ANTIPSYCHOTIC PRESCRIBING PATTERNS ON ADMISSION TO AND
DISCHARGE FROM A TERTIARY CARE PROGRAM FOR TREATMENT-
RESISTANT PSYCHOSIS AT RIVERVIEW HOSPITAL

by

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Abstract

The treatment of psychosis typically requires the use of only one antipsychotic. Even in instances of treatment-resistant psychosis, the atypical antipsychotic clozapine has proven to be effective when used on its own. However, antipsychotic polypharmacy is commonly prescribed despite a lack of evidence for this practice. This concurrent use of two or more antipsychotics can also prolong the time before clozapine is tried. Antipsychotic polypharmacy should be reserved for instances of clozapine-resistant psychosis if it is to be used at all.

In this retrospective study, data were collected from individuals who were referred to a tertiary care program for treatment-resistant psychosis. The main objectives were to compare the use of antipsychotic monotherapy to polypharmacy in treatment-resistant psychosis and to characterize within-individual changes in treatment and symptomatology secondary to hospitalization.

At admission, individuals who were prescribed only one antipsychotic were comparable to those who were prescribed at least two antipsychotics with regard to demographics and symptom severity. The use of drugs other than antipsychotics was also similar between groups. However, the magnitude of antipsychotic utilization was greater in individuals who were receiving antipsychotic polypharmacy. In addition, a greater proportion of these individuals received excessive doses at admission. Similar findings were observed when monotherapy and polypharmacy were compared at discharge.

Three important patterns were identified when investigating within-individual changes. First, fewer individuals were on polypharmacy at discharge. This was accompanied by a general decrease in both the number of antipsychotics prescribed and the magnitude of antipsychotic utilization. Second, the number of individuals who were prescribed clozapine had increased by discharge. Those who were already prescribed clozapine at admission typically had their doses increased. Third, improvements in symptomatology were observed across all of the subscales included in the Positive and Negative Syndrome Scale (PANSS). However, only 57.9% of individuals experienced a relative reduction in PANSS scores greater than 20%.
Based on these findings, it is possible to alleviate the symptoms of psychosis in treatment-resistant psychosis while reducing antipsychotic utilization. Although this may seem counterintuitive, an increase in the use of clozapine and a decrease in antipsychotic polypharmacy may have contributed to clinical improvement.
Lay Summary

Antipsychotics are the only therapeutic drug class approved for psychotic disorders. However, not all individuals will respond favorably to treatment.

The concurrent use of two or more antipsychotics is common in individuals who continue to have symptoms despite conventional treatment, but this practice, termed antipsychotic polypharmacy, is lacking in evidence. Clozapine is the most effective antipsychotic in treatment-resistant psychosis. However, widespread use of this drug is potentially limited by its adverse effect profile and the need for therapeutic drug monitoring.

The goal of this study is to investigate antipsychotic prescribing patterns on admission to and discharge from a program for treatment-resistant psychosis. For most individuals, the medications prescribed at discharge should reflect optimized treatment.

Important findings are as follows:

1) The number of antipsychotics and the total daily dose were reduced in most individuals
2) The number of individuals prescribed clozapine increased from admission
3) Most individuals improved following hospitalization
Preface

This thesis contains unpublished work.

The experimental design was developed in collaboration with Dr. Alasdair Barr, Dr. Ric Procysyn, and Dr. William Honer.

Data were collected by Dr. Geoffrey Smith. I performed the data pre-processing and analysis with input from Dr. Barr.

Ethics approval was obtained from the University of British Columbia Clinical Research Ethics Board (certificate number: H10-02890).
Table of Contents

Abstract.............................................................................................................................................. ii

Lay Summary....................................................................................................................................... iv

Preface.................................................................................................................................................... v

Table of Contents................................................................................................................................. vi

List of Tables .......................................................................................................................................... ix

List of Figures ......................................................................................................................................... x

List of Abbreviations ............................................................................................................................. xii

Acknowledgements ............................................................................................................................... xiii

Chapter 1: Introduction .......................................................................................................................... 1

1.1 Psychosis ......................................................................................................................................... 1

1.1.1 In schizophrenia and other psychotic disorders ......................................................................... 1

1.1.2 In other medical conditions ......................................................................................................... 4

1.2 Pharmacological treatment ............................................................................................................ 4

1.2.1 Typical antipsychotics .................................................................................................................. 5

1.2.1.1 Mechanism of action ............................................................................................................... 5

1.2.1.2 Adverse effects ...................................................................................................................... 6

1.2.2 Atypical antipsychotics ............................................................................................................... 8

1.2.2.1 Mechanism of action ............................................................................................................. 8

1.2.2.2 Adverse effects ...................................................................................................................... 9

1.2.3 Clinical effectiveness .................................................................................................................. 11

1.3 Treatment-resistant psychosis ....................................................................................................... 13
1.3.1 Therapeutic options........................................................................................................ 13
  1.3.1.1 Clozapine .................................................................................................................... 14
  1.3.1.2 Antipsychotic polypharmacy ....................................................................................... 16
1.4 Tertiary care program for treatment-resistant psychosis ................................................. 17
1.5 Rationale, objectives, and hypotheses ............................................................................... 17

Chapter 2: Methods ................................................................................................................. 19
  2.1 Data collection .................................................................................................................. 19
  2.2 Antipsychotic utilization .................................................................................................. 20
  2.3 Statistical analyses ......................................................................................................... 20

Chapter 3: Results .................................................................................................................... 22
  3.1 Comparison of antipsychotic monotherapy and polypharmacy at admission ............. 22
  3.2 Comparison of antipsychotic monotherapy and polypharmacy at discharge ............ 25
  3.3 Within-individual change in antipsychotic prescribing patterns .................................. 28
  3.4 Within-individual change in antipsychotic utilization .................................................... 32
  3.5 Within-individual change in clozapine treatment ............................................................. 42
  3.6 Within-individual change in clozapine utilization ............................................................. 42
  3.7 Within-individual change in symptom severity ............................................................... 44
  3.8 Predictor variables associated with symptom severity at discharge ............................ 49

Chapter 4: Discussion ................................................................................................................. 52
  4.1 Between-group differences at admission and discharge .................................................. 52
  4.2 Within-individual changes in pharmacological treatment .............................................. 54
  4.3 Within-individual changes in symptom severity ............................................................. 56
  4.4 Predictor variables associated with change in symptom severity ................................ 56
4.4.1 Admission PANSS scores ................................................................. 56
4.4.2 Diagnosis .............................................................................................. 57
4.4.3 Sex ........................................................................................................... 57
4.4.4 Age .......................................................................................................... 57
4.4.5 Clozapine .................................................................................................. 58
4.4.6 Antipsychotic polypharmacy .................................................................... 60
4.4.7 Excessive antipsychotic utilization ............................................................ 61
4.4.8 Drugs other than antipsychotics ............................................................... 62
4.5 Limitations .................................................................................................. 63
  4.5.1 DDD method ........................................................................................... 63
  4.5.2 Exclusion of pro re nata medications ....................................................... 64
  4.5.3 Categorizing antipsychotic prescribing patterns ...................................... 64
  4.5.4 Antipsychotic utilization as an approximation of drug concentrations .......... 64
  4.5.5 Changes in diagnostic criteria ................................................................. 65
  4.5.6 Changes in treatment patterns over time ................................................ 66
  4.5.7 Study design .......................................................................................... 66
4.6 Future directions .......................................................................................... 67
4.7 Conclusion .................................................................................................... 67

References ........................................................................................................ 68
List of Tables

Table 1. Antipsychotics prescribed at admission

Table 2. Comparison of antipsychotic monotherapy and polypharmacy at admission

Table 3. Antipsychotics prescribed at discharge

Table 4. Comparison of antipsychotic monotherapy and polypharmacy at discharge

Table 5. Contingency table for antipsychotic prescribing patterns at admission and discharge

Table 6. Contingency table for clozapine treatment at admission and discharge

Table 7. Estimated regression coefficients for predictors of symptom severity at discharge
List of Figures

Fig. 1. Within-individual change in antipsychotic prescribing pattern ........................................ 28
Fig. 2. Number of antipsychotics prescribed at admission and discharge ................................. 29
Fig. 3. Number of antipsychotics prescribed at admission and discharge by clozapine prescribing pattern ................................................................................................................. 30
Fig. 4. Number of antipsychotics prescribed at admission and discharge by extent of utilization .. 31
Fig. 5. Within-individual change in the number of antipsychotics prescribed by extent of utilization ........................................................................................................................................ 32
Fig. 6. Within-individual change in antipsychotic utilization ....................................................... 33
Fig. 7. Antipsychotic utilization at admission and discharge ....................................................... 34
Fig. 8. Within-individual change in antipsychotic utilization by extent of utilization at admission ................................................................................................................................. 35
Fig. 9. Within-individual change in antipsychotic utilization by extent of utilization ............... 36
Fig. 10. Comparison of within-individual change in antipsychotic utilization by extent of utilization ........................................................................................................................................ 37
Fig. 11. Within-individual change in antipsychotic utilization by antipsychotic prescribing pattern ................................................................................................................................. 39
Fig. 12. Comparison of within-individual change in antipsychotic utilization by antipsychotic prescribing pattern ................................................................................................................................. 40
Fig. 13. Within-individual change in antipsychotic utilization by clozapine prescribing pattern 41
Fig. 14. Within-individual change in clozapine utilization ......................................................... 43
Fig. 15. Clozapine utilization at admission and discharge ......................................................... 44
Fig. 16. Within-individual change in positive symptoms .......................................................... 45
Fig. 17. Within-individual change in negative symptoms .......................................................... 46
Fig. 18. Within-individual change in general psychopathology .............................................. 47
Fig. 19. Within-individual change in total symptomatology ..................................................... 48
**List of Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
</tr>
<tr>
<td>ICD</td>
<td>International Statistical Classification of Diseases and Related Health Problems</td>
</tr>
<tr>
<td>cAMP</td>
<td>cyclic adenosine monophosphate</td>
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<tr>
<td>CATIE</td>
<td>Clinical Antipsychotic Trials of Intervention Effectiveness</td>
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<tr>
<td>BPRS</td>
<td>Brief Psychiatric Rating Scale</td>
</tr>
<tr>
<td>CGI</td>
<td>Clinical Global Impression</td>
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<tr>
<td>PANSS</td>
<td>Positive and Negative Syndrome Scale</td>
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<tr>
<td>DDD</td>
<td>defined daily dose</td>
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<td>PDD</td>
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Chapter 1: Introduction

1.1 Psychosis

Psychosis—a condition typified by hallucinations and delusions—is the defining feature of schizophrenia and other psychotic disorders such as schizoaffective and schizophreniform disorder[1]. However, since these diagnoses are ones of exclusion, not all instances of psychosis will warrant a diagnosis of a psychotic disorder. Moreover, subclinical experiences that do not result in distress or functional impairment are unlikely to receive medical attention. These observations have led to the hypothesis that psychotic experiences exist on a continuum spanning from individuals diagnosed with psychiatric disorders to those within the general population[2,3]. Nevertheless, the validity of this transdiagnostic and extended psychotic phenotype as well as the merits of adopting a diagnostic approach based on a continuum or multiple dimensions have been debated[4-8].

1.1.1 In schizophrenia and other psychotic disorders

The current diagnostic approach to psychotic disorders is categorical by design. In the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM), a diagnosis of schizophrenia requires:

“[t]wo (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2), or (3):

1. Delusions.
2. Hallucinations.
3. Disorganized speech (e.g., frequent derailment or incoherence).
4. Grossly disorganized or catatonic behavior.
5. Negative symptoms (i.e., diminished emotional expression or avolition).”[1]”

Alternatively, in the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD), a diagnosis of schizophrenia requires:

“a minimum of one very clear symptom (and usually two or more if less clear-cut) belonging to any one of the groups listed as (a) to (d) [below], or symptoms from at least two of the groups referred to as (e) to (h), should have been clearly present for most of the time during a period of 1 month or more.”[9]

(a) “thought echo, thought insertion or withdrawal, and thought broadcasting;
(b) delusions of control, influence, or passivity, clearly referred to body or limb movements or specific thoughts, actions, or sensations; delusional perception;
(c) hallucinatory voices giving a running commentary on the patient’s behaviour, or discussing the patient among themselves, or other types of hallucinatory voices coming from some part of the body;
(d) persistent delusions of other kinds that are culturally inappropriate and completely impossible, such as religious or political identity, or superhuman powers and abilities (e.g. being able to control the weather, or being in communication with aliens from another world);
(e) persistent hallucinations in any modality, when accompanied either by fleeting or half-formed delusions without clear affective content, or by persistent over-valued ideas, or when occurring every day for weeks or months on end;
(f) breaks or interpolations in the train of thought, resulting in incoherence or irrelevant speech, or neologisms;
(g) catatonic behaviour, such as excitement, posturing, or waxy flexibility, negativism, mutism, and stupor;
(h) “negative” symptoms such as marked apathy, paucity of speech, and blunting or incongruity of emotional responses, usually resulting in social withdrawal and lowering of social performance; it must be clear that these are not due to depression or to neuroleptic medication;
(i) a significant and consistent change in the overall quality of some aspects of personal behaviour, manifest as loss of interest, aimlessness, idleness, a self-absorbed attitude, and social withdrawal.[9]

Common to both diagnostic criteria is the emphasis placed on the symptoms of psychosis. Although there has been a move away from specific types of psychotic experiences (e.g., bizarre delusions; special hallucinations) in the fifth edition of the DSM[10,11], the criteria in the ICD remain a testament to the legacy of Schneider’s first rank symptoms[12] in psychiatry[13]. Originally conceived to be a list of symptoms pathognomonic for schizophrenia, evidence for the continued use of these first rank symptoms (e.g., thought insertion or withdrawal; thought broadcasting) in the ICD has been equivocal owing to the heterogeneity in study populations and design[14]. Even so, it would be unwise to dismiss their clinical utility altogether. While these symptoms may perform poorly in distinguishing schizophrenia from other disorders with psychotic features[15], they can still be of use in settings where the exclusion of organic disorders may not be feasible[11].

Given the difficulty in diagnosing psychotic disorders based on the presentation of psychosis alone, it stands to reason that these disorders are closely related to each other (and to bipolar disorder) as has been suggested by numerous genetic studies[16]. Although the etiology of psychosis in these disorders has yet to be fully elucidated, it is generally accepted to be multifactorial in origin[17]. Several genetic and environmental risk factors have been implicated in increasing the vulnerability to psychosis[18-20]. Exposure to stressors may even increase the behavioral response to future stressors in individuals who are predisposed to psychosis[21]. This
The notion of stress-induced cross-sensitization has direct implications on the pathology of psychotic disorders if similar changes to the physiological response also occur\textsuperscript{[22]}. Nevertheless, it is possible for there to be many different etiologies underlying the same disorder since diagnoses are based solely on symptomatology. Even if the cause of vulnerability were to be considered in isolation, the specific combination of risk factors will invariably differ between individuals\textsuperscript{[23]}.

But given the similarities in symptoms across these disorders, it remains possible that the pathophysiology of psychosis is the same despite these potential differences in etiology\textsuperscript{[23,24]}. The pathophysiology of psychosis has traditionally been conceptualized at the level of neurotransmitters. While the prevailing hypothesis focuses on abnormalities in dopamine within the context of schizophrenia\textsuperscript{[24]}, other neurotransmitters such as glutamate and gamma-aminobutyric acid may also be of importance by virtue of the neural pathways involved in dopaminergic neurotransmission\textsuperscript{[20,22,25]}. Early work on the mechanism of action of antipsychotics led to the speculation that a non-specific increase in dopaminergic activity is involved in the pathophysiology of schizophrenia\textsuperscript{[26,27]}. This abnormality in dopaminergic activity was later localized to subcortical regions of the brain (i.e., mesolimbic dopamine neurons) based on direct evidence from animal models and indirect evidence from humans\textsuperscript{[28]}.

