The Impact of COVID-19 Health Measures on the Utilization of Antipsychotics in Schizophrenia in Manitoba – A Population-Based Study Using Administrative Data

by

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Abstract

Background: During the COVID-19 pandemic, measures were implemented to stabilize access to drugs, yet it is unknown whether those with chronic medical conditions were able to sufficiently access their medications. The purpose of this study was to assess the effects of COVID-19-induced health measures on antipsychotic utility during the pandemic (in 2020 and 2021) compared to the expected trend. This was achieved through three objectives: (1) to describe the overall and individual incidence and prevalence of antipsychotics, (2) to describe the incidence and prevalence of first generation and atypical antipsychotics and (3) to describe the incidence and prevalence of oral and injectable antipsychotics.

Methods: In this repeated cross-sectional study, I used dispensed prescription drug data in Manitobans with schizophrenia. The incident and prevalent dispensation of antipsychotics in schizophrenia was assessed at two time periods (1: April-June 2020, 2: April-June 2021) and were compared with the expected trend from the previous 5 years. I stratified the primary objective results by age categories and sex.

Results: The population with schizophrenia in the first fiscal quarter (April-June) of the corresponding year ranged over the study from 8,196 (2015) to 9,166 (2021). At both time points studied, the prevalent use of antipsychotics remained stable (2020: estimate: -1.7, standard error (SE): 4.3, p = 0.6 and 2021: estimate: 4, SE: 4.3, p = 0.3). Those 65-79 years old showed a significant drop in prevalent antipsychotics in the early stages of the pandemic. In the early stages of the pandemic, the incident use of antipsychotics was reduced (estimate: -1.3, SE: 0.5, p = 0.01), although this effect was no longer significant upon extending the data to include one year later (p=0.7). We noted a significant rise in the atypical antipsychotics and risperidone incident use in April-June 2021. All other findings were non-significant.

Conclusions: The present study highlights the need for further considerations for those newly diagnosed with schizophrenia as well as elderlies during the COVID-19 pandemic and future pandemics regarding access to antipsychotic medications among users of antipsychotics with schizophrenia.

Keywords: *COVID-19, Schizophrenia, Incident antipsychotics, Prevalent antipsychotics, access to healthcare services.*

List of Symbols and Abbreviations

*****	Statistically significant
N/A	Not Available
p	Significance value
SE	Standard error
ATC	Anatomic Therapeutic Classification
COVID-19	Corona Virus Disease of 2019
DPIN	Drug Program Information Network
FGAs	First-Generation Antipsychotics
5-HT2A	5-hydroxy-tryptamine(serotonin)-2A
ICD	International Classification of Diseases
LAIAs	Long-Acting Injectable Antipsychotics
MCHP	Manitoba Centre for Health Policy
MHSAL	Manitoba Health Seniors and Active Living
Q1	First fiscal quarter
Q2	Second fiscal quarter
Q3	Third fiscal quarter
Q4	Fourth fiscal quarter
RNA	Ribonucleic acid
SARS-CoV2	Severe acute respiratory syndrome coronavirus-2
SCZ	Schizophrenia
SGAs	Second-Generation Antipsychotics
USA	United States of America

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Dedication

I dedicate this thesis to my ***beloved family and dear friends****.*
Thank you for your warm and consistent support and encouragement.

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Chapter 1: Introduction

COVID-19

SARS COV2

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV2) is a type of human coronavirus and the cause of the coronavirus disease 2019 (COVID-19) pandemic.[1] Human coronaviruses are single-stranded ribonucleic acid (RNA) viruses responsible for a wide range of respiratory infections in humans.[1] The respiratory system and specifically the alveolar epithelium is the main target of the virus, which leads to its respiratory symptoms. Clinical manifestations of a COVID-19 infection range from mild (80% of cases) including cough, fever, shortness of breath, and diarrhea, to more severe forms (15% of cases) in which hypoxia, dyspnea, and alterations in lung imaging can occur. The presence of the virus target receptor in other organs, in addition to the excessive immune response in advanced cases, can cause septic shock, acute respiratory distress syndrome, coagulopathy, metabolic acidosis as well as multiple organ dysfunction syndrome.[2] Despite the low mutation rate and sequence diversity in SARS-CoV-2, the initial wild-type strain of the virus altered substantially, as a consequence of spreading throughout the globe, which resulted varying levels of pathogenicity. Currently, the variants alpha, beta, gamma, delta, and omicron (and corresponding subvariants) have been detected for SARS-CoV-2 in different regions of the world.[3] In addition to the various vaccines with different mechanisms available in the market as a preventive intervention, antiviral agents and monoclonal antibodies are therapeutics which are available for the treatment of this viral disease.[4 5]

The first COVID-19 cases were detected in Wuhan, China, in December 2019. Subsequently, the virus spread rapidly to other continents[6] placing healthcare systems under considerable pressure around the world.[7] On January 30, 2020, the World Health Organization declared the outbreak as

a public health emergency,[8] and in March 2020, the outbreak was declared a pandemic.[9] Since then, policies have been applied to restrict spread of the virus by governments around the world.[10]

COVID-19 pandemic in Canada

Epidemiology

In Canada, reports of the first COVID-19 case date back to January 25, 2020 in Toronto (Ontario).[11] [12] From January 2020 to August 2021, Canada experienced three COVID-19 waves. Each wave was characterized by infections that were predominating caused by a specific COVID-19 variant. The first wave of COVID-19 in Canada started in January 2020 and lasted for five months,[13] on April 12, 2020, there were 25,000 confirmed cases of COVID-19, with a fatality rate of 50.51/day.[12] [14] From September 2020 to August 2021, the second (57.88 deaths/day)[14] and third (31.25 deaths/day)[14] waves occurred. The third wave, driven by the alpha-variant, overwhelmed hospital intensive care units in Canada. This wave again provoked restrictions in terms of stay-at-home orders and distance learning in Canada.[13] The fourth wave of COVID-19 in Canada was largely due to the delta-variant. This peak further exacerbated the overwhelmed situation of acute care units in some provinces. In November 2021, the number of COVID-19 cases declined and the capacity limitations in public places were removed, but masking mandates remained. The omicron-variant caused the fifth wave of COVID-19 in Canada in December 2021 leading to a re-establishment of health measures. When this wave receded in February 2022, it caused the largest number of hospitalizations in acute care wards and largest overall number of infection cases in Canada since the start of the COVID-19 pandemic.[15] The number of cases decreased drastically until April 2022, when a sub lineage of the Omicron variant drove a sixth peak, which then ended in May 2022. Canada witnessed the seventh wave of COVID-19 in the summer of 2022 caused by

another sub lineage of Omicron variant.[15] Eventually, World Health Organization declared the end of the pandemic related health emergency on May 5, 2023.[16]

After detection of first case of COVID-19 in Canada, federal, provincial, and regional regulations were applied to mitigate the spread of the virus. One crucial regulation was social distancing, which is maintaining a minimum physical distance from others to avoid close contact between individuals,[17] and also closure of public places such as schools and non-essential businesses, limiting social interactions and stay-at home orders, as well as setting fines for individuals and business not abiding to these restrictions. Another regulation was placing restrictions on travelling, such as a mandatory 14-day quarantine for passengers arriving into Canada.[18] The provincial government focused on mandating face masks, detecting infected cases through testing, ensuring social distancing was being maintained, managing school policies, and overseeing issues related to acute and long-term care in health centers. Issues such as controlling borders, developing, and approving COVID-19 vaccines and medications, were among the federal government responsibilities. Between waves, many public health restrictions were reduced or limited.[13]

Pandemic related healthcare policies

Pharmaceutical drug products

Access to pharmaceutical drugs was interrupted during COVID-19 because of global supply chain shortages. A pharmaceutical drug shortage is defined as "a supply issue that affects how the pharmacy prepares or dispenses a drug product or influences patient care when prescribers must use an alternative agent".[19] Ramifications of pharmaceutical drugs supply include limited access to chronic medications, higher workload for healthcare providers (needing to find a proper alternative to a pharmaceutical drug if in short supply), higher costs for patients and insurance provider (if substituting with a more expensive or non-covered drug by insurance services), and,

imposing more risk to patients (if a suitable alternative is unavailable).[19] There were two main reasons for pharmaceutical drug shortage during the COVID-19 pandemic. The first was the rise in the need for pharmaceutical drugs due to increased use of antivirals, respiratory or traditional cold/flu medications therapies related to COVID-19 infections and also stockpiling in response to an anticipated shortage.[20] The second reason for this shortage was the interruption in the supply chain because of government restrictions including limiting transportation across international borders or forcing manufacturers to reduce their workforce for social distancing or facility closures. These factors potentially affected the production and transportation of materials necessary for producing pharmaceutical drugs; thus, resulting in reduced quantity or delayed supply of essential pharmaceuticals.[8 21 22]

At the beginning of the COVID-19 pandemic, Canada reported an alarming increase in drug shortages.[23] One study in Canada showed a surge of 32% in drug shortages in Canada in March and April 2020, which returned to the expected levels in following months.[20] At the early stages of the pandemic, interruptions in the supply chains from China and India (global producers of ~80% of the raw ingredients and pharmaceutical drugs) caused vulnerability in the pharmaceutical drugs market in the country.[19] One study reported that the 30-day average of pharmaceutical drug shortage prevalence in Canada increased from 901 in April, 2017 to 2,345 per 10,000 drug identification number in April, 2020 (during COVID-19).[19]

Drug shortages are tiered, with Tier 1 indicating the least potential effect on drug supplies and health care system in Canada, and Tier 3 indicating the largest effect. The Tier Assignment Committee, which consists of government (federal, territorial and provincial), health care professionals, and industry groups, are responsible for managing drug shortages in Canada.

According to *Drug Shortages Canada* website, no antipsychotics were subject of an actual or expected shortage (Tier 1,2 or 3) from April-June 2020.[20]

In response to the pharmaceutical drug shortages outside that of antipsychotics, the federal, provincial, and territorial bodies implemented new regulations to alleviate the shortages.[24] According to Canadian Pharmacist Association, as of 23 March 2020, pharmacies were recommended to supply a maximum of one month supply of prescriptions, and this reverted back to the original policy (3 months' supply maximum?) in the following months.[20] On March 30, 2020, a new regulation permitted the importation of pharmaceutical drugs authorized in foreign countries but which followed comparable regulatory standards to Canadian requirements. This was amended on March 1, 2021 to clarify how much of the pharmaceutical drugs are allowed to be imported and the length of time they can be sold. It also placed further restrictions on drug exporting those could worsen a shortage. The new regulation also emphasized the established monitoring framework in order to detect and report shortages in the market.[24] [25] [26] In order to manage access to controlled pharmaceutical drugs[27] [28] (e.g., narcotics and benzodiazepines that are controlled to be distributed through only legal organizations)[29] during the pandemic, Canada, for a short time (from April 7, 2020 to April 7, 2022) permitted transferring of prescriptions between pharmacies, and allowing verbal orders to pharmacists [27] [28].

Virtual healthcare

The Canadian federal government announced on May 3, 2020, that $240.5 million dollars had been devoted to the provinces to aid running virtual healthcare defined as "any interaction between patients and/or members of their circle of care, occurring remotely, using any forms of communication or information technologies with the aim of facilitating or maximizing the quality and effectiveness of patient care".[30] This investment occurred a few months after the release of the

Virtual Care Task Force report, which served to outline the need for transformation of the healthcare system to virtual care during the pandemic. This report was revised in 2021 to establish equity in terms of access to virtual care across Canada and ensuring that this mode of care was safe and efficient. The Canadian Medical Association provided tools and resources for the virtual care system aimed at supporting patients and physicians.[30] Virtual care usage rates increased from 10-20% (2019) to 60% (April 2020) across Canada.[31] In Ontario, from March to July 2020, 71.1% of primary care visits were virtual, compared to only 1.2% during the same period in 2019.[30] Using the Ontario Health Insurance Plan claims database (2012-2020), one population-based study revealed that among the chronic conditions evaluated (e.g., mental health, heart failure, and others) mental health showed the highest rate of adoption of tele-healthcare.[32] The virtual visits were predominantly conducted through phone calls.[32] Another study in Ontario showed a drop in overall healthcare provider visits in those with schizophrenia when comparing pre-pandemic (March 2019–2020: 81%) to during pandemic (March 2020-2021: ~40%), but noted an increase in virtual visits (pre-pandemic: 81% vs. during pandemic: 78%).[33] They estimated that during the first year of the pandemic 38.5% of SCZ patients had only virtual visits with their primary healthcare providers.[33]

Effects of COVID-19 infection or public health measures

The COVID-19 pandemic imposed significant changes to an individuals' personal life, such as limited social gatherings and closure of work places.[34] The pandemic also impacted access to healthcare services.[35] Access to healthcare is defined as "the opportunity to identify healthcare needs, to seek healthcare services, to reach, to obtain or use healthcare services and to have the need for services fulfilled".[36] According to the World Health Organization, >100 countries around the world faced interruptions in access to healthcare at various levels including in-patient, out-

patient, and community-based clinics during the pandemic.[36] As a consequence of the healthcare systems focus on COVID-19, there was vulnerability in the delivery of mental and physical healthcare, medical surveillance for patients, diagnosis of new cases, and preventive interventions procedures.[37] [38] [39] [40] Therefore, an increase in the mortality and morbidity rates among individuals with non-COVID-19 medical conditions was identified.[36] A case report of a 48-year-old man who developed a myocardial infarction due to delay in seeking health care because of COVID-19.[41] In another news report, the author discusses that inadequate access to healthcare services brings up the concern of older people with chronic conditions to be unnoticed.[42] In a narrative review between January 2020 and January 2021, researchers discuss that barriers induced by COVID-19 for those with chronic conditions to access to healthcare on primary and specialty levels calls for better management of chronic diseases during the pandemic.[43] A review on direct and indirect effects of COVID-19 infection and pandemic on schizophrenia (SCZ) highlighted the introduction of public health measures imposed issues to the adequacy and continuity of treatment in this group of patients.[44] One aspect of healthcare that was negatively impacted by the COVID-19 pandemic was access to prescription medications among people who live with chronic medical conditions[39] [45] as a consequence of limited access to pharmaceutical drugs (noted above), limited access to medical providers and fear of COVID-19 contagion.

Access to medical providers

COVID-19 caused reduced access to hospitals and primary healthcare services in different parts of world, including Manitoba.[33] [46] This reduction of in-person visits was not only the consequence of public health measures adopted to reduce spreading of the virus, but is also the result of the shift of the healthcare systems priority toward growing demand from the COVID-19 pandemic.[40] During the pandemic, public health measures implemented included cancelling, postponing or

moving to virtual care.[36] Thus, people were less likely to attend medical consultations, which reduced the medications prescribed or dispensed.[45 47] According to a study in 2021, since the beginning of the pandemic, 31% people in Canada had no visits with their healthcare providers (in-person or virtual).[48] Virtual care was introduced as an alternative to in-person medical consultations during the pandemic.[30] This format had its own challenges, such as lack of necessary technology infrastructure and training, which made for initially improper implementation of this alternative method.[49]

Fear of COVID-19 contagion

Avoidance of healthcare can be defined as "missing appointments, failing to adhere to therapy, and delaying or avoiding medical care due to cost, time, fear, or a denial of symptoms, among other variables".[50] Studies have reported on the role of public fear of COVID-19 infection by avoiding seeking healthcare during the pandemic.[36 37] The rate of healthcare avoidance due to fear of COVID-19 ranged from 19% in the Czech Republic (for all ages) to 4% in Slovenia among those 50 or older.[36] Further concerns worsening this fear during the COVID-19 pandemic included loss of face-to-face interaction, job insecurity, and feeling uncertain in the current situation.[51] Fear of COVID-19 contagion could also be attributed to the lack of a cure for the infection.[52] Those who were older, female, from a poor sociodemographic background, and who lived with poor health conditions, were more likely to avoid healthcare due to concern for COVID-19 contagion during the pandemic.[36] Studies demonstrated that avoidance of healthcare as a result of COVID-19 infection could result in higher severity in medical conditions as well as higher rate of mortality in these cases.[50]

COVID-19 pandemic in the province of Manitoba

Epidemiology

In the Canadian province of Manitoba, the first COVID-19 case was reported on March 12, 2020 (***Appendix I***).[53] Public health measures to limit spreading of the virus were first enacted on March 13, and were like those being implemented in other parts of the world, as described previously. On March 20, 2020, Manitoba declared a state of emergency for 1-month based on increasing COVID-19 cases. In terms of the healthcare sector, non-urgent hospital visits were restricted and/or suspended, and a one month limit for drug dispensing was implemented.[46 54]

Introduction of RestartMB (a Pandemic Response System in Manitoba) provided an overview of the status of COVID-19 in Manitoba. According to this color-coded levelled system, trends of COVID-19 infection rates and current public health directions were reported as Red (critical level), Orange (restricted level), Yellow (caution level) and Green (limited risk level). This system was enacted in August, 2020.[46 55]

Due to the reducing number of COVID-19 cases, Manitoba eased some public health restrictions and reopened public places and removed inter-provincial isolation requirements between May 4-July 17, 2020. Following this, in August 2020, COVID-19 cases began increasing, which was followed by mandatory masking in schools and on public transportation, along with 2-weeks of isolation if an individual tested positive for COVID-19 or was a close contact of COVID-19 positive case. At the end of August 2020, Manitoba released a plan for safe return to schools in Fall 2020 but shortly after, in September, Manitoba moved to a restricted level on the Pandemic Response System. From September to October 2020, Manitoba experienced several outbreaks in long-term care and personal care homes. Intensive care units were highly occupied by COVID-19 positive cases. Despite establishment of additional measures, the number of COVID-19 cases

reached a critical level in November 2020. However, the number of cases then decreased and stabilized by February 2021. Vaccinations began in December 2020 for front-line healthcare workers. A decrease in the incident COVID-19 cases led to another phase of easing restrictions during February 2021, but with the continuation of masking and physical distancing mandates. Manitoba was still at a critical level in March 2021 and from April to May 2021, the emergence of another variant (gamma) led to a peak in the number of cases. In June 2021, the province announced re-opening plans across three phases, which progressively relaxed restrictions from June-August 2021. In October 2021, Manitoba experienced the Delta variant surge in cases that was followed by extension of restrictions, requirement of proof of vaccination, and expanding vaccination to children. In December 2021, the Omicron variant spread and peaked in January 2022. This wave decreased to a cautionary level in February 2022, during which restrictions were completely removed with proof of vaccination.[46] (***Appendix I***)

Pandemic related healthcare policies

Pharmaceutical drug products

Following the advice of the Canadian Pharmacists Association, and consistent with other provinces, Manitoba limited drug prescription refills from up to three months (based on direction by prescriber) to only one month maximum. This restriction, effective on March 20, 2020, was to prevent medication stockpiling and reduce the drug shortages. This policy ended on May 11, 2020, because of increasingly stable drug supplies which enabled pharmacies to dispense long-term prescriptions for pharmaceutical drugs not affected by the shortage. Since then, an informal "drug shortage working group" was responsible for making further evidence-based decisions on the pharmaceutical drugs that should continue one-month dispensing restrictions, including those on the Health Canada's list of shortage reports.[56] [57] [58]

Additionally, pharmacists would be able to keep their clients informed about medications subject to this limitation and limited them to <100 days' supply of any pharmaceutical drugs.[57 58] Although to provide safe access to narcotics and other controlled pharmaceutical drugs during the pandemic, in March 2020, the prescriptions were temporarily allowed to be directly faxed by physicians to pharmacies.[28 59]

Virtual healthcare

In Manitoba, from March-April 2020, tariffs were introduced for virtual health care services and virtual visit codes were expanded through following negotiations in Fall 2020.[30] A tariff code is defined as "a specific code used to identify each service provided by a physician or a nurse practitioner as defined in the Physician (Tariff) Manual".[60] The virtual services were possible through telephone or videoconference and were under insurance coverage if the patient and physician were both in the Manitoban province.[30] In summer 2021, the province announced the investing of $342,000 to boost tele-psychiatry services in remote areas with the focus on rural and indigenous adult populations.[61]

Schizophrenia

Overview of the disorder

SCZ is a rare mental illness and the most common psychotic disorders.[62 63] SCZ is characterized by the presence of positive and negative symptoms and cognitive deficits.[64] Positive symptoms of SCZ are known as overly exaggerated ideas about the surrounding world such as delusions and hallucinations, thinking and concentration difficulties, and disorganized speech.[65] Negative symptoms are a lack of normal processes such as pleasure, showing emotions, making and completing plans, and social isolation.[65] Cognitive impairments include deficits in attention, processing speed, executive functioning, and social perception.[65] Executive functions are regarded

as sensitive predictors of social function and of comorbidities which are crucial determinants of quality of life in this group of patients and prognosis of SCZ,[66] and can lead to low engagement in available social supports like friends and family.[65]

SCZ is a chronic and potentially debilitating mental illness that places a significant burden on the lives of those affected, which makes it among the top 10 global causes of disability.[62 63] The overall prevalence of SCZ in the world is 1 in 300 (0.32%).[64] The incident rate of the disorder is higher in urban regions compared with rural regions.[67] In the province of Manitoba, the prevalence of SCZ is 1 in 100, and is higher among men aged 18-44 years old, compared to women of the same age.[68] Prevalence of SCZ in Manitoba is higher in urban areas and among those in low-income levels.[68]

