.9% of patients discharged from pediatric hospitals were taking at least one medication for off-label age category regardless of the indication (46). A high prevalence of off-label use in children has also been reported in other studies, and it has been commonly argued that this is because children are typically excluded from drug trials (11,47–49). Both the FDA and the European Medicine Agency (EMA) introduced initiatives to encourage clinical research in pediatric populations, however their policies seem to have had only marginal effects on off-label use of medications in this age category (50).

In the field of psychiatry, off-label use is more prevalent than most other clinical specialties (8,51–53). Chen et al. (2006) studied off-label use of antidepressants, anticonvulsants, and antipsychotics in Medicaid enrollees in Georgia and reported that among adult patients who were prescribed antipsychotics, 63.6% received at least one antipsychotic for an off-label indication. Off-label doses were not assessed in this study (54). Alexander et al. (2011) reported that visits in which antipsychotics were prescribed for off-label indications almost doubled from 4.4 million in 1998 to 9 million in 2008 in the US (55); off-label doses and use in off-label age categories were not assessed in this study.

In Canada, increasing trends in the use of SGAs for both on- and off-label uses have been examined in different clinical settings across various provinces, including Ontario, British Columbia, Manitoba, and Quebec. The majority of these studies focused on children and youth, and used health administrative databases as their data source. The following estimates are from Canadian studies on the off-label use of SGAs.

Alessi-Severini et al. (2012) studied ten years of antipsychotic prescribing to children and adolescents in Manitoba and reported that despite the lack of approved indication in this population, the prevalence of antipsychotic use increased from 1.9 per 1000 in 1999 to 7.4 per 1000 in 2008, and SGAs were the driver of this increasing trend. They reported that more than 70% of antipsychotic prescriptions were written by family physicians, and the most common diagnoses linked to antipsychotic use were attention-deficit hyperactivity disorder (ADHD) and conduct disorders. They used health administrative data in Manitoba Population Health Research Data Repository to identify those who were prescribed antipsychotics. Diagnoses were obtained

through the use of International Classification of Diseases, ninth and tenth version, Clinical Modification codes (ICD-9-CM and ICD-10-CM) in medical claims. Their data source captured over 90% of outpatient prescriptions dispensed to Manitoban residents without limitations regarding drug coverage, and results could be considered representative of the general youth population of Canada (56).

Bock et al. (2016) conducted a survey of 100 pediatricians and 421 family physicians in 2013 and assessed medication therapy for pediatric insomnia in southwestern Ontario. They reported that antipsychotics were one of the most commonly prescribed medications in children 6 to 12 years of age (57).

Chow et al. (2017) studied off-label use of quetiapine for insomnia in the inpatient child and psychiatry unit, and reported that 11.5% of admissions received a prescription for quetiapine (58). They performed a retrospective chart review after they identified night-time prescriptions of quetiapine to assess indication and doses.

Lachaine et al. (2014) studied healthcare resource utilization (HRU) and costs related to SGAs among children with ADHD who previously received stimulants in Quebec. They concluded that off-label use of SGAs was associated with increased HRU and costs. They used Quebec provincial health care claim data between 2007 and 2012 for their study (59).

Ronsley et al. (2013), studied the antipsychotic prescription trends in children and adolescents in British Columbia (BC) from 1996 to 2011 and reported an exponential rise in SGA prescriptions due to extensive off-label use: the prevalence of SGA prescriptions increased 18-fold (from 0.33 to 5.98 per 1000 population in the study period) and the most common diagnoses associated with antipsychotics were depressive disorders, hyperkinetic syndrome of childhood, and neurotic disorders. They reported that in 2010-2011, psychiatrists, family physicians and pediatricians provided 38.6%, 34.3%, and 15.6% of new antipsychotic prescriptions respectively. They used the BC medication registry of all outpatient prescriptions (BC PharmaNet) to identify prescriptions for antipsychotics, dose and quantity dispensed, duration of treatment, and prescriber information for each prescription. Diagnoses were obtained from a probabilistic linkage between prescriptions and ICD-9 codes in medical claims – for each patient, the last diagnoses from the prescribing physician before the prescription was dispensed was considered the diagnosis associated with the antipsychotic prescription (27).

Iaboni et al. (2016) used linked databases at ICES and studied the changing pattern of sedative use in older adults (≥ 66 years) between 2002 to 2013 in Ontario. The data revealed a shift away from benzodiazepines toward the off-label use of low dose quetiapine and trazodone (an antidepressant agent) in both community and long-term care settings. Diagnostic data were not analyzed in this study, but researchers examined prescribed doses and concluded that the observed low dose pattern is likely consistent with the off-label use of trazodone and quetiapine for sedative effects (60). Lunsky et al. (2018) also used databases at ICES and studied a cohort of adult patients with intellectual and developmental disabilities (IDD) who were prescribed antipsychotic agents (both first and second generation) between 2010 and 2016 in Ontario. Antipsychotic users were identified through Ontario Drug Benefit (ODB) claims, which covers medication costs for people with IDD who are on a disability support program. They also investigated whether patients in the cohort had a history of psychiatric disorders in the two-year period before their first antipsychotic prescriptions. Although they did not classify antipsychotic

users to off-label and on-label users, they reported that almost one-third of users (28.9%) had no recorded psychiatric diagnoses (61).

Peringsheim and Gardner studied dispensed prescriptions for quetiapine between 2005 and 2012 and reported a 300% increase in quetiapine prescriptions by family physicians, from 1.04 million in 2005 to 4.17 million in 2012. Both risperidone and olanzapine prescriptions also increased by 37.4% and 37.1%, respectively, over the study period. The study examined the diagnoses associated with quetiapine only and reported a 10-fold increase in off-label use of quetiapine for sleep disturbances. Mood disorders, psychotic disorders, anxiety disorders and sleep disturbances were reported as the top four diagnoses associated with quetiapine use. Researchers used two different databases in this study: first, they used IMS Brogan CompuScript database, which captures filled prescription data from more than 60% of retail pharmacies across Canada, to determine the quantity of antipsychotic prescriptions per year; second, they used the Canadian Disease and Treatment Index, which collects treatment data from a sample of office-based physicians (n = 652) in Canada, to report on diagnoses associated with quetiapine (23).

Eguale et al. (2012) studied determinants of off-label prescribing to adult populations in primary care in Quebec from 2005 to 2009. They reported that among different classes of medications, off-label use was the highest for central nervous system medications: 66% for anticonvulsants, 43.8% for antipsychotics, and 33.4% for antidepressants. They used data from an electronic health record (EHR) system, which included 113 primary care physicians in urban centers in Quebec and 50,823 patients. The researchers indicated that a major advantage of this database was the accurate capturing of diagnoses. Participating physicians were required to specify the therapeutic indication with every prescription by selecting from a list of on-label and off-label indications or writing in a free-text field, and this uniquely allowed for accurate documentation of off-label use, unlike most other retrospective studies that utilize health administrative data (9). Off-label dose were not assessed in this study, however.

2.5 Concerns with Off-label Prescribing

It has been argued that in most cases, little is known about the effectiveness and safety when a medication is prescribed off-label (8). Eguale et al. (2012) studied off-label prescribing in primary care in Quebec and reported that 79% of the off-label prescriptions lacked strong scientific support, defined as no randomized trial to justify off-label uses (9). Another study by the same group recently reported that off-label prescriptions lead to a 57% increase in adverse drug reactions when compared to approved uses (62).

SGAs are used for a variety of off-label indications in psychiatry, such as depression, obsessive compulsive disorder, personality disorders, post-traumatic stress disorder, Tourette syndrome, behavioral problems in patients affected by dementia, autism, anxiety, ADHD, eating disorders, insomnia, and substance abuse (63). The Agency for Healthcare Research and Quality (AHRQ) in the US published a review on off-label use of SGAs in 2006, and later released an updated version in 2011. The original review (31) concluded that there was no high strength evidence on the efficacy of SGAs for any known off-label use of SGAs. The updated review in 2011 (63) assessed additional published studies in the literature and found that available evidence still did not support the use of SGAs for most off-label indications (Table 2-1). The report adds that evidence on optimal dosage, duration of treatment, and effect of age in the use of SGAs for off-label indications is lacking as well (63).

Aside from the unknown efficacy, safety is another concern regarding off-label use of SGAs. The original AHRQ review reported on strong evidence of an increased risk of adverse events (e.g. mortality in seniors) following off-label use of SGAs. The updated version of the review calculated the number needed to harm (NNH) for some adverse events: risk of death NNH = 87; stroke NNH = 53 for risperidone; and extrapyramidal symptoms NNH = 10 and 20 for olanzapine and risperidone respectively. In April 2005 following analyses of 17 placebo-controlled trials, the US FDA issued a black box warning for off-label use of SGAs in elderly patients with dementia: the risk of death was about 1.6 to 1.7 times that of placebo with various cause of death (heart failure, heart-related sudden death, pneumonia) in this population (64). Increased risk of coronary heart disease and metabolic syndrome in patients treated with SGAs and some typical antipsychotics has also been reported in other studies (32,34,65)(66,67).

The original AHRQ review estimated that Olanzapine users are 6.1 times more likely to gain weight compared to placebo users and 2.6 times more likely compared to FGA users. This conclusion remained unchanged in the updated version. Weight gain is also seen with most other SGAs, but less than olanzapine. Newcomer et al. (2002) reported glucose level elevation with olanzapine, clozapine, and risperidone in comparison with both untreated controlled subjects and those on first generation antipsychotics (68). Guo et al. (2006) also linked SGAs to diabetes and reported that clozapine (Hazard Ratio [HR]: 7.0, 95% CI: 1.7 to 28.9), olanzapine (HR: 3.2, 95% CI: 2.7 to 3.8), risperidone (HR: 3.4, 95% CI: 2.8 to 4.2) and quetiapine (HR: 1.8, 95% CI: 1.4 to 2.4) all increase the risk of developing diabetes (69). The AHRQ report, however, concluded that evidence for endocrine and metabolic risks of SGAs are less certain (63). In 2017, Sagreiya et al. (2017) compared the safety of antipsychotics (first and second generation) in pediatric, adult, and geriatric populations and reported that the frequency and type of adverse events is different in each population. Diabetes is frequently reported as one of the adverse effects of using SGA in adult populations (70).

Table 2-1 Efficacy of Olanzapine, Risperidone and Quetiapine by Off-label Conditions

	Olanzapine	Quetiapine	Risperidone
Anxiety			
Generalized anxiety disorder	-	++	-
Social phobia	+	-	No Trial
Attention-deficit hyperactivity disorder			
No co-occurring disorders	No Trial	No Trial	+
Bipolar children	No Trial	No Trial	No Trial
Mentally retarded children	No Trial	No Trial	+
Dementia			
Overall	+	+	++
Psychosis	+-	+-	++
Agitation	++	+-	++
Depression			
MDD - augmentation of SSRI/SNRI	+	++	++
MDD - monotherapy	-	++	No Trial
Eating Disorders	--	-	No Trial
Insomnia	No Trial	-	No Trial
Obsessive-compulsive disorder			
Augmentation of SSRI	+	- -	++
Augmentation of citalopram	No Trial	+	+
Personality disorder			
Borderline	+-	+	No Trial
Schizotypal	No Trial	No Trial	+-
Post-traumatic stress disorder	+-	+	++
Substance abuse			
Alcohol	-	-	No Trial
Cocaine	-	No Trial	-

Methamphetamine	No Trial	No Trial	No Trial
Methadone clients	No Trial	No Trial	-
Tourette's syndrome	No Trial	No Trial	+

++ = moderate or high evidence of efficacy; + = low or very low evidence of efficacy; +- = mixed results; - = low or very low evidence of inefficacy; - - = moderate or high evidence of inefficacy

MDD: major depressive disorder; SNRI: serotonin norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor

Adapted from: *Maglione M, Ruelaz Maher A, Hu J, et al. Off-label use of atypical antipsychotics: an update. AHRQ comparative effectiveness review no. 43. September 2011*

2.6 Summary of Existing Literature and Current Gaps on Off-Label Use of SGAs

Off-label use of SGAs, especially risperidone, quetiapine, and olanzapine, is reportedly common and widespread in various studies and in different subgroups of the population. Yet, the efficacy of SGAs for most off-label indications is not supported by strong evidence and concerns regarding their safety profile remain. This is of particular concern when a drug treatment is not supported by strong evidence – when the effectiveness of the drug is not established, the prescriber is not able to have a clear estimate of risk-benefit balance. Off-label prescribing in this situation would potentially put a broader patient population at risk of adverse events, while the benefit may not be realized.

Despite concerns regarding the trends in prevalence of off-label use of SGAs, few studies have been done on this subject in Canada. These studies provided valuable data, but they had some limitations: the majority of the studies were restricted to a specific age group (children and adolescents) (27,56–59), or a specific antipsychotic agent (23,60). In Ontario, data are lacking on the current situation of off-label use of antipsychotics in primary care. There is a need to re-evaluate and understand the current prevalence of off-label use of SGAs across age categories in primary care in Ontario. The current study includes all available SGAs in Canada and aims to describe patients of various age categories who received a SGA prescription from their primary care provider in Southwestern Ontario, and investigate their history of diagnoses to evaluate off-label use of SGAs between 2005 to 2015. This will provide an updated insight to policy makers regarding the current patterns of off-label prescribing and potential points of intervention.

Chapter 3

3 Methods

3.1 Research Objectives

The objectives of this exploratory[1] study were:

1) To quantify and describe off-label uses of SGAs among primary care patients in Southwestern Ontario between 2005 and 2015:

> Research Question 1: What proportion of patients were prescribed an SGA for off-label indications in the study population?
>
> Research Question 2: What are the age and sex characteristics of patients who were prescribed an SGA for off-label indications compared to the on-label and reference groups in the study population?
>
> Research Question 3: How is the off-label prescribing changing over time in the study population?

2) To compare history of diagnoses for patients with off-label SGA prescriptions with the on-label and reference group:

> Research Question 4: Which diagnoses are seen more or less frequently in the off-label group as compared with the reference group in the study population?
>
> Research Question 5: Is there an association between the commonly reported off-label uses of SGA in the literature and history of diagnoses of patients in the off-label group, when controlling for age and sex characteristics?

3.2 Data Source

The data for this study were derived from Deliver Primary Health Care Information (DELPHI) database. DELPHI is part of Canadian primary care sentinel surveillance network (CPCSSN) project[2] and is a de-identified research database created from Electronic Medical Record (EMR)

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[1] "Exploratory research is research conducted for a problem that has not been studied more clearly, intended to establish priorities, develop operational definitions and improve the final research design. Exploratory research helps determine the best research design, data-collection method and selection of subjects" (71)

[2] CPCSSN is the first pan-Canadian multi-disease public and population health surveillance system. Health information from electronic medical records in the offices of participating primary care providers (e.g. family physicians) is collected with the purpose of improving the quality of care for Canadians suffering from variety of chronic and mental and neurologic conditions: hypertension, osteoarthritis, diabetes,

data from primary care practices in Southwestern Ontario. It was created for the purpose of improving practice, policy, and research in primary care (72). The DELPHI data includes information on patient characteristics (birth year, sex, postal code, etc.), encounter billing information, medication lists, physical examination, allergy intolerance, family history, laboratory tests, and procedures. One important advantage that DELPHI data has over other data sources (e.g. ICES) is that DELPHI contains fields in regards to the "prescribed medications" for individuals. This information was essential in conducting this study and assessing off-label uses of SGAs.

The DELPI project is currently comprised of 14 primary care practices throughout southwestern Ontario and includes 60 primary care physicians, 64,377 patients, and 1,956,778 encounters. For the purposes of this study, the analyses were limited to data extracted between October 1, 2005 and December 31, 2015. Records before October 2005 or after December 2015 were excluded as data prior or after the specified dates may not be as accurate or complete in DELPHI.

Primary care physicians in DELPHI were recruited through a variety of approaches, as described in detail in previous literature (72). Although the physicians were not selected through a random sampling strategy, they are considered representative of Ontario family physicians by age and sex (Table 3-1). Although, in terms of practice location, participants in DELPHI were less urban compared to Ontario family physicians. Table 3-1 shows the age, sex, and rurality distribution of the physicians as of fourth quarter of 2015. Primary care in Ontario is provided through different paths and by various practitioners other than family physicians (e.g. nurse practitioners, dieticians, pharmacists, etc.). However, DELPHI merely had data on family physicians in the study period whereas no other type of practitioner was included. So DELPHI data reflects only a part of broad services in primary care in southwestern Ontario and this should be considered in any inference made beyond the data.

chronic obstructive pulmonary disease (COPD), depression, Alzheimer's and related dementias, epilepsy and Parkinson's disease

Table 3-1: Comparison of Family Physician Characteristics of the DELPHI Sample and Ontario Family Physicians

Characteristics	DELPHI Family Physicians (n=60) from October 1st 2005 to December 31st 2015[1]	Ontario Family Physicians (National Physician Survey (NPS) 2014; n=3883)
Age[2]		
44 years and under	22 (36.7%)	1275 (32.8%)
45-64 years	13 (21.7%)	922 (23.7%)
55-64 years	13 (21.7%)	957 (24.6%)
65+ years	12 (20.0%)	687 (17.7%)
Unknown	0 (0.0%)	42 (1.1%)
Sex		
Male	36 (60.0%)	2098 (54.0%)
Female	24 (40.0%)	1758 (45.3%)
Practice Location[3,4]		
Urban/suburban	23 (38.3%)	(78.9%)
Small town	24 (40.0%)	(12.4%)
Rural	13 (21.7%)	(4.8%)
Isolated/remote	0 (0.0%)	(0.8%)
No Response	0 (0.0%)	(3.1%)

[1] Not all physicians contributed 10 years of data. Some were retired/deceased or left their practice site before 2015.
[2] We do not have data on age of DELPHI physicians. Year of graduation was used as a proxy for age, with the assumption that most graduates would be approximately 28 years at the time of graduation, and age is measured as of 2015, at the end of the database extract.
[3] Location is measured differently for both DELPHI and the NPS. DELPHI location was classified using the city location and adapted from a Statistics Canada population definition. (Urban 100K+, Suburban 30 - 99K, Small Town 4-29K, Rural <5000).
[4] The NPS asked physicians " with respect to your main patient care/practice setting, describe the population primarily served by you in your practice. " The physicians gave responses in percentages, and not number of patients. No definition was provided for the type of location.