Although this notion of striatal hyperdopaminergia has since been corroborated by neurochemical imaging studies\textsuperscript{[24]}, it is interesting to note that individuals who experience subclinical auditory hallucinations have not been found to differ from healthy controls in terms of dopamine synthesis capacity in functional subdivisions of the striatum, suggesting that subclinical auditory hallucinations may not involve some of the same dopaminergic abnormalities that are characteristic of psychotic symptoms\textsuperscript{[29]}. This could also be interpreted as an inherent neurobiological difference between those who have subclinical psychotic experiences and those who can be diagnosed with a psychotic disorder\textsuperscript{[30]}.

The relationship between striatal hyperdopaminergia in the mesolimbic pathway and the symptoms of psychosis may be explained by the putative role of dopamine in the attribution of salience. Dopamine has been implicated in ascribing motivational value to external stimuli for the purposes of directing behavior when released in response to contextually relevant stimuli\textsuperscript{[31]}.
However, Kapur\textsuperscript{[32]} has proposed that an increase in dopaminergic activity, such as that observed in psychosis, can interfere with this process, leading to the “\textit{aberrant assignment of salience to external objects and internal representations}”. The assignment of salience to internal representations may explain the pathophysiology of hallucinations, while the assignment of salience to external objects and attempts to rationalize these experiences may explain that of delusions. Although this framework offers an explanation for psychosis, it is not without its limitations, the most important of which is the fact that a definitive causal relationship between dopamine and salience has yet to be established\textsuperscript{[33]}.

Regardless of the framework used to contextualize psychosis, it has become abundantly clear that most instances of psychotic disorders are, at best, associated with partial recovery\textsuperscript{[34]}. While the treatment of psychosis (i.e., positive symptoms) is undoubtedly important in attaining favorable clinical outcomes, other aspects of these disorders should not be neglected. Negative symptoms, consisting of affective flattening, anhedonia, avolition, asociality, and alogia, are associated with poor functional outcomes\textsuperscript{[35]}, and the same can also be said of cognitive impairments\textsuperscript{[36]}. Thus, the ideal pharmacological treatment or treatments should alleviate all symptoms and impairments present in these disorders.

\subsection*{1.1.2 In other medical conditions}

As mentioned, psychosis is not limited to psychotic disorders. Individuals diagnosed with other mental disorders, such as bipolar or major depressive disorder, can also present with symptoms of hallucinations and delusions\textsuperscript{[1]}. Psychosis has also been observed in a variety of clinical presentations outside of psychiatry such as temporal lobe epilepsy\textsuperscript{[33,37]} and Alzheimer’s disease\textsuperscript{[38]}. But the fact that psychosis is not present in all instances of these conditions suggests some underlying difference in pathophysiology between those who experience it and those who do not. For this reason, the discussion to follow will focus only on psychotic disorders.

\subsection*{1.2 Pharmacological treatment}

Antipsychotics are the only class of drugs indicated in individuals with schizophrenia or other psychotic disorders. Although they exhibit marked differences in their receptor binding profiles,
these drugs have been dichotomized based on their propensity to cause a number of acute movement disorders that are collectively termed extrapyramidal symptoms.

1.2.1 Typical antipsychotics

Chlorpromazine, the archetypal phenothiazine antipsychotic, was initially synthesized as part of an effort to create drugs with anesthetic-potentiating effects similar to promethazine\(^ {39}\). In assessing its clinical pharmacodynamic profile in patients undergoing surgery, the drug was found to have a calming effect\(^ {40}\), prompting investigation into its use in psychiatry. Early case reports described clinical improvement following the use of chlorpromazine\(^ {41,42}\), but results from an early crossover trial were especially promising since some individuals were shown to improve with chlorpromazine, deteriorate with placebo, and improve once again when treatment was reinstated\(^ {43}\). Although the content of their hallucinations and delusions remained unchanged, these observations demonstrated the potential for symptomatic relief afforded by chlorpromazine. Haloperidol, the archetypal butyrophenone antipsychotic, was synthesized soon after and found to have similar effects as phenothiazine antipsychotics in animal models and in individuals with psychosis\(^ {44,45}\).

1.2.1.1 Mechanism of action

Since these archetypal antipsychotics are the products of serendipitous discovery rather than rational drug design, the elucidation of their mechanism of action took place after their introduction into clinical practice.

Carlsson and Lindqvist\(^ {46}\) were the first to propose a mechanism of action involving receptor blockade based on the results of their \textit{in vivo} study\(^ {47}\). Having pre-treated the mice with nialamide to restrict the metabolism of noradrenaline and dopamine to normetanephrine and 3-methoxytyramine, respectively, they found the concentrations of these O-methylated metabolites to be higher in the brains of mice treated with either low doses of chlorpromazine or haloperidol than in the brains of mice treated with nialamide only. But despite these increases in the concentrations of the metabolites, the concentrations of dopamine and noradrenaline remained unchanged. These observations were hypothesized to be the result of a compensatory increase in
the synthesis and release of these neurotransmitters secondary to the blockade of monoamine receptors.

The scope of this blockade was narrowed based on findings from radioligand studies\(^{[48]}\). Seeman et al.\(^{[49,50]}\) and Creese et al.\(^{[51]}\) each reported that the concentrations required to displace \(^{[3} \text{H}]\)haloperidol in their assays was strongly correlated with the clinical potency of these drugs. This, in addition to the displacement of \(^{[3} \text{H}]\)dopamine by antipsychotics, furthered speculation that the blockade of a single type of dopamine receptor is responsible for their therapeutic effect.

Dopamine D\(_2\) receptors were ultimately identified as the therapeutic target of antipsychotics after a distinction was made between receptors that stimulate the production of cyclic adenosine monophosphate (cAMP) and those that do not\(^{[52]}\). Since the inhibition of dopamine-stimulated increases in cAMP required greater concentrations of antipsychotics than were observed in individuals treated with these drugs\(^{[48]}\) and was also weaker with haloperidol and other butyrophenone antipsychotics than suggested by their clinical potency\(^{[49,53,54]}\), it was determined—in hindsight—that the blockade of dopamine receptors associated with adenylate cyclase (i.e., dopamine D\(_1\) receptors) could not possibly explain the antipsychotic effect of these drugs. Butyrophenone antipsychotics were later shown to be relatively selective for dopamine receptors that do not stimulate the synthesis of cAMP (i.e., dopamine D\(_2\) receptors)\(^{[55]}\), thus explaining the observations that otherwise suggested a different mechanism of action for this chemical drug class. Additional subtypes of dopamine receptors would later be discovered and characterized based on their similarities to either dopamine D\(_1\) or D\(_2\) receptors, but the occupancy of the latter remains necessary for the therapeutic effect of all antipsychotics\(^{[56,57]}\).

### 1.2.1.2 Adverse effects

The blockade of dopamine D\(_2\) receptors also contributes to the commonalities in their adverse effect profiles. For example, the extent of receptor blockade in the basal ganglia of individuals treated with antipsychotics has been shown to be higher in those experiencing extrapyramidal symptoms than in those without these iatrogenic movement disorders\(^{[58]}\). A similar observation has also been made in individuals with first episode schizophrenia who have had little to no
treatment with antipsychotics prior to their enrollment in a prospective study\textsuperscript{[59]}. Although it may be possible to ameliorate extrapyramidal symptoms by switching antipsychotics or prescribing additional drugs such as anticholinergics\textsuperscript{[60]}, clinicians do so at the risk of compromising treatment or introducing new adverse effects.

Hyperprolactinemia is also recognized as an adverse effect that is secondary to the blockade of dopamine D\textsubscript{2} receptors by typical antipsychotics\textsuperscript{[61]}. In fact, much like extrapyramidal symptoms, hyperprolactinemia can be predicted based on the extent of striatal dopamine D\textsubscript{2} receptor blockade\textsuperscript{[59]}. Complications resulting from prolonged elevations in serum prolactin may include disruptions in both endocrine and sexual functioning\textsuperscript{[62-64]}, but clinical manifestations of hyperprolactinemia may not always be readily detected. This pathological increase in prolactin can be managed by lowering the daily dose, switching antipsychotics, or prescribing dopamine agonists. Unfortunately, these options are not always practical or recommended\textsuperscript{[65]}.

Whereas extrapyramidal symptoms and hyperprolactinemia are commonly attributed to the blockade of dopamine D\textsubscript{2} receptors in the nigrostriatal and tuberoinfundibular pathways, respectively\textsuperscript{[66]}, secondary negative symptoms can arise as a consequence of these adverse effects\textsuperscript{[67]}. In comparison to primary (or idiopathic) negative symptoms, secondary negative symptoms are considered to be more amenable to treatment so long as the causes of these symptoms can be resolved\textsuperscript{[68]}. Nonetheless, the reliability in discerning between primary and secondary negative symptoms is lacking when assessments are made by cross-sectional evaluation\textsuperscript{[69]}.

Additional adverse effects can occur with the binding of these drugs to other receptors. The risk of these adverse effects will vary depending on their receptor binding profiles. For instance, antipsychotics that possess a greater affinity for histamine receptors are more likely to produce sedation, whereas those with a greater affinity for adrenergic receptors are more likely to produce orthostatic hypotension\textsuperscript{[70]}. Consequently, antipsychotics have to be individualized based on patient tolerability to these adverse effects.
1.2.2 Atypical antipsychotics

Clozapine, the first atypical antipsychotic, was synthesized in an attempt to create tricyclic compounds that, like imipramine, had antidepressant effects[71]. Upon investigation, it became apparent that the drug possessed pharmacological properties that were reminiscent of antipsychotics[72]. However, unlike typical antipsychotics, clozapine failed to produce catalepsy in animals and extrapyramidal symptoms in humans. This atypicality presented a challenge in marketing clozapine since extrapyramidal symptoms were previously believed to be necessary for therapeutic effect[73,74]. But once this notion was dispelled, clozapine carved a niche in the treatment of individuals with psychosis and paved the way for the development of other antipsychotics that are effective at treating psychosis in the absence of extrapyramidal symptoms.

1.2.2.1 Mechanism of action

The mechanism of action responsible for the therapeutic effect of most atypical antipsychotics is presumed to be no different than that of the typical antipsychotics discussed above—the drugs compete against endogenous dopamine for binding to dopamine D_2 receptors, thus alleviating the mesolimbic hyperdopaminergia implicated in psychosis[56].

However, aripiprazole is unique in that it is a partial dopamine D_2 receptor agonist; it exhibits some intrinsic activity at dopamine D_2 receptors[75]. Partial agonists have long been of interest in the development of antipsychotics[76,77] because they can function as either an agonist or an antagonist depending on the availability of the endogenous ligand and the extent of the receptor reserve[78]. In addition to its antagonist-like activity at postsynaptic receptors, aripiprazole appears to inhibit the synthesis and release of dopamine via its agonist-like activity at presynaptic autoreceptors[79,80]. Furthermore, it also appears to inhibit neuronal firing via its agonist-like activity on somatodendritic autoreceptors in the ventral tegmental area[81]. In theory, these divergent effects on the different isoforms of the dopamine D_2 receptor can stabilize abnormal dopamine neurotransmission by increasing activity under conditions of hypodopaminergia and decreasing activity under conditions of hyperdopaminergia[82].
Nevertheless, other studies have found the pharmacological effects of aripiprazole to differ by cell line. For example, aripiprazole was able to reduce the accumulation of cAMP in C-6 glioma cells expressing the long isoform of dopamine D2 receptors, but not in Chinese hamster ovary cells expressing either the short or the long isoforms of the same receptor\textsuperscript{83}. The intrinsic activity of the drug can also differ depending on the signaling pathway or cellular function under investigation\textsuperscript{84,85}. Consequently, it may be more appropriate to conceptualize aripiprazole as a functionally selective ligand\textsuperscript{86}. Its pharmacological effect would therefore depend on the intracellular milieu of cells expressing dopamine D2 receptors.

Regardless of whether aripiprazole is best classified as a partial agonist or a functionally selective ligand, results from a positron emission tomography study have shown that the degree of striatal dopamine D2 receptor occupancy is much greater with therapeutic doses of aripiprazole than with the lowest therapeutic dose of most other antipsychotics (85-91\% vs. 60-65\%)\textsuperscript{87}.

1.2.2.2 Adverse effects

Extrapyramidal symptoms are also observed in individuals treated with atypical antipsychotics, but these drugs carry a comparatively lower risk for these movement disorders than typical antipsychotics. Opinions differ on the pharmacological basis of this atypicality\textsuperscript{74}. According to Meltzer et al.\textsuperscript{88}, atypical antipsychotics can be differentiated from typical antipsychotics based on their greater affinity for serotonin 5-HT\textsubscript{2A} receptors than for dopamine D2 receptors. The additional blockade of serotonin 5-HT\textsubscript{2A} receptors could reduce the risk of extrapyramidal symptoms by increasing dopaminergic activity in the nigrostriatal pathway\textsuperscript{89}. However, saturation of serotonin 5-HT\textsubscript{2A} receptors occurs at low doses and may limit the protective effects of certain atypical antipsychotics when higher doses are used. This could explain the differences in the propensity for extrapyramidal symptoms between atypical antipsychotics\textsuperscript{90}.

In contrast, Kapur and Seeman\textsuperscript{91} have sought to explain the atypicality of these newer antipsychotics in terms of their dissociation rates from dopamine D2 receptors. They have proposed that the rapid dissociation of atypical antipsychotics from these receptors is sufficient
for explaining their relative lack of extrapyramidal symptoms. Unlike typical antipsychotics, which are characterized by their high affinity for dopamine D\textsubscript{2} receptors, the rapid dissociation of atypical antipsychotics frees up the dopamine binding site with greater frequency, allowing transient and physiologically relevant signals to be transmitted in between periods of receptor occupancy. Although this hypothesis is better able to accommodate the existence of atypical antipsychotics that do not block serotonin 5-HT\textsubscript{2A} receptors at clinically relevant doses\cite{92,93}, it fails to account for atypical antipsychotics that have dissociation rates comparable to typical antipsychotics\cite{94}. Furthermore, a recent reassessment of receptor binding kinetics has cast doubts on this hypothesis since discrepancies between typical and atypical antipsychotics were found to be less pronounced than previously reported\cite{95}.

In any case, the two hypotheses detailed above are not sufficient explanations for the atypicality of aripiprazole. The concept of regional selectivity, which posits that atypical antipsychotics preferentially bind to extrastriatal dopamine D\textsubscript{2} receptors\cite{96,97}, is also unlikely given the conflicting results from positron emission tomography studies\cite{98-100}. Pharmacological properties unique to aripiprazole are likely responsible for its low propensity for extrapyramidal symptoms in spite of its high occupancy of striatal dopamine D\textsubscript{2} receptors at clinically relevant doses. Any detrimental effects that would otherwise result from the blockade of dopamine D\textsubscript{2} receptors in the nigrostriatal pathway may be mitigated by functionally selective or partial agonistic actions at dopamine D\textsubscript{2} receptors.

Since the mechanism underlying antipsychotic-induced hyperprolactinemia also involves the blockade of dopamine D\textsubscript{2} receptors, the fast-off hypothesis has also been used to explain the low incidence of this adverse effect in individuals treated with atypical antipsychotics\cite{91}. But despite this seemingly lower risk of hyperprolactinemia, transient increases in plasma prolactin are still observed with atypical antipsychotics in the hours following drug administration\cite{101}. The distinction between this and hyperprolactinemia, as proposed by Kapur and Seeman\cite{91}, is the duration of receptor occupancy. In addition to their slower dissociation rates from dopamine D\textsubscript{2} receptors, typical antipsychotics tend to produce longer periods of dopamine D\textsubscript{2} receptor occupancy, resulting in an elevation of plasma prolactin that persists between doses.
Although serotonin is capable of stimulating the release of prolactin in rats\textsuperscript{102}, the serotonin-dopamine hypothesis has rarely been used to explain the lower risk of hyperprolactinemia with atypical antipsychotics because the adverse effect is commonly observed with risperidone in spite of its antagonistic activity at serotonin 5-HT\textsubscript{2A} receptors\textsuperscript{103}. The increase in plasma prolactin with risperidone has been attributed to its relatively low permeability across the blood-brain barrier, resulting in a greater occupancy of dopamine D\textsubscript{2} receptors in the anterior pituitary than is expected with other atypical antipsychotics such as olanzapine\textsuperscript{104}. The blockade of serotonin 5-HT\textsubscript{2A} receptors, if it is able to reduce prolactin release in humans, may not be sufficient in overcoming the blockade of dopamine D\textsubscript{2} receptors in the anterior pituitary.