First episode psychosis, a term used to define the first experience of psychosis in a patient,[69] in SCZ occurs predominantly in young adulthood (20-35 years), and younger age of onset is more common among men compared to women.[62 70] Genetic and environmental factors play role in the etiology of the disorder as SCZ heritability is reported around 80% and distribution of the disorder is higher among those with lower socio-economic status.[70 71] The mortality rate is 2-3 times higher among people with SCZ compared to the general population, due to various factors, including cardiovascular and metabolic comorbidities, and suicide.[40 64]

The diagnosis of SCZ is based on the Diagnostic and Statistical Manual of Mental Disorders (DSM). According to the fifth and latest edition of the DSM, there are five specific key symptoms in SCZ: delusions, hallucinations, disorganized speech, disorganized behavior, and negative symptoms; with >2 symptoms required for at least 6 months (during which, active-phase symptoms must be persistent for at least one month).[72 73]

The goal of treatment for SCZ is reducing symptoms, preventing relapses, and helping the patient to better integrate into society by improving adaptive abilities. The typical treatment approach is a

combination of pharmacological medication, psychotherapy, and potentially additional therapeutic options such as peer support groups, education, life and social oriented training, and symptom-focused interventions.[74] [75] Pharmacological treatment for SCZ is aimed at reducing the positive symptoms and improving negative symptoms so that healthy functioning is more attainable. In combination with therapy, improving socialization and self-care, preventing relapses, and managing residual symptoms and boosting adherence to medications is more likely.[74] [75]

Antipsychotics

Antipsychotics are approved by Health Canada for the treatment of SCZ and bipolar disorders. Antipsychotics have several off-label uses[76] such as anxiety,[77] [78] attention deficit hyperactivity disorder (behavioral therapy),[79] and dementia (management of behavioral and psychological symptoms).[80] Antipsychotics are divided into two categories based on when they were introduced into the market and their propensity to cause adverse drug reactions: first-generation antipsychotics (FGAs) (typical or conventional) and second-generation antipsychotics (SGAs) (atypical).[81] The key characterization of typical and atypical antipsychotics is based on the induction of motor adverse events, dopamine 2 receptor properties, and their action on other receptor classes.[82] While incidence of extrapyramidal side effects is higher in typical antipsychotics, atypical antipsychotics administration is associated with higher weight gain as well as metabolic disturbances.[83] [84] The prevalence of antipsychotics utility and their patterns differ from country to country, although most of countries have faced increased usage of antipsychotics, particularly the atypicals, due to new approved indications, new off-label uses, and improved access to these medications.[85] [86]

First-generation antipsychotics (FGAs) or Typical Antipsychotics

First-Generation Antipsychotics were first introduced in the 1950's with chlorpromazine. Most are phenothiazine derivatives, meaning they predominantly act through blocking serotonin-

dopamine.[81] Some studies have shown that FGAs demonstrate their optimal effectiveness when approximately 72% of brain dopamine 2 receptors are blocked.[87] These antipsychotics also have noradrenergic, cholinergic, and histaminergic blocking actions.[87] and pose a high affinity to dopamine-2 receptors which can contribute to movement disorders, for which FGAs are also known, for significant, like extrapyramidal adverse effects acute (such as akathisia, parkinsonism, and dystonia) and delayed ones (such as tardive dyskinesia) as well as hyperprolactinemia.[87 88 89] The adverse effects of these antipsychotics emerge based on the receptors that are affected. Antihistaminergic effects can cause sedation and anticholinergic effects leading to constipation, dry mouth, and urinary retention; their alpha receptor blockage properties can lead to cardiac arrhythmias, neuroleptic malignant syndrome, blood dyscrasia, and photosensitivity.[87 89]

Atypical Antipsychotics

SGAs were introduced following the first-generation antipsychotics, in the 1980's with clozapine. Regarding mechanism of action, they partially agonize dopamine receptors,[81] and pose lower affinity to dopamine receptors[88] meaning a reduction in the extrapyramidal adverse effects compared to FGAs.[87] SGAs also have an effect on serotonin receptors, predominantly the 5-hydroxy-tryptamine(serotonin)-2A (5-HT2A) subtype.[87] Administration of certain atypical antipsychotics is associated with additional adverse effects such as metabolic syndrome and weight gain,[87 90] which require monitoring blood glucose and lipid levels, and waist circumference. Other adverse effects of SGAs include dizziness, somnolence, agitation, arrhythmia and hypotension (though some SGAs, including ziprasidone can cause activating side effects).[87 90] Aripiprazole is a newer antipsychotic, and known as a third generation antipsychotic and a "dopamine stabilizer", as it poses low agonistic effects on dopamine receptors through better control on presynaptic

dopamine receptors. Cariprazine and brexpiprazole are other examples of the third-generation antipsychotics. Third generation antipsychotics are more commonly known as atypical agents.[91]

Routes of administration of antipsychotics

Both generations of antipsychotics include agents that can be administered orally or by injection. Injectable antipsychotics are divided into short-acting intramuscular antipsychotics and long-acting injectable antipsychotics (LAIAs). Short-acting injectables are applied in the treatment of acute agitation episodes in SCZ,[92] whereas LAIA (or "depot" formulations) are preferred for maintenance therapy in SCZ.[93] Administration of short-acting intramuscular antipsychotics in acute agitation episodes in SCZ helps achieve rapid stabilization and transition to oral agents in addition to making sure about the safety of the patient and others[92] Administration of LAIAs range from every two weeks to three months, depending on the drug and dosage.[94 95]

When compared to placebo, LAIAs can significantly increase the likelihood of stable recovery and lead to less relapse and rehospitalization through improving adherence to treatment.[94 95] Compared to placebo, LAIAs also can reduce the progression of the disorder and improve symptoms when used as front-line treatment in acute SCZ cases. In terms of reducing relapse and improvement of symptoms, there is no significant disparity among LAIAs.[95]

Studies demonstrated that LAIAs compared to oral antipsychotics are better able to prevent hospitalization in patients who were switched from an oral antipsychotic to a LAIA, when comparing outcomes in pre- and post-drug conversion periods.[40 62] Studies showed LAIAs in comparison with oral antipsychotics, significantly prevent all-cause discontinuation, relapses, and hospitalization and reduce mortality.[40 62] Studies also demonstrated the superiority of LAIAs to oral agents as the initial therapy in the first episode of SCZ in preventing exacerbation in patients who are prone to non-adherence.[95] Tolerability with LAIAs is generally very high in comparison

to oral agents.[63] Another advantage of the LAIAs to oral agents is less fluctuation in the plasma concentration of drug.[93]

LAIA are administered at clinics, community pharmacies, and health care facilities[96 97] and are more costly compared to oral agents (specifically second-generation LAIA). [94 98 99] Insurance coverage in nearly all Canadian provinces restrict coverage of second-generation LAIA to SCZ cases demonstrating poor antipsychotic adherence, treatment failure or intolerance. In Manitoba, all first-generation LAIA are covered by Manitoba's universal provincial drug benefit program.[100]

Comparative effectiveness of first- and second-generation of antipsychotics

A meta-analysis on randomized controlled trials comparing SGA vs. FGA in SCZ spectrum disorders, revealed the superiority of SGAs. In terms of first episode psychosis, SGAs are associated with lower discontinuation rate (Relative risk: 0.74, 95% confidence interval: 0.62-0.87), intolerability (Relative risk: 0.46, 95% confidence interval: 0.31-0.68), extrapyramidal side effects (relative risk: -0.42, 95% confidence interval: -0.64 to -0.22), and akathisia (pooled effect size: -0.48, 95% Confidence Interval: -0.62~-0.34).[83] A nationwide prospective cohort study in Sweden included ~29,000 SCZ cases, from July 1, 2006, to December 31, 2013, to assess the comparative effectiveness of antipsychotics and found clozapine and LAIAs were associated with lower risk of rehospitalization and treatment failure during the follow-up, compared to the most frequently use antipsychotic in the study (oral olanzapine).[101] Although, the findings related to SGA superiority for cognitive dysfunction is inconsistent.[83] SGAs also have more weight gain and metabolic disturbance propensity compared to FGAs. [83 84] One meta-analysis of 100 randomized clinical trials (25,952 participants) noted among the 18 antipsychotics included in the study, some SGAs such as ziprasidone and aripiprazole showed no evidence of weight gain and metabolic disorders, compared to placebo.[102] Patients with SCZ, younger and women are more prone to

weight gain with SGAs.[83] Long-term studies indicate that lifestyle, genetics, and environment, in the occurrence of the weight and lipid profile side effects, as putative reasons for the observed differences between SGA and FGA.[83] On the other hand, FGAs are more associated with extrapyramidal side effects, tardive dyskinesia, adjunctive treatment with anticholinergics, and prolactin elevation.[83 84] Although the incidence rate of extrapyramidal side effects in SGAs is lower compared to FGAs, pediatric and young users of SGAs are still at considerable risk of extrapyramidal side effects.[83] Roughly estimated, acute extrapyramidal adverse effects occur in the half of patients on high-potency FGAs.[103] One review of 12 long-term incidence trials reported that the likelihood of tardive dyskinesia with FGAs is 5.5 % per year and this rate reduces to 3.9% per year in SGAs.[104] The agent specific risk (highest for risperidone and lowest for clozapine), history of extrapyramidal symptoms and high dose are risk factors of SGAs induced extrapyramidal side effects.[103]

Clinical use of antipsychotic therapy for schizophrenia

Determining the pharmacotherapy of SCZ with antipsychotics is on an individual basis and is impacted by different factors such as patients' preference, symptom patterns of disorder, and drug adverse effects profile. It is important to monitor the response to treatment and side effects after the initiation of treatment.[62 74 105] The rates of inadequate (or no response) and partial response (defined as improved psychopathological aspects with residual positive symptoms, hallucination and delusion, at mild to severe level) to pharmacotherapy with antipsychotics in SCZ are estimated 10-30%, and 30% respectively.[106] Comorbid depressive symptoms in SZC is treated with other classes of drugs.[107] Recommendations regarding the pharmacological treatment of SCZ with antipsychotics are categorized into 5 groups according to the stages of the disorder: first episode

SCZ, acute exacerbation, maintenance treatment, treatment-resistant SCZ and clozapine-resistant SCZ.[107]

For those who experience their first episode of psychosis, guidelines recommend monotherapy with an antipsychotic of a lower effective dose (e.g., olanzapine or risperidone)[62] and the rate of response after one month to one year since the initiation of treatment is reported between 75-87%.[108] In long term studies (>12 weeks), SGAs show improved responses to long-term outcomes (relapse and discontinuation) compared to FGAs, and are thus regarded as pharmaceutical drugs of choice in SCZ first-line treatment, with the exception of clozapine.[62 74] Decision making at this stage should be based on side effect profile of the medications like motor and metabolic adverse effects.[107]

The initial treatment is continued for at least 2 weeks. During this acute phase of treatment, with gradual dose titration, the following are assessed: the duration of treatment, the response and tolerance. Guidelines suggest the continuation of this phase for 4-6 weeks.[107] Generally, physicians begin with lower therapeutic doses and gradually increased the dose in several weeks to reach an adequate dose.[107] The adequate dose is followed for almost 6 weeks.[107] If there is no response after 4 weeks, and the dose was increased, or if the individual was intolerant, switching to another monotherapy (atypical, if the first choice was a typical antipsychotic) with adequate dose is recommended.[62] The case of partial response to the initial treatment should be reassessed after 8 weeks (unless intolerance issues).[107]

When there is an acute exacerbation of SCZ during treatment, adjustment of the dose or switching to another antipsychotic is recommended. Issues such as non-adherence and substance abuse can contribute to failure of treatment and should be addressed appropriately.[107] The rate of response in subsequent treatment with non-clozapine antipsychotics is lower in comparison to the first episode

of psychosis[108] as the rate of response to multiple trials of FGA monotherapy is reported to be 10-30%.[74] Among SGAs, the response rate is 20-80%.[109] The treatment approach for patients with SCZ who experience multiple episodes of psychosis is similar to the first episode psychosis, but in some cases a different antipsychotic agent and higher doses might be needed.[62]

The acute phase of treatment is continued for maintenance after the remission of symptoms, and can last from 12 months to 2-5years.[62 74 107] Some guidelines recommend continuing the same antipsychotics and the same dose for maintenance therapy, while others recommend reducing doses.[62] Although the goal of maintenance therapy is to prevent relapses, current evidence shows that maintenance treatment does not eliminate the risk of relapse.[107]

If there is an inadequate response following two antipsychotic monotherapies (chemically unrelated antipsychotics), the patient is deemed to be treatment resistant. With treatment resistant SCZ, the gold standard of pharmacotherapy is clozapine.[62] On average, 30% of SCZ patients meet the treatment resistance criteria among which 30-60% respond to clozapine.[108 110] One widely used definition for the inadequate response in the treatment resistant SCZ is less than 20% reduction in positive and negative symptoms. Two persistent positive symptoms with moderate severity or one severe or worse persistent positive symptoms is another applied definition for inadequate response. When it comes to monotherapy trials with non-clozapine antipsychotics, the adequacy of the course in terms of dose and duration of treatment as well as medication non-adherence and substance use should be considered before making any decisions on eligibility for clozapine.[107]

If there is a lack of response to clozapine, or there is an impossibility of blood cell monitoring for adverse side effects, olanzapine and risperidone are recommended as an alternative treatment.[62] Other pharmacological treatment options in treatment resistant cases include combining additional antipsychotics to clozapine (combination therapy), adding other mood stabilizers such as

lamotrigine or topiramate to clozapine (augmentation therapy), or monotherapy with a higher dose of a non-clozapine antipsychotic.[62] When assessing adequacy of clozapine response, the dose, duration, non-adherence, and substance use should be considered before making any decisions on meeting clozapine-resistance criteria.[107]

When an individual exhibits non-adherence to an oral antipsychotic, provided adverse effects are the likely reason, switching to another suitable oral antipsychotic with appropriate dosage and adverse effect profile is recommended, for e.g., switching to an atypical one if the first choice was a typical one). Another choice in non-adherent patients is LAIAs which are recommended in SCZ patients non-adherent to other routes of administration of antipsychotics.[62]

Use of antipsychotics for schizophrenia in Manitoba

One study from 1996 to 2006 demonstrated that the introduction of SGAs to the market led to a dramatic change in the utility patterns of antipsychotics and a rise in the number of prescriptions and the users of antipsychotics during the period of study.[99] Young males experienced the fastest increase in the use of antipsychotics (from 16% in 1996 to 88% in 2006), three times more than the adult group. Authors reported that by 2006, 80% of the market share belonged to SGAs. During this 10-year period risperidone had the higher number of prescriptions and although the clozapine use was low compared to other SGAs, it was comparable with the rates seen in treatment resistant SCZ.[99]

According to a study in Manitoba, on the whole population from 1995 to 2015, the first-generation LAIAs use showed a downward trend.[100] They also reported that LAIAs were 2% of overall use of SGAs in the province by 2015. Introduction of second-generation LAIAs to the market broadened the population of LAIAs users. Those 19-35 years experienced the most considerable increase in the incident and prevalent use of LAIAs from the start of the study till the end. Higher

tolerability based on highly qualified evidence compared to first-generation LAIAs, shortage of first-generation LAIAs in the market and growing off-label uses of second-generation LAIAs are contributing factors to the upward trend in second-generation LAIAs administration during the study period in Manitoba.[100]

According to a study conducted from 1998 to 2009 on optimizing use of antipsychotics in those >65 years old in Manitoba, physicians showed a high consistency with guidelines when prescribing antipsychotics for the target group by considering cautions in term of administration of antipsychotics in this age group due to potential adverse effects and drug-drug interactions.[111] Although the use of newer members of this class of medications showed increasing trend in Manitoba province especially in personal care homes, it was for those with severe symptoms and less likely to happen to advanced age and polypharmacy cases who are at a higher risk of antipsychotics administration adverse events.[111]

The importance of sustained access to medications in schizophrenia

Untreated psychosis

Untreated psychosis is the period when psychotic symptoms occur, but no antipsychotic is given. A longer duration of untreated psychosis is a consistent predictor of poor long-term outcomes .[112] [114] It seems that in the first episode of psychosis, the larger duration of untreated psychosis is associated with the higher severity of negative and positive symptoms. In addition to symptom-wise outcomes, remission and social functioning are also negatively associated with increasing duration of untreated psychosis.[113] These finding were also shown in the chronic stages of the disorder (6-12 months of follow-up).[112] Concerning hospitalization, quality of life and employment, a meta-analysis of studies ranging from 2-28 years of follow up, showed no significant relationship between these outcomes and duration of untreated psychosis.[114]

Mental health during COVID-19

COVID-19 led us to experience the greatest challenge in health sector in the current century. Previous experiences show that almost in all disasters in largescale the mental health such as rate of depression or post traumatic disorders are affected negatively.[49] The results of a systematic review revealed that poorer psychological well-being was experienced among the general population during COVID-19 in comparison with pre COVID-19 era.[115] Not only the fear of COVID-19, but also other COVID-19 related stressor such as social isolation and loss of job that the later can lead to feelings of uselessness and hopelessness play as threats for mental health in healthcare providers and general population. So, it seems that the COVID-19-pandemic was coupled with another pandemic but of emotional and behavioral in nature.[51 116]

In comparison with general population, people with mental conditions are more prone to be effected by emotional problems due to COVID-19.[51] According to a case-control study in China, medication delivery delay and limited primary care access were reported, among other factors, to negatively affect the mental health of people with psychiatric disorders during the pandemic.[115] Authors in a report on drug shortages in Canada discussed the effects of drug shortages on the mental health of patients on chronic medication.[117] Increased psychiatric symptoms was reported among people with psychiatric disorders and this group of patients showed higher rates of moderate to severe worriedness about their physical health due to COVID-19 contagion during pandemic.[115] According to a review study, life stress and stressful events are associated with higher level of anxiety and depression and can lead to relapse in people with SCZ.[118]

Non-adherence in schizophrenia

"Medication adherence can be defined as the extent to which a patient's medication-taking matches that agreed with the prescriber".[119] According to one definition full nonadherence, as defined by

not taking the prescribed medication for 1 week and partial nonadherence is taking only 50% of prescribed medications.[120] In general, non-adherence to antipsychotics has been reported to be high among individuals living with SCZ, as compliance rate is estimated 20-72%.[121 122] Risk factors for nonadherence in SCZ fall into three categories: patient-related, medication-related and environment-related.[123] Nonadherence is due to factors such as reluctance of patients to receive pharmacotherapy (poor insight results in that patient does not see itself ill), poor awareness of the medication benefit, complicated regimen, adverse effects, on-going psychiatric symptoms and living alone.[22 123] Non-adherence is as a challenge in the management of SCZ and is negatively affected by COVID-19, according to reports.[124] One study collected data from 18 formulary decision makers through a survey showed that participants reported non-adherence among challenges in SCZ during COVID-19.[124] Another study investigated adherence to antipsychotics before and during COVID-19, and found no significant change.[125] Medication non-adherence in SCZ means worse social and physical functioning and cognitive performance, and increased hospitalizations which leads to more costs in health system.[22 63 122] It can also lead to disorder progression and complications that has deteriorating impact on patients' quality of life. Higher rates of suicide and death are of consequences of non-adherence to treatment in SCZ.[122] In one study of 103 SCZ patients with adherence, the mean score of patients based on Beck Scale for Suicidal Ideation decreased significantly from the start of study to the end of follow six months later (start: 2.51±5.4, end: 1.74±4.4).[126] Authors discussed that the results are suggestive of the role of stable antipsychotic therapy on the control of suicide ideations in SCZ patients.[126] Nonadherence is among contributing factors to deteriorated cardiovascular outcomes in psychotic disorders and cardiovascular events are known as the main cause of mortality among these patients.[127] Substance use disorder, higher rate of violence and arresting are also reported as the

consequences of non-adherence in SCZ.[128] By considering the potential negative effect of interrupted availability of pharmaceutical drugs on medication adherence among people with SCZ, the necessity of drug access management among this group of people during COVID-19 becomes bold.

Risk of COVID-19

People who live with SCZ are more likely to have concurrent physical comorbidities such as hypertension and diabetes which can be contributed to the illness itself or the medication they receive for SCZ.[40 115] The medical comorbidities in people with SCZ are associated with living 15-30 years less compared to general population and higher hospital admissions leading to more hospital-specific costs in healthcare system.[129 130] These comorbidities are contributable to poor habits such as addiction, smoking, lack of exercise and poor diet that occur with higher rate among this group of patients.[130 131] These comorbidities, combined with the sociodemographic characteristics of patients with SCZ like being homeless or imprisoned (level of literacy and hygiene), and poor habits such as smoking , make this group more likely to develop worse outcomes and complications in the case of COVID-19 infection.[40 115 116 132 133] This group of patients also are at higher risk of COVID-19 infection.[44] One study in the USA found that relative to other serious medical and mental condition, such as cancer and heart failure, SCZ was a stronger risk factor for mortality during early COVID-19 pandemic.[134] Moreover, the impaired insight and decision-making function of this population may put them at higher risk of getting an infection due to barriers that make it more difficult for people with SCZ to keep to commands of social distancing during the pandemic.[40 132 133]

Chapter 2: Literature review

In the following section, I review the results of studies concerning utilization pattern of antipsychotics during the COVID-19 pandemic in the general and SCZ population. Overall, most of studies concerning antipsychotic consumption in the general population were indicative of a rise in whole supply (incident and prevalent) of all antipsychotics use after the pandemic. This could call for more research on the effect of the pandemic on psychological health. Investigations focusing on the SCZ population mostly observed a decline specifically in incident LAIAs following COVID-19 but little effect on the prevalent use of antipsychotics.