3.3 Data in DELPHI

Data from several different EMR software products is structured in 34 different tables in DELPHI. Each table has a title and various fields (columns) of several data types (text, date, auto integer, boolean, number, etc.). Tables may be linked through certain key fields to access associated information on specific cases. For example, people who had records for Risperidone in the

"Medication" table may be linked with data in the "Patient" and the "PatientDemographic" table through the mutual key "Patient_ID" to obtain birth year, occupation, and highest level of education for those people. Certain fields in DELPHI tables (identified by "_orig" appended to their field names) contain original text in EMRs with no systematic modifications to unify the information across EMR vendors. To better organize and provide data for research, another type of field is created in DELPHI and distinguished by "_calc" suffix. In these fields, data from "_orig" fields are algorithmically coded and converted to a unified form. For example, in the "Medication" table, which contains data on prescribed medications for patients, the field "Name_orig" has the medication name exactly as it appears in the EMR: this field may read "Seroquel", "Auro-Quetiapine 25mg", "PMS-Quetiapine 50mg tablet", etc. for essentially the same active ingredient "Quetiapine," depending on the particular clinician and EMR software used. In the "Name_calc" field, in the same table, all such variations are converted to a unique medication name "Quetiapine" with no extra indicator regarding strength, form, or producer propriety name. The converting algorithm was not accessible to us to check for conversion accuracy but our visual inspection of data revealed that incorrect conversions existed. Consequently, we implemented measures to authenticate the conversion algorithm.

Table 3-2 presents a summary of the DELPHI tables which are relevant to the current study. Tables with data on laboratory tests, risk factors, allergy intolerance, etc. are not presented here. For the purpose of this study we investigated the described tables to assess how detailed and complete the data were with respect to our study objectives. As the data in EMRs is primarily recorded for care services and not for the research purposes, DELPHI tables varied widely in proportion of missing or invalid data. Further challenges arose when attempting to link records across tables, because keys were not always present. For example, when trying to link the data from the "Billing" table to "Encounter" table by the mutual "Encounter_ID" key field, only 161 out of 61,172 encounters were matched for those who were prescribed any SGA in the study period. In fact, most "Encounter_ID"s in the "Billing" table were not present in the "Encounter" table. After the assessment, we decided to primarily use the "Medication" and "Billing" tables, as they contained the required information to match and link records had relatively more complete data than other tables in DELPHI.

Table 3-2 Summary of Tables in DELPHI

Patient: a list of EMR patients whose primary provider is a consenting physician in the CPCSSN project

- Contains 64,337 patients
- Fields: Patient_ID, Sex, BirthYear, OptedOut, OptedOutDate

PatientDemographic: characteristics and demographics of the patients

- Contains 51,406 patients
- Fields: Patient_ID, Occupation, HighestEducation, HousingStatus, Ethnicity, DeceasedYear, Site_ID, Network_ID, etc.
- Less than 4% of patients had any data in above fields.

Medication: all medications prescribed for the patient.

- Contains 1,311,156 records for 42,857 patients
- Fields: Patient_ID, Encounter_ID, Reason, Name_orig, Name_calc, Strength, Dose, Frequency, DispensedCount, RefillCount, Site_ID, Network_ID, etc.
- The field "Reason" contains no data.

Billing: all billing data submitted to the province for the patient

- 2,933,604 billing records for 54,953 patients
- Fields: Patient_ID, Encounter_ID, ServiceDate, DiagnosisText_orig, DiagnosisText_calc, DiagnosisCode_orig, DiagnosisCode_calc, DateCreated, Site_ID, Network_ID, etc.
- The field DiagnosisText_orig contains no data

DiseaseCase: patients with one or more of the index diseases: chronic obstructive pulmonary disease (COPD), dementia, depression, hypertension, diabetes, epilepsy, osteoarthritis, Parkinson's disease

- Contains 22,283 patients
- Fields: Patient_ID, Disease, DateOfOnset
- Case detection algorithm was based on either history of billing codes or medications history in respective DELPHI tables

Encounter: all encounters of the patient

- 1,956,778 encounter records for 45,780 patients
- Fields: Patient_ID, Provider_ID, EncounterDate, Reason_orig, Reason_calc, Site_ID, Network_ID, etc.
- >45% of encounters had either missing or invalid data in the "Reason_orig" field
- Only 240 of off-label users and 120 of on-label users had any record in this table

EncounterDiagnosis: all diagnoses resulting from an encounter

- 107,539 records for 23,301 patients
- Fields: Patient_ID, Provider_ID, Encounter_ID, DiagnosisText_orig, DiagnosisText_calc, Site_ID, Network_ID, etc.
- Only 11 of off-label users and six of on-label users had any record in this table

HealthCondition: all health conditions of the patient.

- Contains 32,714 records for 4,756 patients
- Fields: Patient_ID, DiagnosisText_orig, DiagnosisText_calc, DateOfOnset, Site_ID, Network_ID, etc.
- Only 77 off-label user and 31 on-label users were in this table

MedicalProcedure: procedures performed on the patient

- 424,160 records for 13,515 patients
- Fields: Patient_ID, Name_orig, Name_calc, PerformedDate, Site_ID, Network_ID, etc.

Referral: includes referrals made for the patient (only referrals made by this provider/practice are included; referrals made by specialists or other providers are not included)

- Contains 158,426 records for 20,586 patients
- Fields: Patient_ID, CompletedDate, Name_orig, Name_calc, Site_ID, Network_ID, etc.

3.4 Definition of Groups and Classification Criteria

3.4.1 SGA in Canada and Approved Indications

A list of SGAs was derived from the FDA website (73) and checked for availability in Canada through "Drug Product Database" on the Health Canada website (74). Approved indications for each SGA were recorded based on official Health Canada drug monographs, which were accessed through electronic database of Compendium of Pharmaceuticals (E-CPS) (75). Table 3-3 shows the available SGAs in Canada during the time period of the study and their approved indications for each age category as of September 2017. Although drug monographs evolve over time and new indications might be added to the list of approved indications in time, we conservatively chose to define off-label use based on current monographs (September 2017), even for uses in earlier years. It is possible though, that some true off-label uses may have been misclassified to on-label use due to this method. Moreover, this study defined off-label use based on indication, and off-label uses of SGAs as defined by age or unapproved dosage were not investigated in our analyses. For example, if quetiapine is used in children (unapproved population) for an approved indication (e.g. schizophrenia), then it was considered as on-label use.

3.4.2 Mapping Approved Indications to OHIP Billing Codes

DELPHI data contains Ontario Health Insurance Plan (OHIP) billing codes for each patient-provider encounter. Approved indications of SGAs (as of September 2017) were mapped to OHIP billing codes to be used in on-label versus off-label classification of SGA users. Table 3-3 shows the approved indications and corresponding OHIP billing codes.

Table 3-3: Approved Indications of SGAs

SGA (Brand Name)	Age Category	OHIP Codes	Health Canada Approved Indications
Aripiprazole **(Abilify®)**	Adult	295 296 311	• Schizophrenia • Bipolar Disorder • Major Depressive Disorder (MDD)
	Pediatrics	295 296	• Schizophrenia (15-17 years) • Bipolar Disorder (13-17 years)
	Geriatrics		• Aripiprazole is not indicated in elderly patients with dementia
Clozapine **(Clozaril®)**	Adult	295	• Treatment-resistant schizophrenia
	Pediatrics		• Clozapine is not indicated in pediatric patients
	Geriatrics		• Clozapine should be used with care in the elderly
Lurasidone **(Latuda®)**	Adult	295 296	• Schizophrenia • Depressive Episodes Associated with Bipolar I Disorder
	Pediatrics	295	• Schizophrenia (15-17 years)
	Geriatrics		• Lurasidone is not indicated in elderly patients with dementia
Olanzapine **(Zyprexa®)**	Adult	295 296	• Schizophrenia and Related Disorders[1] • Bipolar Disorder
	Pediatrics		• Olanzapine is not indicated in pediatric patients
	Geriatrics		• Olanzapine is not indicated in elderly patients with dementia
Paliperidone **(Invega®)**	Adult	295	• Schizophrenia and related psychotic disorders[1]
	Pediatrics		• Paliperidone is not indicated in pediatric patients
	Geriatrics		• Paliperidone is not indicated in elderly patients with dementia
Risperidone **(Risperdal®)**	Adult	295 298	• Schizophrenia • Severe Dementia of the Alzheimer Type—Symptomatic Management of Aggression and Psychotic Symptoms in patients with severe dementia of the Alzheimer type

[1] The indications wording is exactly as it appears in Canadian monographs; the monograph do not have any clarification regarding the "related psychotic disorders". However, the DSM IV lists several conditions (Schizoaffective disorder, delusional disorders, brief psychotic disorder, shared psychotic disorder, etc) under the title "schizophrenia and related psychotic disorders" among which only schizophrenia have a specific OHIP billing code.

			• Bipolar Disorder—Mania
		296	
	Pediatrics		• Risperidone is not indicated in pediatric patients
	Geriatrics		• Physicians are advised to assess risks and benefits of the use of risperidone in elderly patients with dementia.
Quetiapine **(Seroquel®)**	Adult	295 296 311	• Schizophrenia • Bipolar Disorder: • Major Depressive Disorder (XR tablets only)
	Pediatrics		• Quetiapine is not indicated in pediatric patients
	Geriatrics		• Quetiapine is not indicated in elderly patients with dementia
Ziprasidone **(Geodon®)**	Adult	295 296	• Schizophrenia • Bipolar Disorder
	Pediatrics		• Ziprasidone is not indicated in pediatric
	Geriatrics		• Ziprasidone is not indicated in elderly patients with dementia

3.4.3 On-label and Off-label Classification

To classify DELPHI patients into on-label, off-label, and reference group, the data in the "Medication" table were investigated to identify those who were prescribed at least one SGA between October 1st, 2005 and December 31st, 2015 (SGA users). Queries were generated to explore the Name fields in the medication table for brand and generic names of SGAs. The outputs from both fields were inspected to confirm true capture of SGA records. When an inconsistency was observed, the priority was given to the field that contained original EMR data. Patients who had no records for any SGA were classified as the "reference" group. SGA users then were classified to on-label or off-label based on the presence of approved indications (Table 3-3) in their history of OHIP codes in the "Billing" table.

For the on-label versus off-label classification, we considered all available history of codes for each patient, regardless of the timing of codes. Therefore, a patient was classified as on-label even if the patient had any of the approved codes after receiving his/her first SGA prescription. This approach was taken for two reasons. Firstly, in EMR data billing codes that are restricted to a certain period of time may not be a complete reflection of patients' medical conditions (76)(77). We hypothesized that providers may use codes for common health conditions more often, or they may record patients' previously diagnosed conditions more frequently and underuse codes for rare or stigmatizing conditions (e.g. Schizophrenia). In this situation, considering a complete history of billing codes would provide a more comprehensive picture of patients' medical conditions than considering a time-restricted history of codes. Secondly, although it was feasible to define an index date for each patient in the SGA users group and

investigate approved codes prior to the index date, it was not possible to define an index date for patients in the reference group. Comparing the distribution of codes prior to the first SGA prescription in the off-label or on-label group to the distribution of all codes in the reference group could potentially be a source of information bias, as the reference group would have more complete data in such a comparison.

3.5 Definition of Variables

Age: The age for each patient was calculated as of December 31, 2015. Although this might have led to some misclassifications, choosing any other time point for age calculations would lead to negative measures for some patients. Three age categories were defined based on current age classification in official drug monographs:

-Children and Adolescents: age less than 18 years
-Adults: age greater than or equal to 18 and less than 65 years
-Seniors: age greater than or equal to 65 years

Age was used as a categorical variable (Children, Adults, Seniors).

Number of visits: The number of visits for each patient was obtained from the billing table in DELPHI. Billing records occurring on the same day were considered one in-office visit. More than one billing record per day was likely due to multiple services related to the same visit.

To calculate the median number of visits per year within each group (on-label, off-label, reference), the total number of visits for each patient in DELPHI was extracted and divided by the period of time (in years) between the first and last visit in DELPHI, and then the median visits were calculated. Interquartile range (IQR) was also calculated for each group. Patients with only one visit were not included in this analysis as the first and last visit in this case would be the same.

Number of first SGA prescriptions: The annual number of first SGA prescriptions were inferred from the data in medication table in DELPHI. This table contains prescribed medications and respective dates. For each patient, the oldest record of any SGA was considered the first SGA prescription, in contrast to subsequent refill prescriptions. There were two limitations regarding this classification: First, some patients switched from one SGA to another during their presence in DELPHI and therefore had two or more starting records, one for each different SGA; in these cases, the oldest record was considered to be the first SGA prescription, and subsequent changes to other SGAs were ignored. Second, the data did not allow us to check for prescriptions started by psychiatrists or other secondary care specialists; it is plausible that a proportion of what we classified as the first SGA prescriptions were in fact refill continuation of treatments that were initiated by specialists at earlier time.

Sex: The sex for each patient was obtained from the "Patient" table in DELPHI. The field "Sex" had only "Female" and "Male" values and no other sex orientation was recorded in DELPHI. The sex was used as a binary variable (male, female).

History of Anxiety: History of anxiety for each patient was modeled as a dummy variable based on the presence or absence of OHIP diagnostic code 300 in the billing records.

History of Attention Deficit and Hyperactivity Disorders (ADHD): History of ADHD for each patient was modeled as a dummy variable based on the presence or absence of OHIP diagnostic code 314 in the billing records.

History of Dementia: History of dementia for each patient was modeled as a dummy variable based on the presence or absence of OHIP diagnostic code 290 in the billing records.

History of Major Depressive Disorder (MDD): History of MDD for each patient was modeled as a dummy variable based on the presence or absence of OHIP diagnostic code 311 in the billing records.

History of Eating disorders, Sleep disorders, Tourette's syndrome: History of mentioned conditions for each patient was modeled as a dummy variable based on the presence or absence of OHIP diagnostic code 307 in the billing records.

History of Post-Traumatic Stress Disorder (PTSD): History of PTSD for each patient was modeled as a dummy variable based on the presence or absence of OHIP diagnostic code 309 in the billing records.

History of Personality Disorder (PD): History of PD for each patient was modeled as a dummy variable based on the presence or absence of OHIP diagnostic code 301 in the billing records.

History of Substance Abuse: History of substance abuse for each patient was modeled as a dummy variable based on the presence or absence of OHIP diagnostic code 304 in the billing records.

3.6 Missing Data

The completeness of the data is an important consideration when analyzing EMR-derived data. As mentioned before, various fields in DELPHI tables have missing data. This might be due to the fact that no data was recorded originally in the EMR. It could also be a function of the way DELPHI was assembled: data is extracted remotely from several different EMRs using a newly developed process, and the data were unified to a common standard. There are sometimes problems ensuring complete data come into the database in a unified way, and errors can arise in recoding algorithms.

In our study, completeness of six data fields was evaluated for our analyses: "DiagnosisCode_calc" and "ServiceDate" in the "Billing" table, "Sex" and "BirthYear" in the "Patient" table, and "Name_calc" and "StartDate" in the "Medication" table. Forty percent of records in the billing table (980,693 out of 2,471,189 records) had missing "DiagnosisCode_calc" (which itself mainly resulted from the missing or invalid values in the DiagnosisCode_orig field), and 7% and 22% of patients in DELPHI had missing sex and birth year, respectively. Data in the "Name_calc" was almost complete with < 0.1% missingness, and data in the "ServiceDate" and "StartDate" were complete with no missing values.

Records with missing diagnosis codes were excluded from our analysis as imputation techniques could not be reasonably used. Missing data on sex and age category, however, were handled using single and multiple imputation techniques. To do this, all recorded procedures and diagnosis (billing) codes in OHIP coding system were investigated to identify sex-distinguishing

conditions and procedures (Table 3-4 and Table 3-5); if a sex-distinguishing condition had an identical code with a non-sex-distinguishing condition, it was excluded from this list: for example, “Dysmenorrhea” and “Stress Incontinence” are both coded 625 in OHIP coding system and therefore could not be used as a sex distinguishing code for imputation. Patients with sex-distinguishing conditions were first imputed by rule-based single imputation.