Despite their low propensity for extrapyramidal symptoms, treatment with atypical antipsychotics can result in a number of other adverse effects that are unrelated to their occupancy of dopamine D\textsubscript{2} receptors. Perhaps most important are their collective propensity for metabolic adverse effects. Many receptors have been implicated in antipsychotic-induced weight gain, glucose dysregulation, and dyslipidemia\textsuperscript{105}, but while clozapine and olanzapine carry the greatest risk for these adverse effects, aripiprazole and ziprasidone appear to have minimal effect on metabolic parameters\textsuperscript{106}. In terms of adverse effects, atypical antipsychotics are a heterogeneous class of drugs\textsuperscript{107}.

### 1.2.3 Clinical effectiveness

Antipsychotics play an important role in the treatment of psychosis. In individuals with first episode psychosis, shorter durations of untreated psychosis are associated with greater clinical response and better functional outcomes\textsuperscript{108-110}. Furthermore, in patients with psychotic disorders, non-adherence to treatment is associated with greater risk of hospitalization and suicide\textsuperscript{111,112}. Although results from randomized controlled trials comparing chlorpromazine to placebo have been quite variable, comparisons between the two have produced weak evidence in favor of chlorpromazine for outcomes such as relapse prevention and global improvement under certain conditions\textsuperscript{113}. As the authors of this meta-analysis so aptly stated: “Chlorpromazine, in common use for half a century, is a well-established but imperfect treatment.”\textsuperscript{113}
Typical antipsychotics have been largely replaced by atypical antipsychotics in the treatment of psychotic disorders in spite of the fact that superiority has yet to be unequivocally established. For example, olanzapine was reported to have greater clinical efficacy than haloperidol across multiple symptom domains in an international collaborative trial\cite{114}. Yet no differences were found between the two drugs in a smaller randomized controlled trial\cite{115}. This lack of agreement between the two studies may be a result of the difference in the prescribing patterns of anticholinergic drugs. Unlike the international collaborative trial, where anticholinergic drugs were prescribed on an as needed basis for the management of extrapyramidal symptoms, these drugs were prescribed prophylactically to individuals randomized to haloperidol in the smaller trial because akinesia (a type of extrapyramidal symptom) is commonly observed with the use of high-potency typical antipsychotics and is often mistaken for negative symptoms or depression in psychotic disorders\cite{116}. Thus, while olanzapine may possess greater clinical efficacy than haloperidol, it could be argued that the effectiveness of the two drugs are similar when precautionary measures are taken to mitigate the adverse effects of typical antipsychotics\cite{116}.

Comparisons between the clinical effectiveness of atypical and typical antipsychotics were further explored in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)\cite{117}. In the first phase of this study, individuals diagnosed with schizophrenia were randomly assigned to olanzapine, perphenazine, quetiapine, risperidone, or ziprasidone. They were then followed for a total of 18 months or until the assigned antipsychotic was discontinued. Although the atypical antipsychotic olanzapine was generally found to be slightly more effective in terms of the duration of successful treatment, time to discontinuation due to lack of efficacy, time to all-cause discontinuation, and risk of hospitalization secondary to an exacerbation of schizophrenia, the antipsychotic also had the highest rate of treatment discontinuation owing to intolerable adverse effects. In contrast, the low-potency typical antipsychotic perphenazine was found to be similar to the other atypical antipsychotics in most respects, differing most notably in the rate of treatment discontinuation due to extrapyramidal symptoms. Nonetheless, the main finding is that 74% of participants discontinued their drug treatment before the end of the study period. Thus, even if an antipsychotic is able to alleviate symptoms of psychosis, adverse effects may limit their use, necessitating a switch to a different drug with a more tolerable adverse effect profile.
1.3 Treatment-resistant psychosis

Even with the plethora of antipsychotics available today, it is no guarantee that individuals with psychotic disorders will improve with pharmacological treatment. Individuals who do not respond to antipsychotics are said to have treatment-resistant or refractory psychosis. While this may represent a separate pathological entity altogether, there is not enough evidence to support or refute this hypothesis at the present time\textsuperscript{[118,119]}. Based on the results of two neuroimaging studies, it is possible that individuals with treatment-resistant psychosis more closely resemble healthy individuals than those with treatment-responsive psychosis in terms of dopamine activity\textsuperscript{[120]} and glucose metabolism following haloperidol challenge\textsuperscript{[121]}. If the hyperdopaminergia within the mesolimbic pathway is less severe in individuals with treatment-resistant psychosis, then this could explain their lack of improvement when treated with antipsychotics because the underlying pathophysiology may not involve the same abnormalities that are addressed by dopamine D\textsubscript{2} receptor occupancy.

It is difficult to synthesize the existing literature on treatment-resistant psychosis. Consensus diagnostic criteria have remained elusive even though there is an implicit agreement among researchers and clinicians that treatment resistance requires the continued persistence of symptoms despite at least one antipsychotic trial of adequate dose and duration\textsuperscript{[122]}. In an attempt to remedy this issue, the Treatment Response and Resistance in Psychosis working group has come to a consensus on a set of operationalized criteria\textsuperscript{[123]}. Central to their criteria is the need for at least two antipsychotic trials without adequate response. Each drug would have to be prescribed at a therapeutic dose for at least six weeks without a reduction in symptom severity exceeding 20% when assessed using validated rating scales. Ideally, at least one of these trials would involve the use of a long-acting injectable antipsychotic to rule out overt and covert non-adherence. Prospective trials would also help overcome the limitations of assessing treatment response by retrospective evaluation.

1.3.1 Therapeutic options

If the antipsychotic is well-tolerated, then an optimization of the existing dosage regimen may be a worthwhile endeavor. Otherwise, a switch in antipsychotic treatment will almost certainly be
necessary. For example, despite having to stop treatment during the first phase of the CATIE study—with most having to do so because of a lack of efficacy—8 of the 45 individuals who were enrolled in the second phase of the study and randomized to blinded treatment with olanzapine, quetiapine, or risperidone were able to complete either six months of treatment or the time remaining in the 18-month study without having to discontinue the new antipsychotic drug. More importantly, 20 of the 45 individuals who were randomly assigned to open-label clozapine were able to achieve the same outcome described above. Of the individuals who had to discontinue treatment with their new antipsychotics, those who had been randomized to open-label clozapine demonstrated longer times to all-cause treatment discontinuation than those who had been assigned to blinded treatment with either quetiapine or risperidone. Individuals treated with clozapine also had longer times to treatment discontinuation due to lack of efficacy than those who were prescribed olanzapine, quetiapine, or risperidone.

### 1.3.1.1 Clozapine

Although this demonstration of clinical effectiveness is weakened by the open-label use of clozapine, it corroborates the findings of Kane et al. In their randomized controlled trial, individuals who had been prospectively screened for treatment resistance were randomized to six weeks of treatment with either chlorpromazine or clozapine. At the end of the six weeks, a greater percentage of individuals randomized to clozapine met their *a priori* definition of response (30% vs. 4%), which required a reduction in the total Brief Psychiatric Rating Scale (BPRS) score of at least 20% and either a Clinical Global Impression (CGI) severity scale score of 3 or lower or a total BPRS score of 35 or lower after treatment. This study has been credited with helping reintroduce clozapine after it had been withdrawn from several countries following reports of agranulocytosis. In a meta-analysis of randomized controlled trials comparing the efficacy of clozapine to other antipsychotics in treatment-resistant psychosis, the change in positive symptoms was found to favor clozapine regardless of the length of the studies. In contrast, the change in negative symptoms and overall symptomatology only favored clozapine in studies that were less than three months in duration. The impact of study duration on the relative efficacy of clozapine has
also been reported in a meta-analysis comparing clozapine to typical antipsychotics in treatment-resistant psychosis\textsuperscript{127}. While clozapine has only been shown to exhibit greater clinical efficacy in improving positive symptoms over the long term, it is possible that the diminishing returns observed in other symptom domains may not apply under real-world conditions.

Regardless, the reason behind the greater efficacy of clozapine in alleviating positive symptoms in treatment-resistant psychosis remains a matter of speculation. Considering both the potential differences in striatal dopaminergic activity between individuals with treatment-responsive and treatment-resistant psychosis\textsuperscript{119} and the lower occupancy of striatal dopamine D\textsubscript{2} receptors observed with clinical doses of clozapine\textsuperscript{90}, the mechanism of action responsible for therapeutic response may have less to do with the occupancy of dopamine D\textsubscript{2} receptors than in treatment-responsive psychosis. For example, clozapine produces a greater occupancy of striatal dopamine D\textsubscript{1} receptors than olanzapine, quetiapine, and risperidone. The ratio between this and striatal dopamine D\textsubscript{2} receptor occupancy is also highest with clozapine\textsuperscript{128}. But convincing evidence for the role of dopamine D\textsubscript{1} receptor occupancy has yet to emerge.

All things considered, clozapine has become an indispensable drug in managing treatment-resistant psychosis. Mandatory hematological monitoring has allowed for earlier detection of agranulocytosis, making the drug safer to use than ever before. In addition to its relative efficacy in alleviating positive symptoms of psychosis, suicidality has also been reported to be lower with clozapine than with olanzapine\textsuperscript{129}. But a network meta-analysis has recently challenged long-standing preconceptions of its superiority\textsuperscript{130}. Clozapine was only favored over haloperidol and sertindole in improving overall symptomatology, haloperidol and quetiapine in improving positive symptoms, haloperidol in categorical response to treatment, and fluphenazine, haloperidol, quetiapine, and risperidone in treatment discontinuation owing to a lack of efficacy. In fact, olanzapine was found to be better than clozapine in improving negative symptoms. Although the differences between antipsychotics were predominantly small in effect, the investigators have drawn attention to the randomized controlled trial conducted by Kane et al.\textsuperscript{125}. To date, it remains the trial with the greatest effect size in favor of clozapine (-0.88) and results of this magnitude have yet to be replicated. However, the investigators have also
acknowledged that it has become increasingly unlikely for individuals who would benefit most from clozapine to be enrolled in randomized controlled trials. The population in that study may be unique in that it reflected a time when clinical equipoise existed\textsuperscript{130}.

1.3.1.2 Antipsychotic polypharmacy

Another common option in treatment-resistant psychosis is antipsychotic polypharmacy. However, there is little clinical evidence supporting the concurrent use of two or more antipsychotics in those without a history of treatment resistance\textsuperscript{131,132}. In fact, initiatives have been developed to curtail its use outside of situations where the cross-titration of antipsychotics is unavoidable\textsuperscript{133}. Be that as it may, polypharmacy remains prevalent in British Columbia. Of the 435 outpatients who met the inclusion criteria for a Vancouver-based study, 25.7\% had been prescribed the same combination of antipsychotics for at least 90 consecutive days\textsuperscript{134}. The prevalence of polypharmacy has been found to be even higher in psychiatric hospitals. In 2000, 44.7\% of individuals with schizophrenia were discharged from the provincial tertiary referral hospital with at least two antipsychotics\textsuperscript{135}, representing a 17.2\% increase since this was last studied from November 1\textsuperscript{st}, 1996 to October 31\textsuperscript{st}, 1998\textsuperscript{136}.

From a theoretical standpoint, the potential for pharmacodynamic synergism is limited since the putative mechanism of action (i.e., dopamine D\textsubscript{2} receptor occupancy) is common across all antipsychotics. Furthermore, a temporal association between polypharmacy and symptomatic improvement is not necessarily evidence for synergism because it could also be the result of a delayed response to the original treatment, an effect attributable to the new drug, or a pharmacokinetic interaction affecting plasma concentrations of either medication\textsuperscript{132}. Given the many factors capable of affecting response, it is often difficult to determine the reason for improvement with polypharmacy. There is also little incentive for clinicians to adjust the treatment regimen once therapeutic response is observed, even if the original intention was to switch individuals to a different antipsychotic. Consequently, cases of polypharmacy are often inherited from clinician to clinician\textsuperscript{137}. 
However, there may be some value in augmenting clozapine with a second antipsychotic, particularly in individuals who have had limited success with the drug. In a meta-analysis of randomized controlled trials, the addition of a second antipsychotic to clozapine monotherapy was found to have a small benefit on symptom severity in comparison to treatment with clozapine alone\(^\text{[138]}\). Furthermore, the risk for all-cause study withdrawal was no different between individuals receiving polypharmacy and those receiving monotherapy, suggesting comparable tolerability between the two options. However, neither the cost-effectiveness nor the clinical effectiveness of this practice has been established. It is also important to consider the risk of excessive dosing associated with antipsychotic polypharmacy\(^\text{[134,139]}\).

### 1.4 Tertiary care program for treatment-resistant psychosis

Individuals with treatment-resistant psychosis are often referred to tertiary programs for specialized care. Riverview Hospital served as the tertiary care psychiatric hospital for the entire province of British Columbia. The Refractory Psychosis Program (hereafter referred to as the “Program”) was established in 1988 to meet the demands for psychiatric beds dedicated to individuals with treatment-resistant psychosis. Patients referred to the Program would undergo a comprehensive assessment to confirm their diagnosis, assess the extent of resistance, and develop a personalized treatment plan. Since the closure of Riverview Hospital in 2012, the Program has continued to operate out of the University of British Columbia Hospital as the British Columbia Psychosis Program.

### 1.5 Rationale, objectives, and hypotheses

Many atypical antipsychotics have been developed since the reintroduction of clozapine, but none have proven to be consistently more effective in treatment-resistant psychosis. Unfortunately, clozapine remains underutilized in primary and secondary care, in part because of a lack of familiarity with the drug\(^\text{[140]}\). The reluctance to prescribe clozapine may even result in the use of practices that deviate from treatment guidelines such as antipsychotic polypharmacy\(^\text{[141]}\). Owing to their experience in managing treatment-resistant psychosis, clinicians at tertiary care programs are likely to have greater experience initiating and optimizing
the use of clozapine. Thus, it is reasonable to expect the use of clozapine at these programs when it is deemed necessary.

The objectives of this retrospective chart review were threefold: 1) to compare the use of antipsychotic monotherapy to polypharmacy in treatment-resistant psychosis; 2) to characterize within-individual changes in treatment and symptomatology secondary to hospitalization at the Program; and 3) to explore the collected data for variables that are associated with symptom severity at discharge.

It was hypothesized that antipsychotic utilization would be lower in individuals on antipsychotic monotherapy because dose-dependent adverse effects would limit the use of excessive dosing. While it is possible for individuals to receive lower doses of each antipsychotic when the drugs are prescribed as part of polypharmacy, the use of two or more antipsychotics could result in excessive dosing when the cumulative antipsychotic dose is taken into consideration. The majority of individuals were also hypothesized to have switched from antipsychotic polypharmacy to clozapine monotherapy over the course of hospitalization because clinicians at the Program would have greater familiarity with the drug and be better able to monitor patients for its rare but potentially life-threatening adverse effects. The ensuing decrease in the number of antipsychotics prescribed was also expected to reduce the prevalence of excessive dosing for the same reason detailed above.
Chapter 2: Methods

2.1 Data collection

Data from individuals admitted to the Program at Riverview Hospital between September 1994 and November 2010 were collected by retrospective chart review if the severity of their symptoms had been rated by clinicians at admission and discharge using the Positive and Negative Syndrome Scale (PANSS)\textsuperscript{142}. The PANSS is administered as a semi-formalized interview and consists of 30 items; seven to assess positive symptoms (i.e., delusions; conceptual disorganization; hallucinatory behavior; excitement; grandiosity; suspiciousness; hostility), seven to assess negative symptoms (i.e., blunted affect; emotional withdrawal; poor rapport; passive-apathetic social withdrawal; difficulty in abstract thinking; lack of spontaneity and flow of conversation; stereotyped thinking), and sixteen to assess general psychopathology (i.e., somatic concern; anxiety; guilt feelings; tension; mannerisms and posturing; depression; motor retardation; uncooperativeness; unusual thought content; disorientation; poor attention; lack of judgment and insight; disturbance of volition; poor impulse control; preoccupation; active social avoidance). The severity of each item is scored on a seven-point integer scale, with 1 being absent and 7 being extreme. Since these ratings are made based on information from the previous week, they are subject to change over time, making the PANSS an appropriate instrument for assessing the clinical outcome in those treated at the Program.