General population

Kuitunen, et al. (2023) in Finland, in their nationwide register-based study assessed the impact of COVID-19 pandemic on the prevalent psychotropic medications in patients aged 13-24 years old. They observed 396,534 visits, for mental health problems in primary care setting, and compared the annual prevalent rate ratio of antipsychotic medications in 2020 and 2021 with 2019 (as the pre-COVID-19 era). In 2021, they found a significant increase of 19% (prevalence rate ratios: 1.19, 95% confidence interval: 1.16-1.21) in the use of antipsychotics, relative to 2019.[135]

Marengoni, et al. (2023) evaluated the effects COVID-19 on the consumption of 30 categories of medication including antipsychotics and other classes of pharmaceutical drugs, such as antihypertensive and lipid lowering agents in Italy. They included those >65 years of age (~14 million participants) and used the Defined Daily Dose per 1000 inhabitants to compare the dispensation in 2019 and 2020. Comparing 2020 with 2019, a decline was detected in the Defined Daily Dose of all 30 classes (except for anticoagulants) in the population, and this was more considerable among men. Moreover, the Defined Daily Dose showed a decline in those >75 years old compared to other age groups in the study.[136]

Nobili, et al. (2023) in Italy, using the administrative claims database in the Lombardy region, performed an investigation and used medications and diagnostic tests dispensation as indicators of the COVID-19 health effects. They recruited 46,574 cases of COVID-19 who tested negative by June 20, 2020, and were followed for 18 months. The drug dispensations in this group were compared with that of the same participants during July-December 2019. There was a significant increase in whole supply (incident and prevalent) antipsychotics dispensation (adjusted odd ratio: 1.37, 95% Confidence Interval: 1.29-1.46) in the follow up period in 2020 compared to the reference (2019). Although a decrease or stability was seen in the rest of time in the study (January to June 2021 and July to December 2021), the whole supply (incident and prevalent) rate of antipsychotics was still higher compared to 2019 July-December.[137]

Rachidi, et al. (2023) in Lebanon, studied the psychotropic medications utility before and during the pandemic. They conducted two cross-sectional studies, one from May to October 2019 (pre-COVID period) and the other one during pandemic (July to October 2021) and ran a case-control study by interpreting data from them. Data collection was done through surveys and 128 cases (during pandemic) were matched based on age and sex with 256 individuals before the pandemic. They observed significantly less patients using antipsychotics during pandemic. Authors discussed that this reduction could be the consequence of higher antidepressants consumption during COVID-19 (another observation in their study) to control the psychological disorders following the pandemic.[138]

Maguire, et al. (2022) in Northern Ireland, compared the use of antipsychotic medications before (January 2012 to February 2020) and during pandemic (March to October 2020).[139] They used population-based databases with monthly prescribing data. They reported that use of whole supply (incident and prevalent) antipsychotics continued an upward trend (since 2012) during the

pandemic and showed use rate within expected values during the entire period of study. In stratification analysis, antipsychotics uptake increased more than expected in five of the possible eight month follow up period in those live in affluent ereas.[139]

Benistand, et al. (2022) in France, assessed the effect of COVID-19 on the psychotropic medications' uptake. They collected their data through French National Health Insurance from 1 January 2015 to 30 September 2021. When comparing pre-pandemic era (January 2015 to March 2020) with post-pandemic era (March 2020 to the end of September 2021), they found a small but significant increase in the monthly delivery of antipsychotics in the post-pandemic (0.04 boxes (95% Confidence Interval: 0.02~0.06, p = 0.001) per month per thousand population).[140]

Amill-Rosario et al. (2022) looked at monthly psychotropic medications utility among people aged 2-17 years living with mental illness in the USA. They obtained prescribing data from 8,896,713 participants during January 2019-September 2020 and found that in the early stage of the COVID-19 pandemic, the whole supply (incident and prevalent) monthly use of antipsychotics increased, but peaked in April 2020 (41.9% year-over-year percent change compared to April 2019). Although it showed gradual decline after April 2020, in September 2020, the whole supply (incident and prevalent) rate remained higher compared to the pre-pandemic level in September 2019. The authors suggested further investigation of the long-term effects of COVID-19 on the mental health of this age group.[141]

Leong, et al. (2022) in Canada, focused on psychotropic medications usage from January 1, 2015 to December 31, 2020 in Manitoba to assess the effects of COVID-19 public health measures. Using province-wide administrative health data, they evaluated the incident and prevalent use of psychotropic drugs in different age groups and by sex. According to their results they observed an upward trend in incident and prevalent use of antipsychotics during the period of study. Their

findings suggested a significant increase in the prevalent antipsychotics in the last quarter of 2020 for all age groups (≤18, 19–39, 40–64, 65–79, ≥80 years old) and also in 2020Q3 for those 65–79 (Coefficient Estimate: 1.43, Standard Error: 0.35, p=0.02) and ≥80 years old (Coefficient Estimate: 2.70, Standard Error: 0.99, p=0.013). They also noted a significant increase in incident antipsychotics in the last quarter of 2020 among women (Coefficient Estimate: 0.52, Standard Error: 0.12, p=0.0004) and those > 40 years (40-65 years old: Coefficient Estimate: 0.29, Standard Error: 0.11, p=0.02; 65–79 years old: Coefficient Estimate: 0.82, Standard Error: 0.18, p=0.0002; ≥80 years old: Coefficient Estimate: 1.87, Standard Error: 0.38, p<0.0001). Authors discussed that interrupted access to non-pharmacological interventions, and extended social isolation among the elderly and stressors such as home schooling and increased child care for women during the pandemic could have contributed to these results.[28] *Leong, et al*. (2022) in Canada, focused on psychotropic drugs dispensation among Manitoban children 18 years or younger (330,398 eligible participants in the first quarter of 2020) from January 1, 2015, to December 31, 2020 aimed at investigating the association between pandemic and psychotropic drug use in this population. According to their results, in terms of antipsychotic use, there was no significant changes in prevalent and incident dispensing rate.[142]

Bliddal, et al. (2022) in Denmark, through their investigation, studied consumption of psychotropic drugs and rate of incident or prevalent psychiatric disorders during the pandemic in Danish children and adolescents. Using individual-level data from health care registries in Denmark, they investigated those 5-24 years from January 1, 2017 to June 30, 2022 (108,840 incident users in total). Incident use of antipsychotics increased during COVID-19 with rate ratio of 1.08 (95% CI, 1.06-1.11), which was compatible with expected values based on the pre-COVID-19 trends in Denmark, whereas, the prevalent use remained stable.[143]

McKee, et al. (2021) in Canada, conducted a retrospective cohort study using prescribing data from Canadian retail pharmacies from provinces, Alberta, Atlantic, British Colombia, Manitoba, Ontario, Quebec, and Saskatchewan, from January 2019-December 2020. They investigated the association between COVID-19 public health measures and incident LAIAs. They parallelly assessed the switching between antipsychotics and LAIAs discontinuation. Their results showed stable prescription of LAIAs over the time period and was attributed to the alignment of prescribers with recommendations to maintain organizations.[94]

Balestrieri et al. (2021) in Italy, carried out a multi-center study to analyze the psychiatric consultation and medication prescription trends during (between 8 March and 17 May) and after (between 18 May and 30 June) COVID-19 public health measures in 2020, and then compared them with the same period in 2019. They found that the proportion of antipsychotic prescriptions increased during the pandemic (from 12.4% in 2019 to 15.6% during the pandemic, $p<0.001$) and this pattern continued after public health measures were reduced (from 13.6% in 2019 to 17.5% after the pandemic, p: 0.010). The authors discussed that this increase could have implications of increased need for pharmacological intervention for acute psychiatric symptoms since the commence of the pandemic public health measures.[144]

Clement et al. (2021) assessed the effect of COVID-19 induced drug shortages on the filling of six classes of pharmaceutical drugs of importance in chronic conditions, including the FGA, haloperidol in the USA applying Symphony Health data firm as data source. They found a higher likelihood of discontinuing haloperidol among those medications demonstrated increase in the discontinuation after Covid-19 like citalopram and dexmethylphenidate, and haloperidol also showed an increase in the incident use after COVID-19 onset against other drug classes.[145] They did the same analysis for quetiapine (a SGA) and it showed an increase in discontinuation of the

drug 1.49% (95% CI: 1.41% to 1.57%, p<0.001) and a decrease in new starts after COVID-19. The authors discussed that the results are indicative of difference in the usage pattern among different individual pharmaceutical drugs in the same class.[145] Another USA-base study by *Nason et al*. (2021) evaluated incident psychotropic drug prescriptions, including antipsychotics, during the pandemic. They used prescription data from IMS Health Quantiles Via, a longitudinal prescription data provider, from March 13 to August 8, 2020. They found a significant reduction in incident antipsychotics use (2.6% relative to the expected value), with the greatest effects among those younger than 18 years old and in men.[146]

Patel et al. (2021) conducted a study from January 2019 to September 2020 in England to investigate the impact of the COVID-19 pandemic on the number of clinical consultations via remote healthcare system, and additionally, the prescription of mood stabilizers and antipsychotics. They assessed the clinical records of 37,500 participants/week in the South London and Maudsley National Health Service Foundation Trust. They found no significant change in the overall, oral or injectable antipsychotics whole supply (prevalent and Incident) prescriptions up to September 2020. They also found a decline in antipsychotic prescriptions among children and adolescents, while older adults (>65 years old) showed a steady upward trend. In their further investigation on frequently used antipsychotics, they noted a significant increase in clozapine, while oral risperidone showed a significant decrease in April 2020 (early phase of the pandemic).[147]

In summary, among 15 studies concerning antipsychotics utility pattern, in the general population, during the COVID-19 pandemic, seven reported an increase in antipsychotics uptake during the pandemic relative to pre-COVID-19 era, while 5 reported a decrease and 3 reported stabiliy in the use of antipsychotics over this period, respectively.

Schizophrenia Population

Correll et al. (2022) in the US, conducted a review covering the period of January 2020 to March 2021 and roundtable discussion with stakeholders to answer how the access of adults with SCZ and bipolar disorders to LAIAs was changed by the COVID-19 pandemic. Results from the stakeholder discussion and review, they found that less in-person consultations driven by COVID-19 induced measurements interrupted the administration of LAIAs among those who live with SCZ and bipolar disorders.[40]

Barlati, et al. (2022) in Italy, aimed at assessing the initiation of LAIAs, LAIAs discontinuation and total number of patients on LAIAs in pre (2019) and post COVID-19 (2020) eras. Their participants as were patients with SCZ who received services from two mental health centers in Italy. The total number of patients treated with LAIAs in 2019 and 2020 were 233 and 236 respectively with the number of new LAIA users 36 in 2019 and 19 in 2020. Their observations showed a significant decline in the incident use of LAIAs (chi square = 5.255, $p = 0.022$).[63]

Miron, et al. (2022) in Romania, held a study to assess the effect of the pandemic on the incident use of LAIAs. They covered a period of 12 months before (pre-COVID-19) and after March 11, 2020 (post-COVID-19) and included 218 SCZ cases. They found that although those SCZ cases who were hospitalized remained stable, the LAIAs initiation dropped significantly (48.3%) in post-COVID-19 period compared to the pre COVID-19. They discuss the importance of further studies on the effect of this drop on the rate of relapse and other clinical outcomes in those with SCZ on LAIAs.[148]

In 2022, *Kisely et al*. in Australia, conducted a retrospective study to assess the effect of COVID-19 on antipsychotic supply among people with SCZ. The random sample was driven from Department of Human Services Pharmaceutical Benefits Scheme. Individuals at least 18 years old

with SCZ on at least three antipsychotics prescriptions between 1 June 2015 and 31 May 2020 (oral or LAIAs) were included in the study (7,873 participants in April and May 2020), and new and all prescriptions between April 1-May 31 from 2015 to 2020 were evaluated. Although a reduction was seen in new (5.7%) and all prescriptions (3.5%) of antipsychotics in April to May 2020 (the start of public health measures in Australia) compared to 2019, the finding was not significant after adjusting for other covariates (age, sex, class of treatment, residential status and type of provider). They also found that during the period of study, oral SGAs were the most commonly dispensed group compared to oral FGAs, first-generation, and second-generation LAIAs.[149] Regarding incident antipsychotics, between April 1 and May 31 in 2020 compared to the same period in 2019, oral SGAs declined by 6.4%, while the second-generation LAIAs increased by 0.6% (continuing its upward trend). New prescriptions of oral and long acting injectable FGAs were comparatively low between 1 April and 31 May in all years in the study.[149]

Zhdanava, et al. (2022) in the US, held a survey among 104 healthcare providers, with different job titles and based in different clinical settings caring from those with SCZ with LAIAs. The self-report survey focused on health care providers prescription habits and their perception regarding health outcomes of patients to evaluate changes in these factors between pre- and post-COVID-19 periods. Approximately two third of participants reported unchanged trend in overall prescription of LAIAs.[150]

Pesa, et al. (2021) in the USA carried out a study to evaluate utilization of antipsychotics in 578,011 patients with SCZ 17 weeks prior to and following the beginning of the pandemic. The investigators made comparisons among three insured populations: privately-insured, Medicare (a government program targeting access to healthcare in >65 years old, with particular disabilities or chronic conditions), and Medicaid (a government program targeting access to healthcare in those

with low income) populations. In this cross-sectional study, they found an increase in the use of oral whole supply (incident and prevalent) antipsychotics among all three populations (4.3%, 1.8% and 1.4% in commercially-insured, Medicare, and Medicaid populations, respectively), while whole supply (incident and prevalent) injectable antipsychotic use showed a decrease (4.8%, 2.5% and 1.5% in commercially-insured, Medicare, and Medicaid populations, respectively). They discuss that transferring to mail order prescriptions could have led to more oral antipsychotic prescriptions in the early months of the pandemic and that fewer pharmacists affected the uptake injectable antipsychotics after pandemic in all three population groups.[151]

In summary, among the four studies with a quantitative approach concerning antipsychotic use in the SCZ population during the COVID-19 pandemic, three reported a decrease in injectable antipsychotic incidence during the pandemic relative to the pre-COVID-19 period. One study showed no change in incident and prevalent use of whole supply antipsychotics, although a non-significant drop was noted in incident rate, and one noted a rise in incident and prevalent oral antipsychotics.

Knowledge gap

Based on the results of numerous studies, the COVID-19 induced public health measures influenced the pattern of seeking and receiving healthcare services in various groups of individuals, including those with severe mental illnesses such as SCZ.[33 57 152] However, we need to elucidate the extent of the COVID-19 public health measures on the drug utilization in specific populations within specific countries, as this might be important for future pandemics regarding financial and resource management. In the province of Manitoba, the impact of COVID-19 restrictions on the use of antipsychotics has been evaluated in the general population but not specifically in SCZ.[28]

As shown, studies on the utilization of antipsychotics in the general population and specific groups of patient populations such as SCZ have conflicting results[28 94 147 148] and could largely be due to the variation in the pandemic and applied policies by regions and or different research methods applied in these investigations. Moreover, lack of population-based studies, limited follow-up time, and limitations of ascertainment of the accuracy of the data on the prescription of antipsychotics (survey, registry databases and so on) as the limitations of available literatures indicates the need to such investigations.

The present study included a large population with SCZ in Manitoba, without sociodemographic restrictions, and with long period of time (five years before and two years after the establishment of public health measures in Manitoba) by applying data from a governmental registry in the province regarded as a valid source in population-based studies.

Objectives and hypotheses

The overall objective of this thesis is to examine the impact of COVID-19 public health measures on antipsychotic medication use within a population with SCZ.

Objective 1: I aimed to compare the prevalent and incident rates of overall and individual antipsychotics at two time points during COVID-19 (Apr-Jun 2020 and Apr-Jun 2021) compared to the expected trend among individuals living with SCZ in Manitoba. Additionally, I aimed to compare the overall antipsychotics rates stratified by age and sex in Apr-Jun 2020.

> Null hypothesis (H_o): COVID-19 public health measures did not change the prevalent and incident rates for all antipsychotics relative to the expected trend among people with SCZ in Manitoba, nor by age and sex. Alternative hypothesis (H_a): COVID-19 public health measures led to a temporary lowering in the prevalent and incident rates for all

antipsychotics among people with SCZ in Manitoba, and this difference was more pronounced in females and in >80 years of age.

Objective 2: I aimed to compare the rates of prevalent and incident antipsychotics dispensing among the first generation vs. the atypical antipsychotics at two time points during COVID-19 (Apr-Jun 2020 and Apr-Jun 2021) compared to the expected trend among individuals living with SCZ in Manitoba.

Null hypothesis (H_o): COVID-19 public health measures did not change the prevalent and incident rates of first- vs. atypical antipsychotics relative to the expected trend among people with SCZ in Manitoba. Alternative hypothesis (H_a): COVID-19 public health measures led to a temporary lowering in the prevalent and incident rates for all atypical antipsychotics among people with SCZ in Manitoba.

Objective 3: I aimed to compare the rates of prevalent and incident antipsychotics dispensing among oral vs. injectable antipsychotics at two time points during COVID-19 (Apr-Jun 2020 and Apr-Jun 2021) compared to the expected trend among individuals living with SCZ in Manitoba.

Null hypothesis. (H_o): COVID-19 public health measures did not change the prevalent and incident rates of oral vs. injectable antipsychotics compared to the expected trend among people with SCZ in Manitoba. Alternative hypothesis (H_a): COVID-19 public health measures led to a temporary lowering in the prevalent and incident rates for all oral antipsychotics among people with SCZ in Manitoba.

Chapter 3: Materials and Methods

Study design, data sources, participants, and time period

Study design

We conducted a population-based repeated cross-sectional study.

Data sources

We used the Manitoba Population Research Data Repository in the Manitoba Centre for Health Policy (MCHP). This repository is a collection of several governmental administrative datasets such as health care, education, residential and others. Most data in the MCHP repository are updated annually. This anonymized population registry consists of virtual and deidentified records of individuals in Manitoba; an identification number is assigned to each individual in the registry permitting linkage to multiple data sources possible.[68 153 154 155 156 157]

Within MCHP, I used the Drug Program Information Network (DPIN)[158] for antipsychotic prescription drugs (covering prescriptions from 1995; medications received in hospital and nursing station are not included), physician claims data and hospital abstracts[159] for diagnoses (from 1970), and the Manitoba Health Insurance Registry[160] and Statistics Canada[161] for demographic information (from 1970). Manitoba Health Insurance Registry updates MCHP Research Registry as a key component in the MCHP Population Health Data Repository on a twice-yearly basis regarding demographic and insurance coverage data.[162] Canada statistics conduct a census on all Canadian citizens every 5 years (since 1971) in dissemination areas to collect demographic, social and economic characteristics such as age, sex, employment, marital states and income on individual and family level.[163] Complete updates of DPIN, physician claims data and hospital abstracts are sent to the MCHP in Fall each fiscal year (April 1-March 31). The validation of these databases for population health studies is well established.[155 156 157]

Study population

We included all individuals with ≥1 physician or ≥1 hospital claim for SCZ (International Classification of Diseases (ICD)-9-CM: 295, ICD-10: F20, F21, F23.2, or F25).[164] This is a validated case definition for SCZ.[68 165 166] Individuals with a SCZ diagnostic code within five years prior to a quarter or year of interest and listed in the Manitoba Health Seniors and Active Living (MHSAL) registry for at least one day of coverage that quarter or year were included. All individuals meeting these criteria who were prescribed at least one antipsychotic medication within each quarter from 2015 to 2021 fiscal year (from April 1 to March 31)[167] in Manitoba were included. I did not apply any specific exclusion criteria.

Time period

We included data from April 1, 2015, to March 31, 2021. This range of time covered pre-COVID-19 (April 1, 2015-March 31, 2020) and during-COVID-19 periods (April 1, 2020-March 31, 2021). During this time, Manitoba experienced five waves of COVID-19.[15] I specifically defined the first fiscal quarter of 2020 (April 1-June 30) as the primary intervention point for the study because it was two weeks following the implementation of the COVID-19 public health measures in Manitoba. The public health measures enacted in March 2020 were the most severe in terms of affecting the access to prescription medications. The second intervention point was defined as April 1-June 30, 2021. Fiscal quarters were defined as: Quarter 1 (Q1): April to June, Quarter 2 (Q2), July to September, Quarter 3 (Q3), October to December, and Quarter 4 (Q4), January to March for the year 2015 to 2021.

Ethical and privacy committee approval

This study was approved by the Human Research Ethics Board of the University of Manitoba and the Manitoba Health, Seniors, and Active Living Health Information Privacy Committee. Informed

consent was not required with the use of de-identified administrative data. The results and conclusions are those of myself and no official endorsement by Manitoba Health and Healthy Living was intended or should be inferred.

Methods

Exposure, outcomes, and variables

The exposure was the establishment of COVID-19 public health measures, including limiting the number of drug redemptions, enacted March 13, 2020, in Manitoba. Before and including March 30, 2020, is defined as the pre-COVID-19 time and after and including April 1 2020 is during-COVID. I discussed the overall antipsychotics use in the first fiscal quarter of 2021 (April-June) to evaluate the continuation of situation in April-June 2020 after a long time.