Table 3-4: Sex-Distinguishing Conditions and Procedures -Female

OHIP Codes	Description
	Pap smear, Pregnancy test, Insert intra-uterine contraceptive device[a]
174, 180, 181, 183, 184	Malignant neoplasm of cervix, ovary or other female organs
218	Uterine fibroid
220	Ovarian cyst
219	Cervical Polyp or other benign neoplasm of uterus
256	Ovarian dysfunction, polycystic ovaries
289	Adenitis cervical
610	Cystic mastitis, fibro-adenosis of breast
614	Salpingitis, oophoritis, or pelvic inflammatory disease
615, 617	Endometriosis
616	Cervicitis, vaginitis, cyst or abscess of Bartholin's gland, vulvitis
618	Cystocele, rectocele, urethrocele, enterocele, uterine prolapse
621	Retroversion of uterus, endometrial hyperplasia, other disorders of uterus
622	Cervical erosion, cervical dysplasia
623	Stricture or stenosis of vagina
626	Disorders of menstruation (amenorrhea, hypermenorrhea or hypomenorrhea or menorrhagia)
627	Menopause, post-menopausal bleeding
628	Female infertility
629	Other disorders of female genital organs
632	Missed abortion
633	Ectopic pregnancy
634	Cystitis or pyelitis during pregnancy
634	Complete or incomplete abortion
635	Therapeutic abortion
640	Haemorrhage in early pregnancy or threatened abortion
641	Abruptio placentae
642	Toxaemia of pregnancy
642	Pre-eclampsia
643	Vomiting as a complication of pregnancy
644	False labour
645	Prolonged pregnancy (post maturity pregnancy)
646	Cervicitis, vulvitis, vaginitis, varicose veins, pelvic inflammatory disease, anemia or other complications during pregnancy
650	Uncomplicated pregnancy or normal delivery
651	Multiple pregnancy
652	Unusual position of fetus
653	Cephalo-pelvic disproportion
653	Abnormal bony pelvis in pregnancy: 653
656	Fetal distress in pregnancy
658	Premature rupture of membranes in pregnancy
660	Obstructed labour
661	Uterine inertia
662	Prolonged labour
664	Perineal lacerations
666	Post-partum haemorrhage
667	Retained placenta
669	Delivery with other complications
671	Post-partum thrombophlebitis
675	Post-partum mastitis
677	Post-partum pulmonary

OHIP Codes	Description
752	Cervical hyperplasia

a: Procedures in DELPHI are recorded by description and have no corresponding code. History of procedures for patients were investigated for sex distinguishing procedures by using procedure descriptions field.

Table 3-5 Sex-Distinguishing Conditions and Procedures -Male

OHIP Codes	Description
-	Vasectomy[a]
175, 185, 186,187	Malignant neoplasm of prostate or other male genital organs
257	Testicular dysfunction
592	Prostate stone
600	Benign prostatic hypertrophy (BPH)
601	Prostatitis
603	Hydrocele
604	Epididymitis, Orchitis
605	Phimosis
606	Male infertility
608	Undescended testicle, seminal vesiculitis or other disorders of male genital organs
609	Newborn circumcision

a: Procedures in DELPHI are recorded by description and have no corresponding code. History of procedures for patients were investigated for sex distinguishing procedures by using procedure descriptions.

The remaining patients with missing sex or age category were imputed using a specific method of multiple imputation called multivariate imputation by chained equations (MICE). MICE is flexible tool in managing missing data and is capable of handling data of different types (e.g. continuous, binary, or categorical) (78).

Unlike single imputation, multiple imputation techniques create multiple complete datasets "based on the observed values for a given individual and the relations observed in the data for other participants, assuming the observed variables are included in the imputation model" (78). In this approach, each missing value is imputed multiple times based on available information in observed data; if available data are not informative regarding the missing variable, each imputation would vary substantially and the model will take into account the uncertainty in the imputations. On the other hand, if the missing value could be well predicted by the available data, the model will yield more coherent imputations and standard errors will be smaller (78).

To select a subset of billing codes as predictors of sex and age category, the frequency of each code were compared across different strata of sex and age category for those with known sex and age. The codes with largest difference in distribution across different strata were assumed to be most predictive and selected as variables to be included in the imputation model. Table 3-6 shows the selected billing codes that were used.

Table 3-6: Conditions Used in the Multiple Imputation Model

OHIP Codes	Description
057	Roseola
079	Viral disease
153	Malignant neoplasm of large intestine (excluding rectum)

OHIP Codes	Description
174	Malignant neoplasm of female breast
212	Benign neoplasm of respiratory system
216	Seborrheic wart or other skin conditions
217	Benign neoplasm of breast
220	Ovarian cyst
226	Benign neoplasm of thyroid
274	Gout
290	Senile dementia
313	Behavior disorders of childhood and adolescence
332	Parkinson's disease
382	Otitis media
401	Essential hypertension
412	Arteriosclerotic heart disease
428	Congestive heart failure
435	Transient cerebral ischemia
455	Hemorrhoids
492	Emphysema
571	Liver cirrhosis
574	Gallstones
585	Acute renal failure
628	Infertility
643	Vomiting as a complication of pregnancy
600	Benign prostatic hypertrophy
640	Threatened abortion
646	Cervicitis, vulvitis, vaginitis, varicose veins, pelvic inflammatory disease, anemia or other complications during pregnancy
669	Delivery with other complications
696	Psoriasis
715	Osteoarthritis
765	Low birthweight infant
766	High birthweight infant
773	Hemolytic disease of newborn
769	Respiratory distress syndrome
777	Perinatal disorders of digestive system
779	Other conditions of fetus or newborn
895	Family planning advice
896	Immunization
916	Well baby care

3.7 Statistical Analyses

We used descriptive statistics and frequency counts to describe the on-label, off-label, and reference groups. We applied Fisher exact tests to compare the frequency of each OHIP billing code between the groups. Due to the large number of comparisons made, the type I error rate was adjusted by Bonferroni-Holm method for multiple comparisons.

The median number of visits per year for patients in the off-label and other groups were also calculated to compare use of primary care services and check for data contribution of each group in the study population.

A logistic regression model was also developed to evaluate the association between the common off-label indications of SGA and a history of billing codes for our off-label and reference groups. The dependent variable was defined as group association (being in the off-label or

reference group), and dummy variables were created for common off-label indications for SGA and used as the independent variables. These indications were identified from previous literature and mapped to OHIP billing codes (Table 3-7). The logistic model was applied to five MICE-created datasets and pooled results are presented in the "Results" chapter.

Table 3-7: Common Off-label Uses of SGAs and Respective OHIP Billing Codes

OHIP Codes	Description
300	Anxiety disorders
314	ADHD
290	Dementia
311	Major depressive disorder
307	Eating disorders, Insomnia, Tourette's syndrome
309	Post-Traumatic Stress Disorder (PTSD)
301	Personality disorders
304	Substance abuse

As part of the data exploration, we also used a multi morbidity tool to investigate what combination of diagnosis are seen more frequently in the off-label group. This tool was developed by M. Bauer and K. Nicholson at The University of Western Ontario (London, Canada) to find either permutations or combinations (ordered clusters or unordered ones) among a sets of diseases (79). We observed that the codes for anxiety disorders and depressive disorders were recorded more frequently than other combinations in the off-label group. Consequently, we decided to use an interaction term for codes 300 and 311 in our regression analysis to assess the interaction effect of both conditions, compared to each condition alone. All age- and sex-stratified analyses presented in the "Results" chapter are derived from complete-case data with originally known birth year and sex. As a sensitivity analysis, the analyses were also applied to each of five imputed sets and findings were reported in the appendix section. The data analyses for this study were conducted using R statistical software, version 3.4.4 on a Linux-gnu operating system.

Chapter 4

4. Results

4.1. Prescription Patterns of Second-Generation Antipsychotics in DELPHI

Between October 1st 2005 and December 31st 2015, there were 52,138 unique patients in the DELPHI database. Of those, 827 (1.5%) had a record for at least one SGA prescription in their list of prescribed medications. Among SGA users, 596 patients (72%) had no history of a diagnostic code for an approved indication in their records and were classified as the off-label group, whereas 231 (28%) patients had a diagnostic code for an approved indication and were classified as the on-label group. The reference group (comparator group) consisted of the 51,311 patients in DELPHI with no record of an SGA prescription (Figure 4-1).

Figure 4-1 Patient Classification in DELPHI Population

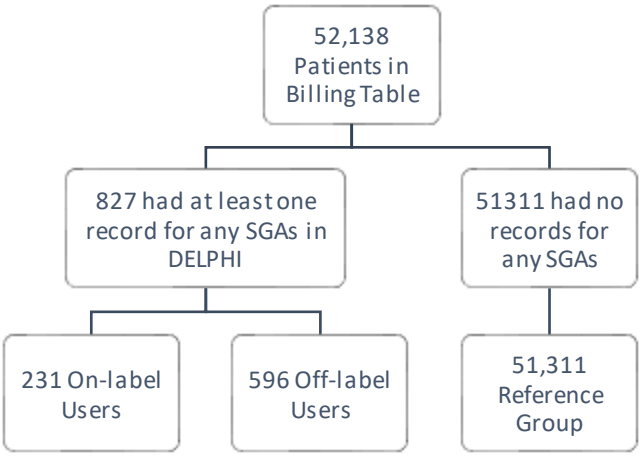


Table 4-1 presents the frequency of first SGA prescriptions recorded in the DELPHI database for the off-label and on-label groups by medication type. The majority of SGA prescriptions were for Quetiapine across both groups (off-label = 69%; on-label = 58%), followed by Risperidone and Olanzapine. These three medications accounted for 96% of all SGA prescriptions. Although Quetiapine and Risperidone prescriptions were more frequent in the off-label group, prescriptions for Aripiprazole were notably more frequent in the on-label group (off-label = 2% vs. on-label = 13%).

Table 4-1: Frequency of First Second Generation Antipsychotic (SGA) Prescriptions by Medication Type

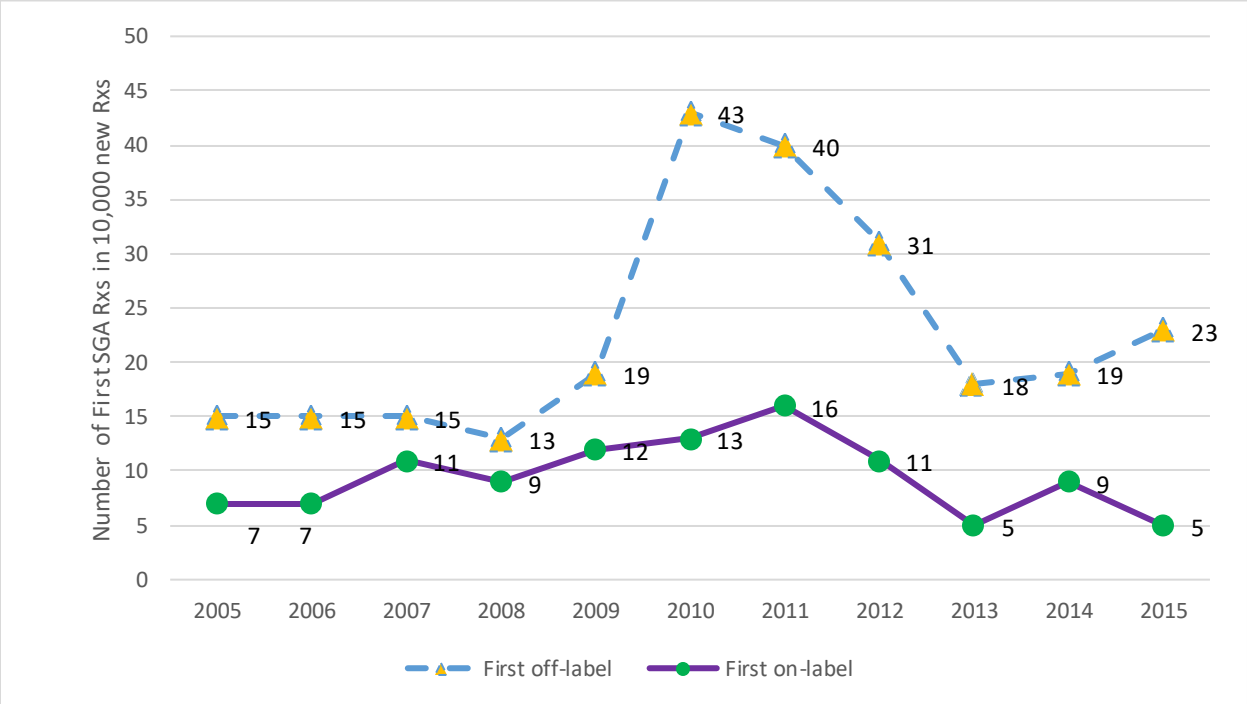
Type of SGA (Year approved in Canada)	Off-Label Group n = 596; n (%)	On-Label Group n = 231; n (%)
Quetiapine (1997)	410 (69%)	133 (58%)
Risperidone (1993)	97 (16%)	31 (13%)
Olanzapine (1996)	67 (11%)	31 (13%)

Aripiprazole (2009)	11 (2%)	31 (13%)
Ziprasidone (2007)	7 (1%)	<6 (<3%)
Paliperidone (2007)	<6 (<1%)	<6 (<3%)
Clozapine (1991)	<6 (<1%)	<6 (<3%)
Lurasidone (2012)	0 (0%)	<6 (<3%)
Asenapine (2011)	0 (0%)	0 (0%)

***Cell sizes less than or equal to 5 suppressed**

To compare the trends in off-label and on-label prescribing over time, the annual number of first SGA prescriptions were divided by total number of first prescriptions in each year. The results are presented in Figure 4-2. In any given year from 2005 to 2015, there was a higher number of first SGA prescriptions in the off-label group compared to the on-label group. In the off-label group, the ratio of first SGA prescriptions is relatively constant between 2005 to 2009 before a sharp increase during 2010, and then it falls gradually between 2011 to 2015. Although the ratio at peak in 2010 (43 per 10,000) is almost 4 times greater than the smallest ratio in 2008 (13 per 10,000) among the off-label group, the trend in the on-label group is more steady with smaller fluctuations over the study period: the ratio increases slowly from 7 per 10,000 in 2005 to 16 per 10,000 in 2011 and then it declines to 5 per 10,000 in 2015.

Figure 4-2: First Off-label and On-label Prescriptions by Year in DELPHI



4.2. Description of the Study Sample

The sex and age of the study sample, by group, are presented in Table 4-2. Across all groups, there were more females than males (off-label: 54% vs. 46%; on-label: 56% vs. 44%; reference: 54% vs 45.9%). In the off-label group, the mean age was 52.5 years (SD: 20.8) and higher than the mean for the on-label (49.4 years, SD: 16.4) and the reference groups (47.4 years, SD: 23.4). Almost half of patients were adults (18 to 64 years) across all groups (off-label = 53.5%; on-label = 51%; reference = 53%). 11% of the

reference group were children (<18 years), whereas only 1.5% of the off-label group were children. There were no children in the on-label group. Nearly 20% of patients in each group were older adults (≥65 years) (off-label = 21%; on-label = 16%; reference = 22%).

Table 4-2: Description of off-label, on-label and reference groups in DELPHI

Group	Characteristics		Frequency (%)
Off-label Users total: 596 Patients	Sex	Male	274 (46%)
		Female	322 (54%)
		Missing	0 (0%)
	Age	Mean (SD)	52.5 years (20.76)
		Range	12-103 years
	Age Distribution	Children and Youth (<18)	9 (1.5%)
		Adult (18-64)	318 (53.5%)
		Seniors (≥ 65)	125 (21%)
		Missing	144 (24%)
On-label Users total: 231 Patients	Sex	Male	101 (44%)
		Female	129 (56%)
		Missing	1 (<1%)
	Age	Mean (SD)	49.4 years (16.4)
		Range	22-89 years
	Age Distribution	Children and Youth (<18)	0 (0%)
		Adult (18-64)	119 (51%)
		Seniors (≥ 65)	37 (16%)
		Missing	75 (33%)
Reference Users total: 51,311 Patients	Sex	Male	23562 (45.9%)
		Female	27712(54%)
		Missing	37 (0.1%)
	Age	Mean (SD)	47.4 years (23.4)
		Range	1-108 years
	Age Distribution	Children and Youth (<18)	5553 (11%)
		Adult (18-64)	27160 (53%)
		Seniors (≥ 65)	11,455 (22%)
		Missing	7143 (14%)

4.3. Comparison of Visit Frequency

The billing records were used to calculate and compare median visit frequency in DELPHI. Age- and sex-stratified results from complete case analysis are presented in Table 4-3 and

Table 4-4.

