A Descriptive Analysis of Antipsychotic Prescribing Patterns for Patients Admitted to Hospital with a Primary Diagnosis of Schizophrenia

by

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The above committee determined that the thesis is acceptable in form and content and that a satisfactory knowledge of the field covered by the thesis was demonstrated by the candidate during an oral examination. A signed copy of the Certificate of Approval is available from the School of Graduate and Postdoctoral Studies.

Abstract

Treatment with antipsychotic medication is recognized as the standard treatment for patients with schizophrenia. While evidence-based recommendations have been made on antipsychotic prescribing patterns for patients with schizophrenia, there is still a disconnect between these recommendations and the prescribing patterns that are seen in clinical practice. This study investigates the current antipsychotic prescribing patterns for inpatients with schizophrenia at Ontario Shores, a specialized mental health hospital in Whitby, Ontario. Most sociodemographic variables had no significant effect on the three outcomes variables: whether patients met a target antipsychotic dose by the second week post-admission; were prescribed an LAI; or whether, pending eligibility, patients were prescribed clozapine as a third-line treatment. Length of stay as well as race/ethnicity were associated with an increased likelihood of receiving treatment with an LAI, however there are a number of unobservable confounding variables which make it difficult to draw conclusions from these findings. Overall, the findings of this study suggest that the provider seen may be an influential factor in determining the type of treatment a patient receives. This study provides a baseline on the current antipsychotic prescribing patterns at Ontario Shores and may be used to inform the implementation of an antipsychotic order set as part of bundled care initiatives within the hospital moving forward. Future studies should investigate whether receiving treatment that aligns with evidence based recommendations correlates with improved symptom scale scores and, whether the successful implementation of an antipsychotic order set improves both the standard of care received and symptom scale scores of patients diagnosed with schizophrenia.

Keywords: mental illness, schizophrenia, antipsychotic prescribing, prescribing patterns

Author's Declaration

I hereby declare that this thesis consists of original work of which I have authored. This is a true copy of the thesis, including any required final revisions, as accepted by the examiners.

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The research work in this thesis was performed in compliance with the regulations of Research Ethics Board / Animal Care Committee obtained from Ontario Shores Centre for Mental Health Sciences #22-029-D.

Statement of Contributions

This research was conducted by Tai Hollingbery while attending Ontario Tech University under the supervision of Dr. David Rudoler and guidance provided by Dr. Chekkera Shammi. All individuals contributed discussions, editing and revisions which led to the final manuscript. Dr. Rudoler, Dr. Shammi and Tai Hollingbery developed the study and oversaw the direction and planning. Tai Hollingbery wrote the manuscript with support from Dr. David Rudoler and Dr. Shammi. They conducted the literature review and interpreted the statistical findings while the analytical methods used were verified by Dr. Rudoler.

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Table of Contents

List of Figures

List of Tables

List of Appendices

Chapter 1. Introduction

Schizophrenia is one of the leading causes of disability worldwide with individuals diagnosed with schizophrenia typically having a lower life expectancy and decreased quality of life (1). Treatment with antipsychotic medication is essential to the effective management of schizophrenia during the acute phase of illness and for relapse prevention (2). Due to the chronic nature of schizophrenia, it is usually necessary to maintain treatment with antipsychotic medication over a long period of time (3). Despite the necessity of medication for optimal treatment, nonadherence is highly prevalent in this patient population with non-adherence rates ranging from 41-55% (2). Poor adherence has been linked to higher levels of residual symptoms, higher risk and rates of relapse, increased hospitalization rates, lower rates of remission, greater mortality and overall a decreased quality of life (2). There are several recommendations that have been made on the prescription patterns and practices for antipsychotic medication in the treatment of schizophrenia; however, research shows that these guidelines and best practices do not always align with what is being done in clinical settings (4). For example, polypharmacy has been found to be high in clinical settings despite the limited evidence to support its use (5). However, more recent studies offer support for the use of combinations of antipsychotics after an inadequate response to serial monotherapy trials, with evidence especially supporting the use of a dopamine partial antagonist as the second agent (6–10).

In addition, clozapine, a medication known to be effective in cases of treatment-resistant schizophrenia, is often underused in clinical practice despite the evidence

describing its effectiveness as a third-line treatment (11). Similarly, long-acting injectables (LAIs) have been shown to be an effective treatment option at many stages of illness due to increased treatment adherence and reduced rates of relapse and rehospitalizations but are also consistently underutilized in clinical practice (12).

A critical problem in mental health services is the gap between what is known about effective treatment and the importance of continuity of care compared to the types and ways that treatment is provided to the patient (13). To address this gap, integrated care pathways (ICPs) are being implemented in order to provide structured, multidisciplinary care plans which detail the essential procedures and interventions when it comes to the care of patients with specific health conditions (14). Currently the clinical services provided to patients with schizophrenia are variable and often poorly defined and, due to the chronic, complex and cost-intensive nature of the illness, makes the use of ICPs particularly relevant for this patient population (14). Use of the ICP framework has the ability to improve the services patients receive and have access to by-way of improving the way services are delivered. An example of this is the use of a medication order set which helps guide the prescription of medications and overall treatment plan to ensure that optimal interventions are implemented (14). However, in order to implement new interventions aimed at improving prescribing practices, an understanding of the current prescribing practices is required.

This thesis will describe and evaluate the antipsychotic prescribing patterns for patients with a primary diagnosis of schizophrenia admitted to Ontario Shores Centre for Mental Health Sciences (“Ontario Shores”), a specialized mental health hospital in Whitby, Ontario. The following chapter will provide background information and context

on the illness of schizophrenia and how antipsychotic medication is used to treat schizophrenia. It will also provide an overview of how advancements in pharmacotherapy have influenced the treatment of schizophrenia. This chapter will also introduce and compare typical and recommended prescribing practices and potentially problematic methods of treating schizophrenia in the acute and chronic stages of the illness.

Chapter 2. Background & Literature Review

This section describes the symptoms of schizophrenia, the impact this complex mental illness has on individuals and society, and how antipsychotic medications are critical in the treatment of schizophrenia. This section will also discuss how advancements in pharmacotherapy have influenced the treatment of schizophrenia over time. Finally, both common and recommended antipsychotic prescribing practices will be discussed and the potentially problematic methods of treating schizophrenia in the acute and chronic stages of the illness will be explored.

Schizophrenia

Schizophrenia is a neurodevelopmental, life-long and chronic illness characterized by classic psychotic symptoms (positive and negative symptoms) and cognitive and perceptual alterations (including delusions and hallucinations) along with other neuropsychiatric manifestations which come about in episodes of acute psychosis followed by periods of partial or full remission (15–19). The Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V) defines schizophrenia as a psychotic disorder characterized by two or more core symptoms, one of which must be hallucinations, delusions or disorganized speech in which the patient has experienced the symptom(s) for at least 1 month (20,21).

Schizophrenia is associated with functional deficits as well as social and/or occupational decline (22–25). It involves the breakdown in links between thought, emotion and behavior which ultimately affects how a person thinks, feels and acts (24). The psychopathology of schizophrenia is complex and patients tend to experience a very broad range of symptoms which usually leads to a loss of function and autonomy with low expectations of recovery (16–18). Generally, schizophrenia manifests in

adolescence or early adulthood with the first episode of psychosis occurring between the ages of 15 and 30 after which the illness follows a chronic life course (26,27).

Globally, the lifetime prevalence of schizophrenia is around 1%, and affects approximately 20 million people around the world (28,29). The recurring course of illness makes schizophrenia one of the leading causes of disability worldwide, falling within the top ten contributors to global burden of disease and disability (16,22,24,28,30,31). Co-occurrence of other psychiatric disorders are common and include substance use disorders which, along with other physical health challenges such as diabetes, obesity and reduced engagement in health maintenance, contribute to the increased mortality rates seen in individuals with schizophrenia (31). Compared to the general population, individuals with schizophrenia are at an increased risk of premature death due to cardiovascular disease and suicide (26,27,31). Estimates put suicide rates at around 4-10% with rates among men being at the higher end of this range (26,27,31).

The highest prevalence rates of schizophrenia are seen in individuals 25-54 years of age which, due to the potential earning capacity of this age range, makes schizophrenia a contributor to notable economic losses through loss of the labor market (16,18,28,31–33). The economic burden imposed by individuals with a diagnosis of schizophrenia comes from both direct and indirect costs (18,34). The chronic nature of schizophrenia often necessitates hospital admissions, prescription drugs and, along with these direct healthcare costs, many indirect costs including unemployment, productivity loss, premature mortality, and caregiver time (16). For example, due to the level of functional impairment caused by the illness, only 10-15% of people with

schizophrenia are employed with many remaining on disability after their initial diagnosis (16,18). The World Health Organization (WHO) has estimated that direct costs of schizophrenia in Western countries range from 1.6-2.6% of total healthcare expenditures (16). It has been shown that young adults incur higher all-cause healthcare costs when compared to older adults (16). Studies often use hospitalizations as a measure of relapse for individuals with schizophrenia, due to the high frequency of hospitalization that occurs in this patient population as a result of the exacerbation of symptoms (19). Furthermore, the costs incurred by patients with schizophrenia during the initial stages of the illness and during relapses are mostly attributed to inpatient costs followed by outpatient visits and pharmacy costs (16). Quantifying the cost of relapse is an important component of evaluating the total cost burden of the disease as well as the cost effectiveness of a variety of treatment options for individuals with schizophrenia which should be explored further (19).

First-episode schizophrenia

The initial effects on social, occupational, and functional aspects of life that come with the onset of schizophrenia are difficult to reverse. For this reason, early illness ------— described as the first 2-5 years following illness onset which typically occurs around adolescence or early adulthood — is a critical period for treatment and for determining long-term prognosis (16,26),18,,21,22,30,31). Greater duration of untreated psychosis in the early stages of illness is associated with poor long-term outcomes which include reduced likelihood of remission, poor symptom control and worse social and overall functioning (27,35). Despite concerns associated with delayed treatment in

the early stages of illness, early intervention for psychosis is not universally available in Canada. While guidelines have been developed to help standardize the delivery of services, there are no government policies or official standards of care for early intervention services (EIS) (35,37,38).

Despite the importance of timely treatment in the early stages of illness, treatment nonadherence to oral antipsychotics is common and can lead to relapse and contribute to the deteriorating course of the illness (27). Patients are known to be more responsive to antipsychotic treatment in the earlier stages of illness (first-episode psychosis); however, treatment nonadherence during this time period has been described as one of the most important obstacles in achieving sustained remission (27,39). Medication nonadherence in first-episode psychosis can be detrimental to achieving optimal treatment outcomes (27,39). Overall, treatment from the early phases of disease may present a key point for preserving neurocognitive abilities, for preventing structural brain changes, and for hindering the progression towards chronic functional deterioration (30).

Antipsychotic Medication

According to national and international guidelines, pharmacological treatment with antipsychotic medications is part of the standard treatment provided to patients experiencing psychosis (17). Antipsychotics are used to address the positive symptoms of psychosis which commonly include hallucinations and delusions (28,40). All antipsychotic medications act downstream at the dopamine D2 receptors on the

postsynaptic terminals to reduce dopamine-mediated signaling which in turn reduces psychotic symptoms (17,40,41). Oral or injectable typical, also referred to as first generation antipsychotic (FGA) or atypical, also known as second-generation antipsychotic (SGA) medications can be used in the treatment of schizophrenia (10,23). In addition, patients diagnosed with schizophrenia may have a treatment plan where antipsychotic medications are used alongside other therapeutic interventions (15,28).

First generation antipsychotics (FGA), also known as typical antipsychotics, weren't introduced until the early 1950s. Prior to the discovery of Chlorpromazine in 1952, treatment for patients with schizophrenia was based around the idea that treatment with a tranquilizer had therapeutic effects by way of reducing aggression, agitation, violence and anxiety in patients (41). However, when the antipsychotic properties of Chlorpromazine were discovered it became apparent that the primary effect was the reduction in psychotic symptoms which ultimately provided a more effective treatment for patients with schizophrenia (41). Despite the beneficial effects of FGAs, it was soon discovered that they were causing drug-induced movement-disorders (42). The prevalence of the symptoms experienced by individuals on these medications was found to be correlated with the degree of dopamine D2 receptor blockade which is largely influenced by the dosage of medication an individual receives (40). These uncontrollable involuntary movements, such as dystonia, parkinsonism, and tardive dyskinesia had notable negative effects on the lives of individuals being treated with FGAs (22).

In an effort to move away from the prescribing of medications that were known to cause serious side effects, second generation antipsychotics (SGAs) were created and

on the market for use in the early 1990s (43). When oral second-generation antipsychotics (SGA) were introduced there were several claims of better tolerance and less severe side effects and they quickly became the recommended treatment due to their lower risk of motor dysfunction (40,43). While SGAs typically provide a lower risk of movement disorders, they are commonly associated with serious metabolic disturbances including pronounced weight gain, dyslipidemia, and diabetes (40). Despite the metabolic concerns associated with many SGAs, they are currently used in approximately 71% of patients diagnosed with schizophrenia due to their efficacy in providing symptomatic relief during episodes of psychosis (28,40,44).

Since the discovery of Chlorpromazine, other than the development of new compounds which have similar mechanisms of action, the field of antipsychotic drug therapy has not seen many innovative advancements or discoveries (41). With most antipsychotics sharing the same dopamine D2 receptor mechanism of action, increasing potency and dosing both raise the risk of a variety of adverse effects while at the same time demonstrate no additional improvements in efficacy (41). Currently, drug development for the treatment of schizophrenia is focused on synthesizing compounds that are capable of alleviating commonly unresponsive negative symptoms, while also attempting to decrease the likelihood and severity of a variety of other adverse effects (22). Overall, antipsychotic medication has been critical in managing the wide range of symptoms experienced by patients diagnosed with schizophrenia and the continuation of effective treatment is critical in reducing the risk of future relapses (45).

Long-Acting Injectable Antipsychotics (LAIs)

Several antipsychotic medications, both typical and atypical, are available in oral or injectable form (28). The introduction of long-acting injectable antipsychotics (LAIs) was a key advancement in the treatment of schizophrenia (41). LAIs are delivered parenterally, allowing them to avoid some of the inter-individual differences in absorption and metabolism (46). The first guidelines on LAI use for patients with schizophrenia were published in 1988 and recommended that LAI antipsychotics be considered as a treatment option for any patient with schizophrenia who requires long term treatment (43,47).

Findings from previous research support the use of LAIs at various stages of illness (48). The use of LAIs decreases the reliance on daily oral medication regimens which can be beneficial in increasing medication adherence rates (41). Poor medication adherence is often considered to be the primary indicator for clinicians to switch to a trial of LAIs; however, several studies have reported that less than 20% of patients with evidence of poor adherence use LAIs (16,49). Studies have compared LAI antipsychotics to oral medications and it has been found that those treated with LAIs experience a lower relapse rate (9.2%) when compared to those treated with oral antipsychotics (42.1%) (29). In addition, other studies have shown a reduction in mean number of hospitalizations and overall shorter lengths of stay in patients with schizophrenia who are treated with LAIs (16). One RCT demonstrated that, over a period of 24 months, patients with schizophrenia who were treated with an LAI experienced a 44% decrease in total hospitalizations compared to those treated with oral medications (50). In another trial, this time in patients with recent onset schizophrenia, reductions in relapse rates and hospitalizations were reported alongside

better psychotic symptom control and better medication adherence after 12 months of treatment with LAIs compared to oral medications (51). Most randomized controlled trials (RCTs) that have compared LAIs to oral antipsychotics have shown superiority of LAIs in regards to adherence, clinical symptomatic improvement, reduction in adverse effects (especially extrapyramidal symptoms) and a reduction in hospitalizations (43). Large scale database studies support RCT findings, showing that compared to those receiving oral antipsychotics, patients receiving SGA LAIs had lower odds of rehospitalizations, ER visits and fewer total days in the hospital (39). Given what is known on LAIs and their positive treatment outcomes, it is important that physicians are willing to use LAIs as part of the treatment plan at time points that present the greatest opportunity for positive outcomes for the patient. The key decision points when a LAI may be considered as a treatment option include: 1) when an individual is newly diagnosed, 2) when an individual has recently relapsed or, 3) when an individual is transitioning out of in-patient care or incarceration (52). Revisiting the decision-making process that goes into creating a treatment plan for individuals at these timepoints may be necessary to improve the quality of treatment received and overall patient outcomes.