In addition to these ratings of symptom severity, demographic data (i.e., diagnosis; sex; age at admission; prior history of clozapine) and regularly scheduled medications at admission and discharge were recorded where available. Pro re nata or ‘as needed’ medications were not included in the analysis. Individuals were excluded if they had a psychiatric diagnosis other than schizophrenia or schizoaffective disorder. If the individual has had more than one admission to the Program, then data from their last available admission were used.
Data pre-processing was completed using R version 3.3.2\textsuperscript{[143]}. In addition to the pre-installed packages, \textit{forcats} (v. 0.1.1), \textit{lubridate} (v. 1.6.0), \textit{stringr} (v. 1.1.0), and \textit{tidyverse} (v. 1.0.0) were used to prepare the data for analysis\textsuperscript{[144-147]}.

### 2.2 Antipsychotic utilization

As outlined by the World Health Organization\textsuperscript{[148]}, the defined daily dose (DDD) was used to quantify antipsychotic utilization at admission to and discharge from the Program. For each individual, the prescribed daily dose (PDD) of each antipsychotic was divided by its DDD, “the assumed average maintenance dose per day for a drug used for its main indication in adults”\textsuperscript{[149]}. The ratios were added together if individuals were prescribed more than one antipsychotic at a given time. If antipsychotic utilization is equal to 1, then the prescribed antipsychotic dose or doses are assumed to be appropriate for the treatment of schizophrenia. But if it exceeds 1.5, then, consistent with the criteria used in previous studies\textsuperscript{[134,139,150]}, excessive dosing of antipsychotics is considered to have taken place. For long-acting injectable antipsychotics, the PDD was determined by dividing the administered dose by the number of days between injections.

### 2.3 Statistical analyses

Statistical analyses were also conducted using R version 3.3.2\textsuperscript{[143]}. A complete-case approach was used to handle missing data. All hypothesis testing was two-tailed. P-values less than 0.05 were considered to be statistically significant.

To compare antipsychotic monotherapy to polypharmacy, the \textit{coin} (v. 1.1-3) implementation of the Wilcoxon-Mann-Whitney test\textsuperscript{[151]} was used to quantify differences in age, antipsychotic utilization, and symptom severity between the two groups. The \textit{exact2x2} (v. 1.5.2) implementation of Boschloo’s test\textsuperscript{[152]} was used to identify associations between polypharmacy and sex, diagnosis, prior clozapine trial, and use of medications.
To characterize within-individual changes following hospitalization at the Program, the *coin* (v. 1.1-3) implementation of the Wilcoxon signed-rank test\[151\] was used to compare antipsychotic utilization and symptom severity at admission and discharge. The *coin* (v. 1.1-3) implementation of the Kruskal-Wallis test\[151\] was used when individuals were categorized according to patterns in treatment and the *Pairwise Multiple Comparison of Mean Ranks* (v.4.1) implementation of Dunn’s test (with Bonferroni adjustment)\[153\] was used for post-hoc analysis where necessary. A mid-p variant of the McNemar test\[154\] was used to examine marginal homogeneity between hospitalization at the Program and the use of antipsychotics.

To explore potential associations between the collected data and symptom severity at discharge, the *stats* package (v. 3.3.2)\[143\] was used to fit four linear regression models, one for each of the three subscales and one for the total PANSS score. Independent variables include demographic data (i.e., diagnosis; sex; age at admission; prior clozapine trial) and changes in the pattern (i.e., monotherapy; polypharmacy), extent (i.e., acceptable; excessive), and magnitude (i.e., PDD:DDD ratio) of antipsychotic utilization. Admission PANSS scores and changes in the prescribing patterns of clozapine, antidepressants, mood stabilizers, benzodiazepines, and anticholinergics were also included as independent variables in the model.

All figures were generated using *ggplot2* (v. 2.2.1)\[155\]. Tables containing estimates of regression coefficients were adapted from those created using *stargazer* (v. 5.2)\[156\].
Chapter 3: Results

3.1 Comparison of antipsychotic monotherapy and polypharmacy at admission

Data were collected from 330 patients, but three were not prescribed any antipsychotics at admission.

Of the remaining 327 individuals, 156 (47.7%) were on monotherapy and 171 (52.3%) were on polypharmacy at admission. The choice of antipsychotics was similar between groups (Table 1); in no particular order, clozapine, olanzapine, quetiapine, risperidone, and the typical antipsychotic loxapine were the five most commonly prescribed antipsychotics. Many of the drug combinations used in polypharmacy involved at least one atypical antipsychotic. The majority of individuals treated with two or more antipsychotics (102; 59.6%) were prescribed a combination of typical and atypical antipsychotics; 46 (26.9%) were treated exclusively with atypical antipsychotics and 23 (13.5%) were treated exclusively with typical antipsychotics.

There is little to suggest that the age at admission or the severity of symptoms were stochastically greater in one group than in the other (Table 2). Furthermore, no statistically significant associations were found between antipsychotic prescribing pattern and sex, diagnosis, or the use of drugs other than antipsychotics. Polypharmacy was associated with a prior clozapine trial (OR = 1.85, P = 0.006) and greater use of antipsychotics by class (typical antipsychotics, OR = 6.11, P < 0.001; atypical antipsychotics, OR = 2.86, P < 0.001) and by agent (i.e., olanzapine, OR = 2.39, P < 0.001; quetiapine, OR = 1.95, P = 0.015; risperidone, OR = 2.23, P = 0.002) at admission. In fact, antipsychotic utilization was significantly different between those who had been prescribed only one antipsychotic and those who had been prescribed two or more antipsychotics (Z = -8.00, P < 0.001). Polypharmacy was associated with excessive dosing (OR = 5.41; P < 0.001). Nonetheless, the use of clozapine was comparable between groups (OR = 1.58, P = 0.121) despite the prescribing of more antipsychotics in the polypharmacy group.
Table 1. Antipsychotics prescribed at admission

<table>
<thead>
<tr>
<th>Drug</th>
<th>Count</th>
<th>Percent</th>
<th>Drug</th>
<th>Count</th>
<th>Percent</th>
<th>Combination</th>
<th>Count</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy</td>
<td></td>
<td></td>
<td>Polypharmacy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 156)a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>olanzapine</td>
<td>27</td>
<td>17.3%</td>
<td>olanzapine</td>
<td>57</td>
<td>33.3%</td>
<td>clozapine, risperidone</td>
<td>13</td>
<td>7.6%</td>
</tr>
<tr>
<td>clozapine</td>
<td>26</td>
<td>16.7%</td>
<td>risperidone (po)</td>
<td>55</td>
<td>32.2%</td>
<td>clozapine, olanzapine</td>
<td>11</td>
<td>6.4%</td>
</tr>
<tr>
<td>quetiapine</td>
<td>26</td>
<td>16.7%</td>
<td>quetiapine</td>
<td>48</td>
<td>28.1%</td>
<td>clozapine, risperidone</td>
<td>11</td>
<td>6.4%</td>
</tr>
<tr>
<td>risperidone (po)</td>
<td>25</td>
<td>16.0%</td>
<td>loxapine</td>
<td>42</td>
<td>24.6%</td>
<td>olanzapine, quetiapine</td>
<td>11</td>
<td>6.4%</td>
</tr>
<tr>
<td>loxapine</td>
<td>13</td>
<td>8.3%</td>
<td>clozapine</td>
<td>41</td>
<td>24.0%</td>
<td>olanzapine, zuclopenthixol</td>
<td>11</td>
<td>6.4%</td>
</tr>
<tr>
<td>haloperidol (po)</td>
<td>7</td>
<td>4.5%</td>
<td>haloperidol (po)</td>
<td>20</td>
<td>11.7%</td>
<td>haloperidol, quetiapine</td>
<td>9</td>
<td>5.3%</td>
</tr>
<tr>
<td>zuclopenthixol (im)</td>
<td>5</td>
<td>3.2%</td>
<td>zuclopenthixol (im)</td>
<td>20</td>
<td>11.7%</td>
<td>loxapine, olanzapine</td>
<td>9</td>
<td>5.3%</td>
</tr>
<tr>
<td>haloperidol (im)</td>
<td>4</td>
<td>2.6%</td>
<td>chlorpromazine</td>
<td>15</td>
<td>8.8%</td>
<td>quetiapine, risperidone</td>
<td>9</td>
<td>5.3%</td>
</tr>
<tr>
<td>risperidone (im)</td>
<td>4</td>
<td>2.6%</td>
<td>methotrimeprazine</td>
<td>14</td>
<td>8.2%</td>
<td>olanzapine, risperidone</td>
<td>8</td>
<td>4.7%</td>
</tr>
<tr>
<td>chlorpromazine</td>
<td>3</td>
<td>1.9%</td>
<td>fluphenazine (im)</td>
<td>10</td>
<td>5.8%</td>
<td>clozapine, quetiapine</td>
<td>7</td>
<td>4.1%</td>
</tr>
<tr>
<td>fluphenazine (im)</td>
<td>3</td>
<td>1.9%</td>
<td>fluphenazine (im)</td>
<td>10</td>
<td>5.8%</td>
<td>loxapine, quetiapine</td>
<td>6</td>
<td>3.5%</td>
</tr>
<tr>
<td>zuclopenthixol (po)</td>
<td>3</td>
<td>1.9%</td>
<td>trifluoperazine</td>
<td>9</td>
<td>5.3%</td>
<td>flupenthixol, loxapine</td>
<td>5</td>
<td>2.9%</td>
</tr>
<tr>
<td>methotrimeprazine</td>
<td>2</td>
<td>1.3%</td>
<td>pipotiazine (im)</td>
<td>6</td>
<td>3.5%</td>
<td>fluphenazine, olanzapine</td>
<td>5</td>
<td>2.9%</td>
</tr>
<tr>
<td>pimozide</td>
<td>2</td>
<td>1.3%</td>
<td>flupenthixol (po)</td>
<td>5</td>
<td>2.9%</td>
<td>haloperidol, risperidone</td>
<td>5</td>
<td>2.9%</td>
</tr>
<tr>
<td>aripiprazole</td>
<td>1</td>
<td>0.6%</td>
<td>zuclopenthixol (po)</td>
<td>5</td>
<td>2.9%</td>
<td>loxapine, methotrimeprazine</td>
<td>5</td>
<td>2.9%</td>
</tr>
<tr>
<td>flupenthixol (im)</td>
<td>1</td>
<td>0.6%</td>
<td>pimozide</td>
<td>4</td>
<td>2.3%</td>
<td>loxapine, zuclopenthixol</td>
<td>5</td>
<td>2.9%</td>
</tr>
<tr>
<td>flupenthixol (po)</td>
<td>1</td>
<td>0.6%</td>
<td>aripiprazole</td>
<td>3</td>
<td>1.8%</td>
<td>methotrimeprazine, risperidone</td>
<td>5</td>
<td>2.9%</td>
</tr>
<tr>
<td>fluphenazine (po)</td>
<td>1</td>
<td>0.6%</td>
<td>fluphenazine (po)</td>
<td>3</td>
<td>1.8%</td>
<td>quetiapine, zuclopenthixol</td>
<td>5</td>
<td>2.9%</td>
</tr>
<tr>
<td>perphenazine</td>
<td>1</td>
<td>0.6%</td>
<td>haloperidol (im)</td>
<td>2</td>
<td>1.2%</td>
<td>chlorpromazine, risperidone</td>
<td>4</td>
<td>2.3%</td>
</tr>
<tr>
<td>pipotiazine (im)</td>
<td>1</td>
<td>0.6%</td>
<td>risperidone (im)</td>
<td>2</td>
<td>1.2%</td>
<td>clozapine, haloperidol</td>
<td>4</td>
<td>2.3%</td>
</tr>
<tr>
<td>thioridazine</td>
<td>1</td>
<td>0.6%</td>
<td>pericyazine</td>
<td>1</td>
<td>0.6%</td>
<td>clozapine, loxapide</td>
<td>4</td>
<td>2.3%</td>
</tr>
<tr>
<td>thiothixene</td>
<td>1</td>
<td>0.6%</td>
<td>perphenazine</td>
<td>1</td>
<td>0.6%</td>
<td>flupenthixol, risperidone</td>
<td>4</td>
<td>2.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>prochlorperazine</td>
<td>1</td>
<td>0.6%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ziprasidone</td>
<td>1</td>
<td>0.6%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

po, oral formulation; im, intramuscular (depot) formulation

a two individuals were prescribed two formulations (i.e., oral and intramuscular) of the same antipsychotic

b the remaining fifty combinations each had counts that were \( \leq 3 \)
Table 2. Comparison of antipsychotic monotherapy and polypharmacy at admission

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Monotherapy (n = 156 (47.7%))</th>
<th>Polypharmacy (n = 171 (52.3%))</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>92 (59.0%)</td>
<td>103 (60.2%)</td>
<td>0.816</td>
</tr>
<tr>
<td>Female</td>
<td>64 (41.0%)</td>
<td>68 (39.8%)</td>
<td></td>
</tr>
<tr>
<td>Age, median (Q1, Q3)</td>
<td>37 (25, 44)</td>
<td>36 (29, 44.5)</td>
<td>0.374</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>105 (67.3%)</td>
<td>122 (71.3%)</td>
<td>0.450</td>
</tr>
<tr>
<td>Schizoaffective Disorder</td>
<td>51 (32.7%)</td>
<td>49 (28.7%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antipsychotics</th>
<th>Monotherapy (n = 156 (47.7%))</th>
<th>Polypharmacy (n = 171 (52.3%))</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior Clozapine Trial</td>
<td>78 (50.0%)</td>
<td>111 (64.9%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Typical</td>
<td>48 (30.8%)</td>
<td>125 (73.1%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Atypical</td>
<td>108 (69.2%)</td>
<td>148 (86.5%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Clozapine</td>
<td>26 (16.7%)</td>
<td>41 (24.0%)</td>
<td>0.121</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>27 (17.3%)</td>
<td>57 (33.3%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>26 (16.7%)</td>
<td>48 (28.1%)</td>
<td>0.015</td>
</tr>
<tr>
<td>Risperidone(^a)</td>
<td>28 (17.9%)</td>
<td>56 (32.7%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Utilization, median (Q1, Q3)(^b)</td>
<td>1.25 (0.80, 2.00)</td>
<td>2.38 (1.55, 3.20)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Excessive dosing(^c)</td>
<td>57 (36.8%)</td>
<td>129 (75.9%)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other Drugs</th>
<th>Monotherapy (n = 156 (47.7%))</th>
<th>Polypharmacy (n = 171 (52.3%))</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergics</td>
<td>26 (16.7%)</td>
<td>40 (23.4%)</td>
<td>0.155</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>33 (21.2%)</td>
<td>37 (21.6%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>55 (35.3%)</td>
<td>52 (30.4%)</td>
<td>0.388</td>
</tr>
<tr>
<td>Mood Stabilizers</td>
<td>53 (34.0%)</td>
<td>71 (41.5%)</td>
<td>0.161</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptom Severity (PANSS ratings)</th>
<th>Monotherapy (n = 156 (47.7%))</th>
<th>Polypharmacy (n = 171 (52.3%))</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive Scale, median (Q1, Q3)</td>
<td>25 (21, 29)</td>
<td>25 (22, 30)</td>
<td>0.140</td>
</tr>
<tr>
<td>Negative Scale, median (Q1, Q3)</td>
<td>26 (21, 29.25)</td>
<td>25 (21.5, 28)</td>
<td>0.416</td>
</tr>
<tr>
<td>General Psychopathology Scale, median (Q1, Q3)</td>
<td>47 (40, 53)</td>
<td>47 (42, 52)</td>
<td>0.728</td>
</tr>
<tr>
<td>Total, median (Q1, Q3)</td>
<td>97.50 (83.75, 110.25)</td>
<td>98 (87, 109)</td>
<td>0.678</td>
</tr>
</tbody>
</table>

PANSS, positive and negative syndrome scale
\(^a\) oral and intramuscular (depot) formulations of risperidone were combined  
\(^b\) two individuals were excluded because data on antipsychotic doses were missing; utilization was calculated using the defined daily dose method  
\(^c\) n = 155 in the monotherapy group; n = 170 in the polypharmacy group (see b); excessive dosing was defined as utilization greater than 1.5
3.2 Comparison of antipsychotic monotherapy and polypharmacy at discharge

Of the 328 patients who were prescribed antipsychotics at discharge, 273 (83.2%) were prescribed one antipsychotic and the remaining 55 (16.8%) were prescribed two antipsychotics. Clozapine was the most frequently prescribed antipsychotic in both groups, but risperidone was also commonly prescribed in the polypharmacy group (Table 3). Most individuals in the polypharmacy group (42, 76.4%) were treated exclusively with atypical antipsychotics, with the combination of clozapine and risperidone being most prevalent (49.1%). Only 12 (21.8%) were treated with a combination of atypical and typical antipsychotics. One person (1.8%) was treated exclusively with typical antipsychotics.