The outcomes were the prevalent and incident rates of antipsychotics. Medications included in the analysis were identified using their Anatomic Therapeutic Classification (ATC) code (antipsychotic agents: N05A except N05AN).[168] [169] The antipsychotics included were all antipsychotics. Four of the most commonly used antipsychotics in Manitoba (quetiapine, olanzapine, risperidone, clozapine) accounted for >76% of antipsychotics dispensed during the study period. Assessing the dispensation of these antipsychotics were meant to indicate prescribing practice during the pandemic in Manitoba. Overall antipsychotics were also categorized by route of administration (***Appendix III***) and by generation (***Appendix III***). The prevalent rate was defined as the number of individuals who use the medication within each quarter during the study period per 1,000 individuals. The incidence rate was defined as the number of individuals with no dispensation of the drug of interest for at least 3 years prior to receiving their first prescription per 1,000 individuals. To compute the drug dispensing rate for each drug in each fiscal quarter, I

divided the number of individuals who were dispensed a prescription for that medication by the total number of individuals with SCZ who lived in Manitoba during that quarter.

The following information on each individual was collected: sex (male/female),[170] age at the start of the quarter of interest (in years and categorized years of age: ≤18, 19-39, 40-64, 65-79 and ≥80), [28 171 172] and residence (urban and rural).[173] Household income is summarized into five quintiles by urban and rural area representing ten total categories and are ranked in increasing order, with the first quintile being the lowest income category: urban-1 (U1) to urban-5 (U5); and rural-1 (R1) to rural-5 (R5). The density rule is used for the urban/rural designation.[174] According to Canada census a rural area has a populations ≤400 persons per square km (urban: Winnipeg or Brandon and rural: elsewhere in Manitoba).[173 175]

We included the following 30 comorbidities to compute the Elixhauser Comorbidity Index per person (***Appendix II***), which is a summary measure of comorbidities:[176 177] congestive heart failure, cardiac arrhythmia, valvular disease, pulmonary circulation disorders, peripheral vascular disorders, hypertension without complications, hypertension with complications, paralysis, other neurological disorders, chronic pulmonary disease, diabetes without complications, diabetes with complications, hypothyroidism, renal failure, liver disease, peptic ulcer disease excluding bleeding, HIV/AIDS, lymphoma, metastatic cancer, solid tumor without metastasis, rheumatoid arthritis/collagen, coagulopathy, obesity, weight loss, fluid and electrolyte disorders, blood loss anemia, deficiency anemia, alcohol abuse, drug abuse, and depression with at least one hospitalization in one year with a diagnosis of verified ICD-9 and ICD-10 codes or at least one physician visit in one year with a diagnosis of verified ICD-9 and ICD-10 codes (Appendix II). Comorbidities were included as a count: 0, 1, 2, 3 or ≥4. The Charlson Comorbidity Index as another widely used comorbidity index was compared to Elixhauser Comorbidity Index in one

study on people with SCZ,[177] but demonstrated that the Elixhauser outperformed the Charlson Comorbidity Index on discriminatory ability and provided better risk adjustment in predicting mortality in those with schizophrenia. Polypharmacy was defined two ways: >5 dispensed medications in three months or >10 dispensed medications in three months[178]. Different drugs classes were identified by the ATC code (with the inclusion of antipsychotics) and over the counter drugs were not included.

Statistical analysis

I described the total SCZ population at the first fiscal quarter of 2020 using the mean (standard deviation) or N (percent) on the following characteristics: age, sex, residence, income quantile, comorbidity count, and polypharmacy use, and stratified the total population by age and sex.

My first objective investigated the antipsychotics overall, and then four of the most used antipsychotics prescribed in Manitoba and stratified by age and sex. Secondly, I investigated first- vs. atypical antipsychotics (***Appendix III***), and third, by route of administration (***Appendix III***).

For all objectives, I used PROC AUTOREG (***Appendix IV***) to estimate the associations between antipsychotic use, time, and the COVID-19 pandemic, using a linear autoregression model fitted using maximum likelihood and estimating the Durbin-Watson statistic up to the 4th order for autocorrelation (***Table 1, Table 2***). Two models were run based on the immediate effect of COVID-19 public health measures (1: 2020-Q1) and then one year into the pandemic (2: 2021-Q1). I tested the autoregression assumptions including linearity, normality, and homoscedasticity. I reported the rate per 1,000 SCZ participants. Regression results were reported as the effect estimate and standard error (SE) and p-value.

I also performed a sensitivity analysis for all objectives including 2 physician or 1 hospital claim (for ICD-9-CM: 295, ICD-10: F20, F21, F23.2, F25) in the 2 years before the quarter or year of

interest to assess the sensitivity of my results to the inclusion criteria and accuracy of SCZ diagnosis.

Analyses was conducted using SAS statistical software (version 9.4). Statistical significance was set at $p < 0.05$.

Chapter 4: Results

Sociodemographic and clinical characteristics

The population in the first fiscal quarter ranged over the study period from 8,196 (2015) to 9,166 (2021, ***Table 3***). At the beginning of the fiscal quarter of interest, April 2020, the average age of the study participants was 46.9 (SD = 17.9) years, and more than half were male (59.67%). Two-thirds of the participants (74.84%, n = 6,769) resided in an urban region and 27.97% (n = 2,530) were from the lowest urban income quantile. Half of the population (51.45%) had 1-2 comorbidities, with almost one-third (29.23%) of the population were on more than five drugs at the start of the quarter of interest. Conducting the sociodemographic analysis by sex showed similar distribution of characteristics among males and female (***Table 3***). Sociodemographic analysis by age groups demonstrated some differences, including an increasing number of comorbidities and polypharmacy with age (***Table 4***).

Dispensation Rate of Antipsychotics

Prevalent Antipsychotics

Prevalent rates – Objective 1

A non-significant decrease was observed in the prevalent use of all antipsychotics between pre- and during-COVID-19 April-June 2020 (estimate: -1.7, SE: 4.3, p=0.6, ***Figure 1***). One year later, in 2021Q1, the prevalent use of antipsychotics increased non-significantly relative to expected trend (p=0.3, ***Table 5***). Compared to the expected trend, quetiapine (estimate: -2.2, SE: 1.9, p = 0.2) and clozapine (estimate: -1.01, SE: 2.6, p = 0.7) experienced a non-significant decrease in the first fiscal quarter of 2020, whereas the opposite was true for risperidone (estimate: 0.1, SE: 3.4, p = 0.9) and olanzapine (estimate: 0.04, SE: 3.6, p = 0.9, ***Table 5, Figure 1***). The most considerable absolute change was seen in quetiapine. In 2021Q1, compared to the expected trend, quetiapine

(estimate: -2.5, SE: 1.9, $p = 0.2$) and clozapine (estimate: -1.8, SE: 2.6, $p = 0.5$) experienced a non-significant decrease while risperidone (estimate: 5.2, SE: 3.4, $p = 0.9$) and olanzapine (estimate: 4.3, SE: 3.6, $p = 0.2$, ***Table 5***) showed the opposite. Risperidone showed the greatest absolute change.

Comparing April-June 2020 with the expected trend from the previous 5 years by age, only those 65-79 years of age experienced a significant change, with a notable decrease in the prevalence of all antipsychotics (estimate: -21, SE: 9.1, $p = 0.02$, ***Table 6, Figure 2***). All remaining age groupings experienced a non-significant decrease in the prevalence of antipsychotics, except for those 40-64 years, which experienced a non-significant increase (estimate: 4.5, SE: 5.6, $p = 0.4$). Those ≤18 years experienced the largest absolute change in 2020Q1 (estimate: -28.7, SE: 35.6, $p = 0.4$, ***Table 6***). Again, stratifying results by sex found no significant change, with a non-significant rise in antipsychotic prevalence in males (estimate: 4.8, SE: 5.6, $p = 0.4$) and a non-significant drop for females (estimate: -11, SE: 8.3, $p = 0.1$), with the latter having a larger absolute change (***Table 6, Figure 3***).

Prevalent rates – Objectives 2 and 3

I observed a non-significant decrease in the prevalent use of FGAs in 2020Q1 relative to the expected trend (estimate: -3.3, SE: 2.9, $p = 0.2$, ***Table 5, Figure 4***), while atypical antipsychotics showed a non-significant increase during this time (estimate: 1.4, SE: 4.7, $p = 0.7$). The absolute change in FGAs prevalent use was more considerable (***Table 5***). While a non-significant decrease was noted in oral antipsychotics prevalent use in 2020Q1 compared to the expected trend (estimate: -1.2, SE: 4.3, $p = 0.7$), injectable antipsychotics experienced a non-significant increase in this quarter (estimate: 0.5, SE: 2.8, $p = 0.8$). The absolute change in the oral antipsychotics prevalent use was more considerable (***Table 5, Figure 5***).

Relative to the expected trend, in 2021Q1, FGAs (estimate: 2.1, SE: 3, p = 0.4) and atypical antipsychotics (estimate: 4.9, SE: 4.7, p = 0.3) experienced a non-significant increase in prevalent rate (more considerable change in SGA, ***Table 5***) that was true about oral and (estimate: 4.6, SE: 4.3, p = 0.3) injectable (estimate: 2.6, SE: 2.8, p = 0.3) antipsychotics (more considerable change in oral antipsychotics, ***Table 5***).

Incident Antipsychotics

Incident rates – Objectives 1

A significant decrease was observed in the incident dispensation of all antipsychotics in April-June 2020 when compared to the expected trend (estimate: -1.3, SE: 0.5, p = 0.01). Extending the analyses to include one year later in 2021Q1, this decrease became non-significant (estimate: -0.2, SE: 0.6, p = 0.7, ***Table 5, Figure 6***). Compared to the expected trend, the incident rates of quetiapine (estimate: -1.08, SE: 1.07, p = 0.3), olanzapine (estimate: -1.6, SE: 0.8, p = 0.08), risperidone (estimate: -0.7, SE: 0.8, p = 0.3) and clozapine (estimate: -0.3, SE: 0.6, p = 0.5) use showed a non-significant decline in 2020Q1, among which the most considerable absolute change was detected in olanzapine (***Table 5***). In 2021Q1, compared to the expected trend, quetiapine (estimate: -1.2, SE: 1.09, p = 0.2) and clozapine (estimate: -0.6, SE: 0.6, p = 0.3) experienced a non-significant decrease while a non-significant increase was observed in olanzapine (estimate: 1.2, SE: 0.9, p = 0.1) and a significant increase was seen in risperidone (estimate: 1.8, SE: 0.8, p = 0.03, ***Table 5***). The most considerable absolute change was seen in risperidone.

All age categories experienced a non-significant drop in antipsychotic incidence with the largest decrease for the 19-39 years group (***Table 6, Figure 7***). Comparing the incidence in 2020 April-June with the expected trend there was a non-significant drop in the incident consumption of

antipsychotics in both males ($p = 0.4$) and females ($p = 0.1$) which was more considerable among males (***Table 6, Figure 8***).

Incident rates – Objectives 2 and 3

A non-significant decline was observed in the incident use of both FGAs ($p = 0.07$) and atypical antipsychotics ($p = 0.09$) in 2020Q1 relative to the expected trend, with the atypical antipsychotics showing a more considerable decrease (***Table 5, Figure 9***). While a decrease was noted in the incident use of oral antipsychotics ($p = 0.09$) in 2020Q1 compared to the expected trend, the incident use of injectables experienced an increase ($p = 0.06$). The absolute change in the incident use of oral antipsychotics was more considerable and both of changes were non-significant (***Table 5, Figure 10***).

A non-significant drop was observed in the incidence of FGAs ($p = 0.6$) while the incidence of atypical antipsychotics ($p = 0.04$) showed a significant increase in 2021Q1, compared to the expected trend. The absolute change was greater for atypical antipsychotics (***Table 5***). Oral ($p = 0.8$) and injectable ($p = 0.4$) antipsychotics showed a non-significant rise and the change in injectables was more considerable.

Sensitivity analyses

In the sensitivity analysis, the population in the first fiscal quarter ranged over the study period from 5,250 (2015) to 5,651 (2021, ***Table 3***). On the examined characteristics distribution, the population used for the sensitivity analyses was broadly like that used in the primary analysis. Sensitivity analysis using a modified inclusion criteria for SCZ demonstrated similar results to the original inclusion criteria for SCZ, showing a non-significant decrease in overall prevalent (estimate: -3.9, SE: 5.8, $p = 0.4$) and incident (estimate: -0.7, SE: 0.6, $p = 0.2$) antipsychotics, albeit non-significant likely due to a smaller cohort (N=5,642, ***Table 7***). In the first fiscal quarter of 2021,

all prevalent (estimate: 6.9, SE: 5.8, $p = 0.2$) and incident (estimate: 0.09, SE: 0.7, $p = 0.8$) antipsychotic use showed a non-significant increase.

Chapter 5: Discussion

Overall findings

The overall objective of this thesis was to examine the impact of COVID-19 public health measures on antipsychotic medication utility patterns within a population with SCZ. Previous studies in this area have been in different parts of the world and different populations; thus, there remains a need for such studies performed in a particular region and population, especially given the differences in COVID-19 public health measures by region. The present study is, to the best of my knowledge, the first and only study on the effect of COVID-19 health measures on the use of antipsychotics among those with SCZ in Manitoba. I compared these rates between the period before the pandemic to either the first 3 months of the pandemic or to the end of the first year of the pandemic. Overall, I hypothesized that the public health measures enacted during the COVID-19 pandemic would not change antipsychotic drug prescribing to people with SCZ in Manitoba, beyond what is normally expected for drug utilization from year to year. During the first few months of the COVID-19 pandemic, I found the prevalent rate of antipsychotic prescribing to those with SCZ did not change, but I noted a significant decrease in the incidence rate of all antipsychotics, thus, I rejected my first null hypothesis in relation to the incident user findings. However, this incident finding was no longer apparent when examining sub-categories of antipsychotics, including by generation or route of administration, which led me to accept my null hypotheses for objectives 2 and 3. Regarding objective 4, I also accepted the null hypothesis since changes in incident and prevalent antipsychotics in 2021Q1 were not significant.

The distribution of the demographic characteristics among my cohort of people with SCZ in the current study is comparable to what has been reported in previous Manitoban studies of SCZ, as well as in other Canadian and global studies in SCZ. *Chartier et al* (2018) in their report on mental

illness in adults in Manitoba, described the epidemiology of SCZ in the province as a male-dominated mental illness most commonly occurring within the ages of 18-44 years and, is more prevalent in urban regions rather than rural, as well as among low-income quantile in both urban and rural areas.[68] These values were similar to my study and to other COVID-19 studies in SCZ performed outside Manitoba, including one in the Canadian province of Ontario, between March 2019-2021, with a mean age of 49.7 years, 54.2% males and 40.1% in the lowest income quantile.[33] The characteristics were similar to a study outside Canada performed by *Kisely et al* in Australia studied 7873 patients with SCZ in April and May 2020, with a mean of age of 44.4 years and males accounted for 54.6% the population.[149] In terms of comorbidity, *Mitchell et al* (2006) reported that more than half of people with SCZ live with at least one concurrent medical condition.[179] *Carney et al*, reported that only 38% of their participant with SCZ had 1 or 2 comorbidities and this differed with my results (~50%) and could be due to recruiting younger participants predominantly from rural areas and mostly women.[180] My sensitivity analysis showed a similar distribution of sociodemographic characteristics in SCZ to that of the primary analyses.

Prevalent Rate of Antipsychotics

Although I did not observe any significant, other than that in one age category (65-79 years), prevalent antipsychotic rate changes during the first 3-12 months of the pandemic, I will discuss the non-significant findings. I observed a non-significant reduction in the prevalent antipsychotics in the first three months of the pandemic in those with schizophrenia, followed by a non-significant increase in the year that followed. These results were compatible with my alternative hypothesis regarding a temporary reduction in the prevalent rate in the first few months of the pandemic. This finding indicates that for those with SCZ in Manitoba, access to antipsychotics was sustained among existing users. It also implies the success of policies to supply the drug market and maintain

access to care providers and pharmacies during the pandemic. *Leong et al* also noted no significant change in prevalent antipsychotics in the general population in Manitoba in April-June 2020 compared to the previous 5 years,[28] with another study finding similar when assessing new and refill antipsychotics prescriptions in the SCZ population between April-May 2020 compared with the same period of time in 2016-2019.[149] *Patel, et al*. studied 37,500 SCZ participants to assess the impact of the pandemic on the antipsychotics prescription rate. They noted no significant change regarding the overall antipsychotics prescription although a decrease was observed among children and adolescents.[147] *Leong, et al*. studied 330,398 eligible children in Manitoba and noted no significant change in prevalent antipsychotics dispensation in April-June 2020, compared to the mean of the same quarters in the pre-COVID era.[142]

The only significant change in prevalent antipsychotics in SCZ in Manitoba in the first three months of the pandemic was observed in those 65-79 years old, which showed a decrease. This may have been due to challenges in the delivery of virtual healthcare or access to pharmacies; and highlighting the potential importance of sustained medications access possibly via family or caregiver support. It might be expected that those in the older age (≥80 years) would also experience a decrease, but I did not find this, and it might be due to the small number of individuals with SCZ in this age group (N=319 individuals). *Leong et al*. in their investigation on general population of Manitoba detected a non-significant increase in the prevalent antipsychotics in 65-79 years in April-June 2020, when compared to the expected trend, which is compatible with the overall non-significant increase in the whole general population observed.[28]

Among the four individual antipsychotics assessed in the present study, quetiapine was the most frequently prescribed antipsychotics in Manitoba, and its prevalent rate experienced a considerable decrease in the first few months of the pandemic, albeit non-significant, of 2.2 per 1,000

individuals. To the best of my ability, there were no studies available that reported the effects of COVID-19 health measures on the prevalent use of the individual antipsychotics that I report here. However, one study by *Patel, et al*. in England noted a significant increase in the overall prescription of clozapine and decrease in oral risperidone respectively during April 2020.[147] Another study by *Clement et al*. in the USA found the new onset of haloperidol, a FGA, was higher during COVID-19 compared to pre-COVID era and may have been because mostly, haloperidol is started for inpatients during hospitalization or limited resources. They also showed a decrease in the incident use of quetiapine, a SGA, after COVID-19, similar to my findings, which itself may justify the rise in the incident haloperidol after COVID-19.[145] The use of haloperidol in my study was not examined individually, given the low number of prescriptions.

Incident Rate of Antipsychotics

In the current study, I observed a significant reduction in the incident antipsychotics from 3.8 per 1,000 SCZ individuals to 2.3/1,000 (***Figure 1***). SCZ individuals in Manitoba in April-June 2020. This reduction appeared to be temporary, because by the end of the first year of the pandemic (Jun 2021), this finding was no longer significant albeit there was still a reduction. These results aligned with my alternative hypothesis regarding a temporary decline in the incident antipsychotics in the first few months of the pandemic. *Lau et al.* in their study showed a significant reduction in pharmaceutical drugs shortage as a driver of interrupted access chain to them in Canada one year after the pandemic.[19] *Nason, et al*. investigated new prescriptions of antipsychotics from March 13 to August 8, 2020, which showed a significant reduction in incident antipsychotics during this time versus pre-COVID-19 era in the USA. They included weekly cumulative incident antipsychotics during this time and compared to the expected rate, where there were 47,467 fewer new prescriptions from March 13 to August 8, 2020.[146] *Kisely, et al*. also noted a non-significant drop

in new antipsychotics prescriptions in Australia in comparison between 1 April to 31 May 2020 and the respective period of time in 2015-2019.[149]

The sensitivity analyses tested whether the primary effects were sensitive to the definition of SCZ. I modified the definition two-fold: to increase the specificity for SCZ, I increased the number of required physician codes from one to two and reduced the timeframe between the diagnostic code and subsequent drug dispensation from 5 years to 2 years. For both the incident and prevalent rate in the period of April-June 2020, I found sensitivity results to be like that of the primary analyses in terms of the effect direction, with both the prevalence and incidence decreasing. However, the incident finding that was significant for the overall effect was no longer significant and was likely related to the smaller number of individuals with SCZ who met this definition (N = 9,045 for the primary compared to N = 5,397 for the sensitivity analyses). This incident result may better reflect those with newly diagnosed SCZ given that the timeframe for a physician or hospital claim code was reduced from 5 years to 2 years prior to the quarter of interest. In 2021Q1, sensitivity analysis showed the same results regarding the statistical significance and all incident and prevalent both showed non-significant increase.