The primary goal of treatment during the first 5 years after illness onset is to prevent subsequent relapse(s) and to restore adequate levels of socio-occupational functioning (43). In the early stages of illness onset medication-naïve individuals are sensitive to antipsychotics and generally respond well to treatment (43). Treatment continuity for FES is important for improving long-term outcomes as decreasing psychosocial deterioration and progressive structural changes in the brain, which have the potential to occur in the early stages of illness (43,53). There are potential clinical

benefits and cost-effectiveness considerations for the use of LAIs in the early stages of illness when compared to oral medications. These benefits include lower rates of relapse and hospitalizations, delays in treatment failure, reduced comorbidities related to schizophrenia and decreased use of healthcare resources (27,44). In addition, several brain imaging studies have shown that treatment using LAI medication early on is associated with the preservation of the frontal lobe, intracortical myelin and white matter volume when compared to treatment with oral antipsychotics (27,54,55). Generally, patients with schizophrenia are most responsive to antipsychotic treatment at illness presentation, therefore using LAIs as early as after the first episode of psychosis is one way that the illness course may be beneficially altered (39,43). While LAIs do not provide a guarantee of treatment, as there is always the risk that a patient may choose to miss an injection, they do provide the treatment team with an immediate awareness of nonadherence (46). If a patient relapses while using an LAI, it becomes easier to identify that non-compliance was not the reason for relapse (43).

Some reports on negative patient perception of LAIs have been described as a reason that clinicians avoid providing LAIs as a treatment option in the early stages of illness, however, it is also possible that clinicians are not providing patients with adequate information on LAI treatment (43,56,57). LAIs offer several advantages to the patient over oral medications including: not having to remember to take daily medication, reducing the risk of intentional and unintentional overdose, and transparency of adherence to family and/or clinicians (43). For these reasons, many patients who have tried using an LAI report that they prefer this method of treatment and describe “feeling better”, “having a more normal life” and “finding injections easier to

remember” (41,56,57). Proper education directed towards mental health staff, patients and families regarding the use of LAIs may reduce the stigma that has historically been associated with this form of medication (23).

Continuity of care plays an important role in reducing the risk of deterioration in individuals with severe mental illness. Sudden changes in the delivery of healthcare, such as transitioning from an inpatient to outpatient setting, could increase the risk of distress and has the potential to lead to treatment nonadherence (52). The use of LAIs in individuals who are transitioning from one healthcare setting to another (i.e., in-patient to outpatient) may help reduce this risk.

LAI use varies in different areas of the world and it has been reported that, worldwide, the proportion of patients being prescribed LAIs ranges from 10-50% (43). Despite the advantages described for their use in early stage illness, LAIs are largely still being limited to use in the treatment maintenance of chronic, recurring schizophrenia (43). Utilization of LAIs is lower in the United States than many other countries despite being widely available to physicians as a treatment option (46). Even with their demonstrated efficacy, the use of LAIs is often delayed in clinical practice until numerous treatment failures, relapses, or hospitalizations have occurred (27). In the United States, LAIs are not considered as a first-line treatment option and clinicians tend to use them sparingly as they are still perceived by some as being a coercive form of treatment and are deemed to be stigmatizing (60). In addition to subjective viewpoints limiting the use of LAIs, the costs associated with LAIs do tend to be higher than those of oral antipsychotics, however, with the initiation of LAIs, patients incur less direct and indirect healthcare costs over time (61). Earlier introduction of long-acting injectables

not only has the potential to provide significant benefits to the patient but is also one way to reduce total healthcare costs incurred by this patient population (62).

The use of LAIs is not without limitations however. Observational studies comparing treatment with LAI antipsychotics compared to oral antipsychotics may, by nature of the illness and treatment progression, be including individuals with a more severe illness presentation in the LAI groups which influences the interpretation of the results (39). While many studies have shown favorable results for the use of LAIs in treatment for individuals with schizophrenia, there are some RCTs that have not been successful in consistently showing superior efficacy of LAIs over oral medications (39,50,51). For example, Liu et al (2015) found no difference in average time to rehospitalization in LAI-treated and oral medication-treated patients (63). An RCT on the difference between LAI and oral risperidone in early phase schizophrenia found that over the course of 2 years both treatments were equally effective and had similar safety profiles for patients in this phase of illness (39). Supporting the findings of this study another RCT, which evaluated 305 patients over a 30-month study period, showed no significant differences in the time to first relapse or hospitalization between those treated with a Risperidone LAI and those treated with an oral SGA (39).

From the perspective of clinicians, appropriate prescribing of LAIs is complicated due to their long half-lives and delayed release (43). There is a lack of data on the dose-response of LAIs which means clinicians have to approximate dosing of LAIs (44). One of the main disadvantages is the slow dose titration and the length of time it takes to achieve steady state levels within the bloodstream, which is not favorable for acutely ill individuals where rapid dose titration is necessary (44,64).

LAIs have now been available for decades and provide an alternative to oral medications. They offer a method of medication administration which may be more reliable than oral medication for some patients (39). The benefits of LAIs mean they could play an important role in the long-term treatment of patients with schizophrenia (43). The potential for improvement in treatment adherence is a key consideration when determining the best treatment plan for certain patient populations, and for this reason, the use of LAIs as a treatment plan should be considered at all stages of illness (23,27). Despite the benefits described, there is a lack of long-term randomized controlled trials comparing the efficacy, tolerability and relapse prevention of LAIs and oral antipsychotics therefore, further exploration of this type of treatment at various stages of illness is required (12,43).

Polypharmacy

Antipsychotic treatment guidelines for schizophrenia recommend monotherapy as the standard of care, particularly in patients with a history of nonadherence to oral antipsychotics and for whom relapse is a concern (25,65–67). This is, in part, due to the risk of nonadherence that is associated with a more complicated medication regimen (68–70). Despite the recommendation of monotherapy, many individuals diagnosed with schizophrenia are treated using polypharmacy.

Antipsychotic polypharmacy is the practice of co-prescribing one or more antipsychotic medications to a patient for the treatment of their mental illness (25,71). Despite a lack of research that supports the long-term use of antipsychotic polypharmacy, surveys have found that the prevalence of antipsychotic polypharmacy in

individuals diagnosed with schizophrenia can be close to 50% in some clinical settings (68). There are several reasons a clinician may choose to use polypharmacy including; 1) achieving a more rapid therapeutic response, 2) targeting a specific symptom of the illness or, 3) avoiding a high dose of one antipsychotic due to concerns of adverse side effects (66,68).

In some acute and emergency situations it may not be realistic to wait several weeks to determine if the initial antipsychotic treatment is effective. Furthermore, previous research has shown that patients who do not experience symptomatic improvement by the second week of treatment are unlikely to respond at all and may benefit from a treatment change (66). In situations where acute schizophrenia patients are experiencing an insufficient response to the initial treatment, a switching strategy may be used to change medications (66). Wait discontinuation is the process of introducing the new medication while maintaining the old one while non-wait discontinuation involves stopping the original medication before introducing the new one, either strategy may be used in clinical practice (66). In situations where wait discontinuation is used, the illness may stabilize during the switching period and as a result, the clinician may be inclined to maintain the transient polypharmacy that occurred during the switching period as it may be associated with the illness stabilization (66). However, in these situations, after the patient stabilizes, research shows that most patients can be safely transitioned off of the secondary antipsychotic and back to antipsychotic monotherapy without experiencing clinical deterioration (66,68). It has been found that the most common use of antipsychotic polypharmacy, indicated by clinicians, was the perceived failure of a single antipsychotic to control

symptoms of psychosis (68). Adding a second antipsychotic in early non-responders may be beneficial in an acute-phase of the illness, however, it is important to consider the impacts that polypharmacy may have on the individual (66). Specifically, side effects such as weight gain, glucose intolerance, hyperlipidemia, extrapyramidal symptoms and sedation should be monitored (66). In addition, it is important to recognize that the available research on antipsychotic augmentation strategies include very short follow up periods meaning these trials cannot address the potential long-term side effects that antipsychotic augmentation may have (66). As a result, there is currently insufficient evidence to support the routine application of augmentation or polypharmacy in clinical practices (66).

Monotherapy may play an important role in controlling total antipsychotic dosages and minimizing adverse effects experienced by individuals, however, it has been found that approximately 15-39% of patients with schizophrenia do not experience an adequate level of symptomatic relief with monotherapy and in turn, a minority of individuals experience benefits with antipsychotic polypharmacy (25,66). A meta-analysis by Correll et al (2009) supports this finding and concluded that combined antipsychotics (polypharmacy) may be superior to monotherapy in certain clinical situations (72). While there are concerns around the risks that polypharmacy may pose to patients, in practice, the range of dosage and combinations of antipsychotics prescribed by clinicians varies to such a large degree that it is difficult to confidently say that the benefits never outweigh the risks in individual cases where other evidence-based strategies have been ineffective (66).

In general, guidelines that address the pharmacological management of schizophrenia acknowledge that there is only limited emerging evidence supporting the routine use of antipsychotic polypharmacy (66). However, the experience and expertise of clinicians plays a role in informing the methods they use in clinical practice. While it is important that pharmacotherapy used in practice for the treatment of schizophrenia be based on RCTs and observational studies done on real-world clinical practice, due to the current lack of evidence, guideline development groups take different strategies and approaches when it comes to translating what the current scientific knowledge says into recommendations for clinical practice (66).

High Dosage Antipsychotics

There is large individual variability in the response to antipsychotic medications and, as a result, the range of dosages prescribed to individuals varies (73). High dose antipsychotic prescription is defined as >1000 mg daily of chlorpromazine equivalents and studies done in Europe as well as the United States show that this occurs in 15-41% of patients with schizophrenia (74). Reports published early on, after the discovery of antipsychotic medications as an effective treatment for individuals with schizophrenia, supported the use of a high dosage antipsychotic regimen, however, later reports found that the dose-benefit relationship decreased with higher doses in many individuals (74). No concrete evidence currently exists on whether treatment using high dose antipsychotic medication is more effective than standard doses however, some studies have found that a higher dose of antipsychotic medication is associated with illness severity and may be required in acute, psychiatric emergency situations (66,73,75). In

practice, a dose increase typically occurs when a patient does not respond in an adequate manner to the initial treatment and/or they need a more immediate therapeutic response (73). The tendency of clinicians to prescribe high doses of antipsychotics has also been described as a way to reduce the risk of relapse (73).

There is a high degree of subjectivity and variability among the opinions of clinicians on what is considered a high or low dose of any given drug and currently, there is no objective method of determining a minimum effective dose of antipsychotics (73). Experience-based opinions on dosing are susceptible to many influences, including national and local dosing practices, manufacturers' recommendations, and the personal views of clinicians on what constitutes a high or low dose (73,76). Clinicians may also adjust dosages based on patient-related factors such as age, sex, nationality, hepatic function impairment, renal function and the severity of psychiatric symptoms (73,76). An international consensus study by Gardner et al (2010) assessed the clinical opinions on the optimal dose of an antipsychotic medication, haloperidol, for treatment of a reference case which highlights the subjectivity that is present in antipsychotic dosing (76). In this reference case psychiatrists agreed upon a "standard" dose of 5-10mg of haloperidol per day, a dose that would result in over 85% of central dopamine D2 receptor blockade, therefore categorizing it as a high dose of antipsychotic medication (73,76). Furthermore, Schill & Olson (2016) explored the inter-rater reliability of antipsychotic dosing between psychiatrists. It was found that a lack of agreement between psychiatrists exists, which may indicate that the dose of antipsychotic medication an individual is prescribed is heavily influenced by which doctor they see

rather than be determined by objective measures such as the severity of their illness (73).

Adverse Effects

Treatment effectiveness is generally defined as maximizing the efficacy while minimizing the negative side effects (77). In schizophrenia, effective treatment primarily involves reducing psychotic symptoms and while symptomatic reduction is important, considering the burden of side effects that effective treatment may cause is also critical (77). The importance of these two factors is demonstrated in the CATIE study which measured treatment effectiveness and time to treatment discontinuation. While the primary reason for discontinuation was due to lack of efficacy, an important factor influencing the reason for discontinuation was poor medication tolerability (77,78).

Most antipsychotics have a similar mechanism of action and act as a dopamine D2 receptor blocker (79). Typical antipsychotics (FGAs) have been shown to be effective in reducing the positive symptoms associated with schizophrenia but show high rates of extrapyramidal motor side effects, hyperprolactinemia and cognitive dulling in many patients (79). Studies using Positron Emission Tomography (PET) scans identified that a high percentage of central dopamine D2 receptor blockade has been shown to produce adverse effects and high dose antipsychotics may cause further exacerbation of the adverse effects experienced by patients on antipsychotic medications (73,79). Van Putten et al (1990) demonstrated that high dose antipsychotics have the potential to cause significant neuro-psychotoxic effects as early as the second week of treatment (66,80). In addition, micrographia, a fine-motor

extrapyramidal symptom that may develop early on in antipsychotic treatment, has been correlated with levels of central dopamine D2 receptor occupancy and contributes to the overall decline in functioning that is typically seen in individuals with schizophrenia (73,81).

Atypical antipsychotics have different pharmacological properties in that they function as Serotonin 5HT-$_{2A}$ antagonists in combination with the D2 receptor antagonism also seen in FGAs (79). While lower rates of extrapyramidal side effects are seen with SGAs, higher rates of metabolic adverse effects frequently occur (79). Metabolic side effects of antipsychotics include weight gain, insulin resistance, hypertension, elevated glucose, dyslipidemia, and cardiovascular disease (77). With the frequent occurrence of metabolic disturbances when being treated with atypical antipsychotic medication, early onset of weight gain and metabolic dysfunction should be closely monitored in all patients (77). Monitoring and early detection of metabolic side effects plays a crucial role in preventing a variety of metabolic diseases, however, Stahl et al (2020) found that the majority of patients on antipsychotic medications were not being properly monitored (77). Excessive weight gain is defined as an increase in weight that is equal to or greater than 7% of an individual's body mass index (BMI) and is a concern in particular for antipsychotic-naïve patients (27,77). Clozapine and olanzapine are most commonly associated with excessive weight gain, while risperidone, paliperidone, asenapine, iloperidone, and quetiapine are only moderately associated with excessive weight gain (77). In addition to metabolic and neurological side effects, sexual dysfunction is commonly seen with antipsychotic treatment and presents most often as impaired libido, orgasmic and arousal function (77). In patients

with first-episode schizophrenia, cardiometabolic risk factors and abnormalities often present early on in the illness and are likely related to the underlying illness, unhealthy lifestyle, as well as antipsychotic medication (18). In general, it has been observed that first-episode patients are more vulnerable to a wide range of side effects, even with lower doses of antipsychotic medications and currently, there is a need to learn more about the adverse cardiometabolic effects in the early stages of schizophrenia in order to implement better monitoring protocols in clinical settings (18).

Antipsychotics, Schizophrenia and Substance Use Disorders

As many as 47% of individuals diagnosed with schizophrenia have a comorbid substance use disorder which may be explained by the following two hypotheses; 1) individuals with schizophrenia often turn to substances as a way to cope with their symptoms and, 2) schizophrenia as an illness shares similar neurobiological pathways with those of substance use illnesses (82,83). While these hypotheses may have some merit neither fully explain the extent of substance use problems in this patient population. A third hypothesis exists and describes the potential for antipsychotic medication to modify the reward circuitry in the brain, therefore enhancing the rewarding properties of illicit substances (82). Findings that support this hypothesis show that chronic exposure to antipsychotic medications can induce super sensitivity to dopamine agonist stimulation which in turn enhances the function of the reward circuits in the brain (82,84,85). While antipsychotic medications have not been shown to promote addiction, results from several animal studies have shown that treatment with antipsychotic medication may play a role in enhancing the motivational properties of reward cues

experienced when using addictive substances (84,85). A caveat to these findings is that it appears to be a more common occurrence in patients treated with typical antipsychotics, and not as much of a problem in those treated with atypical antipsychotics. The clinical implications of these findings are twofold: first, the potential of dopamine supersensitivity occurring provides another reason as to why it is important to avoid using high dose typical antipsychotics, and second, a clinician may wish to keep in mind a patient's predisposition to substance abuse when choosing which medication to use in treatment (82,86).