The median number of visits per year was smaller for patients in the off-label group compared to patients in the reference group (2.1 vs 2.3 visits per year respectively). When results were stratified, male children and adults in the off-label group had a higher median compared to the reference group (male children: 4.0 vs 2.7; male adults: 2.1 vs 1.9). Male seniors in the off-label group had a smaller median (2.7 vs 2.9). For females, adult and seniors in the off-label group had a smaller median of visits per year compared to the reference group (1.9 vs 2.2, and 2.4 vs 2.9 respectively). This analysis was also

performed on each of five imputed datasets and results were generally similar to complete case analysis, with smaller differences in median visit frequencies seen between the off-label and reference groups. Results from analysis on imputed sets are presented in Appendix A. Overall, both off-label and reference groups seemed relatively balanced in terms of visit frequency and amount of data contributed to DELPHI.

Table 4-3 Overall median for visit frequency per patient[a]

	Median number of visits per year	
	Off-label group	**Reference group**
All age categories	2.1 (IQR[b]: 2.8)	2.3 (IQR: 2.9)

[a]Calculated only for those with available birth year and sex data

[b]IQR: interquartile range

Table 4-4 Median visit frequency stratified based on age and sex[a]

	Median number of visits per year			
	Male		**Female**	
	Off-label Group	**Reference Group**	**Off-label Group**	**Reference Group**
Children	4.0 (IQR[b]: 1.5)	2.7 (IQR: 4.2)	-	2.6 (IQR: 4.2)
Adult	2.1 (IQR: 2.7)	1.9 (IQR: 2.4)	1.9 (IQR: 2.8)	2.2 (IQR: 2.4)
Seniors	2.7 (IQR: 3.9)	2.9 (IQR: 3.3)	2.4 (IQR: 1.7)	2.9 (IQR: 3.3)

[a]Calculated only for those with available birth year and sex data

[b]IQR: interquartile range

4.4. Diagnoses Associated with the Off-Label Group

Fisher's exact tests were used to compare the frequency distributions of all recorded diagnostic codes between the off-label users and the reference group. The significance level was adjusted for multiple comparisons using the Bonferroni-Holm method, resulting in a family wise error rate (FWER) of 0.05.

The analyses were stratified by age categories and restricted to those with available birth year (complete case analyses). Within the children and youth age category, we did not find any statistically significant differences in the frequency of diagnostic codes between those with off-label antipsychotic prescriptions and those in the reference group; however, the number of children and youth with off-label prescriptions was very small (n = 9). There were significant differences in the frequencies of several diagnostic codes within both the adult and seniors age categories. The statistically significant results are presented in Table 4-5 and Table 4-6.

For the adult age category, there were 42 significant differences in the frequency of diagnostic codes between the off-label and reference groups, ranging from 1% to 21%. Diagnostic codes for a variety of mental disorders were seen considerably more frequently in the off-label group, including depressive disorders (+21%), anxiety disorders (+12%), and the mixed code for habit spasms, tics, stuttering, tension headache, sleep disorders, anorexia nervosa, enuresis (+10%). Diagnostic codes for acute bronchitis (-10%), immunization (-13%), acute nasopharyngitis (-14%), and annual health examination (-19%) were notably less frequent in the off-label group compared to the reference group. The frequency of alcohol-induced mental disorders, musculoskeletal conditions, disorders of female genital tract, skin conditions, conjunctiva disorders, and digestive symptoms were also significantly different across groups but were generally smaller in magnitude (≤6%).

In the seniors age category, seven significant differences in the frequency of diagnostic codes between the off-label and reference groups were observed. The diagnostic code for dementia was 14% more frequent in the off-label group, whereas the diagnostic codes for hypertension (-19%) and unspecified disorders of back (-11%) were less frequent. Similar to the adult category, diagnostic codes for acute nasopharyingitis (-10%), acute bronchitis (-14%), immunization (-19%), and annual health examination (-21%) were less frequent in the off-label group.

Table 4-5 Fisher's Exact test on diagnosis distributions in off-label and reference groups – Adult (Only statistically significant results are reported, sorted by the difference in prevalence from those most in excess in the off-label group to those most in excess in the reference group.)

Description	Diagnosis Codes	Fisher's Exact Test- p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Depressive disorder, not elsewhere classified	311	<0.001	<0.001	32.7%	11.4%	21
Anxiety, dissociative and somatoform disorders	300	<0.001	<0.001	35.8%	23.5%	12
Habit Spasms, Tics, Stuttering, Tension headache, Sleep disorders, Anorexia nervosa, Enuresis due to mental disorder	307	<0.001	<0.001	13.8%	4.1%	10
Drug dependence	304	<0.001	<0.001	11.0%	2.0%	9
Joint, leg or muscle pain; symptoms involving nervous and musculoskeletal systems	781	<0.001	0.001	22.6%	14.1%	9
Paranoid Personality Disorder; Obessesive Compulsive Personality	301	<0.001	<0.001	6.0%	0.4%	6
Drug-induced mental disorders	292	<0.001	<0.001	5.3%	0.2%	5
Alcohol-induced mental disorders	291	<0.001	<0.001	4.1%	0.2%	4
Specific delays in development	315	<0.001	<0.001	3.8%	0.6%	3
Other disorders of female genital organs	629	<0.001	0.006	3.5%	0.9%	3
Myositis, Muscular Rheumatism, Fibrositic, myositis, muscular rheumatism... , unspecified neuralgia (7292)	729	<0.001	<0.001	4.1%	0.7%	3
Other nonorganic psychoses	298	<0.001	<0.001	2.5%	0.2%	2
Sexual and gender identity disorders	302	<0.001	0.001	2.2%	0.3%	2
Description	Diagnosis Codes	Fisher's Exact Test- p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Erythematous conditions	695	0.003	0.043	3.5%	1.3%	2
Other deficiency anemias	281	0.003	0.039	1.9%	0.4%	1

Unspecified intellectual disabilities	319	0.002	0.033	1.3%	0.2%	1
Dyspareunia, dysmenorrhea, premenstrual tension, stress incontinence	625	0.004	0.049	0.3%	2.6%	-2
Other cellulitis and abscess	682	0.003	0.039	0.3%	2.8%	-2
Contact dermatitis and other eczema	692	0.001	0.017	0.0%	2.3%	-2
Tetanus	37	<0.001	0.006	0.0%	2.7%	-3
Nondependent abuse of drugs	305	<0.001	0.002	0.0%	3.1%	-3
Disorders of conjunctiva	372	0.001	0.011	0.6%	3.9%	-3
Disorders of external ear	380	0.002	0.027	0.3%	2.8%	-3
Sprains and strains of wrist and hand	842	0.001	0.020	0.3%	3.0%	-3
Other diseases due to viruses and Chlamydiae	78	<0.001	0.006	0.9%	4.8%	-4
Inflammatory disease of cervix, vagina, and vulva	616	<0.001	0.008	0.9%	4.7%	-4
Amenorrhea, Hypermenorrhea, Menorrhagia, Oligomenorrhea, Menstruation disorders	626	0.001	0.013	2.5%	7.0%	-4
Atopic dermatitis and related conditions	691	<0.001	0.005	1.3%	5.4%	-4
Hirsutism, scar, or other disorders of skin and subcutaneous tissue	709	0.002	0.027	2.8%	7.0%	-4
Sprains and strains of shoulder and upper arm	840	<0.001	0.001	0.6%	5.0%	-4
Sprains and strains of ankle and foot	845	<0.001	<0.001	0.0%	4.1%	-4

Description	**Diagnosis Codes**	**Fisher's Exact Test- p_value**	**BH adjusted p-value**	**Prevalence in off-label group**	**Prevalence in reference group**	**Difference in prevalence**
Sprains and strains of other and unspecified parts of back	847	0.001	0.013	2.2%	6.5%	-4
Gastritis and duodenitis	535	<0.001	<0.001	0.0%	4.5%	-5
Other and unspecified disorders of back	724	0.003	0.041	7.5%	13.0%	-5
General symptoms including pyrexia of unknown origin, headache, vertigo, ataxia	780	0.001	0.020	3.5%	8.1%	-5

Sprains and strains of knee and leg	844	<0.001	0.001	0.9%	5.7%	-5
Acute sinusitis	461	<0.001	0.001	2.5%	8.6%	-6
Digestive symptoms including anorexia, nausea and vomiting, heartburn, dysphagia, hiccough, hematemesis, jaundice, ascites, abdominal pain, melena, masses	787	0.004	0.050	10.1%	15.8%	-6
Acute bronchitis and bronchiolitis	466	<0.001	<0.001	0.9%	10.7%	-10
Immunization	896	<0.001	<0.001	1.3%	14.2%	-13
Acute nasopharyngitis [common cold]	460	<0.001	<0.001	2.2%	16.5%	-14
Annual Health Examination	917	<0.001	<0.001	10.1%	29.2%	-19

Table 4-6 Fisher's exact test on diagnosis distributions in off-label and reference groups – Seniors (Only statistically significant results are reported, sorted by the difference in prevalence from those most in excess in the off-label group to those most in excess in the reference group.)

Description	Diagnosis Codes	Fisher's Exact Test- P_value	BH Adjusted P-value	Prevalence in Off-label Group	Prevalence in Reference Group	Difference in Prevalence
Dementias	290	<0.001	<0.001	19.2%	5.3%	14
Acute nasopharyngitis [common cold]	460	0.001	0.038	4.8%	15.1%	-10
Other and unspecified disorders of back	724	<0.001	0.010	4.8%	16.3%	-11
Acute bronchitis and bronchiolitis	466	<0.001	<0.001	0.8%	15.2%	-14
Essential hypertension	401	<0.001	0.003	32.0%	50.9%	-19
Immunization	896	<0.001	<0.001	0.8%	19.7%	-19
Annual Health Examination	917	<0.001	<0.001	7.2%	27.8%	-21

The Fisher's exact tests were also performed on each of five datasets with imputed age values to include patients with missing birth year data. The statistically significant results are presented in appendix B. In the adult category, results in all five imputed sets were largely consistent with the complete case analysis; nevertheless, in two imputed sets, cardiovascular symptoms (including chest pain, tachycardia, syncope, etc.) were 4% more prevalent in the off-label group, unlike the complete case analysis.

In the seniors category, 39 to 44 statistically significant differences were detected. In all five imputed sets, the difference in prevalence of anxiety disorders was the highest between the off-label and the reference groups (25% to 26% more prevalent in the off-label group). The difference for dementia was the second highest (19% to 20% more prevalent in the off-label group). Unlike the results from the complete set, a substantial difference in the prevalence of cardiovascular symptoms was seen in all five imputed sets. This condition was 16% to 18% more prevalent in the seniors category, in the off-label group, and in all imputed sets.

In the children category, although the analysis on complete set did not reveal any significant difference, a few differences are evident when the analysis was performed on imputed sets: hyperkinetic syndrome of childhood (ADHD) was 21% to 38% more frequent in the off-label group, in four out of the five imputed sets, whereas the code for well-baby care visits was 49% to 50% less frequent in the same group in all five imputed sets. The analysis on imputed sets also showed differences in some conditions that are specific to adults (e.g. "Menopausal and postmenopausal disorders") or are uncommon in children (e.g., benign neoplasm of skin or disorders of back). Although various age-specific conditions were selected for the imputation process and to avoid age misclassification, such results show that some error was introduced into our imputation process.

4.5. Factors Associated with Off-Label Use of Second Generation Antipsychotics

Univariate and multivariate regression models were used to estimate the association between off-label use of SGAs and conditions most commonly reported to be off-label indications for SGAs in the literature. The multivariate models were fit to each MICE-imputed dataset, and results from all sets were pooled together using the standard Rubin's Rules. The odds ratios (OR), 95% confidence intervals (95% CI), and frequency distributions of each covariate for the univariate and multivariate models are presented in Table 4-7.

The multivariate models suggest that anxiety disorders (OR = 2.7, 95% CI = 2.2, 3.3), senile dementia (OR = 5.02, 95% CI = 3.6, 7.0), depressive disorders (OR =3.9, 95% CI = 3.0, 5.1), personality disorders (OR = 9.2, 95% CI = 5.8, 14.7), and drug abuse (OR = 3.43, 95% CI = 2.5, 4.7) were associated with a higher odds of being in the off-label group, controlling for other covariates. Children and youth had a lower odds of being in the off-label group (OR = 0.3, 95% CI = 0.2, 0.5). Sex, adjustment reactions (PTSD), and hyperkinetic syndrome of childhood (ADHD) were not significantly associated with being in the off-label group in either the unadjusted or fully adjusted models.

Our multivariate models also suggest a significant interaction between depressive and anxiety disorders. The interaction term was significant showing that the OR of being in the off-label group for patients with either of anxiety disorders or depressive disorders depends on the level of the other condition: for those

with no history of anxiety disorders (300-0), the OR (311-1/311-0) would be equal to 3.89 while for those with a history of anxiety disorders (300-1), the OR (311-1/311-0) would be 3.89 * 0.43 = 1.67. (Note that comparing the group having codes for both anxiety and depressive disorders to the group who has neither gives an OR for (300-1,311-1/300-0,311-0) of 3.89 * 0.43 * 2.68 = 4.48.).

Table 4-7: Factors associated with off-label use of SGAs

Characteristics/ Common off-label uses of SGAs	Frequency in the off-label group (%)	Frequency in the reference group (%)	Univariate OR (95% CI)	Adjusted[a] Multivariate OR (95%CI)
Sex				
- Female	322[b] (54%)	27726 (54%)	1	1
- Male	274 (46%)	23585 (46%)	1(0.85-1.18)	1.15 (0.97-1.35)
Age				
- Adult	382 (64%)	30595 (60%)	1	1
- Youth and Children	15 (3%)	7187 (14%)	0.17 (0.1-0.27)	0.26 (0.15-0.45)
- Seniors	199 (33%)	13529 (26%)	1.18 (0.99-1.4)	1.12 (0.89-1.41)
300-Anxiety Neurosis, Claustrophobia, Obsessive Compulsive Neurosis, Suicide Tendencies, reactive depression, neurasthenia	260 (44%)	10653 (21%)	2.95 (2.51-3.48)	2.68 (2.2-3.26)
314- Hyperkinetic Syndrome of Childhood	11 (2%)	538 (1%)	1.77 (0.91-3.08)	1.64 (0.87-3.08)
290- Senile dementia, presenile dementia	56 (9%)	780 (2%)	6.72 (5.01-8.85)	5.02 (3.64-6.93)
311- Depressive or Other Non-Psychotic Disorder not classified elsewhere	159 (27%)	4516 (9%)	3.77 (3.13-4.52)	3.89 (2.97-5.08)
309-Adjustment Reaction	12 (2%)	956 (2%)	1.08 (0.58-1.84)	0.66 (0.37-1.19)
301- Personality Disorders (Obsessive Compulsive, Paranoid, Schizoid)	24 (4%)	182 (<1%)	11.79 (7.46-17.82)	9.24 (5.81-14.69)
304 - Drug Abuse	47 (8%)	836 (2%)	5.17 (3.76-6.94)	3.43 (2.49-4.71)
300*311 interaction term			-	0.43 (0.3-0.63)

a: ORs are adjusted for sex, age and diagnoses codes 300 (Anxiety Neurosis, Claustrophobia, Obsessive Compulsive Neurosis, Suicide Tendencies, reactive depression, neurasthenia), 314 (Hyperkinetic Syndrome of Childhood), 290 (Senile dementia, presenile dementia), 311 (Depressive or Other Non-Psychotic Disorder not classified elsewhere), 309 (Adjustment Reaction), 301 (Personality Disorders: Obsessive Compulsive, Paranoid, Schizoid), 304 (Drug Abuse).
b: Frequency for sex and age categories are presented based on the first imputed set

Chapter 5

5 Discussion

5.1 Prevalence of Off-Label SGA Use

Over the ten-year study period, 1.5% of patients in DELPHI had records for at least one SGA prescription, and 72% of SGA users had no diagnostic record for approved indications. Our estimate of off-label use of SGAs was remarkably higher than what has been found in a comparable study in Quebec (43.8%) (9). The study by Eguale et al. was focused on 50,823 adult patients between 2005 to 2009 and was conducted in the primary care setting, similar to the current study. Their data were derived from an indication-based prescribing system that allowed for accurate and explicit recording of treatment indication for each written prescription. In the Eguale et al. study, however, antipsychotic agents were analysed as a single class and were not sub-categorized to first and second generation. This might be related to the lower estimate reported in their study as it has been argued that compared to SGAs, first generation agents were perceived to have higher risks of adverse events (20); consequently, this may have led to less frequent off-label use of first generation antipsychotics and a lower overall estimate. Nevertheless, we may have overestimated the prevalence, as our measurement of off-label use was mainly inferred based on history of medical records whereas Eguale's study had a more accurate data on the indication for each prescription.

Our estimate of off-label use (72%) was also higher than Chen et al. (2006) found in a somewhat different setting in Medicaid enrollees in Georgia in US. They found that 63.6% of 33,406 antipsychotic recipients among Medicaid enrollees (18 years or older) received at least one antipsychotic for an off-label indication in 2001 (54). Although they used the same classification system to map to approved indications and to match with claim records as in the current study, their patient population was not limited to primary care patients and included claims from physicians, pharmacies, hospitals, and nursing homes. Within this study, the antipsychotic class-specific proportion of off-label use was not presented and instead the overall proportion for both first- and second-generation antipsychotics was reported. However, based on their report on top five prescribed antipsychotics, nearly 80% of total prescribed antipsychotics were for risperidone, olanzapine, and quetiapine, which suggest a significant portion of their estimate might have been related to those three second generation agents.