Although the stable rate of prevalent antipsychotics potentially demonstrates that regular antipsychotics users had sufficient drug supply during the first 3-12 months of the pandemic, my incident results reflect that these services were interrupted among new users. These new antipsychotic users could either be newly diagnosed individuals with SCZ or those who had not received an antipsychotic for 3 years prior. The reduction in the incident rate could have been due to challenges in connecting with newly diagnosed cases of SCZ or contagion fear, which itself could be worsened by uncontrolled psychotic symptoms. The COVID-19 induced health measures limiting immigration of new cases of SCZ to Manitoba from other regions could be another

contributor to this result. In March to April 2020, Canada experienced an increasing pattern in drug shortages that was regarded as an alarming trend.[23] In response to the situation, authorities applied new policies related to the importing and exporting of drugs and established a drugs shortage monitoring and reporting system to avoid the negative consequences of drugs shortage on the market and healthcare sector.[24 25 26] Presumably, the incidence of SCZ did not change during the pandemic, however, this remains to be fully elucidated with one rapid review predicting an increase incidence of psychosis following the pandemic due to extreme psychosocial stress from the pandemic or directly related to the virus.[181]

The significant increase in the incident atypical antipsychotics in April-June 2021, relative to the expected trend, could be the result of new users that were not captured during the initial few months of the pandemic. This change could be the driver of the significant increase in incident risperidone, an atypical antipsychotic, during April-June 2021. Compared to other individual antipsychotics assessed, risperidone was the only with a significant rise, which could be attributed to prescribing practices by the healthcare providers according to the benefit/risk ratio of risperidone (safety profile and price). *Barlati, et al*. observed a significant decline in new start of LAIAs in SCZ outpatients on LAIAs in pre (2019) and post COVID-19 (2020) eras.[63] *Miron, et al*. found that although the admitted SCZ cases stayed stable the LAIAs initiation dropped significantly (48.3%) in the post-COVID-19 period.[148]

Olanzapine, as the second most frequently used antipsychotic in SCZ in Manitoba, experienced the most considerable drop in incident dispensations in April-June 2020 (Olanzapine: 1.6 per 1000 individuals vs. others ranged from 0.3 – 1.08 per 1,000). The only antipsychotic with a significant change in April-June 2021was risperidone, which was the only significant change among the four antipsychotics assessed (1.8/1,000, SE: 0.8, p=0.03). *Clement et al*. in their investigation noted an

increase and a decrease in the incident prescription of haloperidol and quetiapine respectively when compared after COVID-19 with the before COVID-19 era.[145]

Incidence use of the atypical antipsychotics compared to the FGAs showed more considerable non-significant decrease. The atypical antipsychotics are more commonly used than the first-generation drugs.[99] [100] *Kisely et al*. noted that during their study time between April 1-May 31 from 2015 to 2020, oral SGAs were the most commonly used antipsychotics in SCZ.[149] I noted a non-significant increase in the injectable antipsychotic incidence in April-June 2020, compared to the expected trend. This observation could be a consequence of prescribers in Manitoba switching from oral to injectable antipsychotics in new cases of SCZ to avoid frequent visits by considering pandemic situation and health measures.

A more considerable drop in males versus females as well as those 19-39 years old compared to other age groups noted in the present study are compatible with the epidemiology of SCZ in the province. The prevalence of SCZ in Manitoba is higher in males than females in the age range of 18-44 years. *Nason, et al*. detected a significant drop in incident antipsychotics when compared during March 13 to August 8, 2020,and pre-COVID-19 era which was greater among those younger than 18 and in men.[146] *Leong, et al*. observed no significant change in the incident dispensing rate of antipsychotics in April-June 2020 relative to the mean rate of the same quarters in 2015-2019 when focused on 330,398 Manitoban children.[142] *Bliddal, et al*. in their investigation on Danish children and adolescence, covering January 2017 to June 2022, observed an increase, compatible with pre-COVID-19 trend, in incident consumption of antipsychotics during the pandemic.[143] *Leong, et al.* found a significant rise in the incident use of antipsychotics in the general population in Manitoba in April-June 2020 compared to the secular trend among those ≥ 80 years old.[28]

Pandemic measures including controlling drug shortages and maintaining access to healthcare providers likely helped to maintain a stable antipsychotics utility rate in SCZ in Manitoba. The lifting of the maximum one-month supply of prescription medications in May 2020 and increased virtual visits also likely led to a return to the expected drug utilization patterns from any unexpected fluctuations in the early phase of the pandemic.

Strengths

To the best of my knowledge, this study is the first in Manitoba to examine different antipsychotic dispensing in schizophrenia related to COVID-19 public health measures. Compared to similar studies in other countries, the present study covers the entire first year of COVID-19 pandemic. I used an appropriate statistical analysis method to reduce the bias and achieving valid results. Correction for autocorrelation between the rates after fitting autoregression model to the time series data results in more accurate parameter estimation.[9 28 182] Moreover, due to the universal healthcare offered in Canada and Manitoba, I accessed a provincial administrative health database that provided information on the entire Manitoban population regardless of sex, age, or socioeconomic level. This reduces the probability of selection bias and enhances the generalizability of my results across Manitoba and potentially to other countries with universal healthcare access. This study included a large sample of people with schizophrenia (N>9,000).

Limitations

This study also had its limitations, including being conducted on a provincial level and may not be indicative of situation in other provinces in Canada or at national level, given the differences in the COVID-19 public health measures by area. Using administrative health databases has limitations such as missing data in which investigators are not able to capture the values, such as income data in the current study. Not all healthcare providers in Manitoba are paid on a fee-for-

service basis (for e.g., they offer alternative payment plans if the individual does not have provincial healthcare coverage); thus, their billing codes are not captured in the Medical Services data used here, and may result in underreporting in some regions.[159]

Misclassification bias is a potential bias in my study, as I have used physician billing codes to define a SCZ population and this may not reflect true cases of diagnosed individuals. It could lead to the misclassification of individuals as SCZ cases or of antipsychotics dispensed to non-SCZ cases. To address this bias, I conducted a sensitivity analysis which largely pointed to the same conclusion as the primary results. In this study, I accessed data on antipsychotic dispensing from pharmacies, however, I did not assess consumption of medicines, and this could lead us to observe that access was consistent for prevalent antipsychotics in SCZ, but could not assess whether the individuals were actually taking their medicines. I also did not assess the potential adverse effects of COVID-19 public health measures on outcomes in those with schizophrenia during the time of my study and represent a potential future direction. This study also did not consider the association between the prevalent or incident rate of antipsychotics by the different waves of COVID-19 pandemic over the time of this study.

Chapter 6: Conclusions and Future Considerations

According to the present study, new cases of SCZ, males, and those between 19-39 years, were at higher odds of interrupted access to antipsychotics due to COVID-19 pandemic measures. Incident users in this study are both new cases of SCZ and chronic users who had at least a 3-year interruption in their antipsychotic therapy. Findings from this study are of importance for policymakers to continue to take efficient means for ensuring continued access to pharmaceutical drugs in new users of antipsychotics in the SCZ population. Having sustained access to the antipsychotics in SCZ is an important issue by considering the high rate of non-adherence in this group of patients and the negative effects of discontinuing an antipsychotic.[183] Timing of treatment with antipsychotics in the first episode of psychosis is of importance as the initiation of an antipsychotic after one week compared to within that the first week was associated with longer hospital admissions.[184] My results additionally have implications to define the direction of investment in the healthcare sector after the pandemic is over and of the need to direct policies specifically focusing on incident antipsychotics users to facilitate their drug access in future pandemics. This study serves lays the foundation, along with many other studies, to understand medicine resources management during the COVID-19 pandemic in Canada. The next immediate steps would be to determine whether those with newly diagnosed with SCZ in the first months of the COVID-19 pandemic in Manitoba had an increased risk for any severe outcomes such as suicide, hospitalizations, or mortality. There remains a need for further investigation into the focus on COVID-19 induced measures on adherence to pharmacotherapy specifically in schizophrenia, with consideration for the severity of pandemic waves, as a covariate.

Tables

Table 1. Autocorrelation Durbin-Watson test *p*-value (1st, 2nd, 3rd, 4th order)[a]

	Comparison	2020Q1 Durbin-Watson test[b] (1st, 2nd, 3rd, 4th order[c])	2021Q1 Durbin-Watson test (1st, 2nd, 3rd, 4th order)
Prevalence	All antipsychotics	0.0024*; 0.4619; 0.7499; 0.7606	0.0165*; 0.4529; 0.7145; 0.7675
	Quetiapine	0.0296*; 0.0548; 0.0307*; 0.0929	0.0027*; 0.1327; 0.2750; 0.1657
	Olanzapine	< 0.0001*; 0.0002*; 0.0051*; 0.0359*	< 0.0001*; 0.0002*; 0.0102*; 0.0333*
	Risperidone	< 0.0001*; < 0.0001*; 0.0018*; 0.0160*	< 0.0001*; < 0.0001*; 0.0023*; 0.0148*
	Clozapine	< 0.0001*; < 0.0001*; < 0.0001*; 0.0058*	< 0.0001*; < 0.0001*; 0.0002*; 0.0065*
	≤ 18 years	< 0.0001*; < 0.0001*; 0.0027*; 0.0624	
	19-39 years	0.0070*; 0.1412; 0.3331; 0.1634	
	40-64 years	0.0046*; 0.3555; 0.4462; 0.3617	
	65-79 years	0.0028*; 0.1291; 0.0181*; 0.0114*	
	≥ 80 years	0.0062*; 0.0376*; 0.1963; 0.6854	
	Male	0.0050*; 0.1791; 0.2968; 0.2335	
	Female	< 0.0001*; 0.0001*; 0.0191*; 0.1650	
	First-generation	0.0417*; 0.5287; 0.1243; 0.1673	0.0449*; 0.5687; 0.1646; 0.1133
	Atypical	< 0.0001*; 0.0662; 0.4465; 0.5846	0.0002*; 0.0206*; 0.2323; 0.5412
	Oral	0.0005*; 0.1501; 0.4644; 0.3311	0.0061*; 0.1361; 0.4604;0.3125
	Injectable	< 0.0001*; 0.0793; 0.4532; 0.4451	< 0.0001*; 0.0349*; 0.1443; 0.3923
Incidence	All antipsychotics	0.4264; 0.6752; 0.0854; 0.4311	0.1877; 0.6630; 0.4661; 0.5578
	Quetiapine	0.6347; 0.2808; 0.8188; 0.4917	0.3891; 0.2713; 0.9298; 0.3803
	Olanzapine	0.0849; 0.9731; 0.9103; 0.7476	0.1513; 0.8365; 0.7472; 0.8817
	Risperidone	0.8046; 0.2186; 0.1648; 0.2688	0.7940; 0.1666; 0.1910; 0.3906
	Clozapine	0.7305; 0.0026*; 0.5526; 0.5803	0.8418; 0.0011*; 0.4699; 0.6292
	≤ 18 years	N/A	
	19-39 years	0.2886; 0.7134, 0.4855; 0.5181	
	40-64 years	0.1848; 0.9555; 0.8225; 0.3500	
	65-79 years	0.2247; 0.2544; 0.8685; 0.8373	
	≥ 80 years	0.6768; 0.2199; 0.7675; 0.5468	
	Male	0.1116; 0.9275; 0.7115; 0.2685	

Table 1. Autocorrelation Durbin-Watson test *p*-value (1st, 2nd, 3rd, 4th order)[a]

Comparison	2020Q1 Durbin-Watson test[b] (1st, 2nd, 3rd, 4th order[c])	2021Q1 Durbin-Watson test (1st, 2nd, 3rd, 4th order)
Female	0.7470; 0.2788; 0.7368; 0.5371	
First-generation	0.0523; 0.7672; 0.5255; 0.5818	0.0286*; 0.7194; 0.5784; 0.5132
Atypical	0.2470; 0.8686; 0.6994; 0.1003	0.1626; 0.8699; 0.2043; 0.4476
Oral	0.6430; 0.9666; 0.1396; 0.0895	0.5336; 0.9655; 0.1771; 0.1052
Injectable	0.2383; 0.2779; 0.4199; 0.4012	0.2947; 0.2950; 0.3171; 0.2833
Injectable	0.2383; 0.2779; 0.4199; 0.4012	0.2947; 0.2950; 0.3171; 0.2833

*Statistically significant at P<0.05, N/A = not available. [a] The only statistically significant negative autocorrelations Durbin-Watson tests were second order in 2020 for olanzapine incident rate ($p = 0.0269$), all antipsychotics incident rate in 40-64 years age group ($p = 0.0445$), oral antipsychotics incident rate ($p = 0.0334$) and, in 2021 for oral antipsychotics incident rate ($p = 0.0345$). [b] The higher-order tests assume the absence of lower-order autocorrelation. When a significant autocorrelation is detected, further tests at higher orders are not appropriate to decide on the autoregressive order.[c] 4th order autocorrelation test was conducted to diagnose and correct for seasonality

Table 2. Positive autocorrelation Durbin-Watson test *p*-value (1st, 2nd, 3rd, 4th order)[a] in the sensitivity analysis

		2020Q1	2021Q1
	Comparison	**Durbin-Watson test[b] (1st, 2nd, 3rd, 4th order[c])**	**Durbin-Watson test (1st, 2nd, 3rd, 4th order)**
Prevalence	**All antipsychotics**	0.0004*; 0.5735; 0.8925; 0.8394	0.0013*; 0.4993; 0.8445; 0.8954
Incidence	**All antipsychotics**	0.0193*; 0.1922; 0.1910; 0.1360	0.0185*; 0.1976; 0.2076; 0.2644

*Statistically significant at P<0.05. [a] All the negative autocorrelations Durbin-Watson tests were statistically non-significant. [b] The higher-order tests assume the absence of lower-order autocorrelation. When autocorrelation is detected, further tests at higher orders are not appropriate to decide on the autoregressive order. [c] 4th order autocorrelation test was conducted to diagnose and correct for seasonality

Table 3. Characteristics of the schizophrenia population in Manitoba, in the first fiscal quarter (April-June) of 2020

Characteristic	Primary analyses definition	Stratified by sex		Sensitivity analyses definition
		Males	Females	
N	9045 (100)	5397 (59.67)	3648 (40.33)	5642 (100)
Age, years	46.9 (17.9)	44.24 (16.58)	50.90 (19.06)	46.41 (17.12)
≤18 years	172 (1.9)	97 (1.80)	75 (2.06)	80 (1.42)
19-39 years	3360 (37.15)	2307 (42.75)	1053 (28.87)	2142 (37.97)
40-64 years	3879 (42.89)	2319 (42.97)	1560 (42.76)	2499(44.29)
65-79 years	1315 (14.54)	581 (10.77)	734 (20.12)	774 (13.2)
≥80 years	319 (3.53)	93 (1.72)	226 (6.20)	147 (2.61)
Male sex	5397 (59.67)	N/A	N/A	3498 (62)
Urban residence[a]	6769 (74.84)	3985 (73.84)	1960 (78.82)	4355 (76.66)
Residence and income quintile (1 = lowest, 5 = highest)				
Rural 1	650 (7.19)	383 (7.10)	267 (7.32)	389 (6.89)
Rural 2	574 (6.35)	380 (7.04)	194 (5.32)	353 (6.26)
Rural 3	409 (4.52)	263 (4.87)	146 (4.00)	230(4.08)
Rural 4	332 (3.67)	205 (3.80)	127 (3.48)	191(3.39)
Rural 5	261 (2.89)	159 (2.95)	102 (2.80)	135 (2.39)
Urban 1	2530 (27.97)	1489 (27.59)	1041 (28.54)	1639 (29.05)
Urban 2	1213 (13.41)	737 (13.66)	476 (13.05)	762(13.51)
Urban 3	822 (9.09)	487 (9.02)	335 (9.18)	504(8.93)
Urban 4	642 (7.10)	404 (7.49)	238 (6.52)	422 (7.48)
Urban 5	428 (4.73)	250 (4.63)	178 (4.88)	247 (4.38)
Unknown	1184 (13.09)	640 (11.86)	544 (14.91)	770 (13.65)
Elixhauser Comorbidity Index[b]				
0	1303 (14.39)	870 (16.10)	433 (11.86)	509 (9.02)
1	2507 (27.69)	1636 (30.28)	871 (23.86)	1652 (29.27)
2	2151 (23.76)	1312 (24.28)	839(22.99)	1449 (25.67)
3	1432 (15.82)	797 (14.75)	635 (17.40)	930 (16.48)
4+	1660 (18.34)	788 (14.57)	872 (23.89)	1104 (19.56)
Polypharmacy[c]				
>5 drugs	2655 (29.35)	1295 (23.99)	1360 (37.28)	1674 (29.67)

Table 3. Characteristics of the schizophrenia population in Manitoba, in the first fiscal quarter (April-June) of 2020

Characteristic	Primary analyses definition	Stratified by sex		Sensitivity analyses definition
		Males	Females	
>10 drugs	578 (6.39)	255 (4.72)	323 (8.85)	373 (6.61)

Data reported as mean (standard deviation) or n (%). [a] Versus rural residence. [b] Hospital and physician claims data used to compute the Elixhauser Comorbidity Index on a yearly basis with the following denominators: N (primary analyses): 9053, N (sex-stratified): 5403 Males, 3650 Females; N (Sensitivity analyses): 5644. [c] Based on concurrent use in 3 months. The population stratified by age is in Table 4

Table 4. Characteristics of the schizophrenia population in Manitoba, in the first fiscal quarter (April-June) of 2020, by age					
Characteristic	**≤18 years**	**19-39 years**	**40-64 years**	**65-79 years**	**≥80 years**
N	172 (1.9)	3360 (37.15)	3879 (42.89)	1315 (14.54)	319 (3.53)
Age, years	15.38 (3.34)	29.25 (5.68)	52.37 (7.15)	70.62 (4.17)	86.17 (5.13)
Male sex	97 (56.40)	2307 (68.66)	2319 (59.78)	581 (44.18)	93 (29.15)
Urban residence[a]	92 (53.49)	2374 (70.65)	3004 (77.44)	1048 (79.70)	251 (78.68)
Income quintile (1 = lowest, 5 = highest)					
Rural 1	11 (6.40)	261 (7.77)	267 (6.88)	96 (7.30)	15 (4.7)
Rural 2	29 (16.86)	296 (8.81)	181 (4.67)	53 (4.03)	15 (4.70)
Rural 3	15 (8.72)	161 (4.79)	173 (4.46)	50 (3.80)	10 (3.13)
Rural 4	7 (4.07)	151 (4.49)	129 (3.33)	34 (2.59)	11 (3.45)
Rural 5	18 (10.47)	108 (3.21)	113 (2.91)	18 (1.37)	4(1.25)
Urban 1	25 (14.53)	892 (26.55)	1255 (32.35)	303 (23.04)	55 (17.24)
Urban 2	15 (8.72)	491 (14.61)	543 (14)	137 (10.42)	27 (8.46)
Urban 3	16 (9.30)	327 (9.73)	353 (9.1)	102 (7.76)	24 (7.52)
Urban 4	10 (5.81)	271 (8.07)	259 (6.68)	81 (6.16)	21 (6.58)
Urban 5	6 (3.49)	183 (5.45)	151 (3.89)	69 (5.25)	19 (5.96)
Unknown	20 (11.63)	219 (6.52)	455 (11.73)	372 (28.29)	118 (36.99)
Elixhauser Comorbidity Index[b]					
0	53 (30.81)	687 (20.40)	414 (10.67)	102 (7.76)	47 (14.3)
1	61 (35.47)	1120 (33.26)	1017 (26.21)	244 (18.56)	65 (20.38)
2	35 (20.35)	813 (24.15)	949 (24.46)	290 (22.05)	64 (20.06)
3	12 (6.98)	443 (13.16)	683 (17.6)	242 (18.40)	52 (16.3)
4+	11 (6.40)	304 (9.03)	817 (21.06)	437 (33.23)	91 (28.53)
Polypharmacy[c]					
>5 drugs	8 (4.65)	483 (14.38)	1411 (36.38)	613 (46.62)	140 (43.89)
>10 drugs	N/A[d]	57 (1.7)	331 (8.53)	162 (12.32)	26 (8.15)

Data reported as mean (standard deviation) or n (%). [a] Versus rural residence. [b] Hospital and physician claims data used to compute the Elixhauser Comorbidity Index on a yearly basis with the following denominators: N (≤18 years): 172, (19-39 years): 3367, (40-64 years): 3880, (65-79 years): 1315, (≥80 years): 319. [c] Based on concurrent use in 3 months. [d] Cell suppressed due to N≤5

Table 5. Time series using linear autoregression models summarizing the association between COVID-19 health measures and the prevalent and incident antipsychotic use in schizophrenia in Manitoba, in the first fiscal quarter of 2020 and 2021

	2020Q1		**2021Q1**	
	Prevalence	**Incidence**	**Prevalence**	**Incidence**
	Estimate (Standard Error, *p*-value)	**Estimate (Standard Error, *p*-value)**	**Estimate (Standard Error, *p*-value)**	**Estimate (Standard Error, *p*-value)**
All antipsychotics	-1.7 (4.3, $p = 0.6$)	-1.3 (0.5, $p = 0.01$)*	4 (4.3, $p = 0.3$)	-0.2 (0.6, $p = 0.7$)
Quetiapine	-2.2 (1.9, $p = 0.2$)	-1.08 (1.07, $p = 0.3$)	-2.5 (1.9, $p = 0.2$)	-1.2 (1.09, $p = 0.2$)
Olanzapine	0.04 (3.6, $p = 0.9$)	-1.6 (0.8, $p = 0.08$)	4.3 (3.6, $p = 0.2$)	1.2 (0.9, $p = 0.1$)
Risperidone	0.1 (3.4, $p = 0.9$)	-0.7 (0.8, $p = 0.3$)	5.2 (3.4, $p = 0.1$)	1.8 (0.8, $p = 0.03$)*
Clozapine	-1 (2.6, $p = 0.7$)	-0.3 (0.6, $P = 0.5$)	-1.8 (2.6, $p = 0.5$)	-0.6 (0.6, $p = 0.3$)
First-generation	-3.3 (2.9, $p = 0.2$)	-0.3 (1, $p = 0.07$)	2.1 (3, $p = 0.4$)	-0.4 (1.1, $p = 0.6$)
Atypical	1.4 (4.7, $p = 0.7$)	-1.2 (0.6, $p = 0.09$)	4.9 (4.7, $p = 0.3$)	1.4 (0.6, $p = 0.04$)*
Oral	-1.2 (4.3, $p = 0.7$)	-1 (0.5, $p = 0.09$)	4.1 (4.3, $p = 0.3$)	0.1 (0.6, $p = 0.8$)
Injectable	0.5 (2.8, $p = 0.8$)	0.5 (1.1, $p = 0.06$)	2.6 (2.8, $p = 0.3$)	0.8 (1.1, $p = 0.4$)