Withdrawal Effects of Antipsychotics

While antipsychotic medications are critical in the successful treatment and stabilization of schizophrenia, they also come with some concerns. The chronic nature of schizophrenia necessitates long-term treatment; however, long-term use of antipsychotic medication may exacerbate symptoms of withdrawal and make it difficult for individuals to lower, discontinue or switch medications without experiencing withdrawal effects (87). Withdrawal symptoms appear to occur frequently when antipsychotic medications are discontinued abruptly (87). The main mechanism in the development of withdrawal symptoms seems to be the neuroadaptation to the antagonist effects of antipsychotic medications on the receptors in the brain (87). Most withdrawal symptoms occur within 4 weeks of abrupt discontinuation of medication; however, patients experiencing withdrawal symptoms typically do not fulfill the addiction criteria of the International Classification of Disease (ICD) making the implications and ability to address withdrawal symptoms complex. To add to the complexity, it is often

hard to differentiate withdrawal symptoms from the beginnings of a psychotic relapse (87). The current knowledge on the occurrence of withdrawal symptoms highlights the importance of using a proper discontinuation strategy however, this can be challenging due to side effects that occur with discontinuation being dependent upon specific factors related to the patient and treatment plan. These factors include behavioral mechanisms and comorbidities of the patient as well as side effect profiles, pharmacodynamics and kinetics of the medication(s) being used to treat an individual (87). Overall more research is needed to determine the extent to which patients on antipsychotic medication may experience withdrawal symptoms and how best to maximize discontinuation strategies in order to reduce the risk of a patient experiencing withdrawal.

Schizophrenia, Relapse & Medication Non-Adherence

The recommended first line treatment for patients with schizophrenia is antipsychotic medication which is used to enhance long-term functional outcomes and reduce the risk of relapse (3,88–91). Antipsychotic medications make it possible for patients diagnosed with schizophrenia to achieve symptomatic remission, however, relapses are a common occurrence in the disease course of schizophrenia (29,39). Adequate treatment given during the first psychotic episode is critical in helping to reduce the risk of relapse in the early stages of the illness and long-term maintenance treatment with antipsychotics is usually necessary in order to manage schizophrenia (16,29,39). Wiesjahn et al (2013) defines adherence as “taking medication as prescribed at least 75% of the time” and, based on this definition, adherence rates have

been estimated to be around 49.5% (92). Non-adherence to antipsychotic medication is the most frequently reported factor associated with relapse in the early and later stages of the illness, followed by stress/depression and substance use (29,39). Findings by Alphs et al (2022) suggest that a good level of adherence to oral antipsychotic treatment protocols is difficult to sustain long-term for many individuals (27). These findings align with other studies done on patients experiencing first-episode schizophrenia where rates of nonadherence begin to increase around 6-12 months after the initial recovery from an acute phase of psychosis (27).

Despite the well-known effectiveness of antipsychotic medication in reducing psychotic symptoms, adherence to oral medications is often a barrier to long-term symptomatic relief (16). Supporting this finding, Offord et al (2013), found that only 40% of patients with schizophrenia were adherent to their medication (62). When examining the time course of schizophrenia, from illness onset, adherence seems to decline drastically between months 1-6 and months 7-12 in both younger and older adults (16). Increasing rates of relapse, nonadherence to oral antipsychotics can influence rates of rehospitalization, time to remission, and risk of suicide (65). In addition, stigma, adverse side effects, costs and lack of perceived efficacy can also play a role in patient adherence (46). A large portion of nonadherence comes from patients forgetting to take medication which can be further exacerbated by symptoms of the illness itself such as disorganization and cognitive dysfunction (46). With each relapse recovery becomes slower and less complete, eventually leading to the deterioration of social functioning (65). With what is known about the consequences of relapse it is crucial that clinicians

continue to explore ways that will help patients better maintain their antipsychotic treatment plan.

Treatment Resistant Schizophrenia & Clozapine

Patients diagnosed with schizophrenia who experience minimal or no symptomatic response to the commonly prescribed antipsychotic medication and are considered to have treatment resistant schizophrenia (TRS) (1). TRS is defined as patients who fail to respond to two different antipsychotic medications taken at an adequate dose for at least six weeks. It is estimated that TRS occurs in 34% of patients diagnosed with Schizophrenia (1,65,93,94). Clozapine has been accepted within the literature as the gold-standard treatment for TRS and is the evidence-based treatment option that clinicians should look to pursue when creating a treatment plan for these individuals (36).

Clozapine is an atypical antipsychotic that was introduced in the early 1970s and while its use was initially limited due to the risk of agranulocytosis, a drug-induced blood disorder where white blood cells drastically decrease in the circulating blood, it was eventually approved due to its superior efficacy over chlorpromazine in cases of TRS (41,94–96). In Canada and the United States clozapine was unavailable for some time due to the risk of the potentially fatal agranulocytosis and did not re-enter the market until 1990 and 1991 respectively (94). Clozapine has since proven to be more effective than any other antipsychotic medications in cases of severe treatment resistance, violence and suicide in patients with schizophrenia (41,94).

Evidence that supports the use of clozapine as the most effective treatment for individuals presenting with TRS includes a meta-analysis of 12 controlled trials which demonstrated that clozapine consistently produced a greater reduction in symptoms when compared with typical or atypical antipsychotics (95,97). Additional randomized controlled trials support these findings, and help confirm that clozapine is often more effective in alleviating symptoms in patients with TRS compared to other atypical antipsychotic medications (36,95,98). Despite the evidence supporting the use of clozapine for TRS, clozapine is consistently underused in clinical settings (36,99). Epidemiological studies estimate that 16-30% of patients with schizophrenia would benefit from a clozapine prescription however, further the research shows that less than 7% of patients in Canada are taking clozapine. In contrast, the use of clozapine is more widely accepted by both patients and clinicians in New Zealand and as a result, clozapine prescriptions are estimated to be around 32.8% of the patient population (36,99).

The consensus regarding the use of clozapine is that the medication should be introduced at the earliest opportunity once a patient has been diagnosed with treatment-resistant schizophrenia (36). The CUtLASS study helps support this recommendation by demonstrating that patients who failed to achieve a good response in one year on two different antipsychotic trials, had better symptomatic improvement when switched to clozapine then they did when trialing a third antipsychotic other than clozapine (36,100).

A key component of success in early intervention programs for schizophrenia is the use of a rational approach to pharmacotherapy; however, clozapine is underutilized in this early phase (also known as the critical period) of schizophrenia (36). This is often

attributed to the perception that clozapine should be reserved as a last resort, therefore its use is often limited by clinicians to the later stages of illness (36). Revising the phrase ‘treatment resistant schizophrenia’ to a phrase that applies more broadly to various phases of illness may encourage the use of clozapine, to occur in earlier stages of illness, provided eligibility. In fact it has already been proposed that changing “treatment resistant” to “clozapine eligibility” may allow the focus to be placed on the response to medications rather than the chronicity of the illness (36). It is widely accepted that the long-term trajectory of schizophrenia is established during the initial critical period, or the first 2-5 years following symptom onset, where any type of intervention has the greatest impact on symptom improvement (36). Despite this well recognized time frame, the mean time prior to clozapine use is currently 9.7 years (36). While the rate of clozapine use during the critical period of illness is unknown, informal surveys done by the Canadian Consortium for Early Intervention in Psychosis suggest that the rate that clozapine is used is much lower than the rate of antipsychotic medication failure (36). In Canada, researchers have described the underuse of clozapine as one example of the problematic lack of attention to evidence-based medicine being used in clinical practice (99).

Implementing evidence-based treatment into the routine clinical practice of clinicians has historically been a major challenge in mental health care; however, the low rates of clozapine utilization may be explained by several distinct barriers that arise on the side of both patients and clinicians (13,36). Some patients may decline treatment, may not be able to tolerate clozapine or may experience severe side effects (36). Clinicians may have attitudinal bias around the use of clozapine, similar to the bias

that exists around the use of LAIs (36). As a result of the serious side effects that may present with clozapine use, patients put on this medication require close monitoring. This structural barrier where psychiatrists may be unable to take the extra time needed to monitor patients on clozapine may influence the rate at which clinicians are willing to prescribe the medication (2,36). While clozapine has been shown to be effective for cases of TRS, valid clinical and structural barriers exist that may need to be addressed before the prescription of clozapine can better align with evidence-based recommendations and support this subset of patients in the most effective ways.

Alternative Therapies

Pharmacological therapy is the primary treatment for schizophrenia. However, these medications often induce serious side effects and are limited in their efficacy in managing negative symptoms and reducing cognitive decline (101,102). Research has shown that it is common for patients with schizophrenia to present with anxiety which can in turn contribute to the worsening of psychotic symptoms and an overall decrease in quality of life (101). The use of alternative therapies alongside standard antipsychotic treatment has been studied to varying degrees and have been used to address the core symptoms of schizophrenia as well as the secondary symptoms that patients may present with such as increased levels of anxiety. For example, Lu et al. (2019) used progressive muscle relaxation (PMR) for 12 weeks to determine the acute and long-term utility of this self-managed relaxation technique in reducing anxiety in patients with schizophrenia (101). PMR involves relaxing muscles sequentially, usually starting at the head and moving down the body, is a technique that is easy to learn and is generally accessible to all patients (101). In previous research PMR was effective in reducing

anxiety and improving subjective well-being in patients with schizophrenia (101,103). Overall, Lu et al (2019) demonstrated a decrease in PANSS scores in the experimental group from pre to post intervention, however these positive effects did not persist up until the 3-month follow up mark as was initially hypothesized (101). CBT for psychosis (CBTp) is another modality that can be used in tandem with antipsychotic medication. One review found that compared to the control group, those receiving CBTp treatment had significant improvements in overall psychotic, positive and negative symptoms as well as improvement in auditory hallucinations and delusions (104)

Another study examined music therapy and its role in improving mood and behavior while also reducing stress, pain, isolation and anxiety (102). Music therapy has been used as a preferred alternative to talk therapy as it reduces the patients' need to vocalize what they may be feeling. While results from clinical trials utilizing music therapy as a treatment approach are somewhat inconsistent, one meta-analysis concluded that music therapy decreased total symptom scores and negative symptoms while also improving the quality of life scores in patients with schizophrenia (102). Body-oriented psychotherapy (BPT) is another alternative therapy that has shown some promise when used in combination with antipsychotic medications. Galbusera et al (2017) took a patient-first approach on a small group of patients in order to gain insight as to whether BPT was effective in treating negative symptoms. From the interviews six main themes arose. In the patient group, BPT had many positive effects including; 1) shifting the way patients viewed themselves, 2) making patients feel more grounded, 3) gaining self-confidence, 4) accepting themselves as worthy, 5) gaining appreciation for

interpersonal contact with others, 6) feeling more included and less disengaged and, 7) experiencing hope in the treatment process (105).

The research described above demonstrates a multidisciplinary approach to treatment for patients with schizophrenia should be considered. While more research is needed, using alternative therapies in combination with treatment as usual to date has shown some promising results.

Bundled Care and Order Sets

In Canada there are challenges to accessing appropriate and timely treatment for mental health disorders (106). This can be attributed to several factors including: underfunding, the divide that is made between physical and mental health conditions, and deinstitutionalization which is driving patients with mental health conditions to be cared for in the community rather than in a hospital setting (106). In response to these challenges, Canada has had to come up with more innovative models of treatment to address the fragmented delivery of care and to provide adequate treatment to patient populations affected by complex mental health conditions (106,107).

One solution that is being explored is the implementation of bundled care initiatives which involve the use of integrated health care models where interprofessional and interorganizational collaboration is encouraged (108,109). When utilizing the bundled care model, a predetermined payment is made to a group of providers to deliver agreed-upon bundled health care services which incentivizes cost control by way of efficient care delivery, improved care transitions, and fewer

rehospitalizations, all while ensuring that patient-centered care is being provided (108,110–112).

Order sets fall under the bundled healthcare model and are described as collections of medication orders grouped by clinical purpose that have the potential to help reduce medical errors, improve care quality and reduce costs (113–116). Common classifications include admission order sets, order sets related to the diagnosis or treatment of a particular condition, and order sets that outline a particular care process (such as ruling out an illness or treating a diagnosed illness) (114,117). Order sets for prescription medication are a clinical decision support tool that aim to help clinicians prescribe appropriate treatments using a predefined set of guidelines on type and dosage of medications for specific illnesses (114,115,118). Order sets can be created to support protocols and pathways with decision support systems such as prompts and reminders for clinicians (113). The addition of an order set is often used to encourage evidence-based and efficient care by influencing the behavior of the provider and may be one way to decrease the variation in antipsychotic prescribing that exists (114,119–121).

The efficacy of implementing order sets has been observed in a variety of clinical settings. For example, Netley et al. (2020) evaluated an order set which was implemented to optimize non-opioid treatments for acute pain in the emergency department (122). Researchers found that a key component of the order set implementation was education for clinicians which allowed them to gain an understanding of the importance of the order set which was important in creating buy-in (122). Wells & Loshak (2019) conducted a review of 14 studies done in the United

States (10 studies) and Canada (4 studies) between 2014 and 2019 where order sets were implemented in acute clinical settings for a variety of conditions including respiratory and diabetic conditions, laryngectomies, end-of-life care, ischemic stroke, coronary heart failure and congestive heart failure (115). Researchers found that the implementation of order sets helped reduce hospital length of stay, mortality and medication errors (115). Overall, the percentage of patients who returned to the hospital within 30 days was lower and total length of stay was shorter in the group who received care based on the order set, similar trends have been seen in pediatric patients (115). Order sets used in diabetic conditions saw blood glucose levels decrease to a greater extent, studies on the use of order sets for COPD showed a decrease in prescribing errors and a higher percentage of patients with chronic heart failure received an appropriate medication dose when clinicians had an order set to follow (115). Another study looked at the order set implementation in an emergency department for patients with acute coronary syndrome (ACS) where the goal was to provide physicians with easy access to orders that were consistent with the recommended evidence-based treatment guidelines (119). Results from this study suggest that inexperienced physicians found the order set more useful than experienced physicians, however, survey data showed that conceptually most physicians (regardless of experience) viewed the order set as potentially useful (119). Furthermore, Ozdas et al (2006) examined compliance rates of best practices at admission for patients with ACS and found that the use of an admission order set improved admission practices which increased the chance that patients received aspirin and/or beta-blockers (the standard of care) within 24 hours (120). In another pre and post order set evaluation, Brown et al

(2016) demonstrated that the use of an order set was associated with reduced hospital length of stay and reduced prescribing errors for patients with COPD (123). There is minimal research on the use of order sets directly involved in antipsychotic prescribing, however, one study implemented an electronic laboratory order set for patients on antipsychotic medication in order to increase the rates of pre-antipsychotic blood monitoring in patients (124). The implementation of this order set produced small improvements in cardio-metabolic monitoring parameters in early and chronic psychosis (124).

Two studies have investigated the utilization patterns of order sets in clinical settings. McAlearney et al (2006) examined the utilization of three different order sets at a single hospital site. The variability in the use of order sets seemed to be due to how useful clinicians perceived the order sets to be and a high involvement of clinicians throughout the creation of the order set was associated with higher use of order sets (121). Similarly, Wright et al (2010) evaluated the utilization patterns of order sets across several different hospital sites and found that order sets were consistently utilized when compared to the option of entering orders one at a time which suggests that users attached some utility to the convenience of the order sets available to them (114).

Research on the effectiveness of implementation of order sets is present for some conditions and illnesses and lacking for others. Further research investigating the use of order sets for different illnesses is essential for improving the generalizability of order set use (35,115). Despite the inability to generalize findings from order set implementation in different illnesses to that of schizophrenia and antipsychotic

prescription, it is clear that there are components of the implementation process that are critical for success (35). Having clinical mentors and funding to support implementation may be more influential than data from research studies and including some sort of audit in the implementation process may encourage documentation and adherence among clinicians (35). Formal evaluations of program quality and individual patient outcomes have also been identified as fundamental to any kind of healthcare service delivery while the presence of clinical champions has been shown to be essential to carrying a project of this kind forward from creation to adoption in clinical settings (35,116). In addition, other critical components of order set implementation include: 1) wide stakeholder involvement which helps increase buy-in, 2) use of multiple routes for communication and education of the order set and, 3) advocacy from the administration (116).