Again, the only differences observed between the two groups at discharge were restricted to the use of antipsychotics. Polypharmacy was associated with a prior clozapine trial (OR = 2.22, P = 0.014) and greater use of antipsychotics by class (i.e., typical antipsychotics, OR = 2.25, P = 0.028; atypical antipsychotics, OR = 7.43, P = 0.023). However, when antipsychotics were no longer grouped according to their propensity for extrapyramidal symptoms, polypharmacy was only found to be associated with the use of risperidone (OR = 19.66, P < 0.001). Antipsychotic utilization was different between the two groups (Z = -7.21, P < 0.001). Once again, polypharmacy was significantly associated with excessive dosing (OR = 7.83, P < 0.001).
Table 3. Antipsychotics prescribed at discharge

<table>
<thead>
<tr>
<th>Drug</th>
<th>Count</th>
<th>Percent</th>
<th>Drug</th>
<th>Count</th>
<th>Percent</th>
<th>Combination</th>
<th>Count</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy (n = 273)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>165</td>
<td>60.4%</td>
<td>Clozapine</td>
<td>39</td>
<td>70.9%</td>
<td>Clozapine, risperidone</td>
<td>27</td>
<td>49.1%</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>29</td>
<td>10.6%</td>
<td>Risperidone (po)</td>
<td>33</td>
<td>60.0%</td>
<td>Clozapine, sulpiride</td>
<td>7</td>
<td>12.7%</td>
</tr>
<tr>
<td>Risperidone (po)</td>
<td>18</td>
<td>6.6%</td>
<td>Sulpiride</td>
<td>7</td>
<td>12.7%</td>
<td>Quetiapine, risperidone</td>
<td>3</td>
<td>5.5%</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>14</td>
<td>5.1%</td>
<td>Loxapine</td>
<td>6</td>
<td>10.9%</td>
<td>Olanzapine, risperidone</td>
<td>2</td>
<td>3.6%</td>
</tr>
<tr>
<td>Zuclopenthixol (im)</td>
<td>7</td>
<td>2.6%</td>
<td>Olanzapine</td>
<td>5</td>
<td>9.1%</td>
<td>Amisulpride, clozapine</td>
<td>1</td>
<td>1.8%</td>
</tr>
<tr>
<td>Risperidone (im)</td>
<td>6</td>
<td>2.2%</td>
<td>Quetiapine</td>
<td>5</td>
<td>9.1%</td>
<td>Amisulpride, olanzapine</td>
<td>1</td>
<td>1.8%</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>5</td>
<td>1.8%</td>
<td>Haloperidol (po)</td>
<td>3</td>
<td>5.5%</td>
<td>Aripiprazole, quetiapine</td>
<td>1</td>
<td>1.8%</td>
</tr>
<tr>
<td>Flupenthixol (im)</td>
<td>5</td>
<td>1.8%</td>
<td>Risperidone (im)</td>
<td>3</td>
<td>5.5%</td>
<td>Chlorpromazine, clozapine</td>
<td>1</td>
<td>1.8%</td>
</tr>
<tr>
<td>Loxapine</td>
<td>5</td>
<td>1.8%</td>
<td>Amisulpride</td>
<td>2</td>
<td>3.6%</td>
<td>Clozapine, loxapine</td>
<td>1</td>
<td>1.8%</td>
</tr>
<tr>
<td>Fluphenazine (im)</td>
<td>4</td>
<td>1.5%</td>
<td>Aripiprazole</td>
<td>1</td>
<td>1.8%</td>
<td>Clozapine, pipotiazine</td>
<td>1</td>
<td>1.8%</td>
</tr>
<tr>
<td>Pimozide</td>
<td>3</td>
<td>1.1%</td>
<td>Chlorpromazine</td>
<td>1</td>
<td>1.8%</td>
<td>Clozapine, zuclopenthixol</td>
<td>1</td>
<td>1.8%</td>
</tr>
<tr>
<td>Zuclopenthixol (po)</td>
<td>3</td>
<td>1.1%</td>
<td>Methotrimeprazine</td>
<td>1</td>
<td>1.8%</td>
<td>Haloperidol, loxapine</td>
<td>1</td>
<td>1.8%</td>
</tr>
<tr>
<td>Flupenthixol (po)</td>
<td>2</td>
<td>0.7%</td>
<td>Pipotiazine (im)</td>
<td>1</td>
<td>1.8%</td>
<td>Haloperidol, olanzapine</td>
<td>1</td>
<td>1.8%</td>
</tr>
<tr>
<td>Sulpiride</td>
<td>2</td>
<td>0.7%</td>
<td>Trifluoperazine</td>
<td>1</td>
<td>1.8%</td>
<td>Haloperidol, risperidone</td>
<td>1</td>
<td>1.8%</td>
</tr>
<tr>
<td>Amisulpride</td>
<td>1</td>
<td>0.4%</td>
<td>Ziprasidone</td>
<td>1</td>
<td>1.8%</td>
<td>Loxapine, olanzapine</td>
<td>1</td>
<td>1.8%</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>1</td>
<td>0.4%</td>
<td>Zuclopenthixol (po)</td>
<td>1</td>
<td>1.8%</td>
<td>Loxapine, quetiapine</td>
<td>1</td>
<td>1.8%</td>
</tr>
<tr>
<td>Fluphenazine (po)</td>
<td>1</td>
<td>0.4%</td>
<td>Loxapine, risperidone</td>
<td>1</td>
<td>1.8%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol (po)</td>
<td>1</td>
<td>0.4%</td>
<td>Loxapine, ziprasidone</td>
<td>1</td>
<td>1.8%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiothixene</td>
<td>1</td>
<td>0.4%</td>
<td>Methotrimeprazine</td>
<td>1</td>
<td>1.8%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>1</td>
<td>0.4%</td>
<td>Risperidone, trifluoperazine</td>
<td>1</td>
<td>1.8%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Discharge (n = 328)

Polypharmacy (n = 55)

po, oral formulation; im, intramuscular (depot) formulation

*one individual was prescribed two formulations (i.e., oral and intramuscular) of the same antipsychotic
Table 4. Comparison of antipsychotic monotherapy and polypharmacy at discharge

<table>
<thead>
<tr>
<th></th>
<th>Discharge (n = 328)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Monotherapy</td>
<td>Polypharmacy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 273 (83.2%)</td>
<td>n = 55 (16.8%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>% of Group</td>
<td>% of Group</td>
<td>P-value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>163</td>
<td>32</td>
<td>59.7%</td>
<td>58.2%</td>
<td>0.875</td>
</tr>
<tr>
<td>Female</td>
<td>110</td>
<td>23</td>
<td>40.3%</td>
<td>41.8%</td>
<td></td>
</tr>
<tr>
<td>Age, median (Q1, Q3)</td>
<td>36 (27, 45)</td>
<td>38 (30.0, 42.5)</td>
<td>-</td>
<td>-</td>
<td>0.555</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>188</td>
<td>40</td>
<td>68.9%</td>
<td>72.7%</td>
<td>0.611</td>
</tr>
<tr>
<td>Schizoaffective Disorder</td>
<td>85</td>
<td>15</td>
<td>31.1%</td>
<td>27.3%</td>
<td></td>
</tr>
<tr>
<td>Antipsychotics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior Clozapine Trial</td>
<td>149</td>
<td>40</td>
<td>54.6%</td>
<td>72.7%</td>
<td>0.014</td>
</tr>
<tr>
<td>Typical</td>
<td>33</td>
<td>13</td>
<td>12.1%</td>
<td>23.6%</td>
<td>0.028</td>
</tr>
<tr>
<td>Atypical</td>
<td>240</td>
<td>54</td>
<td>87.9%</td>
<td>98.2%</td>
<td>0.023</td>
</tr>
<tr>
<td>Clozapine</td>
<td>165</td>
<td>39</td>
<td>60.4%</td>
<td>70.9%</td>
<td>0.156</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>29</td>
<td>5</td>
<td>10.6%</td>
<td>9.1%</td>
<td>1.000</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>14</td>
<td>5</td>
<td>5.1%</td>
<td>9.1%</td>
<td>0.314</td>
</tr>
<tr>
<td>Risperidone</td>
<td>24</td>
<td>36</td>
<td>8.8%</td>
<td>65.5%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Utilization, median (Q1, Q3)</td>
<td>1.33 (1.00, 1.85)</td>
<td>2.27 (1.70, 2.78)</td>
<td>-</td>
<td>-</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Excessive dosing</td>
<td>107</td>
<td>46</td>
<td>39.5%</td>
<td>83.6%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Other Drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>15</td>
<td>2</td>
<td>5.5%</td>
<td>3.6%</td>
<td>0.729</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>46</td>
<td>11</td>
<td>16.8%</td>
<td>20.0%</td>
<td>0.556</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>25</td>
<td>9</td>
<td>9.2%</td>
<td>16.4%</td>
<td>0.136</td>
</tr>
<tr>
<td>Mood Stabilizers</td>
<td>78</td>
<td>15</td>
<td>28.6%</td>
<td>27.3%</td>
<td>1.000</td>
</tr>
<tr>
<td>Symptom Severity (PANSS ratings)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive Scale, median (Q1, Q3)</td>
<td>18 (15, 21)</td>
<td>20 (16, 23)</td>
<td>-</td>
<td>0.062</td>
<td></td>
</tr>
<tr>
<td>Negative Scale, median (Q1, Q3)</td>
<td>22 (18, 25)</td>
<td>22 (19, 27)</td>
<td>-</td>
<td>0.540</td>
<td></td>
</tr>
<tr>
<td>General Psychopathology Scale, median (Q1, Q3)</td>
<td>40 (34, 46)</td>
<td>39 (36, 47)</td>
<td>-</td>
<td>0.730</td>
<td></td>
</tr>
<tr>
<td>Total, median (Q1, Q3)</td>
<td>80 (68, 91)</td>
<td>80 (71.5, 92.5)</td>
<td>-</td>
<td>0.408</td>
<td></td>
</tr>
</tbody>
</table>

PANSS, positive and negative syndrome scale

\( ^a \) oral and intramuscular (depot) formulations of risperidone were combined

\( ^b \) two individuals were excluded because data on antipsychotic doses were missing; utilization was calculated using the defined daily dose method

\( ^c \) n = 271 in the monotherapy group (see b); excessive dosing was defined as utilization greater than 1.5
3.3 Within-individual change in antipsychotic prescribing patterns

Most individuals who were prescribed at least two antipsychotics at admission were prescribed only one antipsychotic at discharge (Fig. 1). Even among those who were on polypharmacy at admission and discharge, seven individuals saw a reduction in the number of antipsychotics prescribed (Fig. 2). Although there were individuals that were switched from monotherapy to polypharmacy over the course of hospitalization, most individuals remained on monotherapy at the time of discharge. Moreover, the increase in the number of antipsychotics was limited to one since no individuals were prescribed more than two antipsychotics at discharge.

Fig. 1. Within-individual change in antipsychotic prescribing pattern
Each individual who was prescribed at least one antipsychotic at admission and discharge (n = 325) is represented by a line.
Of the 325 patients who were prescribed antipsychotics at admission and discharge, 139 (42.8%) were on polypharmacy at admission and monotherapy at discharge, and 25 (7.7%) were on monotherapy at admission and polypharmacy at discharge (Table 5). Based on these discordant pairs, there is evidence against a lack of association between hospitalization and antipsychotic prescribing patterns ($\chi^2 = 79.24$, df = 1, mid-p < 0.001). A switch from polypharmacy to monotherapy over the course of hospitalization was more likely than a switch from monotherapy to polypharmacy.
Table 5. Contingency table for antipsychotic prescribing patterns at admission and discharge

<table>
<thead>
<tr>
<th>Discharge</th>
<th>Monotherapy</th>
<th>Polypharmacy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission</td>
<td>131</td>
<td>25</td>
<td>156</td>
</tr>
<tr>
<td>Polypharmacy</td>
<td>139</td>
<td>30</td>
<td>169</td>
</tr>
<tr>
<td>Total</td>
<td>270</td>
<td>55</td>
<td>325</td>
</tr>
</tbody>
</table>

When the individuals were grouped according to their use of clozapine at the two time points, the change in the number of antipsychotics was similar between groups ($\chi^2 = 0.75, \text{df} = 3, P = 0.863$; Fig. 3).

![Fig. 3. Number of antipsychotics prescribed at admission and discharge by clozapine prescribing pattern]

Each individual who was prescribed at least one antipsychotic at admission and discharge ($n = 325$) is represented by a point. Points that are clustered around the line represent individuals who were prescribed the same number of antipsychotics at admission and discharge. Those found above the line had more antipsychotics at discharge. Those found below the line had fewer antipsychotics at discharge. Groups are composed of individuals with similar patterns in their use of clozapine.

In contrast, when the 321 individuals who had data on antipsychotic doses were grouped as having received either an excessive or acceptable amount of antipsychotics at admission and
discharge, at least two groups were found to differ ($\chi^2 = 42.78$, df = 3, $P < 0.001$) (Fig. 4). Those who switched from excessive to acceptable utilization were found to differ from all three groups (compared to those who: switched from acceptable to excessive utilization, $P < 0.001$; remained on acceptable utilization, $P < 0.001$; remained on excessive utilization, $P = 0.018$). The only other difference was between those who remained on excessive utilization and those who switched from acceptable to excessive utilization ($P = 0.011$) (Fig. 5).

Fig. 4. Number of antipsychotics prescribed at admission and discharge by extent of utilization
Each individual who had data on antipsychotic utilization at admission and discharge ($n = 321$) is represented by a point. Points that are clustered around the line represent individuals who were prescribed the same number of antipsychotics at admission and discharge. Those found above the line had more antipsychotics at discharge. Those found below the line had fewer antipsychotics at discharge. Groups are composed of individuals with similar patterns in antipsychotic utilization. Utilization was quantified using the defined daily dose method. Excessive dosing is defined as utilization greater than 1.5.
3.4 Within-individual change in antipsychotic utilization

The distribution of the within-individual change in antipsychotic utilization is unlikely to be symmetric about 0 ($Z = 5.05, P < 0.001$) (Figs. 6, 7). Of the 321 individuals who had data on antipsychotic dosing at admission and discharge, the median within-individual change was found to be -0.2 (interquartile range, -1.167 to 0.367). Therefore, in addition to the decrease in the
number of antipsychotics prescribed (see section 3.3), a decrease in utilization was also observed in most individuals.