*Statistically significant at $P<0.05$

Table 6. Time series using linear autoregression models summarizing the association between COVID-19 health measures implementation and prevalent and incident antipsychotic use in the sub-populations with schizophrenia in Manitoba, in the first quarter of 2020

	2020Q1	
	Prevalence	**Incidence**
Sub-population	**Estimate (Standard Error, *p*-value)**	**Estimate (Standard Error, *p*-value)**
Age		
≤ 18 years	-28.7 (35.6, $p = 0.4$)	N/A
19-39 years	-1.7 (5.8, $p = 0.7$)	-2.2 (1.2, $p = 0.7$)
40-64 years	4.5 (5.6, $p = 0.4$)	-0.6 (0.8, $p = 0.4$)
65-79 years	-21 (9.1, $p = 0.02$)*	-1.2 (1.9, $p = 0.5$)
≥ 80 years	-7.4 (14.6, $p = 0.6$)	-1.7 (5, $p = 0.7$)
Sex		
Male	4.8 (5.6, $p = 0.4$)	-1.7 (0.8, $p = 0.06$)
Female	-11 (8.3, $p = 0.1$)	-0.8 (1, $p = 0.4$)

*Statistically significant at P<0.05. N/A = unable to compute due to 0 value

Table 7. Sensitivity analysis utilizing different criteria to define schizophrenia (n=5,642 individuals with schizophrenia in Manitoba**)**

	2020Q1		**2021Q1**	
	Prevalence	**Incidence**	**Prevalence**	**Incidence**
	Estimate (Standard Error, *p*-value)	**Estimate (Standard Error, *p*-value)**	**Estimate (Standard Error, *p*-value)**	**Estimate (Standard Error, *p*-value)**
All antipsychotics	-3.9 (5.8, $p = 0.4$)	-0.7 (0.6, $p = 0.2$)	6.9 (5.8, $p = 0.2$)	0.09 (0.7, $p = 0.8$)

*Statistically significant at P<0.05

Figures

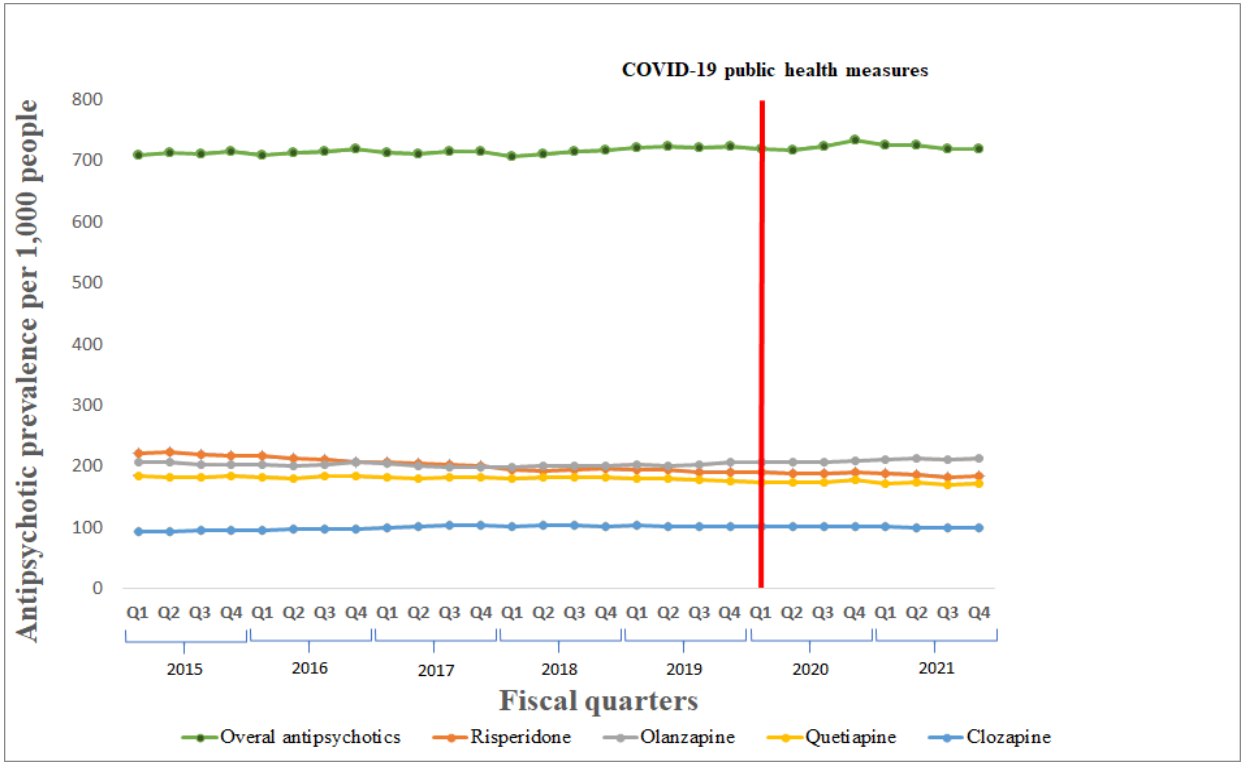

Figure 1. The overall and individual antipsychotic quarterly prevalence (per 1,000) in individuals with schizophrenia in Manitoba, from 2015 to 2021

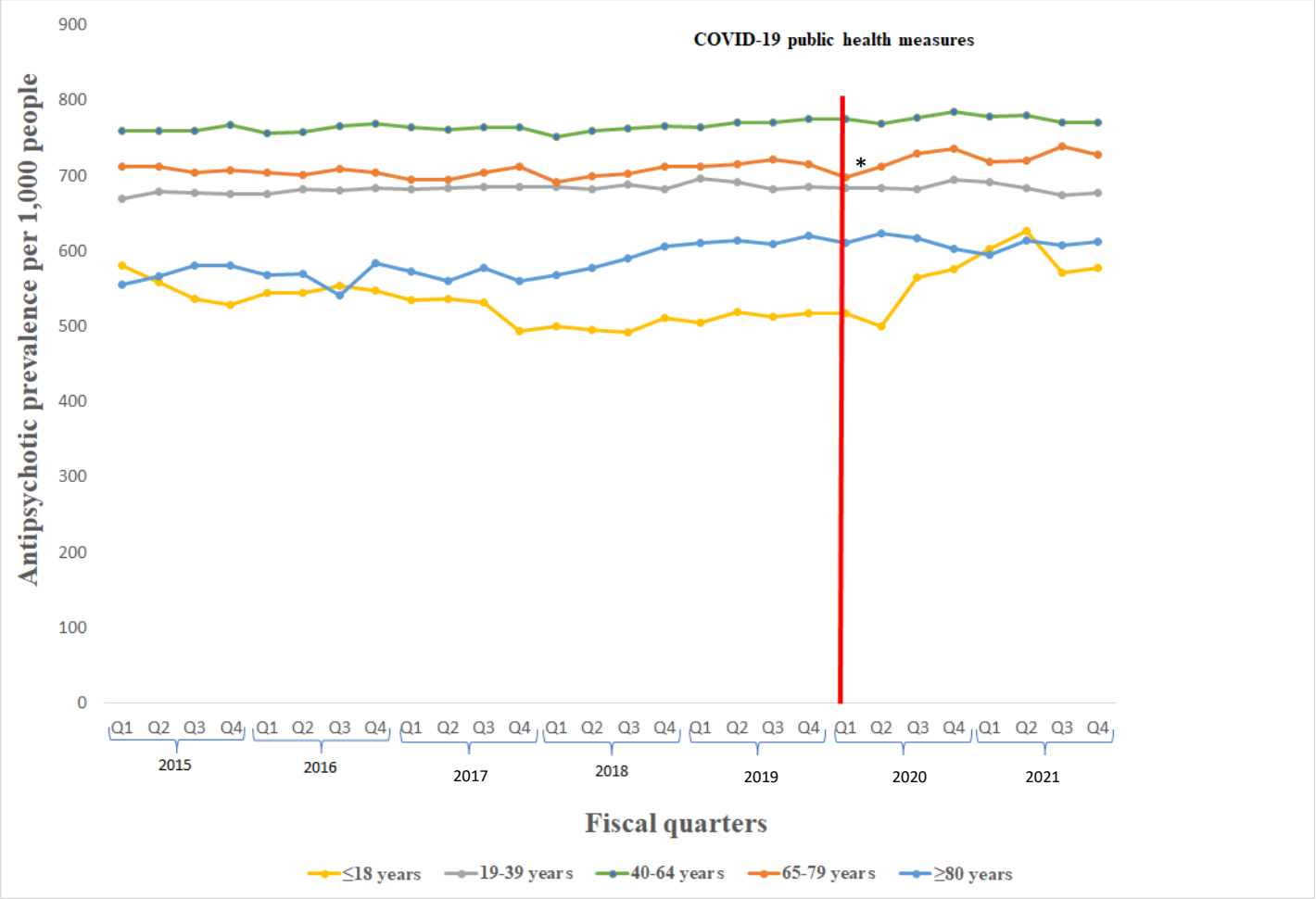

Figure 2. The antipsychotic quarterly prevalence (per 1,000) in individuals with schizophrenia in Manitoba, from 2015 to 2021 by age groups (*Statistically significant at P<0.05)

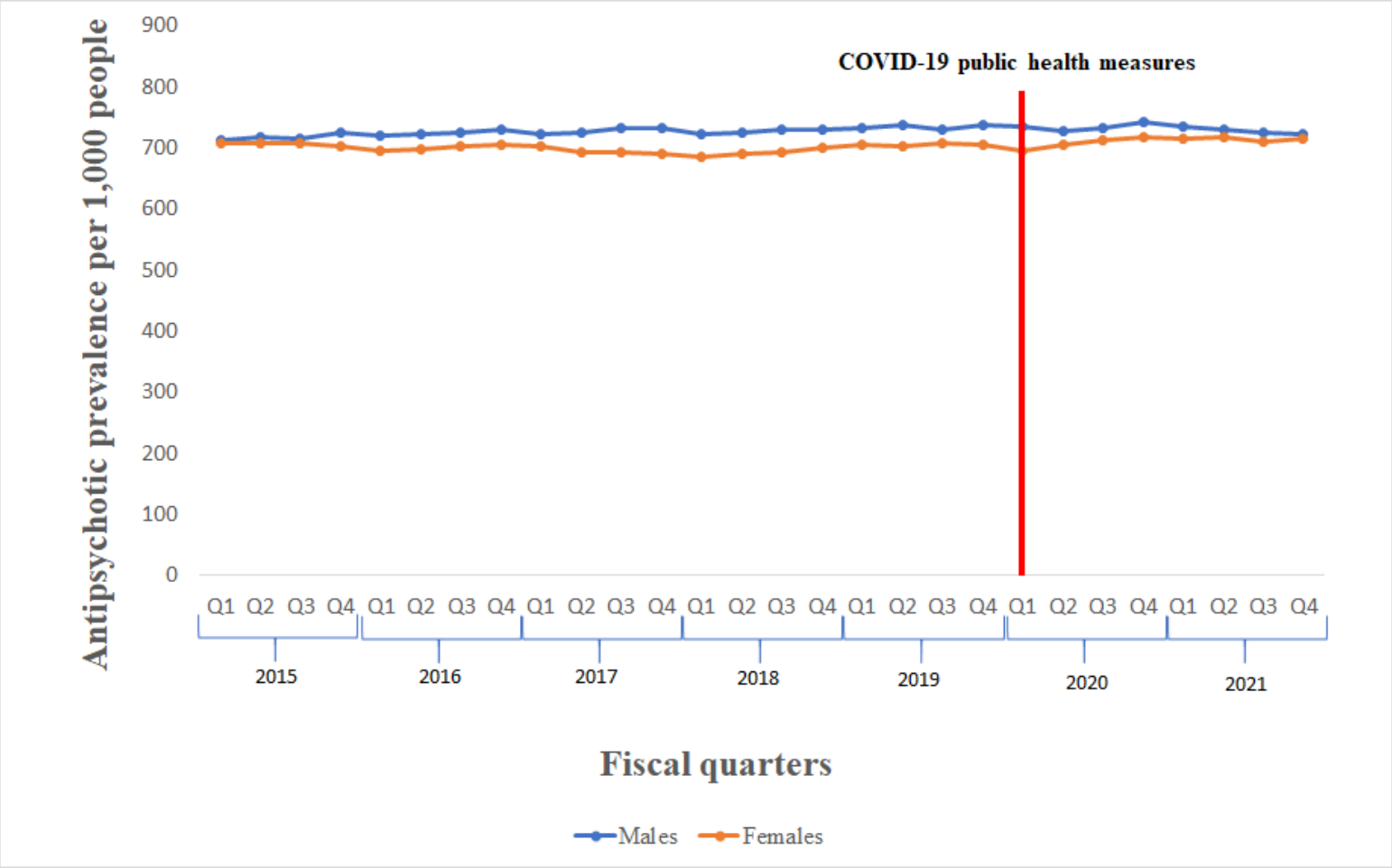

Figure 3. The antipsychotic quarterly prevalence (per 1,000) in individuals with schizophrenia in Manitoba, from 2015 to 2021 by sex

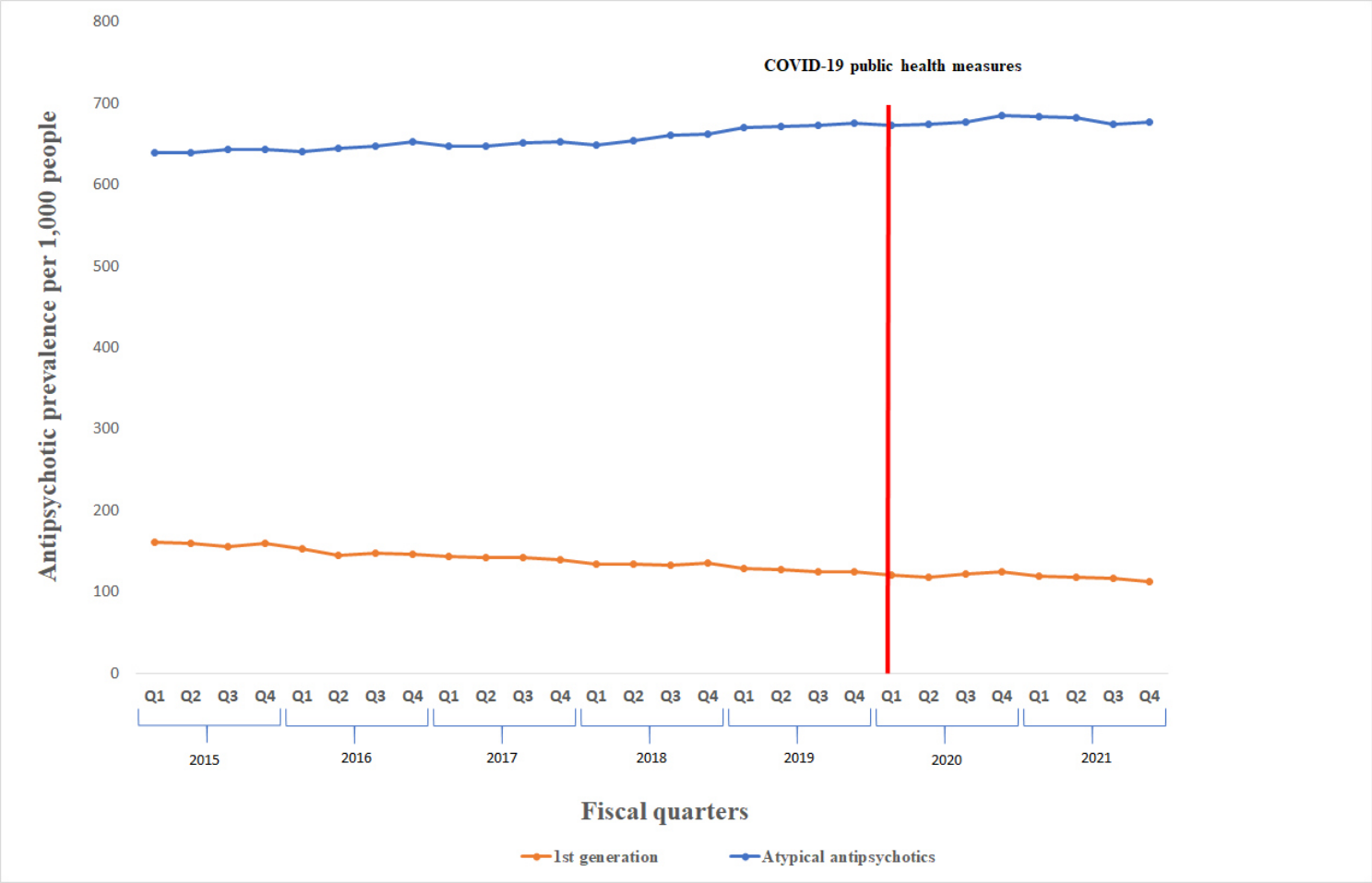

Figure 4. The first-generation and atypical antipsychotic quarterly prevalence (per 1,000) in individuals with schizophrenia in Manitoba, from 2015 to 2021

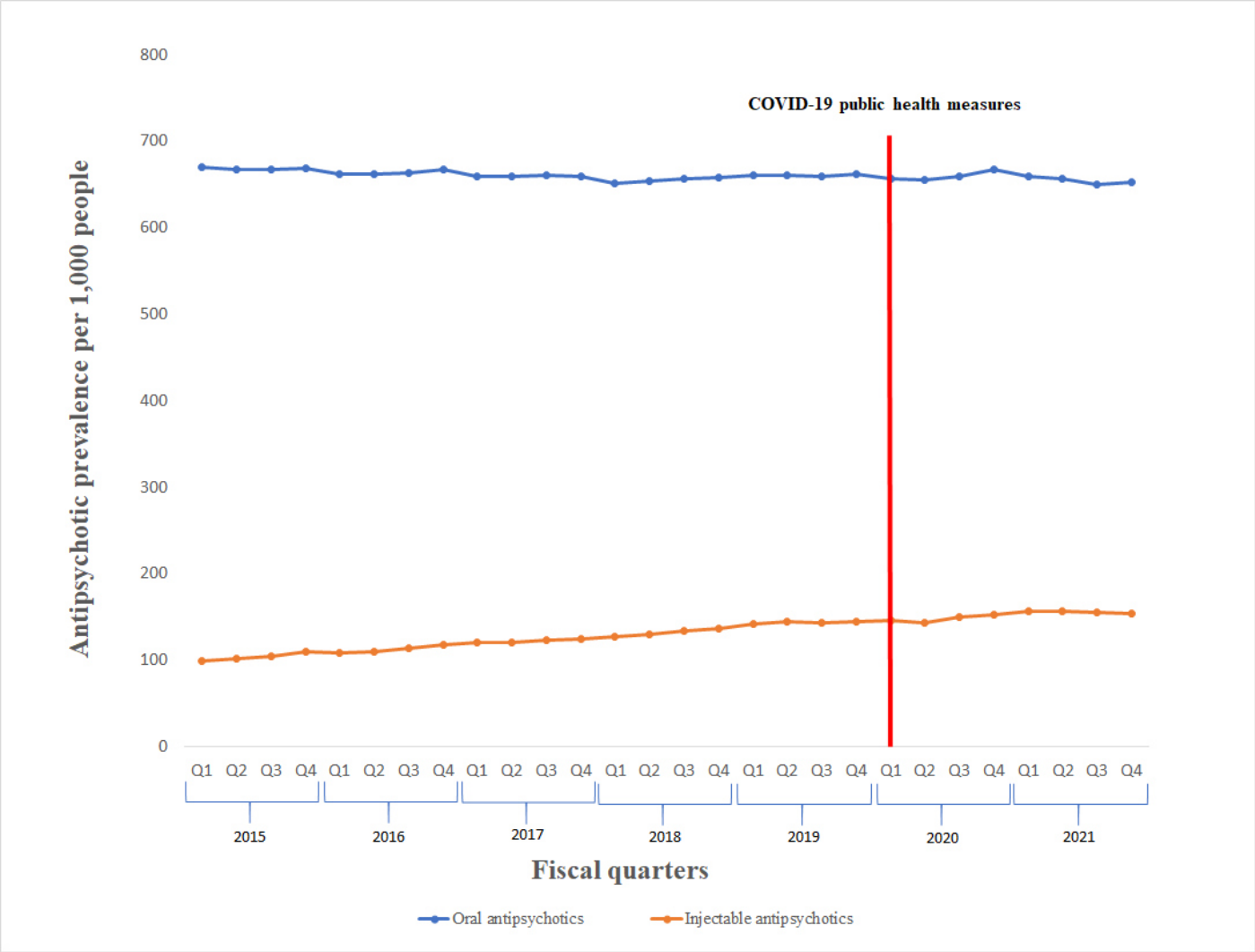

Figure 5. The oral and injectable antipsychotic quarterly prevalence (per 1,000) in individuals with schizophrenia in Manitoba from 2015 to 2021