While order sets can be used to improve care, increase compliance of guidelines and improve resource use for many conditions and illnesses, there are several challenges of implementing order sets in clinical settings. There is a high initial implementation cost and due to the disruption in routine clinical practice, the use of an order set may also be met with some push back from the target users (113,115). Push back from clinicians may be attributed to insufficient funding to support the creation and implementation process and/or refusal by clinicians and other administrators to change established clinical practices (35,123). Other notable challenges to the use of order sets include achieving a consensus and approval in the creation phase (116). At this stage, it may be unclear what is considered “evidence based” and “best practice” especially when these concepts do not align with local practices (116). In these situations it is

important to recognize that order sets cannot be completely standardized and may need to be adapted to the local context (116). While establishing guidelines may be a step in the right direction, it is clear that clinical guidelines need to be accompanied by adequate funding and support from organizations and policy makers (35).

The antipsychotic order set at Ontario Shores is being created by a team of four psychiatrists and one pharmacist. The creation of the order set has involved identifying the most used and most effective antipsychotic medications. Subsequently, best practices, peak dose and fastest time to peak dose are being identified based on expert opinion and published research. The order set is shared with the clinical informatics team at Ontario Shores so it can be built into the electronic health record system. Ultimately the main goals of the order set are to reduce the variability in prescribing practices, achieve optimal symptom reduction at a faster rate, create efficiencies in care, and align clinical prescribing practices with best practices. During implementation of the order set the developing team (psychiatrists, pharmacist and clinical informatics team) will be running education sessions with each of the psychiatry groups to educate clinicians on this new order set. During these sessions a demonstration will be provided along with additional educational material which will be shared through email and on the hospital intranet. In addition, Waypoint and Royal Ottawa Hospital have expressed support towards the concept of the order set however, are not ready to adopt the order set alongside Ontario Shores at this time. Overall the implementation of this antipsychotic medication order set is part of the bundled care initiative at Ontario Shores for inpatients diagnosed with schizophrenia and is being created to provide better support and elevate the standard of care for this patient population.

Summary

Schizophrenia is a mental illness that usually presents in adolescence or early adulthood and follows a chronic life course (16,20,25,26,125). Schizophrenia affects how a person thinks, feels and behaves and patients tend to experience a very wide range of symptoms which often leads to functional impairment affecting their day to day living (18,27,125).

There are two classifications of antipsychotic medication that are used as the primary form of treatment for patients with schizophrenia (20,28,30). While both classifications act in similar ways, targeting the dopamine D2 receptor blockade, SGAs also act as Serotonin 5HT-$_{2A}$ antagonists and have become the more popular form of treatment due to their lower risk of motor dysfunction (31,126). Long-acting injectables (LAIs) were a key development in antipsychotic treatment for schizophrenia and allow for patients to move away from a daily oral medication regimen, potentially increasing the adherence rates and decreasing rehospitalizations due to relapse (16,29,41,43,46,47). Despite the availability of LAIs and guidelines stating their use should be considered at any stage of illness, previous research suggests that they are consistently underutilized in the treatment of patients with schizophrenia (16,41,49). Individuals are classified as having treatment resistant schizophrenia when two antipsychotic medications trials are not producing sufficient symptomatic relief (1,65,93,94). For these patients, clozapine is the gold standard third line treatment; however, similar to LAIs, clozapine has been consistently underutilized in clinical practice. This presents a concern due to the research which shows that the longer a

patient goes experiencing untreated symptoms, the greater long term effects the patient is likely to experience (27,36,95,98,99). Monotherapy is the standard of care for schizophrenia patients on antipsychotic medication however surveys have shown that a high degree of polypharmacy occurs in clinical settings (25,65–67,71). While there may be individual situations that warrant transient polypharmacy to provide rapid symptomatic relief, long-term polypharmacy is known to cause notable adverse effects (66,68). In addition, antipsychotic polypharmacy has the potential to contribute to high dose antipsychotics (defined as >1000 mg chlorpromazine per day), which may contribute to adverse effects (68,72–74). Nonadherence to oral antipsychotics is a common occurrence, in particular in patients experiencing first episode psychosis and can cause relapse, rehospitalization and longer time to remission (17,46,62,64). While pharmacological treatment using antipsychotics is the primary method of treating schizophrenia and has shown a high degree of efficacy in controlling positive symptoms, the use of alternative therapies in conjunction with antipsychotic medication has shown some promise in addressing negative symptoms and improving cognition (101,102,105).

Bundled care is a method of care delivery that focuses on patient centered care and incentivizes efficiency, improves care transitions and decreases rehospitalizations (112–116). Order sets may be one method bundled care initiatives employ as a way to reduce medication error and improve standardization of care in order to help ensure all patients receive the same care regardless of patient-level characteristics or access to facilities or physicians (117–120). While no previous research has been specific to order sets for mental health disorders or antipsychotic medication, previous research has

shown that when there is clinician buy in, proper implementation processes and enough funding to support the creation of order sets, they can be successfully integrated into clinical practice and eventually help improving patient outcomes (119,121,123). The antipsychotic order set being created at Ontario Shores is part of the bundled care pathway being developed for patients with schizophrenia. The rest of this thesis will explore the prescribing patterns and practices of clinicians at Ontario Shores in order to inform and support the implementation of the antipsychotic order set going forward. This research will help provide future direction for other hospitals across Ontario looking to implement similar bundled care pathways.

Chapter 3. Study Design & Methodology

This study investigated the current antipsychotic prescribing patterns of patients admitted to hospital with a primary diagnosis of Schizophrenia. Antipsychotic medication is considered essential in the treatment of schizophrenia for improving both short term and long term outcomes (2). Despite the evidence which indicates that treatment with antipsychotics is almost always necessary for controlling and improving psychotic symptoms, the rates of treatment non-adherence in this patient population tend to be high. There are several evidence-based recommendations on how best to treat symptoms of schizophrenia; however, previous research has consistently shown that the recommendations and best-practices are not always followed in clinical settings (5).

In general, access to appropriate and timely treatment for mental health disorders in Canada can be a challenge. Within the healthcare field, innovative models such as bundled care initiatives are being established to address this lack of access to treatment (106–109). The implementation of an order set is one strategy which falls under bundled care that has been used to help addresses treatment inconsistencies for a variety of other health concerns such as non-opioid treatment for acute pain, respiratory and diabetic conditions, laryngectomies, end-of-life care, ischemic stroke and coronary heart failure (115). While previous research on mental illness has focused on establishing how best to use medication and other treatment modalities to control symptoms, little research has been done to establish the effectiveness of bundled care initiatives to improve timely treatment and continuity of care. For example, the implementation of an order set in clinical settings may improve the efficiency and cost

effectiveness of treatment as well as the objective and subjective outcomes measures for patients.

Despite these predicted improvements that bundled care initiatives offer, currently there is only a vague understanding around the treatment patients receive and whether it reflects the standards of practice described in the literature. In order to move towards new methods of treatment however, it is important first to understand whether factors such as the physician seen, the location treatment is accessed or other sociodemographic factors play a role in the quality of care patients receive.

Based on the findings of the background and literature review, it was hypothesized that the current antipsychotic prescribing patterns for patients with schizophrenia at Ontario Shores would align with the research and demonstrate a low percentage of patients achieving the target dose by 2 weeks post-admission, low rates of LAI prescription and, provided clozapine eligibility, low rates of clozapine prescription as a third-line treatment. In addition, it was hypothesized that there would not be any sociodemographic factors correlated with receiving treatment that aligns with the evidence-based recommendations described in the literature.

Given these hypotheses the present study aims to describe the current antipsychotic prescribing patterns of physicians at Ontario Shores treating patients with a primary diagnosis of schizophrenia and answers the question: what are the current rates of patients who receive treatment that aligns with evidence-based recommendations and are there are any patient-level characteristics that correlate with the treatment received while in hospital? The following chapter will provide a description

of the study population and design, as well as the types of analysis used to address the research questions highlighted above.

Study Population & Design

This study was completed at Ontario Shores Centre for Mental Health Sciences, which is a specialized mental health hospital in Whitby, Ontario, Canada. Clinical staff who work at the hospital have specialized training in caring for people with mental illness. Patients who are admitted to hospital are often dealing with complex cases of mental illness and may have increased illness severity compared to patients treated in other inpatient or outpatient settings. Ontario Shores does not have an emergency department, and so referrals from community care or acute hospitals account for most patient admissions.

This study was a retrospective cohort study designed to describe the prescribing patterns of psychiatrists treating inpatients with a primary diagnosis of Schizophrenia at Ontario Shores. Patients included in the study cohort were all admitted to Ontario Shores (inpatients) with a primary diagnosis of schizophrenia. Patients were excluded if they had any other primary diagnosis (including schizoaffective disorder). Multiple hospital admissions were also excluded if they occurred less than 30 days apart. In this case, data from the most recent hospital admissions was used. This study looked at all antipsychotic prescriptions administered to a patient during their hospital stay. The cohort was constructed using the Meditech electronic health record (EHR) data of patients admitted to Ontario Shores between May 1st, 2021 and August 1st, 2022 and included 407 patients. Approval to access the data was received from the Research

Ethics Board at Ontario Shores and at Ontario Tech University (#22-029-D). A full list of variables extracted from the EHR can be found in the Data Creation Form in Appendix A, which was submitted as part of the REB application for this study.

Outcomes Variables of Interest

The outcomes measured in this study were based on the factors identified in the literature as being important to optimizing the process of care and treatment outcomes for patients diagnosed with schizophrenia in primary care settings. The first two outcome variables were binary indicators for whether a patient was prescribed an antipsychotic medication dosage which met the target dose identified for each medication within the first 2 and 4 weeks of being admitted to an inpatient setting. In order to create the binary indicator for target dose all daily antipsychotic doses were converted into chlorpromazine equivalents in order to allow for the comparison of dosages across individual patients who were on a variety of different medications. For oral antipsychotic medications a multiplier was assigned based on the information contained in the Clinical Handbook for Psychotropic Drugs as well as the expert clinical opinion from a psychiatrist with a specialization in antipsychotic prescribing (127). The conversions for short and long acting injectables were determined based on the American Psychiatric Association (APA) and the United States Substance Abuse and Mental Health Services Administration (SAMHSA) alongside the same expert clinical opinion mentioned above. All conversion factors can be found in the Data Creation Form (DCF) in Appendix A. Once all daily medications were converted to

chlorpromazine equivalents, the binary indicator was created based on whether the medication dosage reached 600 milligram chlorpromazine equivalents or greater by week 2 or 4 post hospital admission.

The third outcome variable was another binary indicator, this time indicating whether an individual had been offered a prescription for a long-acting injectable (LAI) during their hospital admission. The fourth outcome variable focused on a sub-sample of patients who were identified as eligible to receive clozapine as a third line treatment. For this outcome variable a binary indicator was created for whether patients who were eligible, received a clozapine prescription.

Covariates

The exposure variables that were included in the analysis were chosen based on the literature search which indicates they may be factors that impact the antipsychotic prescribing patterns. The data contained the following socio-demographic factors: biological sex, age group, substance use diagnosis, education level and race/ethnicity. The data also included baseline Brief Psychiatric Rating Scale-6 (BPRS-6) scores taken at the time of admission. The BPRS-6 is a measure of psychiatric symptoms and illness severity and its measures of expressed delusions, conceptual disorganization, hallucinations, blunted affect, emotional withdrawal, and poverty of speech are consistent with the DSM-5 diagnostic criteria for schizophrenia (128). Additional information of each variable can be found in Table 1.

Table 1. Description of Covariates

Variables Name	Description	Code
Sex	Sex recorded at the time of admission.	Male = 0 Female = 1
Age Group	Age at the time of admission, grouped into age categories.	<20 20-29 30-39 40-49 50-59 60+
Waist Circumference	First measurement taken at or after admission.	Inches
Weight	First measurement taken at or after admission.	Kilograms
Length of Stay	Total length of stay determined based on admission & discharge dates. Does not take into account days ALC.	Days
Race / Ethnicity	Recorded at the time of admission. Grouped into White & Non-White.	White Non-White
Education	Groupings of the highest level of education completed based on information documented during the intake at admission.	0- Unknown 1- No Schooling, 8 grades or less 2- High School or some High School 3- Technical/Trade School or some College 4- Diploma/Bachelor's or Graduate Degree
Substance Use Diagnosis	First recorded indication of substance use diagnosis at or around the time of admission.	Yes No
Initial BPRS-6 Score	First BPRS-6 score taken after admission, used as an indicator for illness severity at admission.	Range: 0-36

Data Analysis

The demographic data was summarized by calculating proportions for categorical data and means and standard deviations (SDs) for continuous data. The differences in demographic characteristics between those who achieved target dose and those who did not achieve target dose, were prescribed or not prescribed an LAI and received clozapine treatment or did not receive clozapine treatment provided eligibility were assessed using t-tests for continuous variables and chi squared tests for categorical variables. For each of these outcome variables a sensitivity analysis was conducted. This original analysis assumes that those who were admitted for less than 2 weeks had the same likelihood of achieving target dose, being offered or prescribed an LAI and/or being prescribed clozapine as a third-line treatment provided eligibility compared to those who were admitted for 14 days or more. In order to test this assumption a sensitivity analysis was conducted and all tests were run on a sub-sample (n=381) of patients who were all admitted for 14 days or more. Unadjusted and adjusted logistic regression models were used to estimate the independent and dependent associations of the patient-level characteristics and sociodemographic factors with the outcome variables. Statistical significance was set to alpha <0.05 and a 95% confidence interval was used. All analysis was conducted using R (2022.07.02, version 3).

Chapter 4 - Results

The period during which this study was conducted identified all patients admitted to Ontario Shores with a primary diagnosis of Schizophrenia. Patients whose admission files are marked as confidential were excluded from the original data pull. Patients who had a primary diagnosis other than schizophrenia were excluded from the analysis (schizoaffective disorder as a primary diagnosis was excluded for example). In addition, for patients who had multiple admissions occurring less than 30 days apart, only the most recent admission was included in the analysis. After taking into account both the inclusion and exclusion criteria, 407 patients admitted to Ontario Shores with a primary diagnosis of Schizophrenia were identified.

The cohort was made up of 64.1% male subjects. The age of the majority of patients was either 20-29 years (21.4%) or 30-39 years (26.0%). Nearly half (47.9%) of the patients in the cohort identified as white. While education was a variable that was included in the analysis, this data was missing for 23.3% of patients. The limitation of missing data was also a factor in the race/ethnicity variable where 17.4% of patients were missing a classification of race/ethnicity. Of the race/ethnicity data that was captured within the EMR, more patients identified as white compared to non-white (47.9% and 34.6% respectively). There was no missing data for all medication and prescribing data as well as no missing data for initial BPRS6 scores. A detailed summary of all observable sociodemographic characteristics of this patient cohort are presented in Table 2. Patients were assessed for reaching target antipsychotic dosage at weekly timepoints for the first 4-weeks post-admission.