**Fig. 6. Within-individual change in antipsychotic utilization**
Each individual who had data on antipsychotic utilization at admission and discharge (n = 321) is represented by a line. Boxplots depict distribution of antipsychotic utilization at their respective time points. Median utilization at admission was 1.8 (interquartile range: 1.075 to 2.750). Median utilization at discharge was 1.5 (interquartile range: 1.0 to 2.0). Utilization was determined using the defined daily dose method.
Fig. 7. Antipsychotic utilization at admission and discharge
Each individual who had data on antipsychotic utilization at admission and discharge (n = 321) is represented by a point. Antipsychotic utilization was the same at admission and discharge for individuals falling on the line. Those found above the line had higher antipsychotic utilization at discharge. Those found below the line had lower antipsychotic utilization at discharge. Utilization was determined using the defined daily dose method.

However, a difference in the direction of change in antipsychotic utilization was observed when the 321 individuals who had data on antipsychotic utilization at admission and discharge were grouped according to the extent of utilization at admission (Fig. 8). Of the 183 individuals (57.0%) whose utilization at admission was deemed excessive, the median within-individual difference was found to be -1.0 (interquartile range: -1.750 to -0.296). Of the 138 individuals (43.0%) whose utilization was deemed to be acceptable at admission, the median within-individual difference was found to be 0.333 (interquartile range: 0.000 to 0.829). The distribution of these within-individual changes was not symmetric about 0 in both cases (P < 0.001).
Consequently, the decrease in antipsychotic utilization observed across most individuals can be largely attributed to the contributions of those receiving excessive doses at admission.

![Fig. 8. Within-individual change in antipsychotic utilization by extent of utilization at admission](image)

Each individual who had data on antipsychotic utilization at admission and discharge (n = 321) is represented by a line. Boxplots depict distribution of antipsychotic utilization at their respective time points. For individuals with acceptable dosing at admission (n = 138), the median utilization was 1.0 (interquartile range: 0.73 to 1.25) at admission and 1.33 (interquartile range: 1.00 to 1.875) at discharge. For individuals with excessive dosing at admission (n = 183), the median utilization was 2.5 (interquartile range: 2.00 to 3.275) at admission and 1.67 (interquartile range: 1.0 to 2.0) at discharge. The horizontal line corresponding to an antipsychotic utilization of 1.5 represents the threshold for excessive antipsychotic utilization.

Differences in the change in antipsychotic utilization also exist when individuals are grouped by the extent of utilization at admission and discharge ($\chi^2 = 200.91$, df = 3, P < 0.001) (Fig. 9). All pairwise comparisons were found to be statistically significant (P < 0.001) (Fig. 10).
Fig. 9. Within-individual change in antipsychotic utilization by extent of utilization

Each individual who had data on antipsychotic utilization at admission and discharge (n = 321) is represented by a line. Boxplots depict distribution of antipsychotic utilization at their respective time points. For individuals switching from acceptable to excessive utilization (n = 56), the median utilization was 1.06 (interquartile range: 0.79 to 1.30) at admission and 2.00 (interquartile range: 1.75 to 2.26) at discharge. For individuals switching from excessive to acceptable utilization (n = 86), antipsychotic utilization was 2.45 (interquartile range: 2.00 to 3.04) at admission and 1.00 (interquartile range: 0.75 to 1.33) at discharge. For individuals who were prescribed an acceptable amount of antipsychotics at both time points (n = 82), the median utilization was 0.96 (interquartile range: 0.67 to 1.25) at admission and 1.00 (0.75 to 1.25) at discharge. For individuals who were prescribed an excessive amount of antipsychotics at both time points (n = 97), the median utilization was 2.63 (interquartile range: 2.07 to 3.50) at admission and 2.00 (interquartile range: 1.83 to 2.67) at discharge. Utilization was determined using the defined daily dose method and was judged to be excessive when greater than 1.5 (as indicated by the horizontal line).
Fig. 10. Comparison of within-individual change in antipsychotic utilization by extent of utilization
Each individual who had data on antipsychotic utilization at admission and discharge (n = 321) is represented by a point and grouped according to the pattern of antipsychotic utilization. Boxplots depict the distribution of this change. For individuals switching from excessive to acceptable utilization (n = 86), the median change in utilization was -1.47 (interquartile range: -2.13 to -0.93). For individuals with excessive utilization at admission and discharge (n = 97), the median change in utilization was -0.42 (interquartile range: -1.33 to 0.00). For individuals with acceptable utilization at admission and discharge (n = 82), the median change in utilization was 0.06 (interquartile range: -0.17 to 0.27). For individuals switching from acceptable to excessive utilization (n = 56), the median change in utilization was 1.04 (interquartile range: 0.67 to 1.60). Utilization was determined using the defined daily dose method. Values exceeding 1.5 were considered to be excessive.
When the individuals were grouped according to antipsychotic prescribing pattern at admission and discharge, a significant difference emerged ($\chi^2 = 54.13$, df $= 3$, $P < 0.001$) (Fig. 11). Individuals who were switched from monotherapy to polypharmacy were significantly different from those who switched from polypharmacy to monotherapy ($P < 0.001$) and those who remained on polypharmacy ($P < 0.001$), but not those who remained on monotherapy ($P = 0.055$). The only other pairwise comparison that resulted in a statistically significant difference was between those who switched from polypharmacy to monotherapy and those who remained on monotherapy ($P < 0.001$) (Fig. 12).
Fig. 11. Within-individual change in antipsychotic utilization by antipsychotic prescribing pattern

Each individual who had data on antipsychotic utilization at admission and discharge (n = 321) is represented by a line. Boxplots depict distribution of antipsychotic utilization at their respective time points. For individuals switching from monotherapy to polypharmacy (n = 25), the median utilization was 1.33 (interquartile range: 1.0 to 2.0) at admission and 2.23 (interquartile range: 1.667 to 2.767) at discharge. For individuals switching from polypharmacy to monotherapy (n = 136), the median utilization was 2.29 at admission (interquartile range: 1.49 to 3.05) and 1.33 (interquartile range: 1.0 to 2.0) at discharge. For individuals who remained on monotherapy (n = 130), the median utilization was 1.25 (interquartile range: 0.75 to 2.00) at admission and 1.33 (interquartile range: 1.00 to 1.83) at discharge. For individuals who remained on polypharmacy (n = 30), the median utilization was 2.78 (interquartile range: 2.19 to 3.68) at admission and 2.31 (interquartile range: 1.76 to 2.79) at discharge. Utilization was determined using the daily dose method.
Fig. 12. Comparison of within-individual change in antipsychotic utilization by antipsychotic prescribing pattern

Each individual who had data on antipsychotic utilization at admission and discharge (n = 321) is represented by a point and grouped according to the prescribing pattern. Boxplots depict the distribution of this change. For individuals switching from polypharmacy to monotherapy (n = 136), the median change in utilization was -0.85 (interquartile range: -1.61 to -0.17). For individuals who remained on polypharmacy (n = 30), the median change in utilization was -0.48 (interquartile range: -1.45 to 0.17). For individuals who remained on monotherapy (n = 130), the median change in utilization was 0.00 (interquartile range: -0.43 to 0.50). For individuals switching from monotherapy to polypharmacy (n = 25), the median change in utilization was 0.80 (interquartile range: 0.15 to 1.43). Utilization was determined using the defined daily dose method.

But as was the case with the change in the number of antipsychotics prescribed, change in antipsychotic utilization did not vary significantly with clozapine prescribing patterns (Fig. 13).
Each individual who had data on antipsychotic utilization at admission and discharge (n = 321) is represented by a line. Boxplots depict distribution of antipsychotic utilization at their respective time points. For individuals prescribed clozapine only at admission (n = 9), the median utilization was 1.02 (interquartile range: 0.50 to 1.42) at admission and 1.25 (interquartile range: 0.75 to 1.75) at discharge. For individuals prescribed clozapine only at discharge (n = 144), the median utilization was 1.81 (interquartile range: 1.20 to 2.85) at admission and 1.41 (interquartile range: 1.00 to 1.95) at discharge. For individuals prescribed clozapine at both time points, the median utilization was 1.96 (interquartile range: 1.17 to 2.53) at admission and 1.67 (interquartile range: 1.33 to 2.02) at discharge. For individuals who were not prescribed clozapine at either time point (n = 112), the median utilization was 1.81 (interquartile range: 0.96 to 2.78) at admission and 1.37 (interquartile range: 0.99 to 2.00) at discharge. Utilization was determined using the daily dose method.
3.5 Within-individual change in clozapine treatment

Of the 325 individuals who were prescribed antipsychotics at admission and discharge, 10 (3.1%) were prescribed clozapine at admission but not at discharge, and 145 (44.6%) were prescribed clozapine at discharge but not at admission (Table 6). Based on these discordant pairs, there is minimal support for a lack of association between hospitalization and clozapine prescribing practices ($\chi^2 = 117.58, \text{df} = 1, \text{mid-p} < 0.001$). The difference in magnitude suggests that the clinicians at the Program favored the use of clozapine in managing treatment-resistant psychosis.

Table 6. Contingency table for clozapine treatment at admission and discharge

<table>
<thead>
<tr>
<th></th>
<th>Discharge</th>
<th></th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Clozapine</td>
<td>Clozapine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Clozapine</td>
<td>113</td>
<td>145</td>
<td></td>
<td>258</td>
</tr>
<tr>
<td>Clozapine</td>
<td>10</td>
<td>57</td>
<td></td>
<td>67</td>
</tr>
<tr>
<td>Total</td>
<td>123</td>
<td>202</td>
<td></td>
<td>325</td>
</tr>
</tbody>
</table>

3.6 Within-individual change in clozapine utilization

Admission and discharge doses of clozapine were available for 56 of the 57 individuals who were prescribed clozapine at both time points. The change in dose was unlikely to be symmetric about 0 ($Z = -3.83, P < 0.001$) (Figs. 14, 15). The median within-individual difference in the prescribed daily dose was 100 mg (interquartile range, 0 to 231.25 mg), indicating an increase in the prescribed daily dose from admission for most individuals.
Fig. 14. Within-individual change in clozapine utilization
Each individual who had data on clozapine utilization at admission and discharge (n = 56) is represented by a line. Boxplots depict distribution of clozapine doses at their respective time points. The median dose was 350 mg (interquartile range: 250 mg to 500 mg) at admission and 500 mg (interquartile range: 400 mg to 575 mg) at discharge. The defined daily dose of clozapine is 300 mg.
Fig. 15. Clozapine utilization at admission and discharge
Each individual who had data on clozapine utilization at admission and discharge (n = 56) is represented by a point. Clozapine utilization was the same at admission and discharge for individuals falling on the line. Those found above the line had higher doses at discharge. Those found below the line had lower doses at discharge. The defined daily dose of clozapine is 300 mg.

3.7 Within-individual change in symptom severity

The median within-individual differences was -5 (interquartile range: -10 to -2) on the positive scale, -3 (interquartile range: -6 to 0) on the negative scale, -7 (interquartile range: -13 to -1) on the general psychopathology scale and -16 (interquartile range: -27 to -6) in terms of the total PANSS score. Since none of the distributions of the within-individual differences were likely to be symmetric about 0 (Figs. 16-19) (P < 0.001), most individuals had lower ratings of symptom
severity at discharge. A relative reduction in total PANSS scores exceeding 20% was observed in 191 individuals (57.9%).

Fig. 16. Within-individual change in positive symptoms
Each individual who was assessed using the Positive and Negative Syndrome Scale (n = 330) is represented by a line. Higher scores reflect greater symptom severity. Boxplots depict distribution of ratings at their respective time points. The median rating was 25 (interquartile range: 21 to 29) at admission and 18 (interquartile range: 15 to 22) at discharge.
Fig. 17. Within-individual change in negative symptoms
Each individual who was assessed using the Positive and Negative Syndrome Scale (n = 330) is represented by a line. Higher scores reflect greater symptom severity. Boxplots depict distribution of ratings at their respective time points. The median rating was 25 (interquartile range: 21 to 29) at admission and 22 (interquartile range: 18 to 25) at discharge.
Fig. 18. Within-individual change in general psychopathology
Each individual who was assessed using the Positive and Negative Syndrome Scale (n = 330) is represented by a line. Higher scores reflect greater symptom severity. Boxplots depict distribution of ratings at their respective time points. The median rating was 47 (interquartile range: 41 to 53) at admission and 40 (interquartile range: 34 to 46) at discharge.
Fig. 19. Within-individual change in total symptomatology
Each individual who was assessed using the Positive and Negative Syndrome Scale (PANSS; n = 330) is represented by a line. Higher scores reflect greater symptom severity. Boxplots depict distribution of ratings at their respective time points. The median rating was 98 (interquartile range: 85 to 110) at admission and 80 (interquartile range: 68 to 91) at discharge.
3.8 Predictor variables associated with symptom severity at discharge

Estimates of the regression coefficients derived from fitting multiple linear models are presented below (Table 7). Owing to the exploratory nature of this analysis, the P-values associated with each of the regression coefficients were used to identify potential associations rather than to establish statistical significance through hypothesis testing.

Based on the estimated regression coefficients for admission PANSS scores, individuals who had more severe symptoms at admission would tend to have more severe symptoms at discharge. But with all else being equal, the absolute change in symptom severity would also be greater in individuals with more severe symptoms at admission, resulting in a similar degree of improvement if relative change were considered instead. Since these baseline scores were included as independent variables in their respective models, the other regression coefficients can be interpreted as the extent of improvement (or worsening) associated with changing each variable while holding all others constant. A positive coefficient would indicate lesser improvement (or greater worsening) in symptoms.

Consequently, even though most individuals exhibited less severe symptoms by the time of discharge (see section 3.7), the extent of improvement across all symptom domains appears to be lower in individuals diagnosed with schizophrenia than in those with schizoaffective disorder. The change in negative symptoms also appears to be lower in males and in individuals who have tried clozapine prior to admission. Improvement in general psychopathology and overall symptomatology also appear to decline with age.

In terms of antipsychotics, individuals who were prescribed clozapine at discharge showed greater improvement in positive symptoms. Conversely, those who were on polypharmacy at discharge showed less improvement in positive symptoms. Despite this, polypharmacy at admission and discharge may be associated with greater improvement in general psychopathology and overall symptomatology. However, excessive utilization at discharge is likely associated with lesser improvement in general psychopathology.
No associations were found in relation to the use of mood stabilizers or anticholinergics. Antidepressant use at discharge was associated with less improvement across all symptom domains. Benzodiazepine use at both admission and discharge was associated with less improvement across all domains aside from negative symptoms.
Table 7. Estimated regression coefficients for predictors of symptom severity at discharge

<table>
<thead>
<tr>
<th>Change in</th>
<th>Positive Symptoms</th>
<th>Negative Symptoms</th>
<th>General Psychopathology</th>
<th>Total PANSS Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>6.184***</td>
<td>4.071***</td>
<td>8.329***</td>
<td>13.862***</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td><strong>1.669</strong></td>
<td><strong>2.085</strong>*</td>
<td><strong>3.715</strong>*</td>
<td><strong>7.522</strong>*</td>
</tr>
<tr>
<td>Female</td>
<td>-0.703</td>
<td>-1.077**</td>
<td>-0.315</td>
<td>-2.508</td>
</tr>
<tr>
<td>Age</td>
<td>0.043</td>
<td>0.014</td>
<td><strong>0.084</strong></td>
<td><strong>0.140</strong></td>
</tr>
<tr>
<td>Prior clozapine trial</td>
<td>0.444</td>
<td><strong>1.091</strong></td>
<td>1.623</td>
<td>2.707</td>
</tr>
<tr>
<td>Change in antipsychotic utilization</td>
<td>-0.142</td>
<td>-0.177</td>
<td>-0.378</td>
<td>-0.653</td>
</tr>
</tbody>
</table>

**Clozapine**
- Admission: -0.019, 0.408, 0.632, 1.335
- Discharge: -1.375**, -0.653, -0.772, -3.025
- Admission and Discharge: -1.359, -0.695, -0.772, -3.793

**Polypharmacy**
- Admission: -0.113, -0.262, -0.413, -1.040
- Discharge: 2.752**, 0.529, 1.682, 5.003
- Admission and Discharge: -1.855, -1.284, -3.360*, -6.504*

**Excessive utilization**
- Admission: -0.467, 0.715, -0.022, 0.157
- Discharge: 0.729, 1.364, 3.198**, 4.621
- Admission and Discharge: 1.316, 0.983, 1.525, 3.556

**Antidepressants**
- Admission: 0.901, 0.804, 1.732, 3.423
- Discharge: **2.216***, **2.580***, **5.704***, **10.742***
- Admission and Discharge: -0.498, 0.510, 2.243, 2.733

**Mood stabilizers**
- Admission: -0.693, -0.634, -1.285, -2.985
- Discharge: 1.114, -0.077, 1.099, 1.566
- Admission and Discharge: 0.457, -0.329, 1.456, 1.395

**Benzodiazepines**
- Admission: 0.037, -0.166, 0.047, -0.128
- Discharge: 1.384, -1.611, 0.361, -0.067
- Admission and Discharge: **3.245***, 0.398, **5.501***, **8.893***

**Anticholinergics**
- Admission: 0.493, 0.469, 0.088, 1.180
- Discharge: -0.219, 1.005, -1.933, -1.460
- Admission and Discharge: 1.078, -0.085, -4.959, -4.857

**Admission PANSS**
- Intercept: **0.394***, **0.610***, **0.510***, **0.564***
- R²: 0.299, 0.526, 0.394, 0.432
- Adjusted R²: 0.234, 0.483, 0.338, 0.379
- Residual standard error (df = 293): 4.993, 4.333, 7.547, 14.521
- F statistic (df = 27, 293): **4.630***, **12.065***, **7.064***, **8.243***

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

Data from 321 individuals were included in each of the four models.
Those who were missing data on antipsychotic utilization or those who were not prescribed antipsychotics at either admission or discharge were excluded.