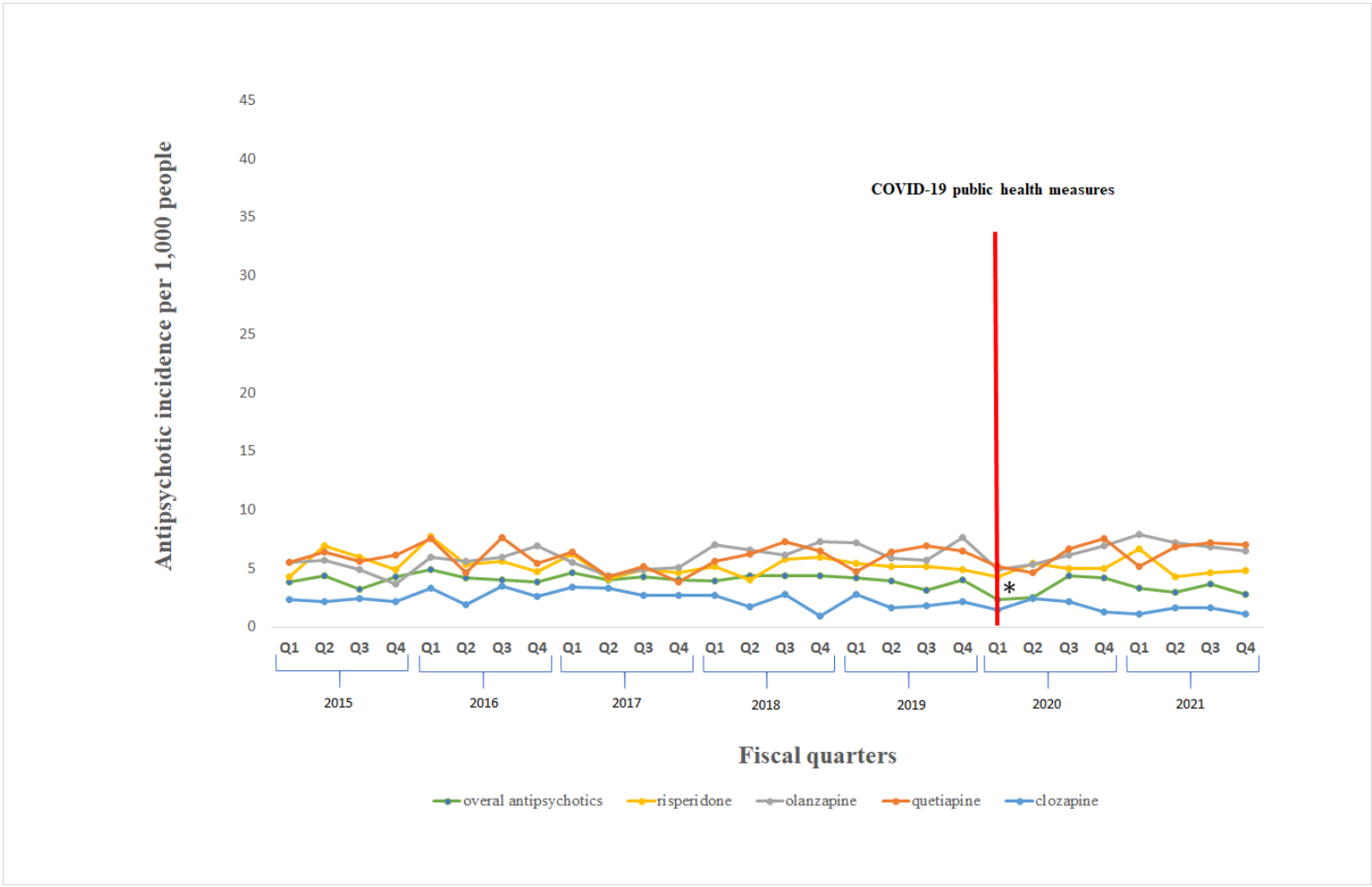

Figure 6. The overall and individual antipsychotic quarterly incidence (per 1,000) in individuals with schizophrenia in Manitoba, from 2015 to 2021 (*Statistically significant at P<0.05)

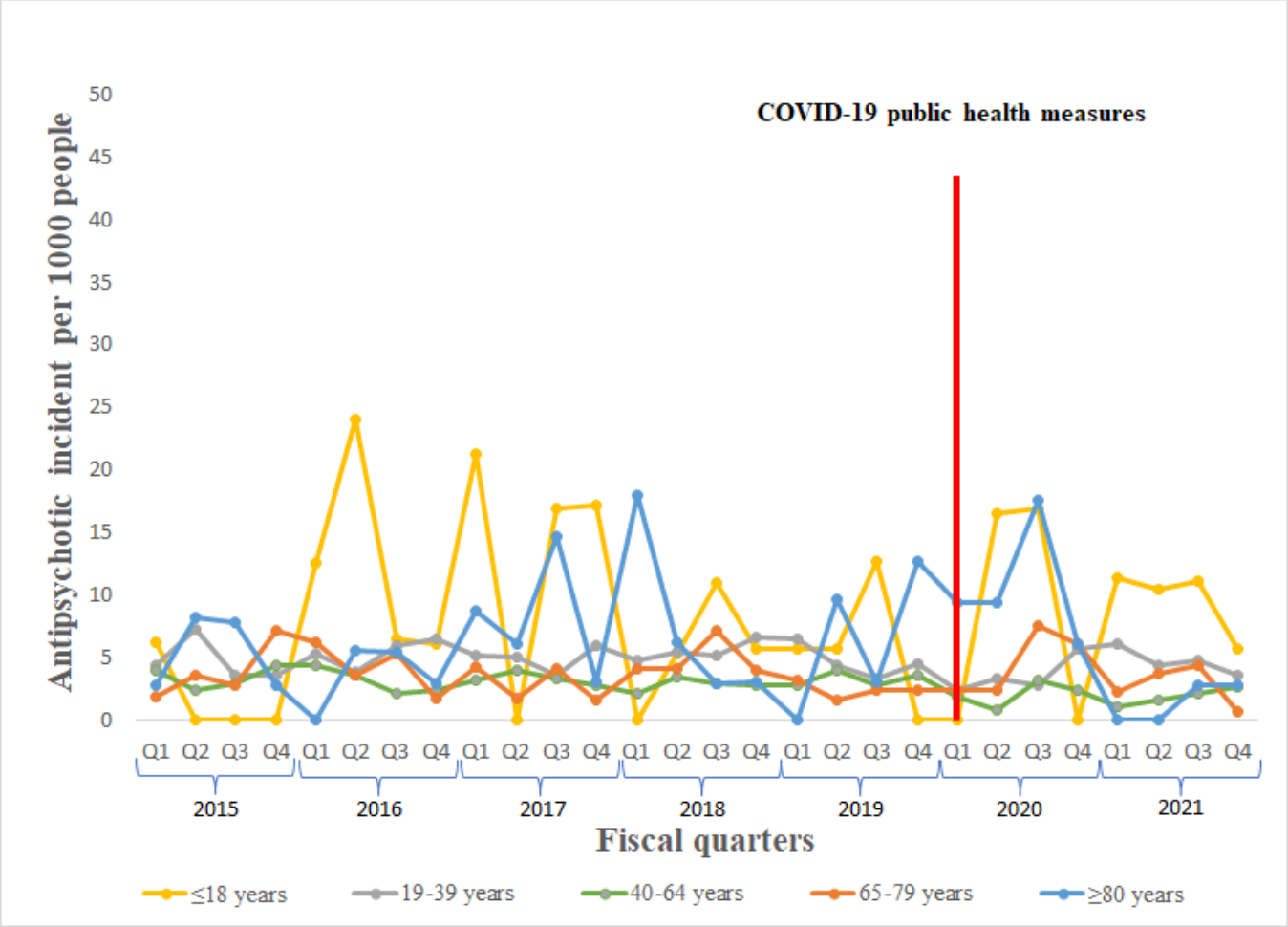

Figure 7. The antipsychotic quarterly incidence (per 1,000) in individuals with schizophrenia in Manitoba, from 2015 to 2021, by age groups

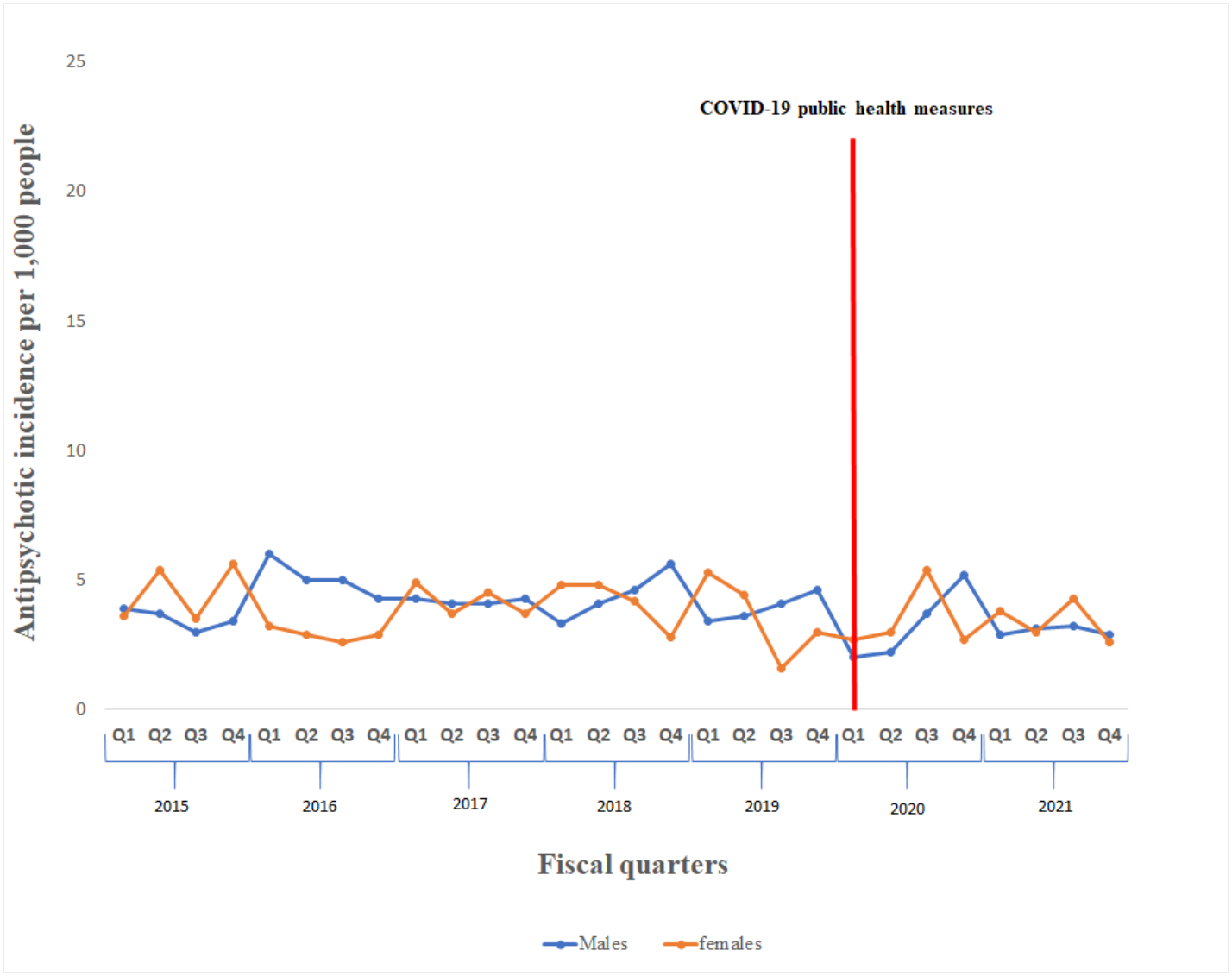

Figure 8. The antipsychotic quarterly incidence (per 1,000) in individuals with schizophrenia in Manitoba, from 2015 to 2021 by sex

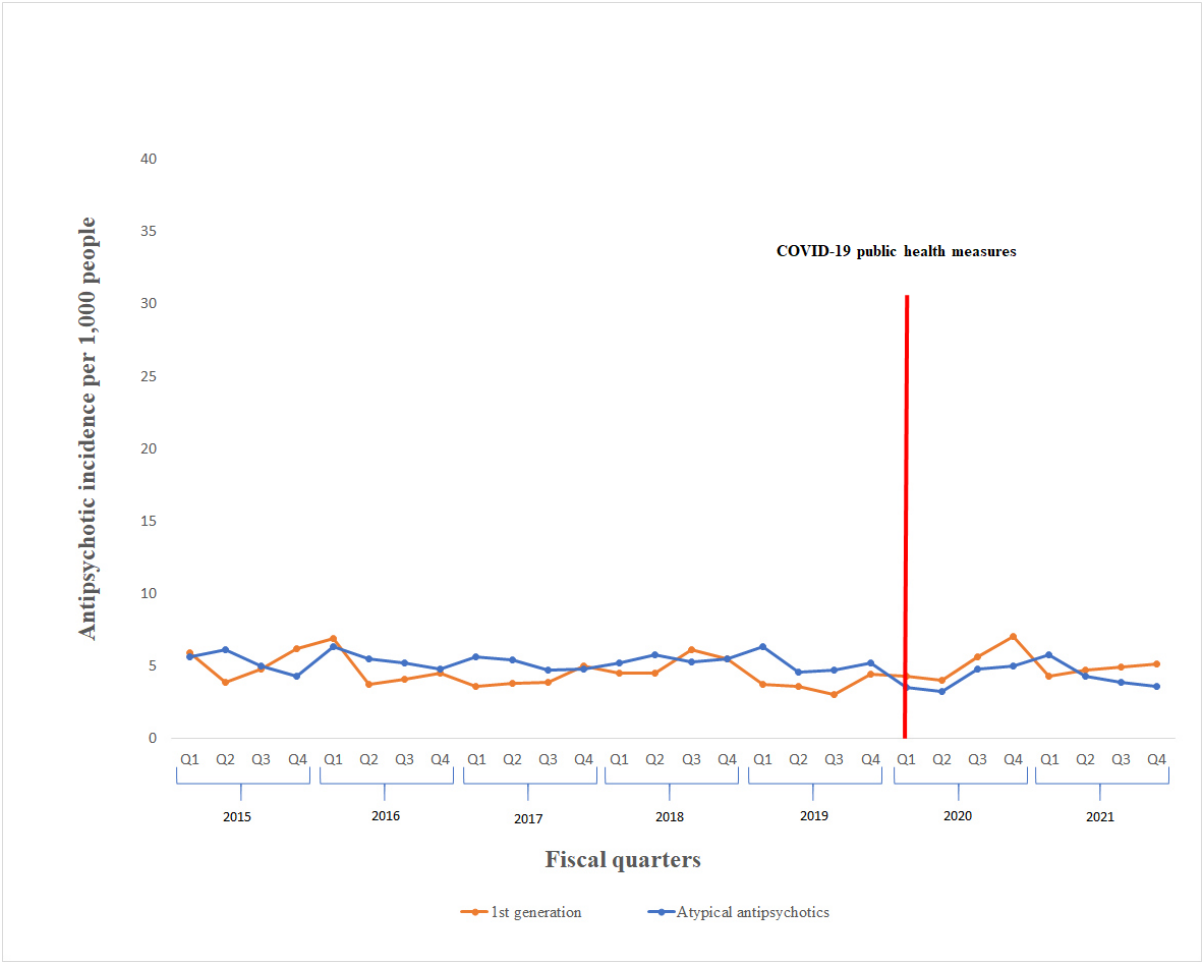

Figure 9. The first-generation and atypical antipsychotic quarterly incidence (per 1,000) in individuals with schizophrenia in Manitoba, from 2015 to 2021

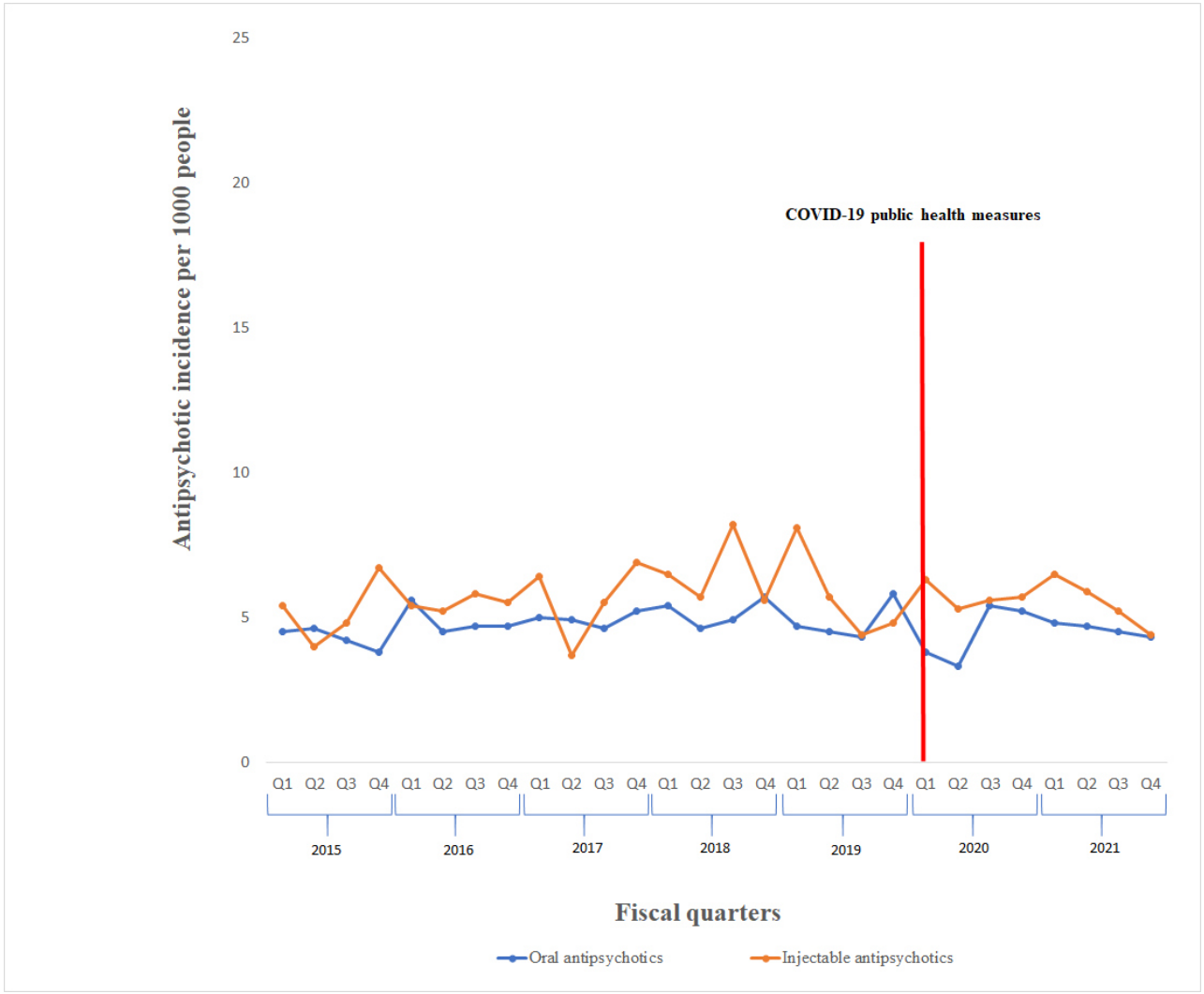

Figure 10. The oral and injectable antipsychotic quarterly incidence (per 1,000) in individuals with schizophrenia in Manitoba, from 2015 to 2021

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Appendices

Appendix I. Measures applied and reported COVID-19 cases in Manitoba (MB) from March 1,2020 to February 28, 2022 (Red line represents the 7-day moving average of reported cases)

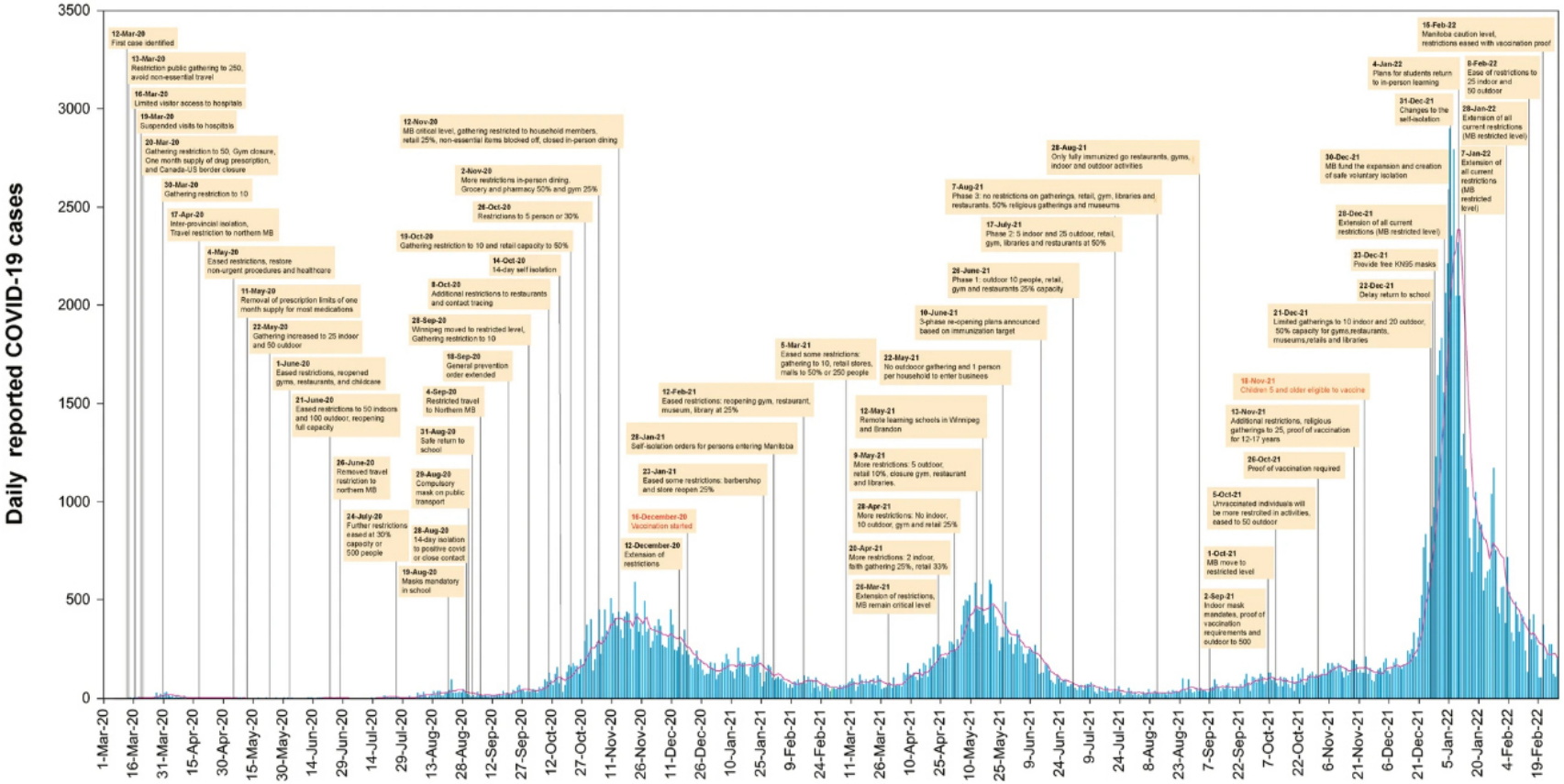

Figure Credit: Aboulatta et al, BMC Research Notes; Link to Creative Commons licence; No changes were made.