The high prevalence of off-label use seen in our study, and in the previous literature, could be related to the lack of safe, effective, and approved treatments, as well as barriers regarding developing new medications for psychiatric disorders. Specifically: a) many psychiatric conditions are not yet well researched and understood; b) animal models are less applicable in psychiatry (80); and c) patients may not map to defined criteria and definitive and differential diagnosis is often hard to reach (36,80). Consequently, the design and conduct of trials to demonstrate the efficacy of psychotropic medications is challenging and many psychiatric conditions currently lack approved treatments (81). Moreover, manufacturers of current medications are often reluctant to conduct costly new trials with the hope of obtaining supporting evidence and follow time consuming regulatory procedures to add new indications to medication labels, especially once their medication is already in the market and could be prescribed off-label by prescribers (3,54).

In the children and youth category, only a small number of patients were prescribed any SGAs in our data (n=9), and none had history of diagnosis for an approved indication. Prevalent off-label use of SGAs in children has been reported in previous literature. As argued by Chen (2006), extensive off-label use of central nervous system medications in pediatric populations largely results from practical challenges and ethical limitations of conducting trials in this population (54). In a recent study in the US, Sohn et al. (2016) investigated national trends in the off-label use of SGAs in children and adolescent outpatient visits. Their findings suggest that among all visits in which a SGA was prescribed, 65% of the prescriptions were for a non-approved indication (82).

In our data, 96% of first SGA prescriptions were for quetiapine, risperidone, and olanzapine in the off-label group (69%, 16% and 11% respectively). Similar patterns have been reported in previous literature, suggesting that that older SGAs tend to be prescribed off-label more frequently (9) perhaps because they are better known and/or perceived safer in medical community compared to newer and less er known agents.

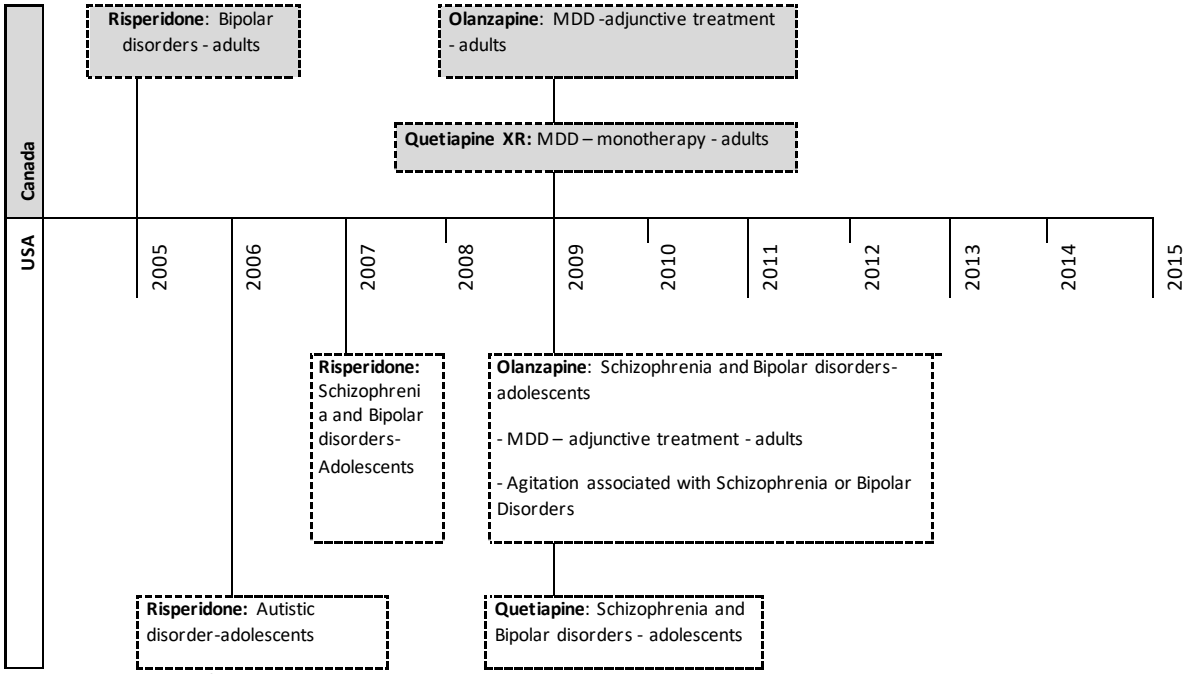
Similarly, Peringsheim et al. (2014) studied dispensed SGA prescriptions in Canada between 2005 to 2012 using pharmacy data, and reported that quetiapine, risperidone, and olanzapine were the most commonly prescribed antipsychotics by primary care physicians in the study period. They reported those three agents accounted for 80% of all SGA prescriptions (23). In another study, Alexander et al. (2011) used survey data from a random sample of office-based physicians in the US and reported quetiapine, risperidone, and olanzapine among the top four antipsychotics prescribed in 2008 (55). These three agents are also the most commonly prescribed antipsychotics for children and youth (≤ 18 years). Ronsley et al. (2013) reported that in 2010/11, 5,791 youths received antipsychotics in British Columbia and 96.1% of all antipsychotic prescriptions were for risperidone (48.0%), quetiapine (36.2%), and olanzapine (5.9%)(27). Alessi et al. (2012) also reported similar frequencies for over 2,100 youth in Manitoba (56).

Although a wide range of estimates of off-label use of SGAs have been previously reported across various clinical settings, our findings are largely in agreement with other studies, which suggest that off-label use of SGAs is prevalent in primary care practice.

When we looked at the trend in SGA prescriptions over time, we observed that off-label users outnumbered the on-label users in any given year between 2005 to 2015. Off-label prescriptions had a relatively constant ratio of 15 per 10,000 first prescriptions for a period of four years (2005 to 2009) before it nearly tripled to 43 per 10,000 during 2010. The ratio then gradually decreased to 23 per 10,000 in 2015. The sharp increase observed was primarily driven by first Quetiapine users, whereas first Olanzapine and Risperidone users had less contribution to the observed peak and decline. A 300% increase in quetiapine prescriptions in primary care was previously reported between 2005 to 2012 by Pringsheim (23), however the increase in that study was gradual with a relatively constant slope and no peak as observed in the current study. In contrast to the first off-label prescriptions, the trend in the on-label group was relatively flat with small fluctuations. It is not entirely clear why the number of first off-label users increased rapidly during 2010 and declined thereafter. Regional and public mental health awareness campaigns in that time period is one factor that could potentially have contributed to the increasing trend. SGA regulatory related events or industry-sponsored promotional programs could be other potential contributing factors.

The increasing trend of first off-label users might be related to the approval updates for SGAs by the US FDA or Health Canada (Figure **5-1**). Quetiapine was approved for bipolar disorders and MDD (for XR tablets) in adults in 2008 and 2009 respectively by Health Canada and for schizophrenia and bipolar disorders in adolescents in 2009 by the US FDA. Olanzapine also received similar approval updates in 2009 by the US FDA. Although it is expected that these regulatory updates would have largely led to an increase in the first on-label prescriptions, the major increase occurred in the first off-label users during 2010. One potential explanation for the observed peak in the first off-label users could be due to a high proportion of first Quetiapine users, who may have been prescribed regular tablets (instead of XR type) for MDD and consequently, they were classified as off-label in our analysis. Pharmaceutical promotional and advertisement activities could be another potential factor that contributed to the observed peak. Following the new approvals, the license holders often run awareness campaigns for prescribers which could potentially increase prescriptions for off-label uses as well. As discussed previously in the second chapter, regulations and policies regarding promotions of off-label use are not always well defined or enforced (3).

Figure 5-1 Health Canada and US FDA approval Updates from 2005 to 2015



Approvals prior and after our study period are not shown in this timeline

MDD: Major Depressive Disorder

Literature regarding the trends over time in the use of SGAs are limited beyond 2010 – of existing studies, none show the gradual decline that we observed between 2010 and 2015. Similar to the increasing phase, the decline phase was mainly affected by quetiapine users. The trend we observed was also related to prescribing patterns among adults and the seniors, as our data had very few children and youth. Overall, the increasing trend for off-label use of SGAs between 2005 to 2015 seems to be similar to the overall trend for the off-label use of SGAs in children and youth in Canada (27).

The proportion of female SGA users was slightly higher than male users across both off-label and on-label groups in our sample, perhaps because some mental disorders are more prevalent in women (83),

and women are generally more likely to seek health care than men. In our data, adult and senior females in the off-label group generally had a smaller median number of visits per year than their male counterparts, whereas in the reference group the opposite was true. We investigated the median number of visits to see if any of the groups lacked data compared to others, but the difference was relatively small (between 0 to 4 visits per 10 years) and did not suggest any significant imbalance in visit frequency for adult and senior patients. Our data for children was very limited.

5.2 Diagnoses Associated with Off-label Prescriptions

We found that the frequencies of some diagnostic codes were significantly different across the off-label and reference groups. Codes for depressive and anxiety disorders were seen considerably more frequently in the adult off-label users (+21% and +12% respectively). A mixed code for habit spasms, tics, stuttering, tension headache, sleep disorders, anorexia nervosa, and enuresis was also seen more frequently in the same group (+10%). In the senior age category, the code for dementia (+14%) and cardiovascular symptoms (+4%) were more frequent in the off-label group. In the children and youth category, ADHD was 21% to 38% more frequent in the off-label group. The association between these conditions and the off-label use of SGAs may suggest that SGAs were prescribed with the intention to treat the above conditions in primary care. Consistent with our findings, previous literature has reported the following conditions as off-label uses of SGAs: depression, obsessive compulsive disorder, personality disorders, post-traumatic stress disorder, Tourette syndrome, behavioral problems in patients affected by dementia, autism, anxiety, ADHD, eating disorders, insomnia, and substance abuse (55,63).

Although the associations observed do not reveal the actual indications for off-label use of SGAs in the study population, they do suggest potential indications of SGAs, common co-morbidities of the off-label users, or potential consequences of SGA use. Codes with lower frequency in the off-label group (e.g. immunization, acute bronchitis, annual health examination, unspecified disorders of back, well baby care visits) might show a lower access to care at some period in life or indicate a lower intention to seek care for perceived minor conditions in presence of mental conditions (e.g. depression). Additionally, prescribers' coding behaviour may also have a role in the observed difference, as prescribers tend to record chronic conditions more often than codes for routine visits.

Our multivariate model also confirmed that history of anxiety disorders, senile dementia, depressive disorders, personality disorders, and drug abuse were strong predictors for the likelihood of being in the off-label group, after controlling for other covariates. Antipsychotics are commonly used off-label for dementia, which is characterized by cognitive decline and memory loss and often associated with non-cognitive neuropsychiatric symptoms like disordered mood, psychosis, inappropriate behavior, and motor symptoms (84). Among several medication classes used in dementia (antipsychotics, anxiolytics, antidepressants, anticonvulsant and mood stabilizers), antipsychotics seem to have better evidence in controlling these intrusive and debilitating symptoms (84). Risperidone, Olanzapine and Aripiprazole bring small but statistically significant benefit for these patients, whereas the evidence for Quetiapine is inconclusive (63,85). On the other hand, their risk profile is broad and brings major concerns. The use of SGAs in this population is shown to be associated with an increased risk of stroke, cardiac events, and mortality (33,84). The US FDA issued a black box warning regarding this in 2005, which was endorsed in

the same year by Health Canada (86,87). However, subsequent research in the US showed that the FDA warning has not led to major change in prescription patterns of antipsychotics among seniors with dementia (88,89). The fourth Canadian consensus conference on the diagnostic and treatment of dementia published a recommendation for family physicians stating that Risperidone, Olanzapine, and Aripiprazole should be considered for severe agitation, aggression and psychosis associated with dementia when there is a risk of harm to the patient or others and when the non-pharmacologic treatments were not effective. They graded this recommendation as a weak or conditional recommendation based on high-quality evidence (90). The latest American Psychiatric Association (APA) practice guideline on this subject also has a similar recommendation (85).

Depression and anxiety disorders are prevalent psychiatric disorders that are both initially treated with two main class of medications as the first line options: selective serotonin and serotonin norepinephrine reuptake inhibitors (SSRIs and SNRIs) (91). However, nearly 50% of patients with depressive disorders or anxiety disorders fail to respond to the first line antidepressant and anti-anxiety medications (92,93). Due to their effects on the serotonin system ($5HT_1A$ and $5HT_2A$ receptors), some SGAs have been seen as alternative options in refractory cases (91). The evidence currently available on their effectiveness in clinic varies, however. According to the AHRQ report, a moderate level of evidence suggests Olanzapine is not effective as monotherapy in depression and anxiety (GAD), whereas Quetiapine has been shown to be effective in some placebo-controlled trials. Risperidone and other SGAs were either not effective or were not examined in clinical trials (63). The Canadian Network for Mood and Anxiety Treatments (CANMAT) guideline for the management of anxiety and related disorders states that SGAs are considered as second-line, third-line, or adjunctive therapies in various anxiety disorders due to the risk profile (risk of diabetes, weight gain, etc.), limited available randomized trial data and lack of clinical experience with them (94). The CANMAT guideline on management of adults with MDD (95) do not recommend monotherapy with SGAs but reports that adjunctive use of aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone were shown to have small to medium effect sizes in Treatment-Resistant Depression (TRD) and these agents may be used as adjunctive options. Although the level of evidence regarding this indication varies for SGAs, these agents generally have the most consistent evidence for efficacy in TRD. These findings were based on four independent meta-analyses (96–99) and a randomized clinical trial (100). The guideline suggests that the decision between switching to another antidepressant agent or adding an adjunctive agent (SGAs or other adjunctive agents) should be individualized and based on several clinical factors (95).

The off-label use of SGA for personality disorders[6] lies in the fact that some of these disorders (paranoid personality disorder, schizotypal personality disorder, borderline personality disorder, etc.) and schizophrenia can share some common symptoms (e.g. delusions, hallucinations, disorganized speech, etc.) (101,102) which are targeted by antipsychotics. Among ten personality disorders defined in DSM-5 (102), SGAs are only studied in schizotypal and borderline personality disorders. According to the AHRQ updated review, Aripiprazole and Quetiapine have been shown to be effective, whereas Olanzapine and

[6] Personality disorders are a class of mental disorders characterized by enduring maladaptive patterns of behavior, cognition, and inner experience, exhibited across many contexts and deviating from those accepted by the individual's culture. These patterns develop early, are inflexible, and are associated with significant distress or disability (ref: DSM-5)

Risperidone have shown mixed results, all based on low and very low strength of evidence (63). There is no approved medication available for this group of disorders yet.

SGAs are used off-label for substance abuse disorders, although current literature in this area is very limited (63). For cocaine and amphetamine abuse, animal studies have shown conflicting results on the role of both first and second generation antipsychotics, but suggested that Clozapine (a SGA) may decrease cocaine and amphetamine self-administration (103–106). Use of Clozapine, one of the most effective SGAs, however, is limited in humans due to a potentially fatal agranulocytosis side effect. Few available human trials on the use of other SGAs have shown that Olanzapine, Risperidone, and Aripiprazole might be ineffective in treating cocaine and amphetamine abuse or dependence (107–109). Aripiprazole and Quetiapine also seem ineffective in treating alcohol dependency (109).

5.3 Strengths of the Study

This study was the first in Ontario to describe the off-label use of SGAs among primary care patients. The study was not limited to a certain antipsychotic agent or a certain age category, which has been the case in previous studies. We included all available SGAs and all age categories to provide a wider and more comprehensive description of off-label use in primary care.

Using electronic medical record data and having access to a large sample of patients made it possible to study SGA users who typically comprise less than five percent of primary care patient population.

5.4 Limitations of the Study

One major limitation of the current study was our inability to capture the diagnosis associated with a SGA prescription within our data source. This limitation arises through several pathways.

Firstly, we were not able to obtain information on visits to psychiatrists. It is possible that a proportion of patients who were assigned to the off-label group were originally prescribed a SGA for an approved indication by a psychiatrist, but the indication was not accurately reflected in the primary care EMR data. Although this might have potentially led to an overestimation of off-label use in primary care, the low frequency of referrals to psychiatrists among off-label users (2%) suggest that this is unlikely to substantially change our estimates.Second, we were not able to differentiate between providers' failure to record a diagnosis and a true lack of a diagnosis or health condition. Providers may have had a different coding behaviours in regards to stigmatized diagnosis (like Schizophrenia) or when patient's symptoms did not meet the complete diagnostic criteria. Physician performance in filling and recording problem lists, chronic disease lists, reason for each visit, and diagnosis for each visit ultimately shapes our data and determines how accurate and detailed the information is that is available to us. Physicians were also limited to record one billing code per visit for each patient and this might also have contributed to the partial recordings of health conditions. However, the on-label and off-label categorization we used considered all recorded diagnoses for each patient, instead of relying on single diagnosis associated with an encounter or within a certain time frame, which may reduce misclassification.

Lastly, our methodology had also limitations in terms of missing data handling, age determination and code assignment to approved indications.