*The admission PANSS score used as the independent variable is determined by the dependent variable of interest (i.e., admission PANSS scores on the positive scale were used when the dependent variable was positive symptoms at discharge)*
Chapter 4: Discussion

4.1 Between-group differences at admission and discharge

Aside from the expected differences related to the use of antipsychotics, individuals who were prescribed only one antipsychotic closely resembled those who were prescribed at least two antipsychotics at admission to the Program. The two groups were not found to differ in terms of age, sex, diagnosis, symptom severity, or the use of other psychotropic medications. But contrary to what has been reported in previous studies[134-136], including one that had excluded individuals who were prescribed typical antipsychotics[157], no association was found between antipsychotic polypharmacy and the use of anticholinergic drugs in this study. Thus, in spite of the tendency toward excessive antipsychotic utilization in those treated with at least two antipsychotics, the prevalence of extrapyramidal symptoms were presumably similar in both groups and did not merit a difference in the use of anticholinergics. Although this may seem unlikely given the relationship between dose and dopamine D$_2$ receptor occupancy, it is possible that the prophylactic use of anticholinergics was uncommon among those who were prescribed at least two antipsychotics at the time of admission. Another explanation is that the anticholinergics were prescribed as pro re nata medications and were therefore excluded from the analysis.

These possibilities notwithstanding, the lack of association between antipsychotic polypharmacy and anticholinergic drug use is perplexing given the method used to compare antipsychotic utilization between the two groups. In a retrospective chart review, Barr et al.[158] reported that the use of chlorpromazine equivalents was better able to distinguish two groups of individuals based on their use of anticholinergic drugs. If the chlorpromazine equivalent method is more sensitive to differences in antipsychotic utilization, then a similar, if not greater, difference is likely to be observed between the two groups in the current study if this method were used instead. Since individuals who were prescribed anticholinergics exhibited a greater degree of antipsychotic utilization than those who did not in the study conducted by Barr et al.[158], the polypharmacy group in this study should be prescribed more anticholinergics on account of the already existing difference in antipsychotic utilization. Nonetheless, this conjecture assumes a
direction of causality that may not actually exist in practice. Furthermore, interpretation of these results is likely complicated by the use of other psychotropic drugs. For example, antidepressants may differ in terms of their propensity for extrapyramidal symptoms\textsuperscript{159}, but neither the drug nor the prescribed daily doses have been accounted for in this study. Although this lack of association between antipsychotic polypharmacy and extrapyramidal symptoms is not novel\textsuperscript{160,161}, conventional wisdom and empirical evidence attribute the risk of extrapyramidal symptoms to the extent of utilization rather than the number of antipsychotics prescribed\textsuperscript{131,132,160}. In fact, after controlling for antipsychotic utilization, Carnahan et al.\textsuperscript{157} reported that polypharmacy was no longer a significant predictor of anticholinergic use in individuals who were prescribed atypical antipsychotics.

Another important finding was the lack of association between the use of clozapine and antipsychotic prescribing patterns at admission. Unlike other atypical antipsychotics such as olanzapine, quetiapine, and risperidone, the proportion of individuals who were prescribed clozapine was similar between the two groups. This likely reflects a reluctance to prescribe clozapine as part of a treatment regimen involving two or more antipsychotic, which is reasonable given the lack of overwhelming support for clozapine-antipsychotic polypharmacy\textsuperscript{162}. Even in a meta-analysis that favors the use of this practice\textsuperscript{138}, the effect size was small (-0.239) and long-term tolerability remains to be seen. However, the fact that the other atypical antipsychotics were so readily used in polypharmacy is emblematic of the underutilization of clozapine in treatment-resistant psychosis. This common practice of polypharmacy may have delayed the initiation of clozapine in individuals who have yet to try the antipsychotic\textsuperscript{141}.

At discharge, the only differences observed between the two groups were also limited to the use of antipsychotics. But unlike before, risperidone was the only atypical antipsychotic found to be associated with antipsychotic prescribing patterns. This likely reflects the interest in risperidone as an adjunct to clozapine monotherapy at the time when many of these individuals were discharged from the Program. The rationale for the addition of risperidone is likely based on the fact that striatal dopamine D\textsubscript{2} receptor occupancy is lower with clozapine than with most other
antipsychotics\textsuperscript{[90]}. The addition of another atypical antipsychotic that is capable of producing greater dopamine D\textsubscript{2} receptor occupancy could theoretically improve therapeutic response. This hypothesis—that risperidone could augment clozapine monotherapy—was tested in a multi-site randomized controlled trial that had recruited participants from Riverview Hospital, the findings of which suggested that clozapine-risperidone polypharmacy was no different than clozapine monotherapy in eliciting response and improving core symptomatology\textsuperscript{[163]}. The frequent use of this particular combination may have been specific to individuals who were treated at Riverview Hospital around the time when this trial took place. Although other tertiary referral hospitals may have also adopted a similar approach in the past, it is unlikely that this combination was ever widely used in primary and secondary care. Thus, the external validity of this finding may be limited.

4.2 Within-individual changes in pharmacological treatment

Two important patterns have emerged in terms of pharmacological treatment at the Program. First, the majority of individuals who were prescribed more than one antipsychotic at admission had a reduction in the number of antipsychotics prescribed by discharge. Second, the extent of antipsychotic utilization was typically lower at discharge than it was at admission. These two changes were most apparent in individuals who went from having excessive to acceptable antipsychotic utilization over the course of hospitalization. In contrast, most individuals who went from monotherapy to polypharmacy saw increases in antipsychotic utilization, which is not particularly surprising given the association between polypharmacy and excessive dosing\textsuperscript{[134,139,150]}.

More surprising is the observation that the majority of individuals who had acceptable doses at admission saw increases in antipsychotic utilization by the time of discharge. In fact, 56 of 138 had transitioned from acceptable to excessive utilization by discharge, but most had experienced symptomatic improvement characteristic of treatment at the Program. This supports the hypothesis that the utilization needed for response is greater in treatment-resistant psychosis than it is for treatment-responsive psychosis. For example, while clozapine may possess greater clinical efficacy than olanzapine at therapeutic doses of both drugs\textsuperscript{[164]}, this does not appear to be
the case when supratherapeutic doses of olanzapine (e.g., 25 to 45 mg or 2.5 to 4.5 DDD) are used instead\textsuperscript{[165]}. Other high-dose treatments may also be of some benefit in treatment-resistant psychosis, but the lack of tolerability, particularly for antipsychotics exhibiting high occupancy of dopamine D\textsubscript{2} receptors at therapeutic doses, likely limits their utility.

Nonetheless, while these two patterns of change bring treatment more in line with evidence-based practice, the central role of clozapine in treatment-resistant psychosis cannot be overstated. For the majority of individuals who were not prescribed clozapine at admission, the drug was prescribed during hospitalization and presumably titrated to effect by the time of discharge. For the majority of individuals who were prescribed clozapine at both time points, the dose at discharge had increased from that at admission. Most importantly, more than half of the individuals admitted to the Program were prescribed clozapine at discharge, thus ameliorating the issue of clozapine underutilization that is observed in primary and secondary care.

This trend in clozapine utilization was not unlike that reported in another naturalistic, retrospective study\textsuperscript{[166]}. Among the 153 patients with treatment-resistant schizophrenia who were admitted to a tertiary psychosis service in the United Kingdom, there were 43 more individuals who were prescribed clozapine at discharge than there were at admission (90 vs. 47; 41 of the individuals who were prescribed clozapine at admission were prescribed clozapine at discharge). In addition, more individuals were prescribed only one medication at discharge (38 vs. 18), reflecting a decrease in psychotropic drug use. However, in individuals who were prescribed more than one antipsychotic at discharge, clozapine was most commonly co-prescribed with amisulpride or quetiapine rather than risperidone.

Although it may be tempting to characterize all of these changes as definitive pathways to symptomatic improvement, this would be a gross oversimplification of the treatment received at the Program. The actual course of treatment is poorly approximated since data were only extracted from the two time points. Individuals who experienced a reduction in the number of antipsychotics may have been prescribed even more antipsychotics at some point during their hospitalization. Likewise, individuals who saw a decrease in utilization may have been
prescribed even lower doses at some point in time. Unfortunately, the process of optimizing pharmacological treatment remains one of trial and error and does not necessarily proceed in a linear fashion. Nonetheless, the patterns here suggest that optimization typically requires clozapine and a departure from antipsychotic polypharmacy and excessive dosing seen at baseline.

### 4.3 Within-individual changes in symptom severity

A decrease in severity across all symptom domains was observed over the course of hospitalization. Based on an equipercentile linking procedure between PANSS and CGI severity scale scores,[167] the median PANSS score was closest to a rating of “markedly ill” at admission and a rating of “moderately ill” at discharge. Similarly, based on the linking of the absolute change in total PANSS score and the CGI improvement scale,[168] the median change most closely resembled someone who was “minimally improved”. To put this into perspective, this degree of improvement (or lack thereof) is not typically considered a response in most randomized controlled trials.[122] However, the rate of response may be lower than expected because the individuals referred to the Program tend to be those with the greatest degree of treatment resistance in the province. Since the options in the pharmacological management of treatment-resistant psychosis are limited, it is understandable that response is not attained in all individuals admitted to the Program.

### 4.4 Predictor variables associated with change in symptom severity

#### 4.4.1 Admission PANSS scores

Individuals who have severe symptoms at admission stand to benefit the most from hospitalization. However, while the absolute change is often lower in individuals with less severe symptoms, clinicians may not perceive this to be a difference in the extent of improvement since change in symptomatology is often judged on a relative basis.[168] Consequently, a relative reduction in PANSS scores greater than 20% may be a more meaningful approach to describing response to hospitalization in treatment-resistant psychosis. In fact, the response rate approaches those observed in randomized controlled trials if this criterion were used instead.[122]
4.4.2 Diagnosis
In terms of diagnoses, individuals with schizophrenia appear to exhibit less improvement than those with schizoaffective disorder across all symptom domains. Woodward et al.\textsuperscript{[169]} reached a similar conclusion using structural equation modeling to study the changes in a five-dimensional unconstrained model of the PANSS in an overlapping cohort of patients from Riverview Hospital. Differences in the underlying pathology that have yet to be identified may explain this discrepancy in response. While the validity of schizoaffective disorder as a distinct pathological entity is contested, individuals with this diagnosis generally have a better prognosis than those with schizophrenia\textsuperscript{[170,171]}. Whether a similar difference in prognosis exists in individuals with treatment-resistant psychosis requires further study.

4.4.3 Sex
The severity of negative symptoms is often greater in males\textsuperscript{[172,173]} . However, if the admission PANSS score is the same between individuals of the opposite sex, then the corresponding model in this study suggests that the reduction in negative symptoms will be greater in females. In one naturalistic study of outpatients with schizophrenia\textsuperscript{[174]} , females who were prescribed clozapine saw a greater improvement in negative symptoms than males who were prescribed the same drug. However, these differences in improvement were also observed across the other symptom domains. In another naturalistic study consisting of inpatients with treatment-resistant psychosis or bipolar disorder, clinical response to clozapine was not found to differ between the two sexes\textsuperscript{[175]} . In an open-label trial of individuals with treatment-resistant schizophrenia, clinical response to clozapine was found to favor males\textsuperscript{[176]} . This lack of consistency between the results of these studies may reflect differences in methodology and baseline characteristics. Thus, this particular finding—that females tend to see greater improvement in negative symptoms following treatment at a tertiary referral hospital—may be specific to this cohort and be of little use in predicting response to pharmacological treatment.

4.4.4 Age
Much as there are sex-related differences in symptom severity, age-related differences in symptomatology also exist. The severity of positive symptoms tends to decrease with age and the
severity of negative symptoms either persists or increases over time\textsuperscript{(172,173)}. But in terms of the change in symptom severity over the course of hospitalization, the corresponding models in this study suggest that the extent of improvement in general psychopathology and overall symptomatology decrease with age. Since these models include the respective admission PANSS scores as predictor variables, an explanation for this phenomenon would likely require either an age-related worsening in symptoms that is less amenable to treatment or an age-related improvement in symptoms that is more amenable to treatment. Among the items found under the general psychopathology scale, a cluster of symptoms consisting of somatic concern, anxiety, guilt feelings, and depression has been reported to be negatively associated with age in schizophrenia and schizophreniform disorder\textsuperscript{(177)}. If these anxiety and depressive symptoms are amenable to treatment, which is possible given the improvement observed in a similar cluster of symptoms following treatment with either risperidone or iloperidone\textsuperscript{(178,179)}, then this could explain the relative lack of improvement with age given the same admission PANSS score on the general psychopathology scale. However, it remains to be seen whether this same association exists in schizoaffective disorder and treatment-resistant psychosis.

4.4.5 Clozapine
While it is true that many individuals who have tried clozapine prior to admission likely experienced little to no clinical improvement (hence their referral to the Program), it would be an oversimplification to categorize all of these individuals as having clozapine-resistant psychosis. Among the individuals who remained on clozapine at admission and discharge, many have had their doses increased so it is possible that a portion of these individuals were prescribed suboptimal doses at admission. Conversely, among the individuals who have not had a clozapine trial prior to admission, approximately 40-70\% will likely meet the criteria for clozapine-resistant psychosis and will require either augmentation or the use of another antipsychotic altogether\textsuperscript{(180)}. Given the suspected heterogeneity within these two groups in terms of their true responsiveness to clozapine, the tentative association between prior clozapine trial and change in negative symptoms is unlikely to be a robust finding.
The greater improvement in positive symptoms observed in individuals who were prescribed clozapine at discharge is more likely to be replicated in future studies. Although the data do not describe treatment at the Program beyond the medications prescribed at admission and discharge, the individuals who were not prescribed clozapine at either admission or discharge are likely those who: have tried clozapine in the past to no success; have tried clozapine during hospitalization to no success; are intolerant of clozapine; or have yet to try clozapine. In contrast, those who were only prescribed clozapine at discharge are likely those who: had yet to try clozapine; had previously tried clozapine to no success; or had previously tried clozapine but found it to be poorly tolerated. Since the Program was intended for the specialized care of individuals with treatment-resistant psychosis, clozapine was most likely regarded as the first-line option if the current treatment had failed to elicit a response. Thus, most individuals who were not prescribed clozapine at either time point were likely intolerant of or nonresponsive to clozapine. Conversely, individuals who were prescribed clozapine at discharge were tolerant and at least partially responsive to clozapine.