Table 2. Descriptive Characteristics of the Patient Cohort

Observable Characteristics	Total Sample (407)
Male, n (%)	261 (64.1)
Age Category, n (%)	
<20	15 (3.7)
20-29	87 (21.4)
30-39	106 (26.0)
40-49	76 (18.7)
50-59	61 (15.0)
60+	49 (12.0)
Missing or Unknown	13 (3.2)
Weight at admission (kg), mean (sd)	80.5 (22.3)
Waist circumference (inches), mean (sd)	38.7 (7.4)
Length of Stay (days), mean(sd)	74.6 (63)
RaceEthnicity, n (%)	
White	195 (47.9)
Non-White	141 (34.6)
Missing or Unknown	71 (17.4)
Education Level, n (%)	
0. Unknown	95 (23.3)
1. 8 grades or less	17 (4.2)
2. High School or Some High School	180 (44.2)

3. College or Technical/Trade School	84 (20.6)
4. Diploma/Bachelor's and/or Graduate Degree	31 (7.6)
Substance Use Disorder (yes), n (%)	148 (36.4)
Initial BPRS-6 Score, mean (sd)	11.5 (7.2)
Target Dose Reached (600mg Chlorpromazine Equivalents), n(%)	
1 week	212 (52.1)
2 weeks	226 (55.5)
3 weeks	240 (58.9)
4 weeks	245 (60.2)
Prescribed Long Acting Injectable, yes, n (%)	253 (62.1)
Eligible and Prescribed Clozapine, yes, n (%)	95 (77.2)

Target Antipsychotic Dose - 2 weeks post-admission

The first outcome variable of interest was achieving target antipsychotic dosage within two weeks post-admission. No significant differences in sex, age category, waist circumference, length of stay, race/ethnicity, education level, substance use diagnosis or initial BPRS-6 score was seen between those who reached target dose and those who did not within the two-week time frame (Table 3). There was a significant difference in weight (in kg) between those who reached target dose (mean = 76.9 kg, sd = 20.2 kg) and those who did not (mean = 83.2 kg, sd = 23.6 kg). Those who did not reach target dose appear to, on average, weigh more than those who reached target dose (Table 3). Looking at the results of the sensitivity analysis, this difference

remained, albeit to a lesser degree than what is seen in the full sample (Appendix C - Table 3-2). In the logistic regression model there were no significant differences in any observable characteristics in either the unadjusted or adjusted odds ratios (Table 6).

Table 3. Descriptive Characteristics of Patients who Reached Target Antipsychotic Dosage by 2-weeks Post-Admission

Characteristics	Did not reach target dose (n = 168)	Reached target dose (n = 226)	p-value
Male, n (%)	99 (58.9)	154 (68.1)	0.075
Age category, n (%)			0.596
<20	6 (3.6)	9 (4.2)	
20-29	31 (18.3)	56 (25.1)	
30-39	44 (26)	62 (26.8)	
40-49	35 (21.3)	41 (18.4)	
50-59	27 (16)	34 (15.5)	
60+	25 (14.8)	24 (10)	
Waist Circumference in inches, mean (sd)	39.5 (7.4)	38 (7.4)	0.063
Weight in kilograms, mean (sd)	83.2 (23.6)	76.9 (20.2)	0.007
Length of Stay in days, mean (sd)	73.0 (58.8)	82.0 (67.9)	0.198
Race / Ethnicity, n (%)			0.266
Non-White	55 (32.7)	83 (36.7)	
White	79 (47.0)	111 (49.1)	
Missing / Unknown	34 (20.2)	32 (14.2)	
Education, n (%)			0.269
0. Unknown	40 (23.7)	53 (23.5)	
1. No Schooling, 8 grades or less	8 (5.1)	9 (4.0)	
2. High School or some High School	66 (39.3)	110 (48.7)	
3. Technical/Trade School or Some College	37 (22)	41 (18.1)	
4. Diploma/Bachelor's or Graduate Degree	17 (10.1)	13 (5.8)	
Substance Use Diagnosis, n (%)			
Yes	61 (36.1)	81 (35.8)	1.000
Initial BPRS-6 score, mean (sd)	11.7(7.3)	11.1 (7.0)	0.379

In addition to the patient characteristics of those who achieved target antipsychotic dosage within the first two weeks post-admission found above, weekly rates of patients who achieved target antipsychotic dosage within the first four weeks post-admission can be found in Figure 1. These results showed that the majority of patients (52.1%) reached target dose within the first week post-admission and that rates of patients who reached target dose only increased minimally in the following three weeks (Figure 1).

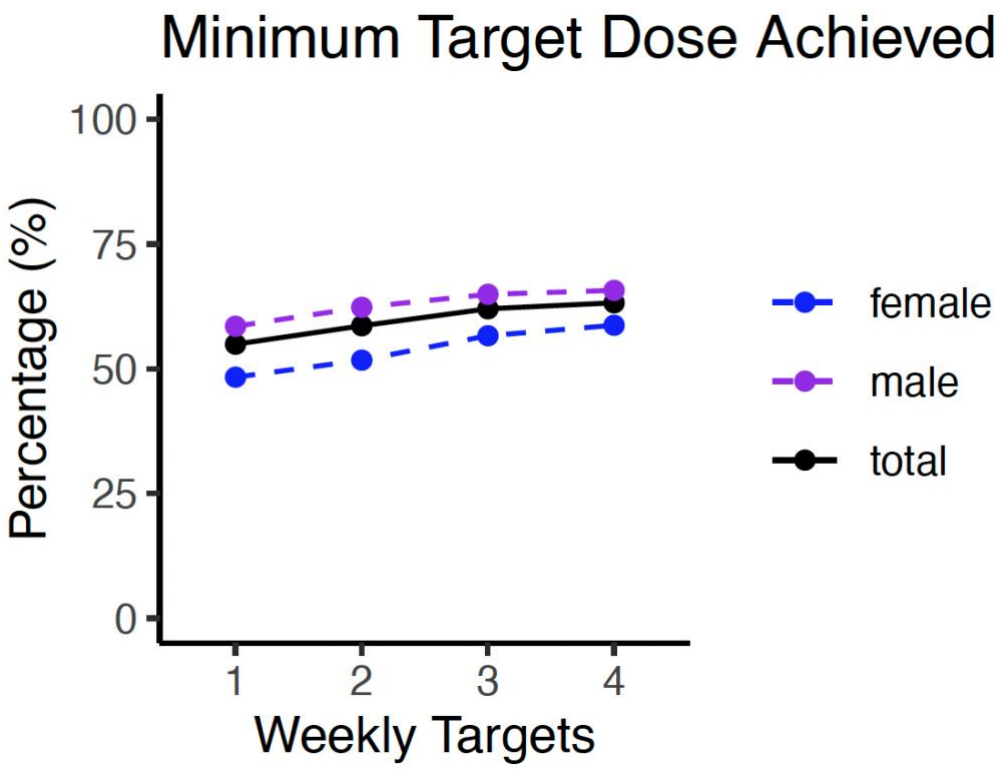

Figure 1. *Percent of Patients who Reached Target Antipsychotic Dosage within the First Four Weeks Post-Admission*

Treatment with Long-Acting Injectables

Receiving treatment with a long-acting injectable was the second outcome variable of interest. Here we saw no statistically significance in sex, age category, waist circumference, weight, education level, substance use diagnosis or initial BPRS-6 score. There was a statistically significant difference in length of stay (in days) and race/ethnicity between those who received treatment with an LAI and those who did not (Table 4). Length of stay is longer in those who were prescribed an LAI (mean = 81.0 days, sd = 64.9 days) compared to those who were not prescribed an LAI (mean = 64.0 days, sd = 58.4 days) (Table 4). Those who were identified as non-white had higher rates of LAI prescription (38.7%) compared to no LAI prescription (27.9%). In contrast, only 40.7% of patients who were identified as white received an LAI prescription while 59.7% of patients who were identified as white did not (Table 4). The results from the logistic regression model indicate that a longer length of stay was significantly associated with a higher likelihood of being prescribed an LAI (OR = 1.005, 95CI [1.001, 1.009]), however, this association was no longer significant in the adjusted regression model (OR = 1.004, 95 CI [1.000, 1.009]). Race/ethnicity was the only other factor associated with an increased likelihood of being prescribed an LAI. Those who were identified as white were less likely to be prescribed an LAI compared to those who were identified as non-white in both the unadjusted (OR = 0.491, 95 CI [0.310, 0.771]) and adjusted (OR = 0.410, 95 CI [0.232, 0.711) logistic regression models (Table 6). Overall, there were few differences in observable characteristics between those who were prescribed a long-acting injectable and those who were not prescribed a long-acting injectable during their hospital admission.

Table 4. Descriptive Characteristics of Patients who were Prescribed a Long-Acting Injectable

Observable Characteristics	Prescribed an LAI (n=253)	Not Prescribed an LAI (n=154)	p-value
Male, n (%)	168 (66.4)	93 (60.4)	0.263
Age in years, n(%)			0.662
<20	7 (2.8)	8 (5.2)	
20-29	57 (22.5)	32 (20.9)	
30-39	73 (28.9)	36 (23.3)	
40-49	49 (19.4)	32 (20.8)	
50-59	37 (14.6)	26 (16.9)	
60+	30 (11.9)	20 (13.0)	
Waist Circumference in inches, mean(sd)	38.7 (7.0)	39.2 (8.2)	0.540
Weight in kilograms, mean(sd)	80.2 (21.7)	81.0 (23.5)	0.727
Length of Stay in days, mean(sd)	81.0 (64.9)	64.0 (58.4)	0.011
Race / Ethnicity, n (%)			0.001
Non-White	98 (38.7)	43 (27.9)	
White	103 (40.7)	92 (59.7)	
Missing or Unknown	52 (20.6)	19 (12.3)	
Education Level, n(%)			0.825
0. Unknown	58 (22.9)	37 (24.0)	
1. No Schooling, 8 grades or less	10 (4.0)	7 (4.5)	
2. High School or some High School	109 (43.1)	71 (46.1)	
3. Technical/Trade School or Some College	54 (21.3)	30 (19.5)	
4. Diploma/Bachelor's or Graduate Degree	22 (8.7)	9 (5.8)	
Substance Use Diagnosis, n(%)			
Yes	97 (38.3)	51 (33.1)	0.339
Initial BPRS-6 score	11.9 (6.9)	10.7(7.6)	0.152

Clozapine as a Third-Line Treatment

The third outcome variable of interest was the prescription of clozapine as a third-line treatment, provided patients were identified as being eligible for clozapine from the data source used. These results, found in Table 5, indicate that there was no significant difference in sex, age category, waist circumference, weight, length of stay, education level or substance use diagnosis. Race/ethnicity was significantly associated with receiving clozapine as a third-line treatment, with those who were non-white having an increased likelihood of receiving clozapine treatment ($p = 0.034$) however, this significance was not present in the sensitivity analysis (Appendix C, Table 5-2).

Initial BPRS-6 scores were significantly different between those who received clozapine as a third line treatment and those who did not ($p = 0.003$), with a higher score (indicating increased illness severity) being associated with an increased likelihood of receiving clozapine treatment (Table 5). This significant difference remained in the sensitivity analysis ($p = 0.034$) (Appendix C, Table 5-2). Additional details on the characteristics of those who received clozapine treatment and those who did not can be found in Table 5. Similar to our findings for the other outcome variables, achieving target dose within 2 weeks post-admission and being prescribed an LAI, there are few observable patient-level characteristics that are associated with receiving clozapine as a third line treatment.

Table 5. Descriptive Characteristics of Patients who were Eligible for Clozapine Prescription

Observable Characteristics	Eligible & Prescribed (n=95)	Eligible & Not prescribed (n=28)	p-value
Male, n (%)	65 (68.4)	17 (60.7)	0.595
Age category, n (%)			0.737
<29	22 (23.2)	8 (28.6)	
30+	73 (76.8)	20 (71.4)	
Waist Circumference in inches, mean(sd)	38.9 (8.1)	39.4 (5.5)	0.700
Weight in kilograms, mean(sd)	80.2 (21.5)	81.1(19.2)	0.845
Length of Stay in days, mean(sd)	91.8(73.5)	88.7 (72.6)	0.857
Race / Ethnicity			0.034
Non-White, Missing or Unknown	46 (48.4)	20 (71.4)	
White	9 (9.5)	8 (28.6)	
Education Level			0.761
0. Unknown	20 (21.1)	7 (25.0)	
1. No Schooling, High School or some High School	55 (57.9)	14 (50.0)	
2. Technical/Trade School or Post-Secondary School	20 (21.1)	7 (25.0)	
Substance Use Diagnosis, n(%)			
Yes	21 (22.1)	9 (31.1)	0.403
Initial BPRS score, mean(sd)	13.1 (6.9)	9.5 (4.6)	0.003

Unadjusted & Adjusted Logistic Regression Models

Unadjusted and adjusted logistic regression models were used to assess the independent and dependent associations of patient-level characteristics on all outcome variables. The unadjusted models included a single predictor (patient level characteristic) to assess whether there was a bivariate association between the predictor and the outcome. Separate unadjusted logistic regression models were estimated for each predictor. The unadjusted models do not take into account other patient level characteristics. In contrast, the adjusted models take into account all patient-level characteristics.. The results of the unadjusted and adjusted logistic regression models for achieving target antipsychotic dosage at week 2 and week 4 post-admission as well as LAI prescription are presented in Table 6. The results of the unadjusted and adjusted logistic regression models for those who were eligible and prescribed clozapine are presented in Table 7.

There were no patient level characteristics in either the unadjusted or adjusted models that were associated with achieving target antipsychotic dosage at either 2 or 4 weeks post-admission. In the unadjusted model we found that length of stay was associated with an increased likelihood of being prescribed a long-acting injectable (OR, 1.005; 95% CI, 1.001 to 1.009) however, this association was no longer significant in the adjusted model (OR, 1.004; 95% CI, 1.000 to 1.009). In addition, it was found that those who were identified as white were less likely to receive a long-acting injectable compared to those who were identified non-white. This association was significant in both the unadjusted (OR, 0.491; 95% CI, 0.310 to 0.771) and adjusted models (OR, 0.420; 95% CI, 0.232 to 0.711). When looking at clozapine prescription amongst the

eligible sub-sample, initial BPRS-6 score was associated with an increased likelihood of receiving clozapine in the unadjusted logistic regression model (OR, 1.102; 95% CI, 1.022 to 1.203) but this association was no longer significant in the adjusted model (OR, 1.090; 95% CI, 0.991 to 1.221).

Table 6. Adjusted and Unadjusted Regression for Patient-Level Sociodemographic Factors for Target Antipsychotic Dosage and LAI Prescription

Observable Characteristics	Reached Target Dose (within 2 weeks)		Reached Target Dose (within 4 weeks)		Recommended and/or Prescribed Long-Acting Injectables	
	n = 407		n = 407		n = 407	
	Unadjusted Odds Ratios (95% CI)	Adjusted Odds Ratios (95% CI)	Unadjusted Odds Ratios (95% CI)	Adjusted Odds Ratios (95% CI)	Unadjusted Odds Ratios (95% CI)	Adjusted Odds Ratios (95% CI)
Initial BPRS-6 Score	1.013 (0.984, 1.043)	1.0111 (0.976, 1.048)	1.014 (0.985, 1.044)	1.012 (0.976, 1.049)	1.023 (0.993, 1.054)	1.017 (0.981, 1.055)
Length of Stay	0.998 (0.994, 1.001)	0.996 (0.992, 1.000)	0.998 (0.995, 1.002)	0.997 (0.993, 1.001)	1.005 (1.001, 1.009)	1.004 (1.000, 1.009)
Age Category						
20-29	1.204 (0.373, 3.659)	1.383 (0.305, 5.724)	0.853 (0.221, 2.757)	1.199 (0.226, 5.164)	2.036 (0.672, 6.312)	1.542 (0.335, 6.553)
30-39	0.939 (0.296, 2.796)	1.031 (0.230, 4.198)	0.576 (0.152, 1.812)	0.795 (0.153, 3.340)	2.317 (0.774, 7.099)	2.198 (0.478, 9.356)
40-49	0.781 (0.241, 2.382)	0.869 (0.191, 3.609)	0.500 (0.129, 1.611)	0.660 (1.125, 2.821)	1.750 (0.574, 5.450)	2.272 (0.485, 9.916)
50-59	0.840 (0.254, 2.622)	1.393 (0.292, 6.150)	0.524 (0.133, 1.728)	1.053 (0.192, 4.792)	1.626 (0.522, 5.182)	1.726 (0.356, 7.836)
60+	0.640 (0.189, 2.048)	0.675 (0.138, 3.030)	0.485 (0.121, 1.643)	0.564 (0.100, 2.608)	1.714 (0.535, 5.625)	2.124 (0.422, 10.094)
Race / Ethnicity						
white	0.931 (0.595, 1.454)	1.030 (0.605, 1.751)	0.828 (0.522, 1.306)	0.916 (0.534, 1.565)	0.491 (0.310, 0.771)	0.410 (0.232, 0.711)
unknown	0.699 (0.336, 1.457)	0.908 (0.393, 2.124)	0.659 (0.361, 1.204)	1.264 (0.535, 3.134)	1.201 (0.642, 2.302)	1.865 (0.683, 6.036)
Substance Diagnosis (yes)	0.980 (0.647, 1.487)	0.686 (0.398, 1.177)	0.898 (0.589, 1.374)	0.738 (0.425, 1.275)	1.256 (0.827, 1.919)	1.162 (0.660, 2.061)
Education Category						
1	1.254 (0.752, 2.087)	1.187 (0.622, 2.247)	1.277 (0.759, 2.139)	1.276 (0.667, 2.425)	0.910 (0.543, 1.513)	1.154 (0.593, 2.227)
3	0.864 (0.468, 1.592)	0.832 (0.393, 1.756)	0.976 (0.526, 1.816)	1.020 (0.479, 2.172)	1.074 (0.580, 1.994)	1.273 (0.582, 2.804)
4	0.596 (0.255,	0.698 (0.260,	0.888 (0.385,	1.042 (0.395,	1.458 (0.616,	1.327 (0.475,