5.5 Implications for Practice

The findings of this study add to the limited body of literature in this area and describe the extent of and trends in off-label use of SGAs, as well as the off-label indications in primary care. From a policy perspective, it is important to promote the evidence-based prescription of medications in practice. Findings from this study indicate that further research is required to produce evidence and fill current evidence gaps especially in regards to the efficacy of SGAs in off-label uses. There might also be a need to develop educational programs to communicate the widespread off-label use of SGAs in diverse populations, as well as to address a potential lack of evidence on their effectiveness and risk of adverse events to the primary care prescribers. Moreover, policymakers and public payers may draw on prior authorization or preferred medication list policies, if available, to alter their prescription pattern of SGAs toward evidence-supported agents. That said, the fundamental challenge is how to address the lack of evidence and determine who should produce evidence, and how, for a multitude of off-label uses in diverse populations and for less well-known mental conditions with low prevalence. Within the current framework, the pharmaceutical industry has little incentive to conduct costly trials after receiving initial approvals, and government research institutions have limited ability to assess numerous off-label uses. The regulator, on one hand, is wisely strict on evidence requirements for medication approvals, while on the other hand there is little control on off-label use of medications in practice. Regardless of whether the former is too restrictive or the latter is too relaxed and lenient, off-label users often lack evidence-based treatments, and this challenge remains to be resolved.

Further efforts in updating policies and exploring innovative solutions are required to enhance the evidence of off-label uses of SGAs. One potential solution may be fostering and expanding the use of real-world data and evidence (110) for safety and effectiveness assessments: If an evidence-based treatment is not available, policymakers can encourage new patient–provider encounters within the EMR framework in such a way that efficacy and safety indicators are defined, monitored, and recorded specifically in each follow-up for each off-label SGA order. Although there would be important methodological limitations to inferring data from such solutions, advances in study designs and statistical methods may support the acceptability of this approach (111).

5.6 Conclusions

The off-label use of SGAs is common in practice, and concerns have been raised regarding their safety and effectiveness in unapproved uses. Our study described patients who were prescribed SGAs with no history of approved indications in primary care in southwestern Ontario, and explored their history of diagnoses between 2005 to 2015 using EMR data. This study found that every 3 out 4 SGAs prescriptions in primary care may be prescribed for off-label indications, and in any given year in the study period SGAs are being prescribed more for off-label than on-label indications. Anxiety, depression, dementia, personality disorders, and drug addiction seem to be common off-label uses for SGAs and were significantly associated with the off-label group, when controlling for other covariates. Off-label prescribing of SGAs seems to have preceded the existence of compelling and supporting evidence on relevant effectiveness and safety. These findings are in agreement with previous literature from other provinces and outside of Canada.

Based on the findings of this study and the previous literature, further research is needed to produce evidence on comparative effectiveness and safety in various clinical populations. Policy makers are encouraged to facilitate and incentivize new psychotropic medication development to address the unmet need for safe and effective treatments for various mental disorders. Primary care physicians are also encouraged to follow evidence-based practice standards.

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7 Appendices

7.1 Appendix A

The tables in this section represent the median visit frequencies of the off-label and reference groups for each of the five imputed sets. These analyses were performed to include patients with missing birth year and sex. Imputation sets are obtained by single and multiple imputation techniques which are described in detail in chapter 3.

Table A-1 Median visit frequency stratified based on age and sex – Imputed Set 1

	Median number of visits per year -Set1			
	Male		Female	
	Off-label Group	Reference Group	Off-label Group	Reference Group
Children	4.2 (IQR[a]: 5.3)	2.9 (IQR: 4.3)	6.7 (IQR: 6.3)	2.9 (IQR: 4.4)
Adult	2.3 (IQR: 3.5)	2.0 (IQR: 2.5)	2.3 (IQR: 3.7)	2.3 (IQR: 2.5)
Seniors	5.6 (IQR: 7.1)	3.1 (IQR: 3.6)	3.5 (IQR: 8.6)	3.2 (IQR: 3.7)

[a]IQR: interquartile range

Table A-2 Median visit frequency stratified based on age and sex – Imputed Set 2

	Median number of visits per year -Set2			
	Male		Female	
	Off-label Group	Reference Group	Off-label Group	Reference Group
Children	4.0 (IQR[a]: 3.7)	2.9 (IQR: 4.3)	5.0 (IQR: 1.8)	3.0 (IQR: 4.5)
Adult	2.4 (IQR: 3.5)	2.0 (IQR: 2.5)	2.3 (IQR: 3.7)	2.3 (IQR: 2.6)
Seniors	5.3 (IQR: 7.2)	3.1 (IQR: 3.6)	3.6 (IQR: 7.9)	3.2 (IQR: 3.6)

[a]IQR: interquartile range

Table A-3 Median visit frequency stratified based on age and sex – Imputed Set 3

	Median number of visits per year -Set3			
	Male		Female	
	Off-label Group	Reference Group	Off-label Group	Reference Group
Children	2.5 (IQR[a]: 2.1)	2.9 (IQR: 4.3)	11.6 (IQR: 3.1)	3.0 (IQR: 4.5)
Adult	2.2 (IQR: 2.9)	2.0 (IQR: 2.5)	2.2 (IQR: 3.7)	2.3 (IQR: 2.6)
Seniors	5.7 (IQR: 7.2)	3.1 (IQR: 3.6)	3.5 (IQR: 8.2)	3.2 (IQR: 3.7)

[a]IQR: interquartile range

Table A-4 Median visit frequency stratified based on age and sex – Imputed Set 4

	Median number of visits per year -Set4			
	Male		Female	
	Off-label Group	Reference Group	Off-label Group	Reference Group
Children	4.2 (IQR[a]: 5.3)	2.9 (IQR: 4.3)	6.7 (IQR: 2.5)	3.0 (IQR: 4.4)
Adult	2.3 (IQR: 3.5)	2.0 (IQR: 2.5)	2.2 (IQR: 3.7)	2.3 (IQR: 2.6)
Seniors	4.0 (IQR: 7.3)	3.1 (IQR: 3.5)	4.0 (IQR: 8.2)	3.2 (IQR: 3.6)

[a]IQR: interquartile range

Table A-5 Median visit frequency stratified based on age and sex – Imputed Set 5

	Median number of visits per year -Set5			
	Male		Female	
	Off-label Group	Reference Group	Off-label Group	Reference Group
Children	3.9 (IQR[a]: 3.7)	2.9 (IQR: 4.3)	6.7 (IQR: 5.4)	2.9 (IQR: 4.4)
Adult	2.3 (IQR: 3.6)	2.0 (IQR: 2.5)	2.3 (IQR: 3.7)	2.3 (IQR: 2.6)
Seniors	4.5 (IQR: 7.4)	3.1 (IQR: 3.6)	3.4 (IQR: 7.3)	3.2 (IQR: 3.7)

[a]IQR: interquartile range

7.1 Appendix B

The tables in this section compares the distribution of diagnosis codes between the off-label and reference groups for each of the five imputed sets. These analyses were performed to include patients with missing birth year and sex. Imputation sets are obtained by single and multiple imputation techniques which are described in detail in chapter 3.

Table B-1 Fisher's Exact test on diagnosis distributions in off-label and reference groups – Imputed Set 1 - Children (Only statistically significant results are reported, sorted by the difference in prevalence from those most in excess in the off-label group to those most in excess in the reference group.)

Description	Diagnosis Codes	Fisher's Exact Test-p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Well Baby Care	916	<0.001	0.034	6.7%	55.9%	-49

Table B-2 Fisher's Exact test on diagnosis distributions in off-label and reference groups – Imputed Set 1 - Adult (Only statistically significant results are reported, sorted by the difference in prevalence from those most in excess in the off-label group to those most in excess in the reference group.)

Description	Diagnosis Codes	Fisher's Exact Test-p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Depressive disorder, not elsewhere classified	311	<0.001	<0.001	31.2%	11.1%	20
Anxiety, dissociative and somatoform disorders	300	<0.001	<0.001	43.2%	23.8%	19
Neuroses and Personality Disorders including Sleep disorders, Tension Headache, Habit Spasms, Enuresis due to mental disorder, Anorexia Nervosa	307	<0.001	<0.001	14.1%	4.2%	10
Drug dependence	304	<0.001	<0.001	10.2%	1.8%	8
Joint, leg or muscle pain; symptoms involving nervous and musculoskeletal systems	781	<0.001	0.003	22.3%	14.8%	8
Drug-induced mental disorders	292	<0.001	<0.001	4.7%	0.2%	5
Paranoid Personality Disorder; Obessesive Compulsive Personality	301	<0.001	<0.001	5.5%	0.4%	5
Myositis, Muscular Rheumatism , Fibrositic, myositis, muscular rheumatism... , unspecified neuralgia (7292)	729	<0.001	<0.001	5.8%	1.0%	5
Alcohol-induced mental disorders	291	<0.001	<0.001	3.4%	0.2%	3
Specific delays in development	315	<0.001	<0.001	3.4%	0.5%	3

Description	Diagnosis Codes	Fisher's Exact Test-p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Migraine	346	<0.001	0.018	5.5%	2.5%	3
Symptoms involving urinary system	788	<0.001	0.011	4.7%	1.9%	3
Other nonorganic psychoses	298	<0.001	<0.001	2.6%	0.2%	2
Sexual and gender identity disorders	302	<0.001	0.003	1.8%	0.3%	2
Alcohol dependence syndrome	303	<0.001	<0.001	2.9%	0.6%	2
Other disorders of female genital organs	629	<0.001	0.005	3.1%	0.9%	2
Other and unspecified anemias	285	<0.001	0.014	1.8%	0.4%	1
Tetanus	37	<0.001	0.004	0.0%	2.4%	-2
Acute tonsillitis	463	0.003	0.049	0.3%	2.3%	-2
Disorders of conjunctiva	372	0.003	0.048	1.6%	4.6%	-3
Gastritis and duodenitis	535	<0.001	0.004	1.0%	4.8%	-4
Amenorrhea, Hypermenorrhea, Menorrhagia, Oligomenorrhea, Menstruation disorders	626	0.002	0.034	3.7%	7.8%	-4
Atopic dermatitis and related conditions	691	0.001	0.028	2.4%	6.0%	-4
Hirsutism, scar, or other disorders of skin and subcutaneous tissue	709	<0.001	0.011	2.4%	6.4%	-4
Other diseases due to viruses and Chlamydiae	78	<0.001	0.001	1.0%	5.2%	-4
Family Planning	895	0.001	0.028	5.0%	9.5%	-5

Description	Diagnosis Codes	Fisher's Exact Test-p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Acute bronchitis and bronchiolitis	466	<0.001	0.004	5.5%	11.4%	-6
Acute nasopharyngitis [common cold]	460	<0.001	<0.001	7.9%	19.7%	-12
Immunization	896	<0.001	<0.001	1.0%	13.3%	-12
Annual Health Examination	917	<0.001	<0.001	19.1%	31.8%	-13

Table B-3 Fisher's Exact test on diagnosis distributions in off-label and reference groups – Imputed Set 1 - Seniors (Only statistically significant results are reported, sorted by the difference in prevalence from those most in excess in the off-label group to those most in excess in the reference group.)

Description	Diagnosis Codes	Fisher's Exact Test- p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Anxiety, dissociative and somatoform disorders	300	<0.001	<0.001	45.2%	20.6%	25
Dementias	290	<0.001	<0.001	25.6%	5.3%	20
Cardiovascular symptoms including chest pain, tachycardia, syncope, shock, edema, masses	785	<0.001	<0.001	32.2%	14.3%	18
Digestive symptoms including anorexia, nausea and vomiting, heartburn, dysphagia, hiccough, hematemesis, jaundice, ascites, abdominal pain, melena, masses	787	<0.001	<0.001	37.7%	21.5%	16
Injury, other and unspecified	959	<0.001	<0.001	20.1%	4.2%	16
Other ill-defined conditions of non-specific abnormal findings including asphyxia, excessive sweating, etc.	799	<0.001	<0.001	30.2%	16.3%	14
adverse effects Of surgical and medical care (e.g., wound infection, wound disruption, other iatrogenic disease)	998	<0.001	<0.001	18.6%	6.5%	12
Depressive disorder, not elsewhere classified	311	<0.001	<0.001	19.1%	7.8%	11
Pneumonia, organism unspecified	486	<0.001	<0.001	18.6%	7.5%	11
Joint, leg or muscle pain; symptoms involving nervous and musculoskeletal systems	781	<0.001	0.015	31.2%	20.9%	10
Senility without mention of psychosis	797	<0.001	<0.001	11.1%	0.7%	10

Description	Diagnosis Codes	Fisher's Exact Test- p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Hematuria, Hemiplegia, or other disorders of urinary tract	599	<0.001	0.009	21.1%	12.2%	9
Other nonspecific abnormal findings	796	<0.001	0.002	18.6%	9.3%	9
Functional digestive disorders, not elsewhere classified	564	<0.001	<0.001	12.1%	4.4%	8
Neuroses and Personality Disorders including Sleep disorders, Tension Headache, Habit Spasms, Enuresis due to mental disorder, Anorexia Nervosa	307	<0.001	0.002	12.6%	5.1%	7
Other disorders of ear	388	0.002693531	0.038	16.6%	9.8%	7
Heart failure	428	<0.001	0.003	12.1%	5.0%	7
Myositis, Muscular Rheumatism , Fibrositic, myositis, muscular rheumatism... , unspecified neuralgia (7292)	729	<0.001	<0.001	8.0%	1.3%	7
General symptoms including pyrexia of unknown origin, headache, vertigo, ataxia	780	0.00315494	0.042	19.6%	12.2%	7
Nonspecific findings on examination of blood	790	<0.001	<0.001	10.6%	3.7%	7
Chronic airway obstruction, not elsewhere classified	496	0.003476031	0.044	13.1%	7.2%	6
Other disorders of intestine	569	<0.001	0.002	10.1%	3.7%	6
Symptoms involving urinary system	788	<0.001	0.005	10.1%	4.1%	6
Other and unspecified malignant neoplasm of skin	173	<0.001	0.005	8.5%	3.1%	5
Other and unspecified disorders of metabolism	277	<0.001	<0.001	5.5%	0.6%	5

Description	Diagnosis Codes	Fisher's Exact Test- p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Iron deficiency anemias	280	0.002463139	0.036	9.0%	4.2%	5
Other local infections of skin and subcutaneous tissue	686	<0.001	0.003	6.5%	1.8%	5
Ill-defined intestinal infections	9	0.003506821	0.044	10.6%	5.3%	5
Poisoning by other and unspecified drugs and medicinal substances	977	0.001161212	0.020	9.0%	3.8%	5
Diseases of esophagus	530	0.00140449	0.024	7.0%	2.7%	4
Other and ill-defined sprains and strains	848	0.001502344	0.024	6.5%	2.4%	4
Malignant neoplasm of trachea, bronchus, and lung	162	0.003104442	0.042	3.5%	0.9%	3
Parkinson's disease	332	0.001726567	0.027	3.5%	0.8%	3
Migraine	346	<0.001	0.008	4.5%	1.1%	3
Other and unspecified disorders of the nervous system	349	0.00259542	0.037	4.0%	1.1%	3
Intestinal obstruction without mention of hernia	560	<0.001	0.009	3.0%	0.5%	3
Secondary malignant neoplasm of other specified sites	198	0.001755283	0.027	2.0%	0.2%	2
Other nonorganic psychoses	298	<0.001	0.001	2.5%	0.2%	2
Keratitis	370	0.003841363	0.047	3.0%	0.7%	2
Immunization	896	<0.001	<0.001	2.5%	17.2%	-15

Table B-4 Fisher's Exact test on diagnosis distributions in off-label and reference groups – Imputed Set 2 - Children (Only statistically significant results are reported, sorted by the difference in prevalence from those most in excess in the off-label group to those most in excess in the reference group.)

Description	Diagnosis Codes	Fisher's Exact Test-p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Hyperkinetic syndrome of childhood	314	<0.001	<0.001	40.0%	2.4%	38
Well Baby Care	916	<0.001	0.016	6.7%	56.2%	-49

Table B-5 Fisher's Exact test on diagnosis distributions in off-label and reference groups – Imputed Set 2 - Adult (Only statistically significant results are reported, sorted by the difference in prevalence from those most in excess in the off-label group to those most in excess in the reference group.)