Appendix II. ICD-9 and ICD-10 Coding Algorithms for Elixhauser's Comorbidity Index

ICD-9-CM and ICD-10 Coding Algorithms for Elixhauser Comorbidities				
Comorbidities	**Elixhauser's original ICD-9-CM**	**Elixhauser AHRQ-Web ICD-9-CM**	**ICD-10**	**Enhanced ICD-9-CM**
Congestive heart failure	398.91, 402.11, 404.11, 404.13, 404.93, 428.x, 402.91, 404.91, 398.91	398.91, 402.01, 402.11, 404.03, 404.91, 402.91, 404.01, 404.11, 404.13, 404.93, 428.x	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, 142.5-I42.9, I43.x, I50.x, P29.0	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4-425.9, 428.x
Cardiac arrhythmias	426.10, 426.11, 426.2-426.53, 426.6-426.8, 427.0, 427.60, 426.13, 427.2, 427.9, 427.31, 785.0, V45.0, V53.3		I44.1-I44.3, I45.6, I45.9, I47.x-I49.x, ROO.O, ROO.1, ROO.8, T82.1, Z45.0, Z95.0	426.0, 426.13, 426.7, 426.9, 426.10, 426.12, 427.0-427.4, 427.6-427.9, 785.0, 996.01, 996.04, V45.0, V53.3
Valvular disease	093.2, 394.0-397.1, 424.0-424.91, 746.3-746.6, V42.2, V43.3	093.2, 394.x-397.1, 397.9, 424.x, 746.3-746.6, V42.2, V43.3	I09.8, I34.x-I39.x, Q23.O-Q23.3, Z95.2, Z95.4	093.2, 394.x-397.x, 424.x, 746.3-746.6, V42.2, V43.3
Pulmonary circulation Disorders	416.x, 417.9	416.x, 417.9	I26.x, I27.x, I28.0, I28.8, I28.9	415.0, 415.1, 416.x, 417.0, 417.8, 417.9
Peripheral vascular disorders	440.x, 441.2, 441.4, 441.7, 441.9, 443.1-443.9, 447.1, 557.1, 557.9, V43.4	440.x, 441.x, 442.x, 443.1-443.9, 447.1, 557.1, 557.9, V43.4	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9	093.0, 437.3, 440.x, 441.x, 443.1-443.9, 447.1, 557.1557.9, V43.4
Hypertension, uncomplicated	401.1, 401.9	401.1, 401.9, 642.0	I10.x	401.x
Hypertension, complicated	402.10, 402.90, 404.10, 404.90, 405.1, 405.9	401.0, 402.x-405.x, 642.1, 642.2, 642.7, 642.9	I11.x-I13.x, I15.x	402.x-405.x
Paralysis	342.0. 342.1, 342.9-344.x	342.x-344.x, 438.2-438.5	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0-G83.4, G83.9	334.1, 342.x, 343.x, 344.0- 344.6, 344.9
Other neurological disorders	331.9, 332.0, 333.4, 333.5, 334.x, 335.x, 340.x, 341.1-341.9,	330.x-331.x, 332.0, 333.4, 333.5, 334.x, 335.x, 340, 341.1-	G10.xG13.x, G20.x-G22.x,	331.9, 332.0, 332.1, 333.4, 333.5, 333.92, 334.x-335.x, 336.2,

ICD-9-CM and ICD-10 Coding Algorithms for Elixhauser Comorbidities				
	345.0, 345.1, 345.4, 345.5, 345.8, 345.9, 348.1, 348.3, 780.3, 784.3	341.9, 345.x, 347.x, 780.3, 784.3	G25.4, G25.5, G31.2, G31.8, G31.9, G32.x, G35.x-G37.x, G40.x, G41.x, G93.1, G93.4, R47.0, R56.x	340.x, 341.x, 345.x, 348.1, 348.3, 780.3, 784.3
Chronic pulmonary disease	490-492.8, 493.00-493.91, 494.x-505.x, 506.4	490x-492.x, 493.x, 494x-505.x, 506.4	I27.8, 127.9, J40.x-J47.x, J60.x-J67.x, J68.4, J70.1, J70.3	416.8, 416.9, 490.x-505.x, 506.4, 508.1, 508.8
Diabetes, uncomplicated	250.0-250.3	250.0-250.3, 648.0	E10.0, E10.1, E10.9, E11.0, E11.1, E11.9, E12.0, E12.1, E12.9, E13.0, E13.1, E13.9, E14.0, E14.1, E14.9	250.0-250.3
Diabetes, complicated	250.4-250.7, 250.9	250.4-250.9, 775.1	E10.2-E10.8, E11.2-E11.8, E12.2- E12.8, E13.2-E13.8, E14.2-E14.8	250.4-250.9
Hypothyroidism	243-244.2, 244.8, 244.9	243-244.2, 244.8, 244.9	E00.x-E03.x, E89.0	240.9, 243.x, 244.x, 246.1, 246.8
Renal failure	403.11, 403.941, 04.12, 404.92, 585.x, 586.x, V42.0, V45.v1, 56.0, V56.8	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 585.x, 586.x, V42.0, V45.1, V56.x	I12.0, I13.1, N18.x, NI9.x, N25.0, Z49.0-Z49.2, Z94.0, Z199.2	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x
Liver disease	070.32, 070.33, 070.54, 456.0, 456.1, 456.2, 571.0, 571.2-571.9, 572.3, 572.8, V42.7	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 456.0, 456.1, 456.20, 571.0, 571.2-571.9, 572.3, 572.8, V42.7	B18.x, I85.x, I86.4, I98.2, K70.x, K71.1, K71.3- K71.5, K71.7, K72.x-K74.x, K76.0, K76.2- K76.9. Z94.4	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 456.0-456.2, 570.x, 571.x, 572.2-572.8, 573.3, 573.4, 573.8,573.9, V42.7

ICD-9-CM and ICD-10 Coding Algorithms for Elixhauser Comorbidities(Continued)				
Comorbidities	Elixhauser's original ICD-9-CM	Elixhauser AHRQ-Web ICD-9-CM	ICD-10	Enhanced ICD-9-CM
Peptic ulcer disease excluding bleeding	531.70, 531.90, 532.70, 532.90, 533.70, 533.90, 534.70, 534.90, V12.71	531.41, 531.51, 531.61, 531.7, 531.91, 532.41, 532.51, 532.61, 532.7, 532.91, 533.41, 533.51, 533.61, 533.7, 533.91, 534.41, 534.51, 534.61, 534.7, 534.91	K25.7, K25.9, K26.7, K26.9, K27.7, K27.9, K28.7, K28.9	531.7, 531.9, 532.7, 532.9, 533.7, 533.9, 534.7, 534.9
AIDS/H1V	042.x-044.x	042.x-044.x	B20.x-B22.x, B24.x	042.x-044.x
Lymphoma	200.x-202.3x, 202.5-203.0, 203.8, 238.6, 273.3, V10.71, V10.72, V10.79	200.x-202.3, 202.5-203.0, 203.8, 238.6, 273.3	C81.x-C85.x, C88.x, C96.x, C90.0, C90.2	200.x-202.x, 203.0, 238.6
Metastatic cancer	196.x-199.x	196.x-199.x	C77.x-C80.x	196.x-199.x
Solid tumor without metastasis	140.x-172.x, 174.x, 175.x, 179.x-195.x, V10.x	140.x-172.x, 174.x, 175.x, 179.x-195.x	C00.x-C26.x, C30.x-C34.x, C37.x-C41.x, C43.x, C45.x-C58.x, C60.x-C76.x, C97.x	140.x-172.x, 174.x-195.x
Rheumatoid arthritis/ collagen vascular diseases	701.0, 710.x, 714.x, 720.x, 725.x	701.0, 710.x, 714.x, 720.x, 725.x	L94.0, L94.1, L94.3, M05.x, M06.x, M08.x, M12.0, M12.3, M30.x, M31.0-M31.3, M32.x-M35.x, M45.x, M46.1, M46.8, M46.9	446.x, 701.0, 710.0-710.4, 710.8, 710.9, 711.2, 714.x, 719.3, 720.x, 725.x, 728.5, 728.89, 729.30
Coagulopathy	286.x, 287.1, 287.3-287.5	286.x, 287.1, 287.3-287.5	D65-D68.x, D69.1, D69.3-D69.6	286.x, 287.1, 287.3-287.5
Obesity	278.0	278.0	E66.x	278.0
Weight loss	260.x-263.x	260.x-263.x, 783.2	E40.x-E46.x, R63.4, R64	260.x-263.x, 783.2, 799.4
Fluid and electrolyte disorders	276.x	276.x	E22.2, E86.x, E87.x	253.6, 276.x
Blood loss anemia	280.0	280.0, 648.2	D50.0	280.0

ICD-9-CM and ICD-10 Coding Algorithms for Elixhauser Comorbidities(Continued)				
Deficiency anemia	280.1-281.9, 285.9	280.1-281.9, 285.2, 285.9	D50.8, D50.9, D51.x-D53.x	280.1-280.9, 281.x
Alcohol abuse	291.1, 291.2, 291.5-291.9, 303.9, 305.0, V113	291.0-291.3, 291.5, 291.8, 291.9, 303.x, 305.0	F10, E52, G62.1, I42.6, K29.2, K70.0, K70.3, K70.9, T51.x, Z50.2, Z71.4, Z72.1	265.2, 291.1-291.3, 291.5-291.9, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, 571.0-571.3, 980.x, V11.3
Drug abuse	292.0, 292.82-292.89, 292.9, 304.0, 305.2, 305.9	292.0, 292.82-292.89, 292.9, 304.x, 305.2-305.9, 648.3	F11.x-F16.x, F18.x, F19.x, Z71.5. Z72.2	292.x, 304.x, 305.2-305.9, V65.42
Psychoses	295.x-298.x, 299.1	295.x-298.x, 299.1	F20.x, F22.x-F25.x, F28.x, F29.x, F30.2, F31.2, F31.5	293.8, 295.x, 296.04, 296.14, 296.44, 296.54, 297.x, 298.x
Depression	300.4, 301.12, 309.0, 309.1, 311	300.4, 301.12, 309.0, 309.1, 311	F20.4, F31.3-F31.5, F32.x, F33.x, F34.1, F41.2, F43.2	296.2, 296.3, 296.5, 300.4, 309.x, 311

Source: Quan H, Med Care. 2005, DOI: 10.1097/01.mlr.0000182534.19832.83.

Appendix III. ATC codes (N05A) and route(s) of administration used for first- and atypical antipsychotics included in the study

Generation	Drug name	ATC code	oral	injectable
1st	Chlorpromazine	N05AA01	√	
1st	Levomepromazine	N05AA02	√	√
1st	Fluphenazine	N05AB02	√	√
1st	Perphenazine	N05AB03	√	
1st	Prochlorperazine	N05AB04	√	
1st	Trifluoperazine	N05AB06	√	
1st	Periciazine	N05AC01	√	
1st	Pipotiazine	N05AC04		√
1st	Haloperidol	N05AD01	√	√
2nd	Ziprasidone	N05AE04	√	
2nd	Lurasidone	N05AE05	√	
1st	Flupentixol	N05AF01	√	√
1st	Tiotixene	N05AF04	√	
1st	Zuclopenthixol	N05AF05	√	√
1st	Pimozide	N05AG02	√	
1st	Loxapine	N05AH01	√	√
2nd	Clozapine	N05AH02	√	
2nd	Olanzapine	N05AH03	√	√
2nd	Quetiapine	N05AH04	√	
2nd	Asenapine	N05AH05	√	
2nd	Risperidone	N05AX08	√	√
2nd	Aripiprazole	N05AX12	√	√
2nd	Paliperidone	N05AX13	√	√
2nd	Brexpiprazole	N05AX16	√	

Appendix IV. Preliminary statistical analyses performed for the primary objective

In the first step, I started with a student *t*-test (the simplest model) comparing the antipsychotic rates in the quarter of interest with the average rate in the same quarter in the five previous years. For example, I computed the average rate across Q1 in 2019, 2018, 2017, 2016, and 2015 and ran a student *t*-test to compare to Q1-2020 (Table Appendix IV below). In the next step, to adjust for the significant change in drug utilization and prescribing preferences during the period, I added time as a continuous covariate to a linear regression model and compared the antipsychotic rates in the quarter of interest with the expected trend (Table Appendix IV below). Finally, correction for any underlying autocorrelation and seasonality led us to fit a linear autoregressive model to our time series data (results in the main thesis).

*** step 1: creating new datasets;**

*** a.** creating a new rx-table sorting by PHIN;

```
proc sort data = project.Minas_thesis_cohort1_rx out = work.sorted_rx;
by SCRPHIN;
run;
```

*** b.** creating a new sorted-rx-table keeping fiscal quarters and dropping some variables;

```
data work.fiscalQ_short;
set work.sorted_rx;
where fyear not in ("2015/16","2016/17","2017/18","2018/19","2019/20","2020/21","2021/22");
drop BIRTHDT canccode covdt enddt p_start P_end resstartdt resenddt postal muncode rha
rha11 urban income;
run;
```

*** c.** creating age-groups tables;

***c.1.** creating age-groups;

```
data work.fiscalQ_short;
set work.fiscalQ_short;
if age <= 18 then age_group = 1;
```

```
else if age >= 19 and age <= 39 then age_group = 2;
else if age >= 40 and age<=64 then age_group = 3;
else if age >= 65 and age<=79 then age_group = 4;
else if age >= 80 then age_group = 5;
run;
* c.2. creating datasets for age-groups;
data data_rate_adepage0018 data_rate_adepage1939 data_rate_adepage4064
data_rate_adepage6579 data_rate_adepage80plus;
set work.fiscalQ_short;
if age_group = 1  then output data_rate_adepage0018;
if age_group = 2  then output data_rate_adepage1939;
if age_group = 3  then output data_rate_adepage4064;
if age_group = 4  then output data_rate_adepage6579;
if age_group = 5  then output data_rate_adepage80plus;
run;
d. creating datasets for sex groups;
data data_rate_adepmale data_rate_adepfemale ;
set work.fiscalQ_short;
if sex = "1" then output data_rate_adepmale;
if sex = "2" then output data_rate_adepfemale;
run;
* step 2: calculating quarterly prevalent and incident antipsychotics;
* a. creating macrovariables;
%let dataset = work.fiscalQ_short;
%let antipsychotics = antipsych_prev;
%let output = antipsych_prev;
* b. calculating prevalent and incident antipsychotics;
proc freq data = &dataset;
table &antipsychotics*fyear/nopercent norow out=&output outpct;
run;
```

```
* c. creating new variables;
data &output;
set &output;
where &antipsychotics = 1;
PCT_COL = PCT_COL*10;
time =_n_;
if fyear = '2020/21Q1' then Q12020I = 1; else Q12020I = 0;
if fyear = '2020/21Q2' then Q22020I = 1; else Q22020I = 0;
if fyear = '2020/21Q3' then Q32020I = 1; else Q32020I = 0;
if fyear = '2020/21Q4' then Q42020I = 1; else Q42020I = 0;
if fyear = '2021/22Q1' then Q12021I = 1; else Q12021I = 0;
if fyear = '2021/22Q2' then Q22021I = 1; else Q22021I = 0;
if fyear = '2021/22Q3' then Q32021I = 1; else Q32021I = 0;
if fyear = '2021/22Q4' then Q42021I = 1; else Q42021I = 0;
if fyear <= '2019/20Q4' then pandlock = 0; else pandlock = 1;
if fyear <= '2019/20Q4' then interaction = 0; else interaction +1;
keep &antipsychotics fyear PCT_COL time pandlock interaction Q12020I Q22020I Q32020I
Q42020I Q12021I Q22021I Q32021I Q42021I;
label Q12020I = 'Indicator: 1 for 2020-Q1, 0 for all other quarter';
label Q22020I = 'Indicator: 1 for 2020-Q2, 0 for all other quarter';
label Q32020I = 'Indicator: 1 for 2020-Q3, 0 for all other quarter';
label Q42020I = 'Indicator: 1 for 2020-Q4, 0 for all other quarter';
label Q12021I = 'Indicator: 1 for 2021-Q1, 0 for all other quarter';
label Q22021I = 'Indicator: 1 for 2021-Q2, 0 for all other quarter';
label Q32021I = 'Indicator: 1 for 2021-Q3, 0 for all other quarter';
label Q42021I = 'Indicator: 1 for 2021-Q4, 0 for all other quarter';
label PCT_COL = 'utility rate';
label pandlock = 'pandemic lockdown started in March 2020';
label time = 'Time (2015Q1-2021Q4)';
label interaction = 'interaction term for time and intervention';
```

run;

*** step 3: conducting preliminary analyses (*t*-test, linear regression) and final analysis (linear autoregression test);**

*** a.** preliminary analyses;

*** a.1.** doing **one-sample t-test** to compare time indicator variable with the average of corresponding quarters in the previous 5 years;

*** short-term (i.e., Q1-2020);**

proc ttest data = &output H0 = 719.3;

var PCT_COL;

where fyear in ("2015/16Q1","2016/17Q1","2017/18Q1","2018/19Q1","2019/20Q1");

run;

*** a.2.** doing **linear regression test** to compare time indicator variable with the expected trend;

*** short-term;**

proc reg data = &output;

model PCT_COL = time Q12020I

run;

*** b.** doing **linear autoregression test** to compare time indicator variable with the expected trend (diagnosis and correction of autocorrelation and seasonality);

*** short-term;**

PROC AUTOREG DATA = &output;

MODEL PCT_COL = time Q12020I/method = ml dw = 4 dwprob loglikl;

run;

*** long-term (i.e., Q1-2021);**

PROC AUTOREG DATA=&output;

MODEL PCT_COL=time Q12021I/method = ml dw = 4 dwprob loglikl;

run;

Table Appendix IV. Preliminary results summarizing the association between COVID-19 health measures and the prevalent and incident antipsychotic use in schizophrenia in Manitoba, in the first fiscal quarter of 2020, by two statistical tests		
	Student *t*-test (Estimate, t-value, *p*-value)	**Linear regression, with adjustment for time (Estimate, standard error, *p*-value)**
Prevalent rate	6.7 (2.6, $p = 0.056$)	-1.7 (4.3, $p = 0.6$)
Incident rate	-1.9 (-9.5, $p < 0.001$)*	-1.3 (0.5, $p = 0.01$)*
*Statistically significant at $p \leq 0.05$		