In this study, clozapine was only found to be more effective in reducing positive symptoms when prescribed at discharge. If the duration of treatment with discharge medications was uniformly greater than three months, then the lack of separation between clozapine and other antipsychotics in the improvement of other symptom domains would match the findings of the meta-analysis conducted by Siskind et al.\textsuperscript{126}. If the duration of treatment with discharge medications was less than three months, the fact that clozapine was not found to be more effective in reducing negative symptoms in this study does not have to be incompatible with the findings of the meta-analysis. In reviewing the studies of shorter duration that were included in the meta-analysis (i.e., those less than three months), the randomized controlled trial with the greatest influence on the results was the one comparing clozapine to haloperidol in treatment-resistant schizophrenia\textsuperscript{181}. However, of the 328 patients who were prescribed antipsychotics at discharge from the Program, only four were prescribed haloperidol. Moreover, three were prescribed haloperidol in combination with another antipsychotic. Therefore, there are considerable challenges extending the results of the meta-analysis to this naturalistic study.
Individuals who were prescribed clozapine at admission and discharge failed to show greater improvement than those who were not prescribed clozapine at either admission or discharge. If clozapine is indeed more effective at reducing the severity of positive symptoms, then the most likely explanation for this observation is that the individuals who were prescribed clozapine at admission were already showing signs of improvement relative to when they were not prescribed clozapine at all. Over the course of hospitalization, further improvement in positive symptoms would only be derived from the optimization of clozapine treatment. Given all of this, it would not be unreasonable to expect lesser improvement in positive symptoms within this group.

4.4.6 Antipsychotic polypharmacy
According to the regression analysis, individuals who were switched to polypharmacy at discharge generally experienced lesser improvement in positive symptoms. This suggests that, given the same degree of change in total antipsychotic utilization, it may be better to adjust the dose of one antipsychotic than to add a second antipsychotic to the treatment regimen. However, without knowing the actual course of treatment that has taken place at the Program, it is impossible to determine whether this approach had previously been tried to no success during hospitalization. Polypharmacy may well have been the therapeutic option of last resort for the majority of individuals who had switched from monotherapy at admission. Although randomized controlled trials aimed at reducing the prevalence of antipsychotic polypharmacy have found that some individuals are able to tolerate the switch from polypharmacy to monotherapy with no deterioration in clinical presentation\textsuperscript{[182-184]}, there will always be individuals whose symptoms worsen when switched from polypharmacy to monotherapy\textsuperscript{[185]}. While it is possible that these individuals require a greater number of antipsychotics for the treatment of positive symptoms, switching to a different antipsychotic that has not yet been tried may produce similar clinical outcomes.

But contrary to the above, being on polypharmacy at both time points may be associated with greater improvements in general psychopathology and overall symptomatology over the course of hospitalization. This benefit could be the result of specific combinations of receptor occupancy that are more easily achieved when two or more antipsychotics are used together.
Unlike positive symptoms, which only require the occupancy of dopamine D$_2$ receptors for therapeutic effect, symptoms falling under the general psychopathology scale of the PANSS may require the occupancy of other receptors that cannot be achieved with certain antipsychotics when used in isolation. Even if an antipsychotic were able to bind to the relevant receptors, the degree of occupancy may be insufficient at therapeutic doses of the drug.

However, this raises the question as to why greater improvements in general psychopathology and overall symptomatology were not observed in the regression analysis for individuals who were on monotherapy at admission and polypharmacy at discharge. Although an improvement across all symptom domains is the desired clinical outcome, priority is likely given to the treatment of positive symptoms since the pervasiveness of these symptoms is central to most definitions of treatment-resistant psychosis\cite{112}. Furthermore, evidence-based approaches for the treatment of general psychopathology are lacking. Consequently, improvements in general psychopathology may be viewed as a serendipitous byproduct of the treatment for positive symptoms. The greater improvement associated with individuals who were on polypharmacy at both time points could very well be a chance observation.

4.4.7 Excessive antipsychotic utilization

Excessive antipsychotic utilization at discharge but not at admission may be associated with lesser improvement in general psychopathology. Given that excessive utilization increases the risk for dose-dependent adverse effects, a parsimonious explanation for this association could be that the onset of new dose-dependent adverse effects hinders improvement in general psychopathology. Based on a secondary analysis of data from the CATIE study, there is evidence to suggest that impairments in cognition may be more pronounced in individuals exhibiting greater occupancy of dopamine D$_2$ receptor occupancy (as estimated from the plasma concentrations of antipsychotic drugs)\cite{186}. Since the extent of occupancy depends on the dose, it may be reasonable to expect a worsening in items on the general psychopathology scale such as poor attention if someone had previously been prescribed an acceptable dose of antipsychotics at admission. Similarly, new-onset extrapyramidal symptoms such as akinesia can be mistaken for depression\cite{116}, another item on the general psychopathology scale. But considering that
approximately half of the items on the PANSS are grouped under the general psychopathology scale, it is worth noting that this lesser improvement in general psychopathology is not reflected in the change in overall symptomatology.

4.4.8 Drugs other than antipsychotics

The use of psychotropic medications other than antipsychotics suggests a more complex clinical presentation. Antidepressants are commonly used in psychotic disorders to treat persistent negative or depressive symptoms. If someone was prescribed antidepressants at discharge but not at admission, then it is likely that these symptoms became apparent during hospitalization at the Program. While a meta-analysis of randomized controlled trials has found small but statistically significant improvements across negative and depressive symptom domains in individuals who have been co-prescribed antidepressants in the treatment of psychotic disorders\textsuperscript{187}, the estimated regression coefficients in each of the four models of this study suggest otherwise; the use of antidepressants at discharge was associated with lesser improvement across all symptom domains. This again could simply be the result of response dictating treatment. Those who were not prescribed antidepressants at admission or discharge may have also had negative or depressive symptoms, but treatment with antipsychotics may have been sufficient. In contrast, individuals who had to be prescribed antidepressants at discharge likely had symptoms that were persistent and difficult to alleviate with antipsychotics alone. Thus, even with antidepressants, the extent of improvement may have been limited.

While there is limited evidence to suggest that benzodiazepines are comparable to antipsychotics in the short-term treatment of psychosis\textsuperscript{188}, the use of benzodiazepines at admission and discharge was associated with lesser improvements in all but negative symptoms. Again, this could be the result of differences in symptomatology between individuals needing to be prescribed benzodiazepines at both time points and those who do not. If these drugs were used for their anxiolytic or sedative effects, then it would be reasonable to expect the scores on related items of the PANSS to be higher at admission. But since the benefits derived from their combined treatment are transient\textsuperscript{188}, appearing shortly after drug administration and dissipating
soon after, any improvement in symptoms may not be recognized as such when the PANSS is administered at discharge.

It is worth noting that no associations were observed between the use of mood stabilizers and changes in symptom severity. While mood stabilizers are commonly prescribed in treatment-resistant psychosis, there is little evidence for their use in augmenting clinical response to antipsychotics such as clozapine\textsuperscript{[189,190]}. In a retrospective study, mood stabilizers appeared to hasten improvements in symptom severity\textsuperscript{[191]}. But after six months of treatment, overall symptomatology was comparable between individuals on clozapine monotherapy, those receiving adjunctive lithium, and those receiving adjunctive valproate despite lower baseline BPRS scores in the group receiving lithium.

4.5 Limitations

4.5.1 DDD method

Owing to the differences in clinical potency, comparisons of antipsychotic utilization can only be made after standardizing the dose of each drug. The DDD method was used in this study, but it has its limitations. For example, while the values correlate well with chlorpromazine equivalents\textsuperscript{[192]}, another method commonly used to standardize antipsychotic doses\textsuperscript{[193,194]}, the DDD method may be less reliable in detecting differences in antipsychotic utilization between individuals who have been prescribed anticholinergics for extrapyramidal symptoms and those who have not\textsuperscript{[158]}. This may have to do with the fact that chlorpromazine equivalents are based on fixed or flexible dose trials whereas the DDD values are based on product monographs and available literature\textsuperscript{[195]}. Although the latter may be suitable for establishing “the assumed average maintenance dose per day for a drug used for its main indication in adults”\textsuperscript{[149]}, the values are unable to account for differences between drugs\textsuperscript{[148]}. Therefore, the DDD method may have limited utility as a means of establishing dose equivalence, but it remains a useful tool for standardizing drug utilization\textsuperscript{[196]}. 
4.5.2 Exclusion of pro re nata medications

While pro re nata antipsychotics are often administered sporadically, the exclusion of these drugs could bias estimates of utilization. This is particularly true if they were administered with regularity around the time of admission or discharge. However, based on preliminary results from the British Columbia Psychosis Program, there is no reason to believe that the use of pro re nata antipsychotics affects the total utilization to an appreciable degree in tertiary care programs (2015 conversation from RM Procyshyn to LH Lee; unreferenced). Further investigation into this topic is warranted.

4.5.3 Categorizing antipsychotic prescribing patterns

Polypharmacy was judged based on the use of two or more antipsychotics at a single point in time. Individuals who were being cross-titrated to another antipsychotic may have been falsely categorized as having received antipsychotic polypharmacy when, in reality, they were transitioning from one drug to another. Since it is more likely for individuals to be incorrectly categorized as having received polypharmacy than it is to incorrectly categorize them as having received monotherapy, the differences in antipsychotic utilization between the two groups may be even more pronounced had more data been collected around the time of admission and discharge.

4.5.4 Antipsychotic utilization as an approximation of drug concentrations

The change in antipsychotic utilization was not associated with any changes in symptomatology. This could be a consequence of the heterogeneity in treatment prior to admission—the extent of utilization may have been too high in some individuals and too low in other individuals. Consequently, optimization of antipsychotic therapy would require changes in both directions depending on whether antipsychotics were initially under- or over-prescribed. Nonetheless, it is also important to note that the prescribed daily dose is a convenient but flawed metric in approximating the concentration of drugs at their site of action. It does not account for the pharmacokinetic differences that may exist between individuals or drug-drug interactions that are common in psychiatry. For example, polycyclic aromatic hydrocarbons in cigarette smoke are inducers of cytochrome P4501A2\textsuperscript{[197]}. Since this isozyme contributes to the metabolism of
clozapine\textsuperscript{[198]}, plasma concentrations of the drug can decrease if one were to start smoking or increase the number of cigarettes smoked per day\textsuperscript{[199]}. Conversely, fluvoxamine is an inhibitor of cytochrome P4501A2 and can increase plasma concentrations of clozapine if the two drugs are administered concurrently\textsuperscript{[200]}. This particular combination of psychotropic drugs was only observed in two individuals at the time of discharge, but it is a common approach to augmenting response in individuals exhibiting partial response to clozapine\textsuperscript{[201]}. Had it been used with even greater frequency at the Program, antipsychotic utilization would have been an even poorer estimate of the true concentration of antipsychotics within the brain.

4.5.5 Changes in diagnostic criteria

The diagnostic criteria for schizophrenia have changed since these individuals were hospitalized at the Program\textsuperscript{[10]}. While bizarre delusions and special hallucinations were previously thought to be pathognomonic for schizophrenia, having only one of these first rank symptoms is no longer sufficient for a diagnosis of schizophrenia in the fifth edition of the DSM. Furthermore, a lack of positive symptoms (i.e., delusions; hallucinations; disorganized speech) also precludes a diagnosis of schizophrenia. But despite these changes, few individuals meeting the old criteria are expected to receive a different diagnosis upon reassessment\textsuperscript{[202]}. In fact, when Mattila et al.\textsuperscript{[203]} repurposed the scores on the BPRS to approximate symptom severity in individuals who had participated in short-term efficacy trials, they found that more than 99.5\% of individuals would still be diagnosed with schizophrenia under the new diagnostic criteria.

The diagnostic criteria for schizoaffective disorder have also changed since individuals were hospitalized at the Program\textsuperscript{[10]}. In attempts to improve the reliability of the diagnosis, affective symptoms meeting the criteria for a major mood episode must now be present for the majority of the duration of illness\textsuperscript{[204]}. Thus, if the duration of the episode does not meet the above criterion, then individuals who have had a diagnosis of schizoaffective disorder in this study would now be diagnosed as having schizophrenia with mood symptoms. The number of patients affected by this change cannot be ascertained. However, if schizoaffective disorder is associated with a better prognosis, then it would be reasonable to expect an even greater difference in the estimated regression coefficients of the four models.
4.5.6 Changes in treatment patterns over time

The pharmacological approach to treatment-resistant psychosis has also changed over time. While the combination of clozapine and risperidone was prevalent at discharge from the Program, evidence for the co-administration of these two antipsychotics has proven to be equivocal\textsuperscript{[189]}. Thus, it is unlikely to be used to the same extent today. On the contrary, aripiprazole was only approved by Health Canada in 2009 so its use has certainly increased since these individuals were hospitalized at the Program. Consequently, there may be difficulties extrapolating the results of this study to other refractory psychosis programs.

4.5.7 Study design

Several limitations are inherent to retrospective chart reviews. First, the quality of the data is dependent on the source material. In this study, data were extracted from booklets that contained information on each patient and the course of treatment they had received from the Program. Since the data within these booklets were abstracted from medical records, there were opportunities for error in the records, the booklets, and the dataset. Errors in the dataset were minimized by data pre-processing. Inconsistencies and irregularities were identified and cross-referenced with the information in the booklets. Unfortunately, the original medical records were not available for reference.

Second, it is not possible to collect data that do not already exist. Information on the history of clozapine use are devoid of meaning if the rationale and outcome of these trials are not available. Antipsychotic utilization, as quantified by prescribed daily dose, is less informative than plasma concentrations of each drug. The duration of treatment with discharge medications affects the extent of response, but this cannot be ascertained using the booklets alone. A prospective follow-up study will offer more insight into the changes in treatment over the course of hospitalization if variables of interest were specified beforehand.

Lastly, missing data remain a challenge. In this study, the prescribed daily dose of antipsychotics was the most frequently missing piece of information in the dataset. Thus, in addition to the five individuals who were not prescribed antipsychotics at either admission or discharge, the four
individuals who were missing prescribed daily doses at either admission or discharge were routinely excluded from analyses requiring data on antipsychotic utilization. Although complete-case analysis simplified the task of analyzing the data, it is biased if the data were not missing completely at random. More specifically, if the data were missing at random, then complete-case analysis would be biased towards the null hypothesis\textsuperscript{[2051]}. However, alternative methods of handling missing data such as multiple imputation were not used because the number of individuals excluded from analyses was relatively small (i.e., at most 9 of 330 or 2.7%) and the data may not have been missing at random; hence explaining the lack of emphasis placed on the estimated regression coefficients in each of the four models. These results are preliminary and will require follow-up studies.

4.6 Future directions

Since the patient population is similar to that of the British Columbia Psychosis Program, follow-up studies should be completed to determine if these findings can be replicated using a different dataset. Given the increasing prevalence of augmentation strategies involving drugs other than antipsychotics, the methods will need to be adapted to reflect these changes in treatment. Prospective studies may also be beneficial in overcoming some of the limitations inherent in this study design. Randomized controlled trials could be conducted in this population if a promising treatment is identified.

4.7 Conclusion

The use of antipsychotics in treatment-resistant psychosis is greater in primary and secondary care than it is in tertiary care at the Program. The overall reduction in the use of antipsychotics suggests that antipsychotic polypharmacy and excessive utilization may not be necessary for a reduction in symptom severity. However, treatment strategies should always be personalized if the goal is to achieve the best possible response. While the co-administration of certain psychotropic drugs may be associated with lesser improvements in symptom severity, it is possible that the removal of these drugs could result in an even further worsening of symptoms.
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77


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