	1.368)	1.847)	2.078)	2.797)	3.673)	3.904)
Sex (male)	1.491 (0.984, 2.261)	1.498 (0.883, 2.549)	1.303 (0.853, 1.987)	1.378 (0.806, 2.354)	1.296 (0.855, 1.963)	1.327 (0.763, 2.304)

Table 7. Adjusted and Unadjusted Regression for Patient-Level Sociodemographic Factors for patients who were Eligible and Prescribed Clozapine

Observable Characteristics	**Eligible and Prescribed Clozapine**
	n = 123
	Unadjusted Odds Ratios (95% CI)
Initial BPRS-6 Score	1.102 (1.022, 1.203)
Length of Stay (days)	1.001 (0.995, 1.007)
Age Category (<29)	
30 +	1.327 (0.493, 3.353)
Race / Ethnicity	
white	2.152 (0.821, 5.946)
unknown	0.281 (0.061, 1.213)
Substance Diagnosis (yes)	0.248 (0.054, 1.064)
Education Category	
1	0.599 (0.240, 1.565)
3	1.447 (0.487, 4.050)
4	1.197 (0.297, 5.351)
Sex (male)	0.860 (0.178, 4.838)

Chapter 5 - Discussion

The aim of this study was to evaluate the current antipsychotic prescribing patterns of physicians at Ontario Shores for patients admitted to hospital with a primary diagnosis of Schizophrenia. We used EHR data collected at Ontario Shores to assess the prescribing patterns of physicians and determine whether any correlations exist between antipsychotic prescribing and sociodemographic factors of patients. In this chapter, I provide a summary of the findings based on the evaluation of this data and how it aligns or differs with previous research in the field of mental health, antipsychotic prescribing patterns and the care that patients diagnosed with schizophrenia receive in clinical settings. I also highlight the clinical implications of these findings. Finally, I discuss the strengths and limitations of this study and propose some ideas for how future research may continue to help improve the standard of care that patients with a diagnosis of schizophrenia receive in clinical settings.

Summary of Findings

The findings of this study suggest that approximately 41.3% patients admitted to Ontario Shores with a primary diagnosis of Schizophrenia are not reaching target antipsychotic dose within two weeks of admission. Severity of illness upon admission, which in this study was based on initial BPRS-6 scores, did not seem to impact the prescription patterns of physicians working with those diagnosed with schizophrenia. This finding is supported by previous research that describes the subjectivity that exists in antipsychotic dosing and prescribing among physicians (76). A lack of objective measurements used to influence antipsychotic dosing for patients with schizophrenia

may be a contributing factor (73). Based on the results of the data collected, a lack of influence from sociodemographic factors on antipsychotic prescription patterns may suggest that antipsychotic prescribing for patients with schizophrenia may rely largely on subjective observations and be influenced more by which physician a patient sees rather than by objective measurements related to the individual patient or status of illness. However, it should be taken into account that this observation is made knowing that not all objective factors were available in the data that was used for this study.

In Figure 1 we see that the majority of patients received the target dosage of antipsychotic medication within the first week post-admission and that these rates only increased minimally in weeks two, three and four post-admission. This finding may indicate that reaching target dose in a shorter time frame, as previous research on evidence-based practice recommends (23,27,35,36), is important for optimizing treatment as well as illness prognosis in the long term. These findings align with the literature which highlights that receiving adequate and timely treatment during the early stages of illness or presentation of psychosis may be associated with better long-term patient outcome (23,27,35,36).

Findings specific to the subset of patients identified as having treatment resistant schizophrenia (TRS) differed in some ways to the findings of the full cohort which have been described above. In this subset of patients, illness severity increased the likelihood that eligible patients were prescribed clozapine as a third-line treatment. These findings demonstrate alignment with previous research which has established clozapine as the evidence-based third line treatment for patients with TRS (129). Despite evidence-

based recommendations for the use of clozapine as the most effective third line treatment for improving long-term outcomes in those with TRS, there has been research showing that, in general, clozapine is still consistently under-utilized in clinical practice (1,65,93,94). Current research on clozapine prescription rates in Canada state that fewer than 7% of patients who are eligible, receive clozapine treatment (36).
The results from this study, which indicate that 77.2% of patients who were eligible, received clozapine as a third-line treatment during their hospital admission may indicate that clozapine use is more accepted and being better integrated into clinical practices. However, it is important to note that these rates of clozapine treatment reflect the care being provided at a specialized mental health hospital and may not be a reflection of the care being provided at other health care settings.

Hospital admissions in this patient population are often due to the presence of psychosis due to illness onset or relapse (29). Evidence-based recommendations for clinical practice suggest that one important decision point for prescribing an LAI as part of a treatment plan is when a patient is newly diagnosed or has recently relapsed (52). Since individuals with a primary diagnosis of schizophrenia are most likely to be hospitalized when experiencing symptoms of psychosis due to illness onset or relapse, LAI prescriptions around the time of admission should be present to demonstrate that evidence-based practice is happening in clinical settings. Further research is needed to identify how many trials of oral medication are used for treatment prior to an individual being offered and/or prescribed an LAI. Furthermore, a recent study by Groenendaal et al. (2023) found that illness severity and duration of illness appear to influence a physician's choice to use an LAI for treatment over an oral antipsychotic (130). The

present study did not evaluate length of illness, in part due to lack of access to data on a patient's history of illness. However, BPRS-6 scores at admission were used as a proxy for illness severity. Results from the full patient cohort showed that severity of illness was not correlated with an increased likelihood of being prescribed an LAI, which does not align with the findings of Groenendaal et al. (2023). Length of stay, however, was associated with an increased likelihood of being prescribed an LAI. It may be that being in hospital longer, regardless of any other factors, may increase a patient's likelihood of receiving an LAI. Another possible explanation which has been supported by previous research is that a greater length of stay may be associated with illness severity (134,135). Therefore, those who demonstrate markers of increased illness severity have longer hospital stays which allows clinicians more time to explore a variety of treatment options. However, without accurate information on the number of days ALC that make up a patient's total length of stay as well as other unobserved confounding factors, it is not clear whether length of stay is a reflection of illness severity, sociodemographic factors, or a combination of both.

Despite the evidence supporting the prescription of LAIs in the early stages of illness or around the time of relapse, there have been reports on negative patient perceptions of LAIs as well as clinicians avoiding the use of LAIs due to the time and financial costs associated with the start of treatment (43,56,57). These factors may influence rates of LAI prescription globally, with estimates showing that LAIs are consistently under-utilized. Specifically in Canada, LAI prescription rates are around 6.3% (64). This study, however, found that 62% of patients admitted to hospital with a primary diagnosis of schizophrenia were offered or prescribed an LAI during their

admission. This may suggest that in contrast to previous research done on the rates of LAI prescription across different clinical settings, the physicians at Ontario Shores are more likely to follow evidence-based prescribing practices. This could be due to the Ontario Shores being an institution specializing in mental illness where, in theory, clinicians would be better trained on the specific standards of care for a variety of mental illnesses and have access to more resources to provide a higher level of care to those experiencing serious mental illness when compared to other clinical settings.

Prior research on access to mental health care services suggests that, in Canada, access is limited and long waitlists often prevent individuals from accessing specialized services (133) . When patients are not able to access specialized services, often, the only other option they have is to seek out care through their primary care provider (133). However, primary healthcare providers may have difficulty in diagnosing and providing adequate treatment for mental illnesses due to factors such as a lack of training in particular for more cases of more complex mental illness and constraints on resources such as time available to allocate to individual patient visits (134,135). This may help explain the drastic differences in LAI rates taken from a pool made up of a variety of primary healthcare clinics and hospitals compared to the findings of the present study which are based on data specific to a hospital specializing in the treatment of mental illness.

In addition to general LAI prescription, findings from this study indicate that those who are non-white are more likely to be prescribed an LAI or clozapine, pending eligibility. This could be related to sociodemographic factors where those identified as white have increased support at home and may be more likely to be discharged sooner.

Currently, however, there is not adequate research specific to race and related sociodemographic factors that help explain how these factors may be associated with hospital admissions, illness severity and/or treatments received. Future research is needed to support the findings from this study and help further investigate the role race/ethnicity plays in receiving support for mental illness, in this case specifically schizophrenia.

The observation window of our study coincided with the hospital's attempt to roll out an Antipsychotic Prescribing Order Set, an initiative that falls under the hospital's goal of creating bundled care pathways for a variety of mental health disorders. The order set focuses on ensuring that all patients receive the same evidence-based treatment which is determined using expert opinion as well as the most recent research being done. In the case of schizophrenia, experts suggest that effective antipsychotic treatment occurs as early as possible. This may present the best opportunity for limiting the deterioration of a patient's mental state and improving the long-term prognosis for the individual (23,27,30,35,129). Findings from this study align with current research on antipsychotic prescribing which point to the gaps that exist when it comes to the treatment of mental illness. These results help provide supporting information on how the investments in time and resources needed to implement an antipsychotic order set into clinical practice are worthwhile for hospitals, physicians and patients.

Clinical Implications

Given the variation in provider-level prescribing patterns demonstrated in this and other studies, tools that can standardize may improve adherence to evidence-based

guidelines. An order set is often used to encourage evidence-based and efficient care by influencing the behavior of the provider and has other indirect benefits such as decreasing rates of polypharmacy, a controversial and common treatment approach despite the limited of evidence to support its benefits in this patient population (114,119–121).

The findings of this study help confirm that treatment received by patients can be largely dependent on the physician that is seen, rather than on objective measures of illness. In a clinical setting, implementing an order set to guide decisions around prescribing patterns based on illness-related measurements of the individual patient, can help improve rates of relapse and rehospitalizations (25,65–67,71). Previous research which investigates the opinions of physicians as well as impact on treatment processes and outcomes have shown that physicians do in fact find benefit in the implementation of an order set within clinical practice (119). While order sets have been successfully implemented for other health conditions, there are currently no known order sets which have been implemented for antipsychotic prescribing practices. The order set itself is an important step that hospitals, both specialized mental health hospitals and standard hospitals as well as other primary care settings, should consider implementing. For an order set to be effective there are considerations that need to be taken into account when it comes to its implementation into clinical practice. The field of implementation science offers some insight into the factors that promote the effective implementation of evidence-based guidelines. At the level of the clinic, these factors include: increasing physician buy-in, using a variety of modalities and techniques to

educate clinicians about the change in clinical procedures and, and advocacy from the administration and senior leadership (116).

Strengths & Limitations

This study has some limitations including a relatively short time period whereby data from the electronic health records was collected and used for analysis. This time period was initially chosen to reflect the data available 6 months pre/post order set implementation which was set to take place at Ontario Shores. However, it became evident early on that the order set was not actually being used during the study time period. This shifted the focus of the study to describing the prescribing practices of physicians at Ontario Shores. Mental illness is often multifactorial and the number of confounding variables that are not observed are many. As such, this presence of unobserved confounding variables means that the results can only indicate correlation and not causation.

The data used was limited to the data currently being collected in the electronic health records (EHR) at Ontario Shores. Research on EHRs and their use within a variety of healthcare settings have highlighted limitations including data fields being used inconsistently as well as inaccurate or inconsistent coding practices. Inconsistent collection of data, and subsequently greater amounts of missing data, make it challenging to answer important clinical questions. Possible explanations as to why some data is collected less consistently than others could be that certain fields within the EHR are not mandatory and therefore it is up to the clinician collecting the data to decide whether or not they ask or record the answers to a given question. Ultimately

this can impact the quality of the data and the ability for certain analyses to be performed (136). In the original proposal for this study BPRS-6 scores were slated to be used as an objective measurement to assess whether patient outcomes were improving. The symptom scale scores were going to be used to assess whether patients who were achieving target dose were also showing symptomatic improvement. This required BPRS-6 scores to be taken and recorded every 2-weeks, consistently across patients; however, the symptom scale score data that was available did not reflect the frequency or consistency needed in order to have sufficient data to run this type of analysis. This study had a relatively small sample size due to the time period chosen and the number of inpatients with a primary diagnosis that Ontario Shores is able to accommodate, which is an additional limitation that must be acknowledged. However, while a larger sample size may have enabled outliers to be detected or helped limit the margin of error, the results from this cohort align in many ways with previous research on the subject of antipsychotic prescribing and the treatment of schizophrenia.

Despite the limitations, this thesis did have some strengths including the quality of the prescribing data which had no missing data and was collected and recorded in the EHR on a daily basis. This allowed for the prescribing and dosage data to be accurately synthesized, interpreted and compared among patients. In addition, the work done to create a dataset conducive to being used for analysis may be used to provide recommendations to the information systems department at Ontario Shores and other hospitals on how best to collect key variables in a way which allows future research to be more time efficient. To the best of our knowledge, a detailed descriptive analysis on

the current antipsychotic prescribing patterns for inpatients with schizophrenia has not previously been done in Canada on this particular population or for any other mental illness, making this study novel. By establishing a baseline on the prescribing patterns that are currently being used, this study provides a starting point for future implementation of order sets which have the potential to improve clinical practice and patient outcomes. Ontario Shores may use this information to continue to improve the bundled care pathways that are implemented for various mental illnesses and patient populations going forward.

Gaps in Literature & Recommendations for Future Research

The literature reviewed in this thesis, alongside expert opinion, identifies that while there is a general consensus on what constitutes evidence-based antipsychotic prescribing practices for patients with schizophrenia, it also highlights that this consensus is not always followed in clinical practice. This work highlights some gaps that exist in the literature pertaining to why the agreed upon standards of care are not always taking place within clinical practice for patients with schizophrenia. Some factors that may play a role in creating this disconnect between what the literature describes as evidence-based practice and what is often seen in clinical practice include; complex cases of illness where standard practices are not sufficient, a lack of time or resources on the side of clinicians, or a general misunderstanding of the importance of following a stricter prescribing protocol in order to optimize long-term patient outcomes (4,5,12,14).

Some key opportunities for future research highlighted by the gaps identified are two-fold; 1) how best to implement an order set for antipsychotic prescribing and, once

successful implementation has been established 2) to investigate whether an antipsychotic order set is in fact effective in improving objective measurements of illness severity using tools such as symptom scale scores.

There are other important components at play when it comes to improving the standard of care given by physicians and received by patients for complex mental illness. Examining in greater detail the cost of relapse compared to a more costly treatment approach or medication may help provide important information to the policy makers. At the level of the organization, requiring the care team to regularly complete a clearly defined set of evaluations to track objective measurements of illness will be helpful and arguably essential to the evaluation process of new decision-making tools, such as an order set, being implemented into clinical practice.

While research on order sets exists and it could be hypothesized that the success of other order sets pertaining to different health conditions may indicate that an order set would be effective in the treatment of mental illness, no research describing how or whether an antipsychotic order set has actually been effective in clinical practice exists. In order to build an understanding around the potential efficacy and/or challenges of an antipsychotic order set, and whether this is a viable direction to take for improving, on a larger scale, the treatment for complex mental illness available to the public, an effective implementation needs to be evaluated. Some important considerations that researchers should keep in mind when implementing and evaluating the effects of an order set include objective outcomes such as hospital length of stay, rates of readmission and changes in symptom scale scores throughout the prescribing period outlined within the order set. Subjective measurements should also be taken into

account when evaluating the effectiveness of new practice guidelines being implemented in a clinical setting. From the perspective of a clinician these may include clinician perception around ease of implementation and helpfulness when it comes to their individual practices. Ultimately the success of a treatment, in particular for those with mental illness, depends largely on a patient's willingness to cooperate and follow a specified treatment protocol (137). With this in mind, subjective measurements relating to the perception of patients on the treatment they receive for their mental illness may help in clarifying whether stricter prescribing guidelines aid or hinder their illness trajectory and quality of life in any way.