Description	Diagnosis Codes	Fisher's Exact Test-p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Depressive disorder, not elsewhere classified	311	<0.001	<0.001	30.8%	11.0%	20
Anxiety, dissociative and somatoform disorders	300	<0.001	<0.001	43.2%	23.8%	19
Neuroses and Personality Disorders including Sleep disorders, Tension Headache, Habit Spasms, Enuresis due to mental disorder, Anorexia Nervosa	307	<0.001	<0.001	13.9%	4.3%	10
Joint, leg or muscle pain; symptoms involving nervous and musculoskeletal systems	781	<0.001	<0.001	23.4%	14.7%	9
Drug dependence	304	<0.001	<0.001	10.3%	1.8%	8
Paranoid Personality Disorder; Obessesive Compulsive Personality	301	<0.001	<0.001	5.5%	0.4%	5
Myositis, Muscular Rheumatism , Fibrositic, myositis, muscular rheumatism... , unspecified neuralgia (7292)	729	<0.001	<0.001	6.1%	0.9%	5
Diabetes mellitus	250	0.002	0.031	11.3%	6.9%	4
Drug-induced mental disorders	292	<0.001	<0.001	4.5%	0.2%	4
Cardiovascular symptoms including chest pain, tachycardia, syncope, shock, edema, masses	785	0.002	0.037	11.1%	6.8%	4
Alcohol-induced mental disorders	291	<0.001	<0.001	3.4%	0.2%	3

Description	Diagnosis Codes	Fisher's Exact Test-p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Other nonorganic psychoses	298	<0.001	<0.001	3.2%	0.2%	3
Specific delays in development	315	<0.001	<0.001	3.4%	0.5%	3
Symptoms involving urinary system	788	0.002	0.037	4.5%	1.9%	3
Dementias	290	<0.001	<0.001	1.8%	0.2%	2
Sexual and gender identity disorders	302	<0.001	0.003	1.8%	0.3%	2
Other disorders of female genital organs	629	<0.001	0.006	3.2%	0.9%	2
Benign neoplasm of other parts of digestive system	211	0.003	0.046	0.5%	0.0%	1
Other and unspecified anemias	285	0.003	0.045	1.6%	0.4%	1
Unspecified intellectual disabilities	319	0.003	0.045	1.1%	0.1%	1
Senility without mention of psychosis	797	0.003	0.045	1.1%	0.1%	1
Tetanus	37	<0.001	0.006	0.0%	2.4%	-2
Acute tonsillitis	463	<0.001	0.008	0.0%	2.3%	-2
Disorders of conjunctiva	372	<0.001	0.017	1.3%	4.6%	-3
Gastritis and duodenitis	535	<0.001	0.004	1.1%	4.7%	-4
Atopic dermatitis and related conditions	691	0.001	0.030	2.4%	6.0%	-4
Hirsutism, scar, or other disorders of skin and subcutaneous tissue	709	0.001	0.030	2.6%	6.4%	-4

Description	Diagnosis Codes	Fisher's Exact Test-p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Other diseases due to viruses and Chlamydiae	78	<0.001	<0.001	0.8%	5.3%	-4
Sprains and strains of knee and leg	844	0.003	0.045	3.2%	6.8%	-4
Family Planning	895	0.002	0.036	5.0%	9.5%	-4
Acute bronchitis and bronchiolitis	466	<0.001	0.006	5.8%	11.5%	-6
Acute nasopharyngitis [common cold]	460	<0.001	<0.001	8.7%	19.8%	-11
Immunization	896	<0.001	<0.001	1.1%	13.4%	-12
Annual Health Examination	917	<0.001	<0.001	20.3%	31.8%	-12

Table B-6 Fisher's Exact test on diagnosis distributions in off-label and reference groups – Imputed Set 2 - Seniors (Only statistically significant results are reported, sorted by the difference in prevalence from those most in excess in the off-label group to those most in excess in the reference group.)

Description	Diagnosis Codes	Fisher's Exact Test-p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Anxiety, dissociative and somatoform disorders	300	<0.001	<0.001	45.8%	20.7%	25
Dementias	290	<0.001	<0.001	23.9%	5.3%	19
Cardiovascular symptoms including chest pain, tachycardia, syncope, shock, edema, masses	785	<0.001	<0.001	29.9%	14.0%	16
Digestive symptoms including anorexia, nausea and vomiting, heartburn, dysphagia, hiccough, hematemesis, jaundice, ascites, abdominal pain, melena, masses	787	<0.001	<0.001	35.3%	21.5%	14
Injury, other and unspecified	959	<0.001	<0.001	17.9%	4.3%	14
Other ill-defined conditions of non-specific abnormal findings including asphyxia, excessive sweating, etc.	799	<0.001	<0.001	29.4%	16.5%	13
Depressive disorder, not elsewhere classified	311	<0.001	<0.001	19.9%	7.8%	12
adverse effects Of surgical and medical care (e.g., wound infection, wound disruption, other iatrogenic disease)	998	<0.001	<0.001	18.4%	6.6%	12
Pneumonia, organism unspecified	486	<0.001	<0.001	18.4%	7.5%	11
Hematuria, Hemiplegia, or other disorders of urinary tract	599	<0.001	0.008	20.9%	12.0%	9
Joint, leg or muscle pain; symptoms involving nervous and musculoskeletal systems	781	0.003	0.040	29.9%	20.8%	9

Description	Diagnosis Codes	Fisher's Exact Test-p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Senility without mention of psychosis	797	<0.001	<0.001	10.0%	0.7%	9
Neuroses and Personality Disorders including Sleep disorders, Tension Headache, Habit Spasms, Enuresis due to mental disorder, Anorexia Nervosa	307	<0.001	<0.001	12.9%	5.0%	8
Functional digestive disorders, not elsewhere classified	564	<0.001	<0.001	11.9%	4.3%	8
General symptoms including pyrexia of unknown origin, headache, vertigo, ataxia	780	0.002	0.032	19.9%	12.1%	8
Nonspecific findings on examination of blood	790	<0.001	<0.001	11.4%	3.8%	8
Other nonspecific abnormal findings	796	<0.001	0.007	17.4%	9.3%	8
Benign neoplasm of skin	216	0.002	0.027	17.9%	10.6%	7
Heart failure	428	<0.001	0.003	11.9%	5.0%	7
Chronic airway obstruction, not elsewhere classified	496	0.003	0.044	12.9%	7.1%	6
Myositis, Muscular Rheumatism , Fibrositic, myositis, muscular rheumatism... , unspecified neuralgia (7292)	729	<0.001	<0.001	7.5%	1.3%	6
Symptoms involving urinary system	788	<0.001	0.004	10.0%	4.0%	6
Poisoning by other and unspecified drugs and medicinal substances	977	<0.001	0.003	10.0%	3.8%	6
Other and unspecified disorders of metabolism	277	<0.001	<0.001	6.0%	0.6%	5
Migraine	346	<0.001	<0.001	6.0%	1.0%	5

Description	Diagnosis Codes	Fisher's Exact Test-p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Other disorders of intestine	569	0.001	0.018	9.0%	3.8%	5
Other local infections of skin and subcutaneous tissue	686	<0.001	0.004	6.5%	1.9%	5
Other and ill-defined sprains and strains	848	<0.001	0.011	7.0%	2.5%	5
Alcohol dependence syndrome	303	<0.001	<0.001	4.0%	0.5%	4
Diseases of esophagus	530	<0.001	0.015	7.0%	2.6%	4
Malignant neoplasm of trachea, bronchus, and lung	162	<0.001	0.013	4.0%	0.9%	3
Parkinson's disease	332	<0.001	0.008	4.0%	0.8%	3
Benign neoplasm of other and unspecified sites	229	0.003	0.045	3.0%	0.7%	2
Other nonorganic psychoses	298	<0.001	0.010	2.0%	0.2%	2
Intestinal obstruction without mention of hernia	560	0.003	0.040	2.5%	0.5%	2
Fracture of ankle	824	0.001	0.018	3.0%	0.5%	2
Encephalitis, myelitis, and encephalomyelitis	323	0.001	0.019	1.0%	0.0%	1
Immunization	896	<0.001	<0.001	2.5%	17.2%	-15

Table B-7 Fisher's Exact test on diagnosis distributions in off-label and reference groups – Imputed Set 3 - Children (Only statistically significant results are reported, sorted by the difference in prevalence from those most in excess in the off-label group to those most in excess in the reference group.)

Description	Diagnosis Codes	Fisher's Exact Test-p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Hyperkinetic syndrome of childhood	314	<0.001	0.004	31.2%	2.2%	29
Other nonorganic psychoses	298	<0.001	0.004	12.5%	0.0%	12
Well Baby Care	916	<0.001	0.005	6.2%	56.0%	-50

Table B-8 Fisher's Exact test on diagnosis distributions in off-label and reference groups – Imputed Set 3 - Adult (Only statistically significant results are reported, sorted by the difference in prevalence from those most in excess in the off-label group to those most in excess in the reference group.)

Description	Diagnosis Codes	Fisher's Exact Test-p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Depressive disorder, not elsewhere classified	311	<0.001	<0.001	32.7%	11.0%	22
Anxiety, dissociative and somatoform disorders	300	<0.001	<0.001	42.5%	23.8%	19
Drug dependence	304	<0.001	<0.001	10.6%	1.8%	9
Neuroses and Personality Disorders including Sleep disorders, Tension Headache, Habit Spasms, Enuresis due to mental disorder, Anorexia Nervosa	307	<0.001	<0.001	13.1%	4.3%	9
Joint, leg or muscle pain; symptoms involving nervous and musculoskeletal systems	781	<0.001	<0.001	23.7%	14.7%	9
Paranoid Personality Disorder; Obessesive Compulsive Personality	301	<0.001	<0.001	5.7%	0.4%	5
Myositis, Muscular Rheumatism , Fibrositic, myositis, muscular rheumatism... , unspecified neuralgia (7292)	729	<0.001	<0.001	6.0%	0.9%	5
Drug-induced mental disorders	292	<0.001	<0.001	4.6%	0.2%	4
Alcohol-induced mental disorders	291	<0.001	<0.001	3.5%	0.2%	3
Other nonorganic psychoses	298	<0.001	<0.001	2.7%	0.2%	3
Specific delays in development	315	<0.001	<0.001	3.5%	0.5%	3

Description	Diagnosis Codes	Fisher's Exact Test-p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Other and unspecified anemias	285	<0.001	0.012	1.9%	0.4%	2
Sexual and gender identity disorders	302	<0.001	0.002	1.9%	0.3%	2
Alcohol dependence syndrome	303	0.002	0.035	2.2%	0.6%	2
Other disorders of female genital organs	629	<0.001	0.014	3.0%	0.9%	2
Symptoms involving urinary system	788	0.003	0.047	4.4%	1.9%	2
Unspecified intellectual disabilities	319	0.003	0.047	1.1%	0.1%	1
Tetanus	37	<0.001	0.006	0.0%	2.4%	-2
Disorders of conjunctiva	372	<0.001	0.009	1.1%	4.5%	-3
Disorders of external ear	380	0.002	0.030	0.8%	3.6%	-3
Sprains and strains of ankle and foot	845	0.001	0.022	1.6%	5.1%	-3
Gastritis and duodenitis	535	<0.001	<0.001	0.3%	4.7%	-4
Atopic dermatitis and related conditions	691	<0.001	0.017	2.2%	6.0%	-4
Hirsutism, scar, or other disorders of skin and subcutaneous tissue	709	0.001	0.022	2.5%	6.4%	-4
Other diseases due to viruses and Chlamydiae	78	<0.001	0.001	1.1%	5.2%	-4
Sprains and strains of knee and leg	844	<0.001	0.017	2.7%	6.8%	-4
Acute bronchitis and bronchiolitis	466	<0.001	0.015	6.0%	11.4%	-5

Description	Diagnosis Codes	Fisher's Exact Test-p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Acute nasopharyngitis [common cold]	460	<0.001	<0.001	8.7%	19.7%	-11
Immunization	896	<0.001	<0.001	1.4%	13.4%	-12
Annual Health Examination	917	<0.001	<0.001	17.4%	31.8%	-14

Table B-9 Fisher's Exact test on diagnosis distributions in off-label and reference groups – Imputed Set 3 - Seniors (Only statistically significant results are reported, sorted by the difference in prevalence from those most in excess in the off-label group to those most in excess in the reference group.)

Description	Diagnosis Codes	Fisher's Exact Test-p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Anxiety, dissociative and somatoform disorders	300	<0.001	<0.001	46.9%	20.6%	26
Dementias	290	<0.001	<0.001	23.9%	5.3%	19
Cardiovascular symptoms including chest pain, tachycardia, syncope, shock, edema, masses	785	<0.001	<0.001	31.5%	14.3%	17
Digestive symptoms including anorexia, nausea and vomiting, heartburn, dysphagia, hiccough, hematemesis, jaundice, ascites, abdominal pain, melena, masses	787	<0.001	<0.001	37.6%	21.6%	16
Injury, other and unspecified	959	<0.001	<0.001	17.8%	4.3%	14
adverse effects Of surgical and medical care (e.g., wound infection, wound disruption, other iatrogenic disease)	998	<0.001	<0.001	21.1%	6.9%	14
Other ill-defined conditions of non-specific abnormal findings including asphyxia, excessive sweating, etc.	799	<0.001	<0.001	30.0%	16.6%	13
Benign neoplasm of skin	216	<0.001	<0.001	20.7%	10.8%	10
Depressive disorder, not elsewhere classified	311	<0.001	<0.001	18.3%	7.9%	10
Pneumonia, organism unspecified	486	<0.001	<0.001	17.8%	7.5%	10
Senility without mention of psychosis	797	<0.001	<0.001	10.3%	0.7%	10

Description	Diagnosis Codes	Fisher's Exact Test-p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Neuroses and Personality Disorders including Sleep disorders, Tension Headache, Habit Spasms, Enuresis due to mental disorder, Anorexia Nervosa	307	<0.001	<0.001	14.6%	5.1%	9
Hematuria, Hemiplegia, or other disorders of urinary tract	599	<0.001	0.008	20.7%	12.2%	8
Other disorders of synovium, tendon, and bursa	727	<0.001	0.003	16.0%	7.9%	8
Nonspecific findings on examination of blood	790	<0.001	<0.001	11.7%	3.8%	8
Other nonspecific abnormal findings	796	<0.001	0.003	17.8%	9.4%	8
Other disorders of ear	388	0.002	0.020	16.9%	9.8%	7
Functional digestive disorders, not elsewhere classified	564	<0.001	<0.001	11.7%	4.4%	7
General symptoms including pyrexia of unknown origin, headache, vertigo, ataxia	780	0.004	0.049	19.2%	12.3%	7
Iron deficiency anemias	280	<0.001	0.008	9.9%	4.3%	6
Heart failure	428	<0.001	0.005	11.3%	5.0%	6
Chronic airway obstruction, not elsewhere classified	496	0.002	0.023	13.1%	7.1%	6
Other disorders of intestine	569	<0.001	0.005	9.4%	3.8%	6
Myositis, Muscular Rheumatism , Fibrositic, myositis, muscular rheumatism... , unspecified neuralgia (7292)	729	<0.001	<0.001	7.5%	1.3%	6
Symptoms involving urinary system	788	<0.001	0.006	9.9%	4.1%	6

Description	Diagnosis Codes	Fisher's Exact Test-p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Ill-defined intestinal infections	9	<0.001	0.009	11.3%	5.3%	6
Poisoning by other and unspecified drugs and medicinal substances	977	<0.001	0.003	9.9%	3.9%	6
Other and unspecified malignant neoplasm of skin	173	<0.001	0.007	8.0%	3.1%	5
Other and unspecified disorders of metabolism	277	<0.001	<0.001	5.6%	0.6%	5
Migraine	346	<0.001	<0.001	6.1%	1.2%	5
Diseases of esophagus	530	<0.001	0.005	7.5%	2.7%	5
Diverticula of intestine	562	0.001	0.014	6.6%	2.5%	4
Other local infections of skin and subcutaneous tissue	686	<0.001	0.005	6.1%	1.9%	4
Other and ill-defined sprains and strains	848	<0.001	0.012	6.6%	2.4%	4
Malignant neoplasm of trachea, bronchus, and lung	162	0.001	0.019	3.8%	1.0%	3
Parkinson's disease	332	<0.001	0.009	3.8%	0.8%	3
Secondary malignant neoplasm of other specified sites	198	0.002	0.030	1.9%	0.2%	2
Other nonorganic psychoses	298	<0.001	0.010	1.9%	0.2%	2
Alcohol dependence syndrome	303	<0.001	0.011	2.8%	0.5%	2
Intestinal obstruction without mention of hernia	560	<0.001	0.009	2.8%	0.4%	2
Intracranial injury of other and unspecified nature	854	0.004	0.048	3.3%	0.9%	2

Description	Diagnosis Codes	Fisher's Exact Test-p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Encephalitis, myelitis, and encephalomyelitis	323	0.001	0.019	0.9%	0.0%	1
Immunization	896	<0.001	<0.001	1.9%	17.2%	-15

Table B-10 Fisher's Exact test on diagnosis distributions in off-label and reference groups – Imputed Set 4 - Children (Only statistically significant results are reported, sorted by the difference in prevalence from those most in excess in the off-label group to those most in excess in the reference group.)

Description	Diagnosis Codes	Fisher's Exact Test-p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Anxiety, dissociative and somatoform disorders	300	<0.001	0.013	41.2%	7.8%	33
Benign neoplasm of skin	216	<0.001	0.013	23.5%	1.4%	22
Sprains and strains of wrist and hand	842	<0.001	0.013	23.5%	1.7%	22
Hyperkinetic syndrome of childhood	314	<0.001	0.023	23.5%	2.3%	21
Depressive disorder, not elsewhere classified	311	<0.001	0.023	17.6%	0.9%	17
Symptoms involving urinary system	788	<0.001	0.023	17.6%	0.9%	17
Sprains and strains of shoulder and upper arm	840	<0.001	0.023	17.6%	1.0%	17
Acquired hypothyroidism	244	<0.001	0.023	11.8%	0.2%	12
Myositis, Muscular Rheumatism , Fibrositic, myositis, muscular rheumatism... , unspecified neuralgia (7292)	729	<0.001	0.013	11.8%	0.1%	12
Well Baby Care	916	<0.001	0.008	5.9%	56.0%	-50

Table B-11 Fisher's Exact test on diagnosis distributions in off-label and reference groups – Imputed Set 4 - Adult (Only statistically significant results are reported, sorted by the difference in prevalence from those most in excess in the off-label group to those most in excess in the reference group.)

Description	Diagnosis Codes	Fisher's Exact Test-p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Depressive disorder, not elsewhere classified	311	<0.001	<0.001	32.0%	11.1%	21
Anxiety, dissociative and somatoform disorders	300	<0.001	<0.001	42.0%	23.9%	18
Neuroses and Personality Disorders including Sleep disorders, Tension Headache, Habit Spasms, Enuresis due to mental disorder, Anorexia Nervosa	307	<0.001	<0.001	13.6%	4.3%	9
Joint, leg or muscle pain; symptoms involving nervous and musculoskeletal systems	781	<0.001	<0.001	23.8%	14.6%	9
Drug dependence	304	<0.001	<0.001	10.3%	1.8%	8
Paranoid Personality Disorder; Obessesive Compulsive Personality	301	<0.001	<0.001	5.4%	0.4%	5
Myositis, Muscular Rheumatism , Fibrositic, myositis, muscular rheumatism... , unspecified neuralgia (7292)	729	<0.001	<0.001	5.7%	1.0%	5
Drug-induced mental disorders	292	<0.001	<0.001	4.6%	0.2%	4
Alcohol-induced mental disorders	291	<0.001	<0.001	3.5%	0.2%	3
Other nonorganic psychoses	298	<0.001	<0.001	3.0%	0.2%	3
Specific delays in development	315	<0.001	<0.001	3.8%	0.5%	3

Description	Diagnosis Codes	Fisher's Exact Test-p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Sexual and gender identity disorders	302	<0.001	0.002	1.9%	0.3%	2
Alcohol dependence syndrome	303	0.002	0.040	2.2%	0.6%	2
Other disorders of female genital organs	629	<0.001	0.004	3.3%	0.9%	2
Other and unspecified anemias	285	0.002	0.043	1.6%	0.4%	1
Unspecified intellectual disabilities	319	0.003	0.044	1.1%	0.1%	1
Tetanus	37	<0.001	0.006	0.0%	2.4%	-2
Acute tonsillitis	463	<0.001	0.008	0.0%	2.3%	-2
Dyspareunia, dysmenorrhea, premenstrual tension, stress incontinence	625	0.002	0.039	0.3%	2.5%	-2
Disorders of conjunctiva	372	<0.001	0.008	1.1%	4.6%	-3
Other cellulitis and abscess	682	0.002	0.033	0.8%	3.6%	-3
Sprains and strains of ankle and foot	845	0.003	0.044	1.9%	5.2%	-3
Atopic dermatitis and related conditions	691	<0.001	0.006	1.9%	6.1%	-4
Hirsutism, scar, or other disorders of skin and subcutaneous tissue	709	0.002	0.043	2.7%	6.4%	-4
Other diseases due to viruses and Chlamydiae	78	<0.001	<0.001	0.8%	5.2%	-4
Sprains and strains of knee and leg	844	0.002	0.042	3.0%	6.8%	-4
Sprains and strains of other and unspecified parts of back	847	0.001	0.029	2.7%	6.5%	-4

Description	Diagnosis Codes	Fisher's Exact Test-p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Family Planning	895	0.003	0.047	5.1%	9.5%	-4
Gastritis and duodenitis	535	<0.001	<0.001	0.0%	4.7%	-5
Acute bronchitis and bronchiolitis	466	<0.001	<0.001	4.6%	11.4%	-7
Acute nasopharyngitis [common cold]	460	<0.001	<0.001	7.6%	19.9%	-12
Immunization	896	<0.001	<0.001	1.4%	13.3%	-12
Annual Health Examination	917	<0.001	<0.001	16.8%	31.8%	-15

Table B-12 Fisher's Exact test on diagnosis distributions in off-label and reference groups – Imputed Set 4 - Seniors (Only statistically significant results are reported, sorted by the difference in prevalence from those most in excess in the off-label group to those most in excess in the reference group.)

Description	Diagnosis Codes	Fisher's Exact Test-p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Anxiety, dissociative and somatoform disorders	300	<0.001	<0.001	46.7%	20.6%	26
Dementias	290	<0.001	<0.001	24.8%	5.3%	19
Cardiovascular symptoms including chest pain, tachycardia, syncope, shock, edema, masses	785	<0.001	<0.001	32.4%	14.2%	18
Digestive symptoms including anorexia, nausea and vomiting, heartburn, dysphagia, hiccough, hematemesis, jaundice, ascites, abdominal pain, melena, masses	787	<0.001	<0.001	37.6%	21.5%	16
Other ill-defined conditions of non-specific abnormal findings including asphyxia, excessive sweating, etc.	799	<0.001	<0.001	31.9%	16.3%	16
adverse effects Of surgical and medical care (e.g., wound infection, wound disruption, other iatrogenic disease)	998	<0.001	<0.001	21.4%	6.8%	15
Injury, other and unspecified	959	<0.001	<0.001	18.6%	4.3%	14
Pneumonia, organism unspecified	486	<0.001	<0.001	18.6%	7.5%	11
Depressive disorder, not elsewhere classified	311	<0.001	<0.001	18.1%	7.8%	10
Senility without mention of psychosis	797	<0.001	<0.001	10.5%	0.7%	10

Description	Diagnosis Codes	Fisher's Exact Test-p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Neuroses and Personality Disorders including Sleep disorders, Tension Headache, Habit Spasms, Enuresis due to mental disorder, Anorexia Nervosa	307	<0.001	<0.001	13.8%	5.0%	9
Hematuria, Hemiplegia, or other disorders of urinary tract	599	<0.001	0.005	21.0%	12.1%	9
General symptoms including pyrexia of unknown origin, headache, vertigo, ataxia	780	<0.001	0.005	21.4%	12.3%	9
Other nonspecific abnormal findings	796	<0.001	0.002	18.1%	9.4%	9
Benign neoplasm of skin	216	<0.001	0.007	19.0%	10.7%	8
Other disorders of ear	388	<0.001	0.007	17.6%	9.7%	8
Functional digestive disorders, not elsewhere classified	564	<0.001	<0.001	12.9%	4.4%	8
Nonspecific findings on examination of blood	790	<0.001	<0.001	11.4%	3.8%	8
Other disorders of synovium, tendon, and bursa	727	<0.001	0.005	15.2%	7.7%	7
Migraine	346	<0.001	<0.001	7.1%	1.1%	6
Heart failure	428	<0.001	0.004	11.4%	5.0%	6
Diseases of esophagus	530	<0.001	<0.001	8.6%	2.7%	6
Other disorders of intestine	569	<0.001	0.001	10.0%	3.7%	6
Myositis, Muscular Rheumatism , Fibrositic, myositis, muscular rheumatism... , unspecified neuralgia (7292)	729	<0.001	<0.001	7.1%	1.2%	6

Description	Diagnosis Codes	Fisher's Exact Test-p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Symptoms involving urinary system	788	<0.001	0.001	10.5%	4.0%	6
Ill-defined intestinal infections	9	<0.001	0.008	11.4%	5.3%	6
Other and unspecified malignant neoplasm of skin	173	<0.001	0.007	8.1%	3.1%	5
Other and unspecified disorders of metabolism	277	<0.001	<0.001	5.7%	0.6%	5
Iron deficiency anemias	280	<0.001	0.010	9.5%	4.2%	5
Other local infections of skin and subcutaneous tissue	686	<0.001	0.002	6.7%	1.9%	5
Poisoning by other and unspecified drugs and medicinal substances	977	<0.001	0.011	9.0%	3.8%	5
Other and ill-defined sprains and strains	848	0.002	0.026	6.2%	2.4%	4
Malignant neoplasm of trachea, bronchus, and lung	162	0.001	0.015	3.8%	0.9%	3
Alcohol dependence syndrome	303	<0.001	0.002	3.3%	0.5%	3
Parkinson's disease	332	<0.001	0.007	3.8%	0.8%	3
Other and unspecified disorders of the nervous system	349	0.003	0.031	3.8%	1.1%	3
Other nonorganic psychoses	298	<0.001	0.007	1.9%	0.1%	2
Paranoid Personality Disorder; Obessesive Compulsive Personality	301	<0.001	0.008	1.9%	0.2%	2
Intestinal obstruction without mention of hernia	560	<0.001	0.008	2.9%	0.5%	2
Encephalitis, myelitis, and encephalomyelitis	323	0.001	0.017	1.0%	0.0%	1

Description	Diagnosis Codes	Fisher's Exact Test-p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Immunization	896	<0.001	<0.001	1.9%	17.2%	-15

Table B-13 Fisher's Exact test on diagnosis distributions in off-label and reference groups – Imputed Set 5 - Children (Only statistically significant results are reported, sorted by the difference in prevalence from those most in excess in the off-label group to those most in excess in the reference group.)

Description	Diagnosis Codes	Fisher's Exact Test-p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Other and unspecified disorders of back	724	<0.001	0.007	26.7%	1.3%	25
Hyperkinetic syndrome of childhood	314	<0.001	0.027	26.7%	2.2%	24
Menopausal and postmenopausal disorders	627	<0.001	0.007	13.3%	0.0%	13
Well Baby Care	916	<0.001	0.011	6.7%	56.0%	-49

Table B-14 Fisher's Exact test on diagnosis distributions in off-label and reference groups – Imputed Set 5 - Adult (Only statistically significant results are reported, sorted by the difference in prevalence from those most in excess in the off-label group to those most in excess in the reference group.)

Description	Diagnosis Codes	Fisher's Exact Test-p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Depressive disorder, not elsewhere classified	311	<0.001	<0.001	31.3%	11.1%	20
Anxiety, dissociative and somatoform disorders	300	<0.001	<0.001	42.7%	23.8%	19
Neuroses and Personality Disorders including Sleep disorders, Tension Headache, Habit Spasms, Enuresis due to mental disorder, Anorexia Nervosa	307	<0.001	<0.001	13.3%	4.3%	9
Joint, leg or muscle pain; symptoms involving nervous and musculoskeletal systems	781	<0.001	<0.001	23.9%	14.7%	9
Drug dependence	304	<0.001	<0.001	10.1%	1.8%	8
Paranoid Personality Disorder; Obessesive Compulsive Personality	301	<0.001	<0.001	5.3%	0.4%	5
Myositis, Muscular Rheumatism , Fibrositic, myositis, muscular rheumatism... , unspecified neuralgia (7292)	729	<0.001	<0.001	6.1%	0.9%	5
Drug-induced mental disorders	292	<0.001	<0.001	4.5%	0.2%	4
Cardiovascular symptoms including chest pain, tachycardia, syncope, shock, edema, masses	785	0.002	0.048	10.9%	6.7%	4
Alcohol-induced mental disorders	291	<0.001	<0.001	3.4%	0.2%	3
Other nonorganic psychoses	298	<0.001	<0.001	3.2%	0.2%	3

Description	Diagnosis Codes	Fisher's Exact Test-p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Specific delays in development	315	<0.001	<0.001	3.7%	0.5%	3
Poisoning by other and unspecified drugs and medicinal substances	977	<0.001	0.015	4.2%	1.6%	3
Sexual and gender identity disorders	302	<0.001	0.002	1.9%	0.3%	2
Other disorders of female genital organs	629	<0.001	0.005	3.2%	0.9%	2
Other and unspecified anemias	285	<0.001	0.015	1.9%	0.4%	1
Tetanus	37	<0.001	0.006	0.0%	2.4%	-2
Disorders of conjunctiva	372	<0.001	0.002	0.8%	4.6%	-4
Gastritis and duodenitis	535	<0.001	0.005	1.1%	4.7%	-4
Atopic dermatitis and related conditions	691	0.002	0.039	2.4%	6.0%	-4
Hirsutism, scar, or other disorders of skin and subcutaneous tissue	709	0.001	0.030	2.7%	6.4%	-4
Other diseases due to viruses and Chlamydiae	78	<0.001	0.001	1.1%	5.2%	-4
Family Planning	895	0.002	0.039	5.0%	9.5%	-4
Acute bronchitis and bronchiolitis	466	<0.001	<0.001	5.0%	11.4%	-6
Acute nasopharyngitis [common cold]	460	<0.001	<0.001	8.8%	19.8%	-11
Immunization	896	<0.001	<0.001	1.3%	13.3%	-12
Annual Health Examination	917	<0.001	<0.001	18.0%	31.7%	-14

Table B-15 Fisher's Exact test on diagnosis distributions in off-label and reference groups – Imputed Set 5 - Seniors (Only statistically significant results are reported, sorted by the difference in prevalence from those most in excess in the off-label group to those most in excess in the reference group.)

Description	Diagnosis Codes	Fisher's Exact Test-p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Anxiety, dissociative and somatoform disorders	300	<0.001	<0.001	46.1%	20.7%	25
Dementias	290	<0.001	<0.001	25.0%	5.3%	20
Cardiovascular symptoms including chest pain, tachycardia, syncope, shock, edema, masses	785	<0.001	<0.001	29.9%	14.2%	16
Digestive symptoms including anorexia, nausea and vomiting, heartburn, dysphagia, hiccough, hematemesis, jaundice, ascites, abdominal pain, melena, masses	787	<0.001	<0.001	36.8%	21.6%	15
Injury, other and unspecified	959	<0.001	<0.001	19.1%	4.4%	15
adverse effects Of surgical and medical care (e.g., wound infection, wound disruption, other iatrogenic disease)	998	<0.001	<0.001	19.6%	6.8%	13
Pneumonia, organism unspecified	486	<0.001	<0.001	19.1%	7.6%	12
Other ill-defined conditions of non-specific abnormal findings including asphyxia, excessive sweating, etc.	799	<0.001	<0.001	28.9%	16.4%	12
Depressive disorder, not elsewhere classified	311	<0.001	<0.001	19.1%	7.8%	11
Senility without mention of psychosis	797	<0.001	<0.001	10.3%	0.7%	10

Description	Diagnosis Codes	Fisher's Exact Test-p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Neuroses and Personality Disorders including Sleep disorders, Tension Headache, Habit Spasms, Enuresis due to mental disorder, Anorexia Nervosa	307	<0.001	<0.001	14.2%	4.9%	9
Hematuria, Hemiplegia, or other disorders of urinary tract	599	<0.001	0.005	21.6%	12.2%	9
Other nonspecific abnormal findings	796	<0.001	0.002	18.1%	9.3%	9
Benign neoplasm of skin	216	<0.001	0.015	18.6%	10.8%	8
Other disorders of ear	388	0.003	0.037	16.7%	9.8%	7
Heart failure	428	<0.001	0.003	11.8%	5.0%	7
Functional digestive disorders, not elsewhere classified	564	<0.001	<0.001	11.8%	4.4%	7
Symptoms involving urinary system	788	<0.001	<0.001	11.3%	4.0%	7
Other disorders of synovium, tendon, and bursa	727	0.001	0.022	14.2%	7.7%	6
Myositis, Muscular Rheumatism , Fibrositic, myositis, muscular rheumatism... , unspecified neuralgia (7292)	729	<0.001	<0.001	7.4%	1.3%	6
Nonspecific findings on examination of blood	790	<0.001	0.001	10.3%	3.8%	6
Ill-defined intestinal infections	9	0.001	0.022	10.8%	5.2%	6
Other and unspecified disorders of metabolism	277	<0.001	<0.001	5.4%	0.6%	5
Iron deficiency anemias	280	0.001	0.022	9.3%	4.2%	5

Description	Diagnosis Codes	Fisher's Exact Test-p_value	BH adjusted p-value	Prevalence in off-label group	Prevalence in reference group	Difference in prevalence
Migraine	346	<0.001	<0.001	5.9%	1.1%	5
Other disorders of intestine	569	0.003	0.036	8.3%	3.8%	5
Other local infections of skin and subcutaneous tissue	686	<0.001	0.001	6.9%	1.9%	5
Diseases of esophagus	530	0.002	0.024	6.9%	2.7%	4
Other and ill-defined sprains and strains	848	<0.001	0.009	6.9%	2.4%	4
Malignant neoplasm of trachea, bronchus, and lung	162	<0.001	0.015	3.9%	0.9%	3
Alcohol dependence syndrome	303	<0.001	<0.001	3.9%	0.5%	3
Parkinson's disease	332	<0.001	0.009	3.9%	0.8%	3
Secondary malignant neoplasm of other specified sites	198	0.002	0.032	2.0%	0.2%	2
Paranoid Personality Disorder; Obessesive Compulsive Personality	301	<0.001	0.011	2.0%	0.2%	2
Intestinal obstruction without mention of hernia	560	<0.001	0.010	2.9%	0.5%	2
Encephalitis, myelitis, and encephalomyelitis	323	0.001	0.021	1.0%	0.0%	1
Immunization	896	<0.001	<0.001	2.0%	17.1%	-15

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