Chapter 6. Conclusion

Schizophrenia is one of the leading causes of disability worldwide and standardizing treatment protocols for schizophrenia can help optimize treatment outcomes while decreasing the long term direct and indirect healthcare costs incurred by this patient population (1). The aim of this thesis was to describe the current antipsychotic prescribing patterns of physicians at Ontario Shores treating patients with a primary diagnosis of Schizophrenia. In addition, this thesis explored whether any patient-level factors such as age, race/ethnicity, education level, diagnosis of a substance use disorder or illness severity, were correlated with patients who achieved certain treatment targets based on what prior research has deemed to be an effective treatment protocol. Through the description of the current state of antipsychotic prescribing patterns at one institution, this thesis helps reinforce previous research findings on where the gaps lie in the treatment of Schizophrenia.

The findings of this thesis highlight gaps in the rates of evidence-based treatment being received by patients regardless of sociodemographic factors. Based on these findings, this research can be used to emphasize the importance of working within a bundled care model and implementing initiatives such as an antipsychotic order set. It is important to take these findings and recognize that, currently, the treatment received by a patient is largely dependent on which physician they see. This opens up the door to conversations around how barriers to accessing treatment and specialized facilities can influence whether an individual receives timely and appropriate treatment and ultimately how access to treatment may influence a patient's quality of life as well as life expectancy over the long-term. A decision tool such as an antipsychotic order set

implemented within a clinical setting is one way to standardize and keep track of the details around the treatment and care each individual patient receives. However, the findings from this study as well as information from the literature reviewed remind us that, in order for initiatives such as the antipsychotic order set to be effective, creating physician buy-in is essential and helps influence the short and long-term success of a new initiative. In addition, the findings of this thesis may also be beneficial in providing objective data and information to physicians on the current landscape of antipsychotic prescribing for patients with Schizophrenia and where and why opportunities exist for the implementation of an order set as part of a bundled care model can be effective at the level of the organization, the physician and, most importantly, the patient.

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Appendices

Appendix A - Data Creation Form

Project Details	
Project Title:	Evaluation of the antipsychotic order set implemented at Ontario Shores for in-patients diagnosed with schizophrenia
Project Objectives: *Insert Project Objectives as listed in protocol (Eg: outcome, main exposure/risk factor, baseline characteristics, etc.)*	Objectives: 1) To determine if the order set of antipsychotic prescription for patients diagnosed with schizophrenia is being followed by clinicians through the evaluation of antipsychotic dosage in mg equivalents over time. 2) To evaluate the effectiveness of the order set implementation on symptom reduction in patients diagnosed with schizophrenia using BPRS-6, mini-FROGS and the Positive Symptom Scale (PSS) Outcomes: - antipsychotic dosage (mg equivalents) - BPRS-6 scores, mini-FROGS scores, Positive Symptom Scores (PSS) - Length of stay minus days ALC Main Exposure: Objective 1: implementation of the order set Objective 2: implementation of the order set, antiosychotic dosage in mg equivalents
PI or delegate to discuss plan: (name/email/extension)	David Rudoler / david.rudoler@ontariotechu.ca
Date Required for REB Submission:	May 13, 2022
Requested Date of Data Delivery (post REB approval): ***Please note we will do our best to accommodate the date requested, but turnaround time**	

is also based on complexity of data pull*	

Study Cohort

Study Design	☒ **Cohort study** ☐ **Matched cohort study** ☐ **Case-control study** ☐ **Cross-sectional study** ☐ **Other** (specify):
Timeframe and Event of Interest (Eg: index event, accrual period, max follow-up period, look-back period, etc.)	Accrual period: May 1st , 2021 – April 30th, 2022 Follow up max date August 1st, 2022 (all medication variables required up to this date if not already specified) Index event: date of admission to Ontario Shores
Inclusion & Exclusion Criteria ***Please specify order of inclusion and exclusion criteria**	– Inclusion: patients diagnosed with schizophrenia at admission – ICD-10-CA: F20 (excluding F20.4), F22, F23, F24, F25, F28, F29, F53.1; – DSM-IV: 295.xx (10, 20, 30, 40, 60, 70, 80, 90 and 295), 297.1, 297.3, 298.8, 298.9 – PROVDX1: 5 **Exclusion: Individuals that have their EMR listed as Confidential**
Level of Data	☐ **Aggregate** ☒ **Raw Data** ☐ **Other** (specify):
Final Destination of Data for Analysis	☒ **Internal** ☐ **External**
If data will be analyzed externally, is there a data sharing agreement in place?	☐ **Yes** ☒ **No**

Variables Requested
(Add additional rows for additional variables)

Variable (Please list each variable that is being requsted from any assessments)	*Time Frame (year, number of timepoints etc.)*	*Data Source (if known)*	*Availability (to be completed by Decision Support)*
Patient ID	N/A	EHR	Yes
Visit ID	N/A	EHR	Yes
Account Number	N/A	EHR	Yes
Primary Diagnosis (ICD-10, DSM-IV)	At admission	EHR	Yes

Primary Diagnosis (ICD-10, DSM-IV)	At discharge	EHR	Yes
Secondary diagnosis (ICD-10, DSM-IV)	At admission	EHR	Yes
Secondary diagnosis (ICD-10, DSM-IV)	At discharge	EHR	Yes
Medical Diagnoses (problem list)	At admission	EHR	Yes
Medical Diagnoses (problem list)	At discharge	EHR	Yes
Average Antipsychotic Dosage (mg equivalents) *Do not include PRN medication	Daily for first 4 weeks, weekly from week 5 until discharge/end-of-follow-up.	EHR	Yes
Reason for change of medication	Weekly	EHR	Yes
Long-Acting Injectable Offered (yes/no)	Weekly	EHR	Yes
Long-Acting Injectable Administered (yes/no)	Weekly	EHR	Yes
Clozapine Offered (yes/no)	Weekly	EHR	Yes
Clozapine Administered (yes/no)	Weekly	EHR	Yes
Length of Stay	At discharge / end of follow-up period	EHR	Yes
Days ALC	At discharge / end of follow-up period	EHR	Yes
BPRS-6 Scores (all questions, take the most recent score)	Weekly	EHR	Yes
Mini-FROGS (all questions, take the most recent score)	Weekly	EHR	Yes
Long Positive Symptom Scale	Weekly	EHR	Yes

(all questions, take the most recent score)			
Weight	Weekly	EHR	Yes
Height	At admission or first measurement	EHR	Yes
Age	At admission	EHR (MPI)	Yes
Sex	At admission	EHR (MPI)	Yes
Substance related disorder (any diagnosis) - ICD-10-CA: F55, F10 to F19; - DSM-IV: 291, 292, 303, 304, 305	At admission	EHR	Yes
Race & Ethnicity	At admission	EHR	Yes
Income	At admission	EHR (from psychosocial assessment - PSA)	Yes
Education admit	At admission	EHR	Yes
Antipsychotic PRN Medication (mg equivalents)	Daily for first 4 weeks, weekly from week 5 until discharge/end-of-follow-up.	EHR	Yes
Benzodiazapine PRN Medication (yes / no)	Daily for first 4 weeks, weekly from week 5 until discharge/end-of-follow-up.	EHR	Yes
Benzodiazapine Scheduled Medication (yes/no)	Daily for first 4 weeks, weekly from week 5 until discharge/end-of-follow-up.	EHR	Yes
Clozapine Blood Level	Weekly	EHR	Yes
Hba1c	Weekly	EHR	Yes
Waist Circumference	Weekly	EHR	Yes
Lipid Tests (Blood Lipids)	Weekly	EHR	Yes
Medication History List	Within 5 days of admission	EHR	Yes

Medication Reconciliation List - Pt prescribed clozapine? - All sections under long acting injection - Was pt/caregiver interviewed by pharmacy?	At admission	EHR	Yes

Additional Notes:

For mg equivalents conversion:

Drug - Generic	Chlorpromazine Equivalents (100mg)	Formulation	Source	Multiplier
First Generation Antipsychotics				
Chlorpromazine	100mg	PO	CPNP, Handbook	1
Flupenthixol	2mg	PO	Not included in CPNP	50
Fluphenazine HCL	2mg	PO	CPNP, Handbook	50
Haloperidol	2mg	PO	CPNP, Handbook	50
Haloperidol lactate	1mg (short-acting IM)	IM	Not in CPNP, Handbook	100
Loxapine	10mg	PO	CPNP, Handbook	10
Loxapine hydrochloride	5mg (short-acting IM)	IM	CPNP, Handbook	20
Perphenazine	8mg	PO	Handbook	12.5
Pimozide	2mg	PO	CPNP, Handbook	50
Thioridazine	100mg	PO	CPNP, Handbook	1
Thiothixene	5mg	PO	Handbook	20
Trifluoperazine	5mg	PO	CPNP, Handbook	20
Zuclopenthixol	12mg	PO	Not included in CPNP	8.33

Zuclopenthixol	30mg	IM	Not included in CPNP	3.33
Second Generation Antipsychotics				
Aripripazole	7.5mg	PO	CPNP, Handbook	13.33
Asenapine	5mg	PO	CPNP, Handbook	20
Brexpiprazole	2mg	PO	N/A:CPNP; Handbook	50
Clozapine	50mg	PO	CPNP, Handbook	2
Iloperidone	3mg	PO	CPNP, Handbook	33.33
Lurasidone	20mg	PO	CPNP, Handbook	5
Olanzapine	5mg	PO	CPNP, Handbook	20
Olanzapine	2.5mg	IM	Not in CPNP, Handbook	40
Paliperidone	1.5mg	PO	CPNP, Handbook	66.67
Quetiapine	75mg	PO	CPNP, Handbook	1.33
Seroquel XR	75mg	PO	CPNP, Handbook	1.33
Risperidone	2mg	PO	CPNP, Handbook	50
Ziprasidone	60mg	PO	CPNP, Handbook	1.67
Long-Acting Injectables – First Generation				
Flupenthixol Decanoate	40mg	IM, Q2 weeks	Not in CPNP; Handbook OLE	2.5
Fluphenazine Decanoate	25mg	IM, Q2 weeks	Not in CPNP; Handbook OLE	4
Haloperidol Decanoate	150mg	IM, Q4 weeks	Not in CPNP; Handbook OLE	0.67
Zuclopenthixol Decanoate	200mg	IM, Q2 weeks	Not in CPNP; Handbook OLE	0.5
Long-Acting Injectables – Second Generation				
Paliperidone Palmitate (Invegga Sustenna)	75mg	IM, Q4 weeks	Not in CPNP or Handbook	1.33
Paliperidone Palmitate (Invega Trinza)	225mg	IM, Q12 weeks	Not in CPNP or Handbook	0.44

Aripriprazole (Abilify Maintena)	25mg	IM, Q2 weeks	Not in CPNP; Handbook	4
Risperidone (Risperidone Consta)	400mg	IM, Q4 weeks	Not in CPNP; Handbook	0.25
Benzodiazapine				
ALPRAZOLAM				
BROMAZEPAM				
CHLORDIAZEPOXIDE				
CHLORDIAZEPOXIDE HCL				
CHLORDIAZEPOXIDE HCL & CLIDINIUM BROMIDE				
CHLORDIAZEPOXIDE HCL & CLIDINIUM HCL				
CLOBAZAM				
CLONAZEPAM				
CLORAZEPATE DIPOTASSIUM				
DIAZEPAM				
DIAZEPAM & METHYLCELLULOSE				
ESTAZOLAM				
EXTEMPORANEOUS MIXTURE				
FLURAZEPAM HCL				
FLURAZEPAM HYDROCHLORIDE				
KETAZOLAM				
LORAZEPAM				
MIDAZOLAM				
MIDAZOLAM HCL				
NITRAZEPAM				
OXAZEPAM				
TEMAZEPAM				
TRIAZOLAM				
ZALEPLON				
ZOPICLONE				

Daily data set for the first 4 weeks after admission

Weekly data set from week 5 until discharge/end of follow-up period

Thank you for your request. Following review, the Decision Support team will contact you for further details.

To be completed by Decision Support Analyst prior to REB submission:

Date Ticket Submitted To Decision Support: May 3/2022

Date Approved: May 12/2022

Responsible Analyst: Eshta Bhardwaj

Ticket Number: N/A

Request Complexity:

☐ **Low Complexity (~5 business day turnaround post REB approval and request for data extraction)**

☐ **Medium Complexity (10-15 busines day turnaround post REB approval and request for data extraction)**

☒ **High Complexity (~15-20 busines day turnaround post REB approval and request for data extraction)**

Appendix B - Mock Antipsychotic Order Set

Order Sets

1) Antipsychotics for Schizophrenia

- Rapid titration: consider in patients with severe symptoms of psychosis, and/or treatment resistant illness, and/or past exposure to antipsychotic medications. Preferred approach especially in inpatients and those being monitored closely (i.e. more frequent intervals) as an outpatient.
- Regular/Slower titration: consider based on clinical factors such as age (e.g. older populations), comorbid medical issues, if treatment naïve, or a history of sensitivity to antipsychotic medications.
- If BPRS-6 score does not improve by 20% by day 14 consider a switch in medication, and by 50% at day 28, consider optimization (pushing to the maximum dose tolerated) and/or augmentation, and if the improvement has plateaued or shows worsening at subsequent assessments consider switching.
- If sequential trials with optimization, switching, and augmentation are not sufficiently effective, then proceed to a trial of clozapine.
- In order to eliminate nonadherence as being a factor in inadequate antipsychotic response, ideally at least one trial should be using a LAI formulation prior to clozapine.
- Even in patients who show a good response to oral medications, consider change to LAIs in all patients (in order to facilitate adherence), and provide this recommendation and information.
- LAIs: ensure that the patient receives a test dose of the appropriate antipsychotic if a LAI order set is to be used and they are naïve to the therapy.
- Genetic testing: consider in patients who are sensitive to medication side-effects (possible poor metabolizer) or those who don't respond to medications, even high doses (possible ultra rapid metabolizer).
- Please consult the product monographs for information on breastfeeding and pregnancy.

a) Monitoring Parameters

Vital Signs, Height/Weight and Waist Circumference are already part of the patient's Standard of Care with a frequency of q 28 days. If increased monitoring is required as part of initiating this medication, please enter a new order.

❑ AIMS Assessment weekly for four weeks then q 180 days

b) Aripiprazole Oral
UpToDate: Link
RxTx: Link
Target Dose: 20-30mg/day

Max Dose: 30mg/day

i) ☐ Rapid Titration

☐ Aripiprazole 10mg PO QAM, Order duration: 3 dose(s) First dose: T; 0800

☐ Aripiprazole 15mg PO QAM, Order duration: 3 dose(s) First dose: T+3; 0800

THEN

☐ Aripiprazole 20mg PO QAM, First dose: T+6; 0800

ii) ☐ Titration

☐ Aripiprazole 5mg PO ONCE, Order duration: 1 dose(s) First dose: T; 0800

☐ Aripiprazole 10mg PO QAM, Order duration: 3 dose(s) First dose: T+1; 0800

☐ Aripiprazole 15mg PO QAM, Order duration: 5 dose(s) First dose: T+4; 0800

THEN

☐ Aripiprazole 20mg PO QAM, First dose: T+8; 0800

c) Abilify Maintena

UpToDate: Link

RxTx: Link

Target Dose: 400mg Q28D

Max Dose: 400mg Q21D (off-label usage)

i) ☐ Rapid Initiation

☐ Aripiprazole 20mg PO QAM, Order duration: 16 dose(s) First dose: T; 0800

☐ Abilify Maintena 400mg IM Q28D, First dose: T+2; 0900

ii) ☐ Rapid Initiation Alternative (IM given in two different sites)

☐ Aripiprazole 20mg PO QAM, Order duration: 1 dose(s) First dose: T; 0800

☐ Abilify Maintena 800mg IM ONCE, Order duration: 1 dose(s), First dose: T; 0900

THEN

☐ Abilify Maintena 400mg IM Q28D, First dose: T+28; 0900

iii) ☐ Initiation

☐ Aripiprazole 10mg PO QAM, Order duration: 3 dose(s) First dose: T; 0800

☐ Aripiprazole 15mg PO QAM, Order duration: 3 dose(s) First dose: T+3; 0800

☐ Aripiprazole 20mg PO QAM, Order duration: 21 dose(s) First dose: T+6; 0800

☐ Abilify Maintena 400mg IM Q28D, First dose: T+14; 0900

d) Risperidone oral

UpToDate: Link

RxTx: Link

Target Dose: 6-8mg/day

Max Dose: 12mg/day

i) ☐ Rapid Initiation

☐ Risperidone 2mg PO QHS, Order duration: 1 dose(s) First dose: T; 2100

☐ Risperidone 4mg PO QHS, Order duration: 1 dose(s) First dose: T+1; 2100

THEN

☐ Risperidone 6mg PO QHS, First dose: T+2; 2100

ii) ☐ Initiation

☐ Risperidone 1mg PO QHS, Order duration: 1 dose(s) First dose: T; 2100

☐ Risperidone 2mg PO QHS, Order duration: 2 dose(s) First dose: T+1; 2100

☐ Risperidone 4mg PO QHS, Order duration: 2 dose(s) First dose: T+3; 2100

THEN

☐ Risperidone 6mg PO QHS, First dose: T+5; 2100

d) Risperdal Consta

UpToDate: Link

RxTx: Link

Target Dose: 25mg Q14D

Max Dose: 50mg Q14D

i) ☐ Low Dose Initiation

☐ Risperidone 1mg PO QHS, Order duration: 1 dose(s) First dose: T; 2100

☐ Risperidone 2mg PO QHS, Order duration: 22 dose(s) First dose: T+1; 2100

☐ Risperidone 25mg IM Q2W, First dose: T+2; 0900

i) ☐ High Dose Initiation

☐ Risperidone 2mg PO QHS, Order duration: 1 dose(s) First dose: T; 2100

☐ Risperidone 4mg PO QHS, Order duration: 22 dose(s) First dose: T+1; 2100

☐ Risperidone 50mg IM Q2W, First dose: T+2; 0900

e) Paliperidone

UpToDate: Link

RxTx: Link

Target Dose: 6-12mg/day

Max Dose: 12mg/day

i) ☐ Rapid Initiation

☐ Paliperidone 6mg PO QHS, Order duration: 1 dose(s) First dose: T; 2100

☐ Paliperidone 9mg PO QHS, Order duration: 1 dose(s) First dose: T+1; 2100

THEN

☐ Paliperidone 12mg PO QHS, First dose: T+2; 2100

ii) ☐ Initiation

☐ Paliperidone 3mg PO QHS, Order duration: 3 dose(s) First dose: T; 2100

☐ Paliperidone 6mg PO QHS, Order duration: 3 dose(s) First dose: T+3; 2100

☐ Paliperidone 9mg PO QHS, Order duration: 3 dose(s) First dose: T+6; 2100

THEN

☐ Paliperidone 12mg PO QHS, First dose: T+9; 2100

f) Invega Sustenna

UpToDate: Link

RxTx: Link

Target Dose: 150mg Q28D

Max Dose: 150mg Q21D (off-label) | 150mg Q14D (off-label, clinician discretion)

i) ☐ Rapid Initiation

☐ Invega Sustenna 150mg IM ONCE, First dose: T; 0900

☐ Invega Sustenna 100mg IM ONCE, First dose: T+7; 0900

☐ Invega Sustenna 150mg IM Q28D, First dose: T+35; 0900

ii) ☐ Initiation

☐ Paliperidone 6mg PO QHS, Order duration: 1 dose(s) First dose: T; 2100

☐ Paliperidone 9mg PO QHS, Order duration: 13 dose(s) First dose: T+1; 2100

☐ Invega Sustenna 150mg IM ONCE, First dose: T+14; 0900

☐ Invega Sustenna 100mg IM ONCE, First dose: T+21; 0900

☐ Invega Sustenna 150mg IM Q28D, First dose: T+56; 0900

g) Clozapine

Note: Before prescribing, the MD must receive confirmation from CSAN that the client/patient has been approved to receive cloZAPine. The client/patient must have an active CSAN number before the first prescription is entered. Please caution with seizure risk at higher doses of 500-600mg/day.

i) Initiation

☑ cloZAPine
12.5 mg, Oral, Form: Tab, qNOON, Order Duration: 1 dose(s), First Dose: T;1200

☑ cloZAPine
25 mg, Oral, Form: Tab, qHS, Order Duration: 1 dose(s), First Dose: T+1;2100

☑ cloZAPine
50 mg, Oral, Form: Tab, qHS, Order Duration: 1 dose(s), First Dose: T+2;2100

☑ cloZAPine
75 mg, Oral, Form: Tab, qHS, Order Duration: 1 dose(s), First Dose: T+3;2100

☑ cloZAPine

100 mg, Oral, Form: Tab, qHS, Order Duration: 1 dose(s), First Dose: T+4;2100

☑ cloZAPine
125 mg, Oral, Form: Tab, qHS, Order Duration: 1 dose(s), First Dose: T+5;2100

☑ cloZAPine
150 mg, Oral, Form: Tab, qHS, Order Duration: 1 dose(s), First Dose: T+6;2100

☑ cloZAPine
175 mg, Oral, Form: Tab, qHS, Order Duration: 1 dose(s), First Dose: T+7;2100

☑ cloZAPine
200 mg, Oral, Form: Tab, qHS, Order Duration: 1 dose(s), First Dose: T+8;2100

☑ cloZAPine
225 mg, Oral, Form: Tab, qHS, Order Duration: 1 dose(s), First Dose: T+9;2100

☑ cloZAPine
250 mg, Oral, Form: Tab, qHS, Order Duration: 1 dose(s), First Dose: T+10;2100

☑ cloZAPine
275 mg, Oral, Form: Tab, qHS, Order Duration: 1 dose(s), First Dose: T+11;2100

THEN

☑ cloZAPine
300 mg, Oral, Form: Tab, qHS, First Dose: T+12;2100

ii) Slow Initiation

☑ cloZAPine
12.5 mg, Oral, Form: Tab, qNOON, Order Duration: 1 dose(s), First Dose: T;1200

☑ cloZAPine
25 mg, Oral, Form: Tab, qHS, Order Duration: 1 dose(s), First Dose: T+1;2100

☑ cloZAPine
50 mg, Oral, Form: Tab, qHS, Order Duration: 2 dose(s), First Dose: T+2;2100

☑ cloZAPine
75 mg, Oral, Form: Tab, qHS, Order Duration: 2 dose(s), First Dose: T+4;2100

☑ cloZAPine
100 mg, Oral, Form: Tab, qHS, Order Duration: 2 dose(s), First Dose:

T+6;2100

☑ cloZAPine
125 mg, Oral, Form: Tab, qHS, Order Duration: 2 dose(s), First Dose: T+8;2100

☑ cloZAPine
150 mg, Oral, Form: Tab, qHS, Order Duration: 2 dose(s), First Dose: T+10;2100

☑ cloZAPine
175 mg, Oral, Form: Tab, qHS, Order Duration: 2 dose(s), First Dose: T+12;2100

☑ cloZAPine
200 mg, Oral, Form: Tab, qHS, Order Duration: 2 dose(s), First Dose: T+14;2100

☑ cloZAPine
225 mg, Oral, Form: Tab, qHS, Order Duration: 2 dose(s), First Dose: T+16;2100

☑ cloZAPine
250 mg, Oral, Form: Tab, qHS, Order Duration: 2 dose(s), First Dose: T+18;2100

☑ cloZAPine
275 mg, Oral, Form: Tab, qHS, Order Duration: 2 dose(s), First Dose: T+20;2100

THEN

☑ cloZAPine
300 mg, Oral, Form: Tab, qHS, First Dose: T+22;2100

h) Quetiapine XR
UpToDate: Link
RxTx: Link
Target Dose: 600-1200mg/day
Max Dose: 1200mg/day

i) ☐ Initiation

☐ Quetiapine XR 300mg PO QPM, Order duration: 1 dose(s) First dose: T; 1700

☐ Quetiapine XR 600mg PO QPM, Order duration: 1 dose(s) First dose: T+1; 1700

THEN

☐ Quetiapine XR 800mg PO QPM, First dose: T+2; 1700

i) Quetiapine
UpToDate: Link
RxTx: Link

Target Dose: 400-800mg/day
Max Dose: 800mg/day

i) ☐ Initiation

☐ Quetiapine 100mg PO QHS, Order duration: 1 dose(s) First dose: T; 2100

☐ Quetiapine 200mg PO QHS, Order duration: 1 dose(s) First dose: T+1; 2100

☐ Quetiapine 300mg PO QHS, Order duration: 1 dose(s) First dose: T+2; 2100

☐ Quetiapine 400mg PO QHS, Order duration: 1 dose(s) First dose: T+3; 2100

☐ Quetiapine 500mg PO QHS, Order duration: 1 dose(s) First dose: T+4; 2100

THEN

☐ Quetiapine 600mg PO QHS, First dose: T+5; 2100

j) Olanzapine

UpToDate: Link
RxTx: Link
Target Dose: 20mg
Max Dose: 40mg (off-label)

i) ☐ Rapid Initiation

☐ Olanzapine 10mg PO QHS, Order duration: 1 dose(s) First dose: T; 2100

THEN

☐ Olanzapine 20mg PO QHS, First dose: T+1; 2100

ii) ☐ Initiation

☐ Olanzapine 5mg PO QHS, Order duration: 1 dose(s) First dose: T; 2100

☐ Olanzapine 10mg PO QHS, Order duration: 3 dose(s) First dose: T+1; 2100

☐ Olanzapine 15mg PO QHS, Order duration: 3 dose(s) First dose: T+4; 2100

THEN

☐ Olanzapine 20mg PO QHS, First dose: T+7; 2100

k) Labs

❑ Glucose Random ONCE

❑ Glucose Random in 84 days then annually q 336 days

❑ Alanine Transaminase (ALT) ONCE

❑ Alanine Transaminase (ALT) q168 days

❑ Lipid Profile ONCE

❑ Lipid Profile in 84 days then annually q 336 days

❑ Complete Blood Count (CBC) ONCE

❑ Complete Blood Count (CBC) annually q 336 days

❑ Electrolytes ONCE

❑ Electrolytes annually q 336 days

❑ Hba1c ONCE

❑ Hba1c in 84 days then annually q 336 days

l) Diagnostic Imaging

❒ ECG - *As clinically indicated*

m) Scales Parameters

☒ BPRS: T
☒ BPRS: T+7;
☒ BPRS: T+14;
☒ BPRS: T+28;
THEN
☒ BPRS: Q56D

Medication Costs (Approx. 28 Days of Therapy)
Aripiprazole Oral 20mg - $28.05
Abilify Maintena 400mg - $456.18
Risperidone Oral 6mg - $40.21
Risperdal Consta 50mg - $340.50
Paliperidone 6mg - $161.93
Invega Sustenna 150mg - $635.83
Clozapine 300mg - $222.15
Quetiapine XR 800mg – $74.31
Quetiapine IR 600mg - $21.63
Olanzapine 20mg - $39.69

Appendix C - Sensitivity Analysis Tables 3-2, 4-2, 5-2

Table 3-2. Descriptive Characteristics of Patients who Reached Target Antipsychotic Dosage by 2-weeks Post-Admission: A sensitivity analysis

Observable Characteristics	Did not reach target dose (n = 135)	Reached Target Dose (n = 175)	p-value
Female, n (%)	60 (44.4)	58 (33.1)	0.056
Age category, n (%)			0.337
<20	6 (4.4)	9(5.1)	
20-29	26(19.3)	46 (26.3)	
30-39	33 (24.4)	43 (24.6)	
40-49	30 (22.2)	28 (16.0)	
50-59	18 (13.3)	30 (17.1)	
60+	22 (16.2)	19 (10.9)	
Waist Circumference in inches, mean (sd)	38.0(7.3)	39.1 (7.6)	0.244
Weight in kilograms, mean (sd)	77.04 (19.3)	82.28 (23.6)	0.038
Length of Stay in days, mean (sd)	89.7(66.7)	79.78(57.5)	0.172
Race / Ethnicity, n (%)	89.7(66.7)	79.78(57.5)	0.825
Non-White	46 (34.1)	65 (37.1)	
White	66 (48.9)	82 (46.9)	
Missing / Unknown	14 (10.4)	16 (9.1)	
Education, n (%)			0.771
0. Unknown	33 (24.4)	38 (21.7)	
1. No Schooling, 8 grades or less	8 (5.9)	9 (5.1)	
2. High School or some High School	55 (40.7)	83 (47.4)	
3. Technical/Trade School or Some College	27 (20.0)	34 (19.4)	
4. Diploma/Bachelor's or Graduate Degree	12 (8.9)	11 (6.3)	
Substance Use Diagnosis, n (%)			0.724
Yes	49 (36.3)	59 (33.7)	
Initial BPRS score, mean (sd)	12.1(7.2)	11.0(6.8)	0.177

Table 4-2. Descriptive Characteristics of Patients who were Prescribed a Long-Acting Injectable: A sensitivity analysis

Observable Characteristics	Prescribed an LAI (n=204)	Not Prescribed an LAI (n=111)	p-value
Female, n (%)	48 (23.5)	72 (64.9)	0.205
Age in years, n (%)			0.362
<20	7 (3.4)	8 (7.2)	
20-29	51 (25.0)	22 (19.8)	
30-39	54 (26.5)	23 (20.7)	
40-49	39 (19.1)	21 (18.9)	
50-59	28 (13.7)	21 (18.9)	
60+	25 (12.3)	16 (14.4)	
Waist Circumference in inches, mean (sd)	38.3 (6.8)	39.0(8.5)	0.466
Weight in kilograms, mean (sd)	80.2(23.6)	79.66 (21.1)	0.839
Length of Stay in days, mean (sd)	87.1(63.9)	76.17(57.01)	0.121
Race / Ethnicity, n (%)			0.001
Non-White	81 (39.7)	31 (27.9)	
White	84 (41.2)	67 (60.4)	
Missing or Unknown	39 (19)	13 (11.7)	
Education Level, n(%)			0.582
0. Unknown	42 (20.6)	30 (27.0)	
1. No Schooling, 8 grades or less	10 (4.9)	7 (6.3)	
2. High School or some High School	92 (45.1)	49 (44.1)	
3. Technical/Trade School or Some College	44 (21.6)	18 (16.2)	
4. Diploma/Bachelor's or Graduate Degree	16 (7.8)	7 (6.3)	
Substance Use Diagnosis, n (%)			0.292
Yes	76 (37.3)	34 (30.6)	
Initial BPRS score	12.1(6.8)	10.87(7.56)	0.190

Table 5-2. Descriptive Characteristics of Patients who were Eligible for Clozapine Prescription: A sensitivity analysis

Observable Characteristics	Eligible & Prescribed (n=71)	Eligible & Not prescribed (n=23)	p-value
Female, n (%)	24 (33.8)	9 (39.1)	0.831
Age category, n (%)			1.000
<29	20 (21.1)	6 (26.1)	
30+	51 (53.7)	17 (73.9)	
Waist Circumference in inches, mean(sd)	38.3(8.3)	38.89(5.49)	0.703
Weight in kilograms, mean(sd)	80.0(21.5)	77.5(18.01)	0.595
Length of Stay in days, mean(sd)	99.00(72.0)	95.57(71.63)	0.843
Race / Ethnicity			0.073
Non-White, Missing or Unknown	37 (38.9)	16 (57.1)	
White	34 (35.8)	7 (25.0)	
Education			0.750
0. Unknown	14 (14.7)	5 (17.9)	
1. No Schooling, High School or some High School	43 (45.3)	12 (42.9)	
2. Technical/Trade School or Post-Secondary School	14 (14.7)	6 (21.4)	
Substance Use Diagnosis, n(%)			1.000
Yes	18 (19.0)	6 (21.4)	
Initial BPRS score, mean(sd)	13.11 (7.0)	10.19 (4.8)	0.034